HAZZARD'S Geriatric Medicine and Gerontology



SEVENTH EDITION

Jeffrey B. Halter • Joseph G. Ouslander
Stephanie Studenski • Kevin P. High • Sanjay Asthana
Christine S. Ritchie • Mark A. Supiano

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Hazzard's Geriatric Medicine and Gerontology

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Seventh Edition

Hazzard's Geriatric Medicine and Gerontology

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Foreword

It has been my privilege as Editor Emeritus of this latest edition to follow its progress over the past 3 years from design at the first meeting of the editorial board to publication. I am pleased to predict that the seventh edition of *Hazzard's Geriatric Medicine and Gerontology* will solidify its reputation as the leading "go to" source for readers seeking the latest, most comprehensive, in-depth, and reliable treatise in research and practice that optimizes the care of our aging and older patients. Moreover, this edition will further expand its influence toward worldwide enhancement in the care of those patients, whose numbers are expanding dramatically as population aging becomes a global phenomenon.

Especially gratifying in my association with this textbook has been its widespread use as core material in geri-atric fellowship training programs. I am frequently flattered to be asked to autograph the latest volume for fellows who have come to value the book highly during their training for its accessibility, breadth, depth, and authenticity as a single source for their scholarly education in our field.

Their appreciation brings me special satisfaction. From the genesis of this textbook in its first edition over 30 years ago, our focus has been steadily maintained on geriatric fellows in training as our primary target audience. This approach was adopted because we envisioned our textbook as complementing the prior education that physicians received in medical school, graduate training in residency, and then maintained in continuing education programs, education which forms the foundation of care for all patients. Through our textbook we have hoped that physicians will be enriched and continuously kept current from its concentration upon the special needs of their older patients. This has been integrated with chapters summarizing the aging process across the lifespan from conception to death (gerontology), but honing down on those above 65, 75 (my personal definition as the threshold to old age), and, perhaps most germane to our special contributions as geriatricians, the "oldest old," those over 85, in whom the art and science of caring for the most complex and vulnerable can be most appreciated. And with the "Aging Tsunami" of retiring baby-boomers looming ever nearer to the seawall of limited resources, our mission to enhance the practice of all professionals and caregivers in managing such patients through our textbook is all the more urgent.

Thus geriatric fellows appropriately remain our primary target audience for this edition, for it is through their added education and expertise that our contribution can be best applied, amplified, and broadly disseminated. This is true whether their training (as for most American fellows) is compressed into a single, full-time year of clinical fellowship following 3-year residencies in Internal Medicine or Family Medicine or extended to acquire additional academic skills and experience in research, education, clinical practice, public health, public policy, or health care systems. This special expertise will serve them well as future leaders in health care as it becomes progressively skewed toward caring for older patients. Thus it will be incumbent upon editors of future editions of this textbook to remain abreast of leading edge developments in our field, which promises to become ever more sophisticated and challenging as aging citizens continue to enjoy increasing healthspan as well as lifespan.

It is with pride and confidence that I predict that these goals will be reflected and continuously enhanced in all future editions of this textbook.

William R. Hazzard, MD

Preface

On behalf of the Editors, it is an honor and privilege to provide this preface to *Hazzard's Geriatric Medicine and Gerontology*, Seventh Edition. This textbook has become a mainstay of the rapidly developing field of geriatric medicine. Building on the textbook's already rich history since it was first published in 1985, the seventh edition emerges renewed and vibrant. This is the second edition of this textbook to carry the name of its founding editor Bill Hazzard in its title. What we and our publisher McGraw-Hill have simply done is to formalize the reality of the imprint that Bill Hazzard has made, as the textbook has been known informally as *Hazzard's Textbook* for many years. We are pleased that Bill has contributed a foreword to the seventh edition, providing his view of the critical importance of fellowship training in geriatrics to the future of our field.

The seventh edition is substantially different from its predecessors, reflecting the continued growth and increasing sophistication of geriatrics as a defined medical discipline. Vitality and continued rejuvenation have been enhanced through the addition of six new chapters (Chapter 23: Quality of Care, Chapter 57: Common Non-pain Symptoms, Chapter 58: Strategies of Effective Communication Around Advanced Illness, Chapter 59: Palliative Medicine Across the Continuum of Care Including Hospice, Chapter 106: Coagulation Disorders, and Chapter 107: Plasma Cell Disorders) and recruitment of new authors for nearly 40% of the chapters. Despite adding new chapters, we have modified and combined others to maintain a total of 130, as in the sixth edition. This is the first edition of the book to be published in full color, thereby greatly enhancing the many illustrations and figures included. We recognize the increasing evidence regarding the care of older adults with serious illness(es) near the end of life and the integral role of palliative care in geriatric medicine. Therefore, we have established Principles of Palliative Medicine as one of the five major parts of the seventh edition, expanded the number of chapters addressing this topic, and added new palliative care content to many other chapters. To promote and facilitate the book's utility as an educational resource for Geriatric Medicine fellows in training and others, each chapter now includes learning objectives and key clinical points. These have been linked to one or more of the Geriatric Fellowship Curriculum milestones to allow easy access by readers. This new educational emphasis is highly relevant to Bill Hazzard's comments in the foreword.

Two new editors have played a critical role in the revitalization of this textbook: Christine Ritchie, who has led the palliative medicine expansion, and Mark Supiano, who has led the added focus on the book's role as an educational resource. In addition to Christine and Mark, the seventh edition's editorial team includes me (my fifth edition); Joe Ouslander (his fourth edition); and Sanjay Asthana, Kevin High, and Stephanie Studenski (their second edition). We acknowledge the effort and contributions of retired editor Mary Tinetti (the fifth and sixth editions). Fortunately for all of us, Bill Hazzard has stayed actively involved as editor emeritus and senior advisor. The seventh edition acknowledges and recognizes the worldwide growth of the field of geriatric medicine. We are very pleased that in the seventh edition 35 authors who are in countries outside of the United States contributed to 13 of the chapters. Overall, our authors are a large and diverse group including many geriatricians but also a substantial number of subspecialists from a range of medical and surgical disciplines. In addition, multiple health profession disciplines are represented among the authors. Two of the textbook's editors are women, and women contributed to over 60% of the chapters, most as lead or senior author.

A major step forward for this textbook is the electronic version, which is now widely available online and will continue to be available as the seventh edition. One of the original goals of working with McGraw-Hill as the publisher of this textbook was to provide a link with *Harrison's Principles of Internal Medicine*. This link was greatly strengthened with the electronic version of the sixth edition of *Hazzard's Geriatric Medicine and Gerontology*, which became part of McGraw-Hill's *AccessMedicine.com* collection. Access Medicine includes not only our textbook and *Harrison's Principles of Internal Medicine*, but also multiple other important books in the clinical library of McGraw-Hill. There are a number of key implications of our textbook being a part of McGraw-Hill's *AccessMedicine.com*. First, it adds a living presence to the textbook as additional material can be added as online updates as needed. We anticipate that such updates will be available for many chapters of the textbook on a regular basis. Second, we are especially pleased that students of the health professions, both undergraduate and postgraduate, now have full access to our textbook through the electronic version if they are at an institution that subscribes to *AccessMedicine*. Finally, our authors can provide supplementary material and illustrations as well as educational materials, which will be accessible

through the online version.

Thus just as our population is inexorably aging, and medicine is faced with an ever-growing number of older patients with multiple and complex problems, we have been able to bring together the best minds and leaders in the field to provide authoritative guidance. Our authors present a highly diverse and dynamic range of thinking, that has not previously existed in our textbooks of geriatric medicine. We are now reaching a broader audience through the availability of the electronic version of the textbook. We have kept it a living and growing document that encompasses the rapid stream of new information, which is helping us to provide more compassionate and effective care to the rapidly growing population of older adults.

Putting together a textbook of this magnitude requires enormous effort by many people. On behalf of the editors, I wish to particularly thank the many chapter authors who have contributed to the book. We especially recognize Jeffrey H. Silverstein, MD, senior author of the chapter on Anesthesia, who passed away prior to publication of the seventh edition. For decades, Dr. Silverstein was a passionate advocate for geriatrics, as well as a highly respected leader in the field of ethics.

The strong and effective working relationship that we have with McGraw-Hill is made possible by the outstanding efforts of Karen G. Edmonson, Senior Editor for the McGraw-Hill geriatrics publishing program; Kim J. Davis, Managing Editor; and their McGraw-Hill colleagues who have ensured the progress of the publication and the important next steps in the textbook's evolution. We are grateful for the continued support of James F. Shanahan, publisher at McGraw-Hill, who was instrumental in the initial publication of this textbook and served as its Managing Editor for the first six editions. We especially appreciate the efforts of Nancy Woolard from Wake Forest University School of Medicine, who has served as a senior editorial project manager for multiple previous editions. Her role for the current edition has been critical to provide a strong link to our past history and as the final common pathway for assembly of the seventh edition. We thank Drs. Alexandra Meier, Brett Porter, and Michelle Sorweid, Geriatric Medicine fellows at the University of Utah, for their helpful advice mapping the fellowship curricular milestones to relevant chapters in the textbook. We also acknowledge the staff who provide support for editorial efforts from our academic offices: Julie Kozak Seeger at the University of Michigan, Catherine Gouchenour at Florida Atlantic University, Eva Gray at the University of Wisconsin, and Helen Colombo at the University of California, San Francisco.

Jeffrey B. Halter, MD

Part

Principles of Gerontology

Chapter 1.	Biology of Aging and Longevity
Chapter 2.	Genetics of Age-Dependent Human Disease
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Chapter 1

Biology of Aging and Longevity

David B. Lombard, Richard A. Miller, Scott D. Pletcher

Learning Objectives

- Describe how biological aging induces progressive functional decline and loss of homeostatic capacity.
- Understand how diet, genetics, and pharmacologic intervention can affect the rate of aging.
- Explain how genetic or pharmacologic interventions affect intracellular signaling pathways such as insulin/insulin-like growth factor (IGF), mTOR, and sirtuins to extend mammalian lifespan.

Key Clinical Points

1. **Biological aging predisposes older individuals to disease and increased mortality risk.**
2. **Dietary restriction (DR) extends lifespan and promotes late life health in diverse taxa, including mammals.**
3. **Interventions that slow the aging rate also delay or even prevent multiple age-associated pathologies simultaneously, such as cancer, neurodegeneration, metabolic syndrome, renal dysfunction, and many others.**

Aging is the process that converts young adults, most of them healthy and in no need of assistance from physicians, into older adults whose deteriorating physiologic fitness leads to progressively increasing risks of illness and death. The effects of aging are so familiar to health professionals and aging adults that they are viewed by both parties as immutable, taken for granted, an arena in which diseases and their treatments take place, but not subject to intervention or modulation. The major discovery in biogerontology, gradually emerging from decades of work in animal model systems, is that this old-fashioned viewpoint is wrong, and that the aging process can be delayed or decelerated in mammals, built very much like human beings, by simple manipulations of nutritional signals and genetic circuits similar to those already well-documented in people. It is now routine to extend lifespan, in rats and mice, by about 40%. This effect is, remarkably, 10 times greater than the increase in active life expectancy that would ensue from a complete elimination of all neoplastic illnesses, or all heart attacks, in a human population. Work in mice is also just starting to show that drugs, including some already in clinical use, can produce meaningful increases in mouse lifespan. As importantly, genetic and pharmacologic interventions that increase longevity typically delay or even prevent many classes of age-associated diseases, such as cancer, metabolic decline, and neurodegeneration. It thus seems likely that a more detailed understanding of the factors that determine aging and the processes by which aging increases the risk of such a wide range of lethal and nonlethal illnesses and disabilities could, in the foreseeable future, have a profound impact on human health and preventive medicine.

Aging is a mystery, in the same sense that infectious disease was once a mystery, and consciousness still is: an area of investigation in which well-informed researchers cannot be certain that they have selected a line of investigation bound to be productive. For a long time, most published papers in biogerontology journals consisted of descriptions of the ways in which young mice, rats, or people differed from older ones. This descriptive era has been superseded by one focused on specific molecular hypotheses about the key factors that regulate aging. The foundation of this modern approach to the biology of aging was the development of genetic models and nutritional manipulations that could delay aging, and the exploitation of this leverage to test molecular ideas about the basis for the retardation of

the aging process.

WHAT IS AGING?

This question—what is aging?—is posed not as an invitation to semantic quibbling, but to initiate reexamination of facts so familiar that they are seldom examined. A case history of an individual who has mild arthritis, some loss of hearing acuity, some evidence of incipient cataract, loss of muscle mass and strength, a progressive decline in capacity for aerobic exercise, troubles with learning and remembering, and an increased vulnerability to infectious illness would lead any physician to assume that the individual described is a man or woman of 60 or more years. But the list of signs and symptoms refers with equal accuracy to a 20-year-old horse, a 10-year-old dog, or a 2-year-old mouse. The specific list of deficits and impairments shifts a bit from person to person, and from species to species, but it is extremely rare to find an 80-year-old person, a 3-year-old mouse, or a 14-year-old dog that has avoided all of these age-associated problems. The aging process is synchronized, in that it is common to see all of these difficulties in older people, horses, dogs, and mice, but rare to encounter any of them in young adults just past puberty. This synchrony, though entirely familiar to schoolchildren, physicians, and scientists alike, is the central challenge in biological gerontology: how is it that such a process affects so many cells, tissues, organs, and systems at a rate that varies, even among mammals, over a 100-fold range from the shortest-lived shrews to the longest-lived whales? Structural features of shrews, mice, dogs, and people are remarkably similar at scales from the arrangement of DNA and histones in the nucleus, to the architecture of the kidney, heart, and thymus, to the role of the central nervous system (CNS) and endocrine systems in regulating responses to heat and cold, hunger and thirst, infection, and predators. Why, then, in molecular terms, will the eye, kidney, immune system, brain, and joints of a mouse last only 2 to 3 years under optimal conditions, while the same cells and organs and systems persevere for 50 or more years in people, and longer still in some species of whales?

The definition proposed at the beginning of this chapter—aging as a process for turning young adults into distinctly less healthy old ones—is straightforward enough to appear simple-minded, but in practice draws some prominent distinctions. In this view, aging is not a disease. Diseases are certainly among the most salient consequences of aging, but aging produces many changes not classified as diseases, and many diseases also affect young people. Similarly, lifespan and mortality risks are influenced by many factors besides aging. Thus, evidence that a gene or diet or public health measure has altered life expectancy, upwards or downwards, does not imply that the effects have been achieved by an effect on aging. In the context of the whole organism definition of aging used in this chapter, it is hard to interpret the meaning of changes that occur as individual cells “age” in tissue culture. Ongoing studies in genetically engineered mice are aimed at evaluating the contribution of cellular “senescence” to the aging of the entire organism, a topic covered in greater depth in a subsequent section.

From a biological standpoint, a critical distinction is the difference between aging and development. Development creates a healthy young adult from a fertilized egg, and is strongly molded by natural selection. Genetic mutations that impair development, creating a slower falcon, a near-sighted chipmunk, or a chimpanzee uninterested in social cues, are rapidly weeded from the gene pool. But the force of natural selection diminishes dramatically at ages that are seldom reached. Mice, for example, typically live only 6 months or so in the wild, before they succumb to predation, hypothermia, starvation, or other natural hazard. There is strong selective pressure against mutations that cause cataracts in the first few months of mouse life, but little or no pressure against genotypes that postpone cataract formation for 2 years, an age seldom reached by mice in their natural environment. Mice protected, in a laboratory setting, against predation, starvation, and other risks typically do develop cataracts in their second or third year. In wolves, however, a genotype that delayed cataracts for only 2 years would be a disaster; natural selection favors wolf genes that preserve lens transparency for a decade or more. A similar process, working on our ancestors in environments where survival to 15 was common, but survival to 55 distinctly uncommon, has filled our own genome with alleles that postpone cancer, osteoarthritis, coronary disease, Alzheimer disease, presbycusis, cataracts, sarcopenia, immune senescence, and many other familiar maladies, for about 50 to 60 years. Thus, although aging and development seem, superficially, to be similar processes in that both lead to changes in form and function, they are different in a fundamental and critical way: Development is molded directly by the forces of Darwinian selection, and the changes of aging are the consequence of the failure of these selective processes to preserve function at ages seldom reached by individuals in any given species.

Aging as a Coordinated, Malleable Process

The definition of aging as a process that turns young adults into old ones conflicts with a view of aging as instead a collection of processes, some that lead to arterial disease, some that affect endocrine function, some that impair cognition or cause neoplastic transformation, etc. Because each of these ailments is itself the outcome of a complex interaction among many factors, including genes, diet, accidents, viruses, toxins, and physicians, and because each of these diseases, and many others, seems an inextricable part of aging, it originally seemed implausible to regard aging as less complex than its (apparent) constituents. Considering aging as a process, rather than a collection of complex processes, has thus seemed, to some, to be an oversimplification.

However, two lines of evidence support the merits of the view of aging as a unitary process, with its own (still incompletely defined) physiologic and molecular basis, which underlies and tends to synchronize the multiple changes seen in older individuals. The first of these discoveries was caloric restriction (CR): the observation that rodents allowed to eat only 60% of the amount of food they would voluntarily consume live 40% longer than controls permitted free access to food. This observation, first made in the 1930s, has been repeated in more than a dozen species in scores of laboratories. Studies in rhesus monkeys have produced suggestive evidence that similar benefits may accrue in our own order of mammals. The key point is not merely that lifespan is extended, but that nearly all of the consequences of aging are coordinately delayed. CR delays changes in cells that proliferate continuously (such as gut epithelial cells), cells that can be triggered to proliferate when called upon (such as lymphocytes), and those that never proliferate (such as most neurons), as well as on tissues that are extracellular or acellular (such as lens tissue and extracellular collagen fibrils). It delays aspects of aging characterized by excess proliferation, such as neoplasia, and also those characterized by failure to proliferate (such as immune senescence). It delays or decelerates age change at the tissue level (such as degradation of articular cartilage) and those involving complex interplay among multiple cells and tissues (such as loss of cognitive function and endocrine control circuits). Because CR alters, in parallel, so vast an array of age-associated changes, it seems inescapable that these many changes, distinct as they are, must be in some measure timed, that is, synchronized by a mechanism altered by caloric intake. This synchrony does not reflect a "clock" that turns on molecular and cellular damage at a set time, producing programmed changes of the sort common in development. Synchrony reflects, instead, processes that can, through unknown links, delay and decelerate age-associated damage in multiple cells and tissues in parallel, to an extent that varies widely across species.

A second, more recent, set of experiments leads to the same inference. In 1996, Bartke and his colleagues reported that Ames dwarf mice, in which a developmental defect in the pituitary impairs production of growth hormone (GH), thyrotropin, and prolactin, show an increase of more than 40% in both mean and maximal lifespan compared to littermates with the normal allele at the same locus. Since then studies of this mutant, and the closely similar Snell dwarf mouse, have documented delay in kidney pathology, arthritis, cancer, immune senescence, collagen cross-linking, cataracts, and cognitive decline, making a strong case that these genetic changes in endocrine levels do indeed modulate the aging process as a whole, with consequent delay in a very wide range of age-synchronized pathology. Since 1996, mouse researchers have documented increased lifespan in dozens of other genetically altered mouse strains, some of which show lower levels of or responses to GH, and/or its downstream mediator IGF-1.

These observations, on CR rodents and then later in mutant mice, justify a sea change in thinking about aging and its relationship to disease. The new framework includes three key tenets: (1) the aging process, despite the complexity of its many effects, can usefully be considered as a single, coordinating mechanism; (2) the rate at which aging progresses can be decelerated in mammals as well as in other taxa; and (3) the time of onset and pace of many age-associated diseases are closely linked to the aging rate. From this perspective, a fundamental challenge to biogerontologists is to develop and test models of how age-dependent changes are themselves coregulated, during middle age, to produce old people or old mice or old worms. Studies of aged individuals, as opposed to studies of aging, are relevant to this challenge only insofar as they are exploited to generate or test ideas about coregulation and synchrony, rather than disease-specific pathogenesis. The key resource for meeting the challenge is not comparisons between young and old donors, but rather comparisons between young or middle-aged adults who are known to be aging at different rates because of genetic differences or exposure to dietary or pharmacologic intervention. Fortunately, the same experiments that have documented the malleability of aging rate have produced sets of animals that do indeed age at slower-than-normal paces. With luck, future studies may produce at least tentative answers to the two key questions in biogerontology: How does aging produce the signs and symptoms of aging, and what controls the rate of this process in mammals?

MODERN STUDIES OF AGING USING ANIMAL MODELS

Modern aging biology might be considered to begin in the early 1990s, when studies of genetically tractable invertebrate models, principally the budding yeast *Saccharomyces cerevisiae*, the nematode roundworm *Caenorhabditis elegans*, and the fruit fly *Drosophila melanogaster*, began to identify ways in which the lifespan of these simple organisms can be extended. Two decades of work in these systems have led to a set of guiding principles: (1) single-gene mutations—lots of them—can extend lifespan, (2) groups of genes with related functions often influence lifespan through common mechanisms, thereby revealing defined biological pathways that modulate aging, (3) many biological processes regulate aging in a conserved manner, in diverse phyla separated by billions of years of evolutionary time, and (4) consequently, aging studies in simple model organisms—with all of their advantages in terms of facile genetics and rapid experimental turnaround—are a valuable "breeding ground" for directed studies of similar processes in vertebrate animals such as mice. Together, aging research in both invertebrate and vertebrate systems has uncovered over 100 genetic and environmental manipulations that prolong healthy lifespan, a handful of which are discussed below because they appear to be clinically relevant and potentially promising targets for intervention in humans.

Diet

As mentioned above, one of the earliest manipulations to prolong healthy lifespan involved diet. Mice or rats fed approximately 30% or 40% less food than they would ordinarily consume typically live up to 40% longer than freely fed animals. Fruit flies intermittently starved are also long-lived. Remarkably, rodents and flies exposed to DR stay healthy and active, with intact physical, sensory, and cognitive function, at ages at which most of the controls have already died. In mice, caloric restriction extends lifespan if initiated at very young ages (eg, at weaning), or when started early in adulthood (eg, at 6 months, in a species where puberty occurs at 2 months and median survival is normally about 28 months). Whether CR diets extend lifespan when initiated in animals already older than half the median lifespan is controversial, with some early studies suggesting little or no response, and some more recent experiments showing a beneficial effect. Lifespan extension by dietary manipulations appears to represent an evolutionarily conserved effect, and it occurs in taxa as diverse as daphnia, worms, flies, spiders, and rodents.

Historically, the beneficial effects of dietary manipulations have been attributed to a reduction in the caloric content of the food. Indeed, most of the early rodent and fly studies were performed by reducing availability of all dietary components (eg, protein, carbohydrates, and lipids). More recently, however, comprehensive experiments in flies and mice that cover a broad dietary landscape suggest that individual macronutrients do not act independently, nor is caloric value the primary predictor of dietary effects on lifespan. Nutrients interact, and it is their balance that appears to be critical (**Figure 1-1**). In particular, the ratio of protein to nonprotein energy in the diet is particularly significant, affecting traits as diverse as total energy intake, growth, and body composition. A diet containing relatively low protein (in relation to other macronutrients) commonly results in the longest lifespan. This broader view of dietary composition as a major determinant of health and lifespan had led to the term "dietary restriction" largely replacing the traditional term "caloric restriction."

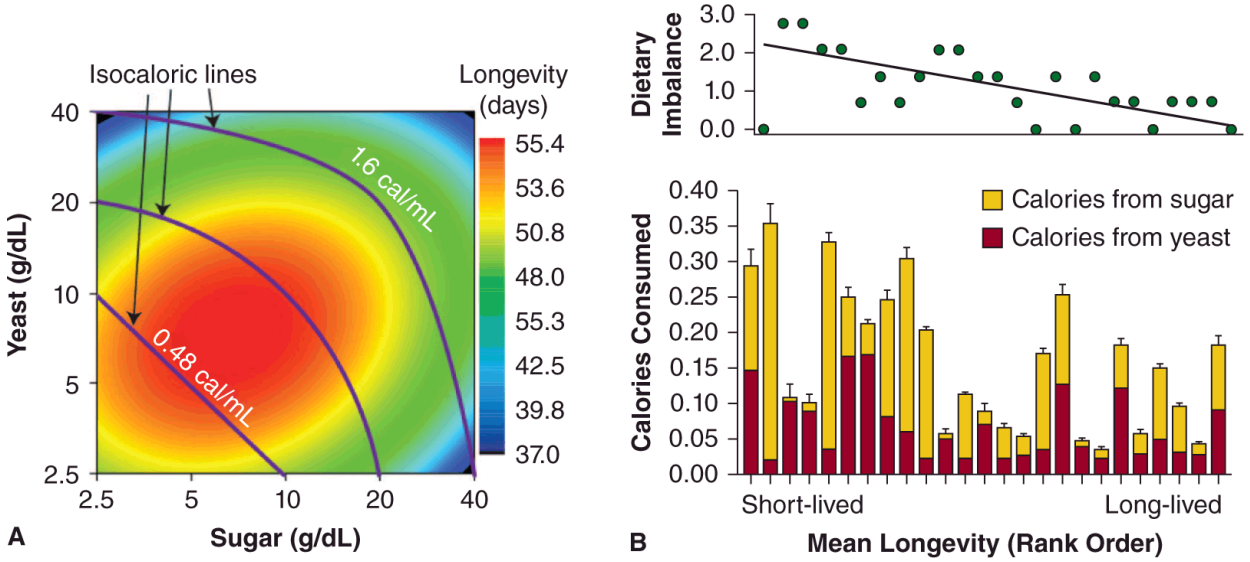


FIGURE 1-1. Dietary composition, not caloric value, specifies lifespan in *Drosophila*. (**A**) A diet response surface that characterizes the

lifespans of female fruit flies across a range of 25 different diets composed of different concentrations of sugar and yeast, which are the two macronutrients in the *Drosophila* diet. Longevity is maximized at intermediate concentrations of both nutrients, and trends in lifespan are not coincident with differences in the caloric value of the food, as evidenced by the significantly different lifespans observed in isocaloric diets. (Adapted from Skorupa DA, Dervisefendic A, Zwiener J, Pletcher SD. Dietary composition specifies consumption, obesity, and lifespan in Drosophila melanogaster. *Aging Cell.* 2008;7:478–490, Figure 2B.) (**B**) When lifespans from each of the 25 diets are rank-ordered, there is little association with amount of calories the flies consume (bottom panel), but there is a significant negative correlation between lifespan and a measure of dietary imbalance, which is proportional to the difference in nutrient concentrations (top panel). (Adapted from Skorupa DA, Dervisefendic A, Zwiener J, Pletcher SD. Dietary composition specifies consumption, obesity, and lifespan in Drosophila melanogaster. *Aging Cell.* 2008;7:478–490, Figure 3D.)

While comprehensive analysis of the dietary landscape is prohibitively expensive in species more closely related to humans, diminished food intake in rhesus monkeys can delay many indices of aging and age-related disease. However, conflicting results on lifespan extension have been observed. Given the impact of diet composition discussed above, the effect of diminished food intake on longevity in rhesus monkeys may depend on subtle differences in diet composition, as well as food intake by control animals, and the intensity with which early aspects of disease are detected and treated by veterinarians. In humans, DR leads to dramatic improvements in lipid profile, blood pressure, and other cardiovascular parameters. Whether or not DR would extend longevity in humans is unknown, though population studies hint that the answer is likely to be yes.

How DR promotes longevity mechanistically remains uncertain, but is the subject of active investigation. Invertebrate models have revealed that the health benefits and extended lifespan associated with DR represent the consequences of an active response by the organism, requiring coordinated changes in specific signaling pathways and in gene expression. Biological processes that have been implicated in the response include stress resistance, mitochondrial respiration, and protein synthesis. Some of the effects of DR also appear to be independent of differential nutrient consumption, suggesting that animals may respond proactively to the perception of reduced nutrient availability in a way that promotes survival.

Whether any of the candidate mechanisms of DR identified in invertebrates translate to mammalian systems is currently unknown. What is likely, however, is that the effects of severe DR on rodent lifespan do not depend solely on avoidance of obesity. Although DR rodents are less obese than control animals, this is not due simply to a global reduction in the overall metabolic rate. In fact, in some tissues, mitochondrial respiration actually increases in response to DR. DR does, however, increase the efficiency of the mitochondrial electron transport chain, and reduces levels of damage attributable to reactive oxygen species (ROS) in certain tissues such as the liver. Possible mechanisms of DR effects in rodents include alterations in nutrient-responsive signaling pathways, increases in stress-resistance pathways including resistance to oxidative injury, diminished inflammatory responses, changes in stem cell self-renewal, alterations in the ratio of visceral to subcutaneous fat, alterations in cellular properties related to protein metabolism, and many others, each plausible, but none of them proven at this point. Short-term DR (ranging from days to months) induces beneficial effects in vitro and in vivo on clinically relevant endpoints including surgical stress, insulin resistance, and inflammation. Further work on the early- and midlife effects of DR is among the most attractive avenues for testing basic ideas about aging in mammals.

The benefits of specific nutrient manipulations have been highlighted by experiments that alter the availability of individual amino acids, either acutely or throughout the lifespan. Rats fed a diet containing much reduced levels of the essential amino acid methionine live 40% longer than rats on a standard diet, and there is a similar, though smaller, effect in mice. The lifespan effect in mice is seen even when methionine restriction (MR) is not begun until the mice are well into adulthood, roughly the equivalent of a 35-year-old person. These animals are not calorically restricted—they eat more calories, per gram of lean body mass, than control rats, and rats pair-fed normal food to match the total caloric intake of an MR rat show a much smaller degree of lifespan extension. Diets in which amino acids are restricted could, in principle, affect tissue health and organism aging by causing changes in protein translation or rate of protein turnover, by changes in DNA methylation (which depends on metabolites of methionine), by alterations in levels or distribution of the antioxidant glutathione (also a metabolite of methionine), by changes in hormone levels (MR mice show low levels of insulin, glucose, and IGF-1), by changes in hydrogen sulfide production, and/or by induction, through hormesis, of augmented stress response pathways at the cellular level. Work in flies suggests that methionine might be more influential than other amino acids in this context, though parallel studies in mammals have not been attempted. Comparisons of similarities and differences between amino acid restriction and full DR in rodents are likely to prove highly informative. Restriction of food, or of protein alone, for a period of several days prior to ischemic or surgical injury, or prior to chemotherapy, leads to better outcomes in rodents, but the extent to which such benefits reflect the same pathways through which long-term DR extends lifespan is not yet clear.

Broadly speaking, mice and rats on DR diets show delay or deceleration in a very wide range of age-dependent

processes, including neoplastic and nonneoplastic diseases, changes in structure and function of nearly all tissues and organs evaluated, endocrine and neural control circuits, and ability to adapt to metabolic, infectious, and cardiovascular challenges. Mouse stocks that have been engineered for vulnerability to specific lethal diseases, such as models of lupus or early neoplasia, also tend to live longer when placed on a DR diet. Thus, understanding the molecular basis for DR may have profound positive consequences for human health.

Insulin/IGF Signaling

In 1993, the Kenyon laboratory first noted that mutations in the nematode *C elegans* insulin/IGF receptor homolog, *daf-2*, provoked large increases in lifespan in this organism. Subsequent work revealed that long life was also observed in worms with loss of function in an insulin-responsive kinase and was dependent on a FoxO transcription factor that is regulated by insulin signaling. This body of work was the first to identify a pathway in any organism that can delay aging, and conserved elements of this pathway were soon shown to have similar effects on lifespan in the fly and in brewer's yeast (**Figure 1-2**). FoxO proteins regulate expression of genes involved in stress resistance, DNA repair, cell cycle arrest, apoptosis, metabolism, and other processes, in a cell- and tissue-specific manner. Over subsequent decades, dozens of studies in worms and flies have revealed that signaling by invertebrate insulins play a major, evolutionarily conserved role in limiting longevity.

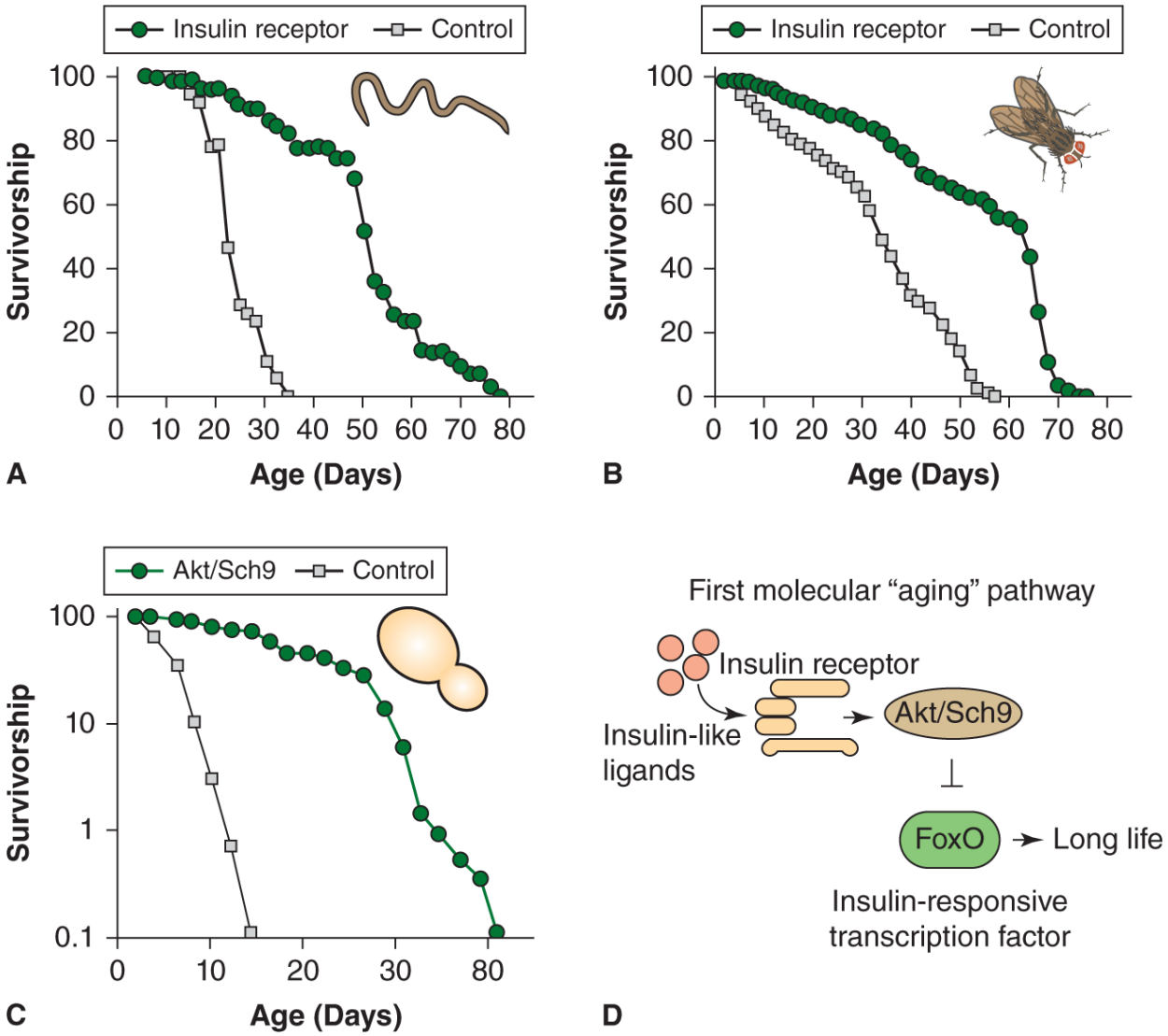


FIGURE 1-2. Research in simple model systems reveals the first molecular pathway that modulates aging. (**A**) One of the first single-gene manipulations capable of significantly extending the lifespan of an organism was discovered in the nematode worm, *Caenorhabditis elegans*. When a mutation was introduced into the gene *daf-2*, which encodes the only insulin-like growth factor (IGF) receptor in the worm, the animals lived over twice as long as the control animals. (**B, C**) Subsequent studies in (**B**) the fruit fly, *Drosophila melanogaster*, which also targeted its sole insulin-like receptor, and in (**C**) the brewer's yeast, *Saccharomyces cerevisiae*, which targeted the insulin-responsive Akt

protein kinase, revealed that disruption of insulin/IGF-like signaling extended the lifespan of these organisms as well. (**D**) A member of the FoxO transcription factor family was soon found to be required for these life-extending effects, thus establishing the first evolutionarily conserved molecular pathway that influences aging. (Data reproduced from Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang R. A *C. elegans* mutant that lives twice as long as wild type. *Nature.* 1993;366(6454):461–464; Fabrizio P, Pozza F, Pletcher SD, Gendron CM, Longo VD. Regulation of longevity and stress resistance by Sch9 in yeast. *Science.* 2001;292(5515):288–290; and Tatar M, Kopelman A, Epstein D, Tu MP, Yin CM, Garofalo RS. A mutant *Drosophila* insulin receptor homolog that extends life-span and impairs neuroendocrine function. *Science.* 2001;292(5514):107–110. Part D prepared by Scott Pletcher.)

In mammals, the family of signals implicated in lifespan extension in worms and flies has diversified: both insulin and IGF signaling pathways can trace their lineages to this simpler invertebrate system. Indeed, the observation that longevity in mice could be improved by reduction of hormones in the insulin/IGF family provided a key foundation for exploiting comparative cell biology in biogerontology research. Subsequent work then showed that similar degrees of lifespan extension could be seen in Snell dwarf mice, whose endocrine defects are very similar to those of Ames dwarfs, and also in mice that lack the GH receptor (GHR-KO mice). This last observation, together with documented lifespan extension in mice producing low levels of GH-releasing hormone (GHRH), the hypothalamic factor that stimulates GH secretion by the pituitary, and in mice lacking the receptor for GHRH, suggests that longevity of the Snell and Ames dwarf mice is due mainly to loss of GH and/or IGF-1 signals. Studies of Snell and Ames dwarf mice, and of GHR-KO mice, have shown that the exceptional longevity of these mice is accompanied by a delay or deceleration of age-dependent changes in T lymphocytes, skin collagen, renal pathology, lens opacity, cognitive function, and neoplastic progression. Taken with the lifespan data, these observations suggest strongly that these mutations, like the DR diet, act to slow the aging process itself (**Figure 1-3**). These mutations increase healthy lifespan in both male and female mice, with some evidence for stronger effects in females.

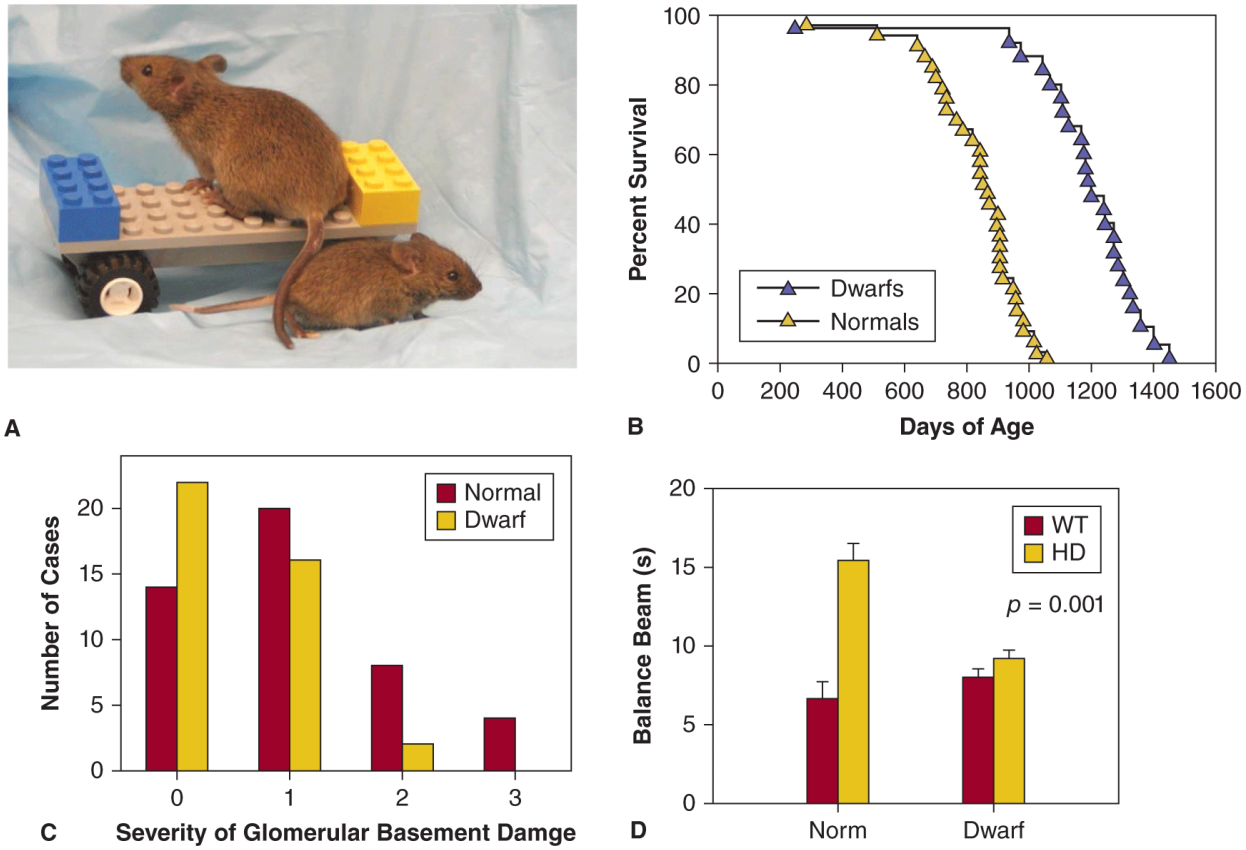


FIGURE 1-3. Mice carrying the Snell dwarf mutation are one-third of the size of their normal littermates, because the mutation diminishes production of growth hormone by the pituitary (**A**). This mutation increases mean and maximum lifespan by about 40% (**B**), and reduces the severity of kidney lesions at death among many other forms of late-life illness (**C**). Mice carrying a dominant mutation for Huntington disease (HD) perform less well than wild-type (WT) control mice on a balance beam task (**D**), but the HD gene does not produce corresponding symptoms when it is placed on a Snell dwarf background. (Part A prepared by Richard Miller. Part B adapted from Flurkey KJ, Papaconstantinou J, Miller RA, Harrison DE. Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. *Proc Natl Acad Sci USA.* 2001;98:6736–6741, Figure 1. Part C data from Vergara M, Smith-Wheelock M, Harper JM, Sigler R, Miller RA. Hormone-treated Snell dwarf mice regain fertility but remain long-lived and disease resistant. *J Gerontol A Biol Sci Med Sci.* 2004;59:1244–1250, Table 4. Part D data from Tallaksen-Greene SJ, Sadagurski M, Zeng L, et al. Differential effects of

delayed aging on phenotype and striatal pathology in a murine model of Huntington Disease. *J Neurosci.* 2014;34:15658–15668.)

It is uncertain whether longevity in these mutant or engineered mice reflects loss of GH signals per se, or a decline in levels of IGF-1, whose production by the liver is GH-dependent. Mice with lower levels of the receptor for IGF-1 have inconsistent findings, ranging from a lifespan benefit in female mice, to little or no benefit in either sex.

Perhaps the strongest evidence for a direct role of IGF-1 comes from reports of increased lifespan in mice lacking the protease pregnancy-associated plasma protein A (PAPP-A). PAPP-A is thought to increase levels of free, active IGF-1 in many tissues by removal of binding proteins that ordinarily sequester IGF-1 and inhibit its activity. Thus genetic deletion of PAPP-A would be expected to diminish IGF-1 action in some tissues, without an effect on circulating or local GH levels. There is, however, also evidence against a role for IGF-1 as the key factor in enhanced survival of mice with lowered GH action, since mice in which GH responses are diminished in liver only, but not in other organs, have a 90% reduction in serum IGF-1 levels but no increase in lifespan. It is likely that feedback circuits in specific tissues may sense GH or IGF-1 effects elsewhere in the body to elicit compensatory adjustments. Production of GH in the brain of Ames dwarf mice, for example, remains high even at ages at which brain GH production, and stem cell turnover, have begun to decline in normal mice. Clarifying details of local control of GH and IGF-1 action could have important implications for human applications, if it proves possible to target inhibition of GH or IGF-1 signals specifically to cell types that modulate aging rate, and thus avoid side effects that might occur if GH or IGF-1 signals were blocked throughout the body.

Some of the longevity effects in Ames and Snell dwarf mice appear to reflect adjustments to limits in GH levels in the first few weeks of life, between birth and weaning 3 weeks later. Ames dwarf mice injected daily with GH, starting at 2 weeks, fail to show the increased lifespan characteristic of this mutation, and also resemble nonmutant control mice in other ways, including lowered cellular stress resistance and diminished hypothalamic inflammation. GH injections started at 4 weeks, however, do not produce such an effect. Conversely, restricting the amount of milk available to normal mice, in their first 3 weeks of life, can lead to a 10% to 20% increase of lifespan; such mice show lower than normal levels of IGF-1 at the end of the nursing period. Thus it appears that the availability of nutrients, perhaps reflected as higher levels of circulating GH and IGF-1 in the first few weeks of life, may produce long-lasting changes in cellular and hormonal properties that persist throughout adult life and affect mortality risks in old age (**Figure 1-4**).

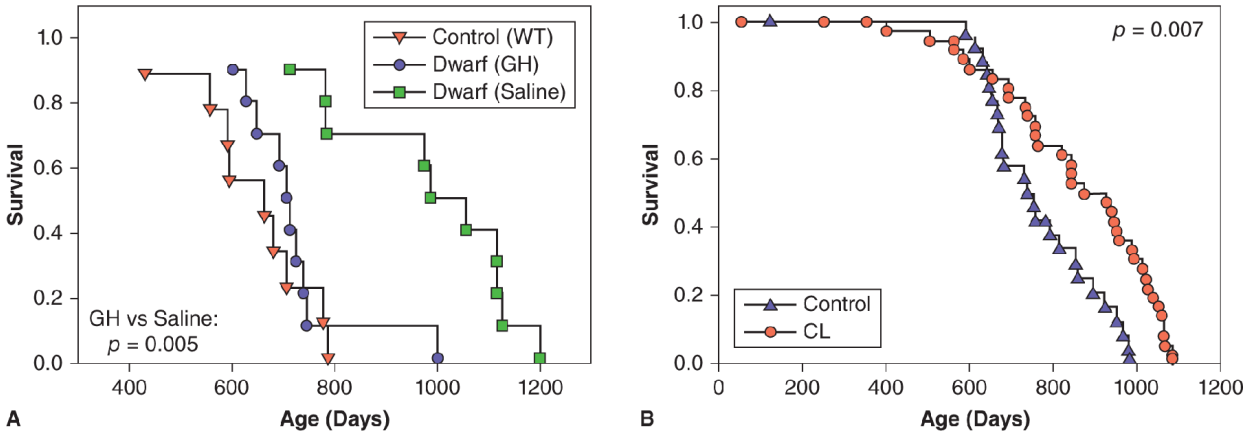


FIGURE 1-4. Early-life hormonal and nutritional status can have major effects on late-life survival and disease. The left panel shows an experiment in which Ames dwarf mice were given injections of growth hormone (GH) for an 8-week period beginning at 2 weeks of age. These hormone-injected mice had survival patterns similar to that of normal mice (WT controls), and therefore much shorter than Ames mutant mice (green) that had only saline injections at early ages. The right panel shows a complementary experiment, in which genetically normal mice were partially deprived of milk ("CL" for "crowded litter") by adding extra pups during the suckling phase, from birth to 3 weeks. This transient milk deprivation led to a substantial increase in lifespan in the CL mice. (Part A adapted from Panici JA, Harper JM, Miller RA, Bartke A, Spong A, Masternak MM. Early life growth hormone treatment shortened the longevity and decreased cellular stress resistance in long-living mice. *FASEB J.* 2010;24:5073–5079, Figure 1. Part B adapted from Sun L, Sadighi Akha AA, Miller RA, Harper JM. Life-span extension in mice by pre-weaning food restriction and by methionine restriction in middle age. *J Gerontol A Biol Sci Med Sci.* 2009;64:711–722, Figure 5.)

TOR/Proteostasis

A second nutrient-sensing pathway, the amino acid–sensing TOR pathway, interacts extensively with insulin and IGF

signaling in complex ways, some of which are diagrammed in **Figure 1-5**. TOR plays a major role in regulating protein translation rates in response to both external cellular stress and the available supply of amino acids. Downregulation of TOR signaling was initially shown to extend lifespan in nematode worms, with evolutionary conservation later demonstrated in fruit flies and then in yeast. It has been proposed that DR may influence lifespan through its effects on TOR signaling. This model has garnered some support from experiments in yeast, worms, flies, and rodents, and it remains an area of active research. It is likely that many dietary interventions that extend lifespan recruit TOR-related mechanisms to affect aging, and inhibition of TOR function by the drug rapamycin can extend longevity in rodents and invertebrates (as discussed in a later section). TOR exists in two distinct molecular complexes, called TORC1 and TORC2, which have a wide range of effects on cell size and shape, responses to stress and nutrient levels, as well as protein synthesis and responses to glucose and insulin. Experimental work to distinguish the distinct, but interacting, effects of TORC1 and TORC2 activation in specific cell and tissue types is now under way. Pharmacologic tools to regulate each TOR complex independently will help to dissect the involvement of TOR in aging and provide new tools for prevention of late-life decline. Signals mediated by the TOR complexes interact with those generated through insulin action.

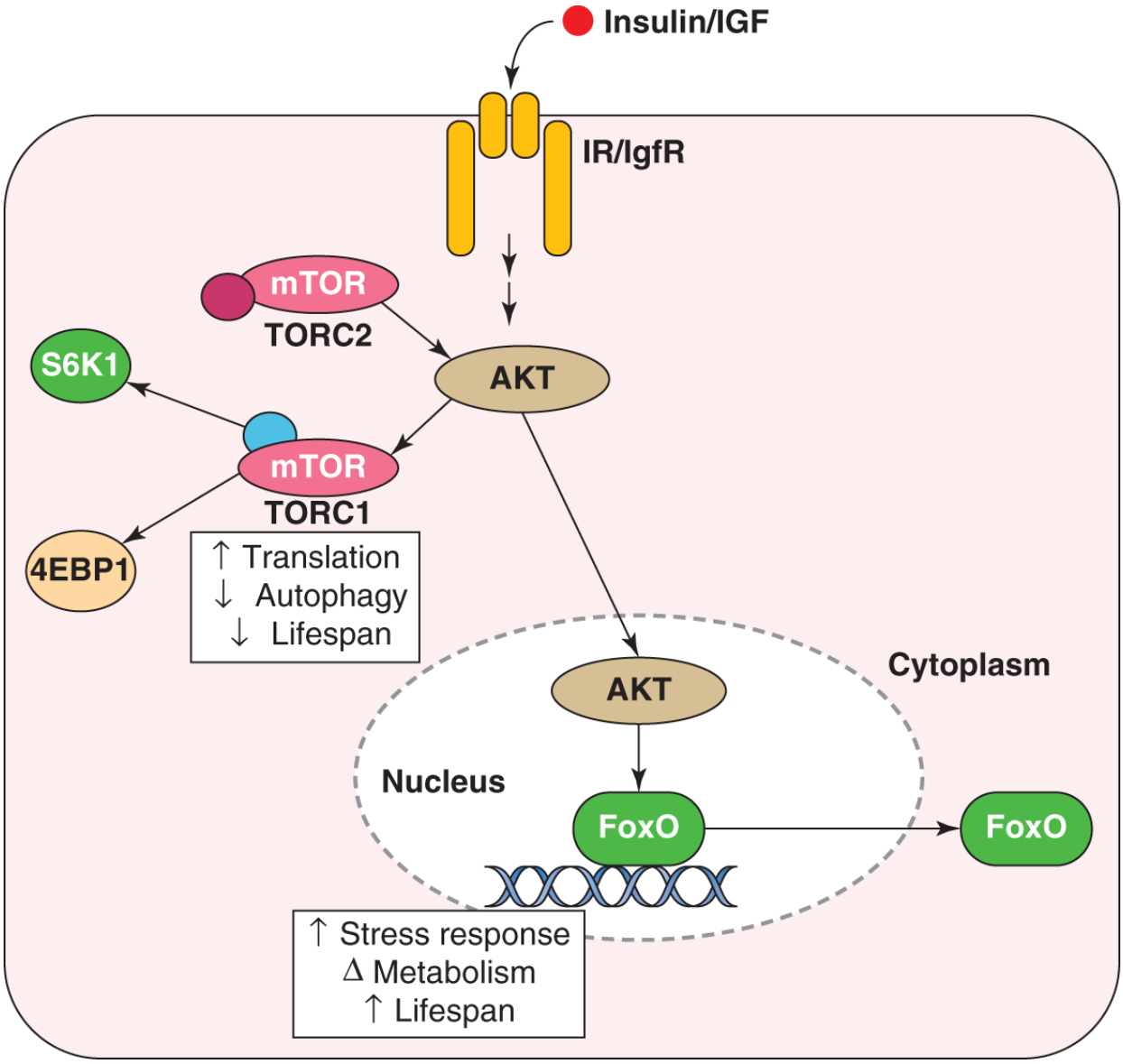


FIGURE 1-5. Insulin–IGF-like signaling (IIS) and mTOR signaling regulate lifespan. Insulin and IGF binding to their cognate receptors activates the intracellular kinase AKT. AKT in turn phosphorylates a large number of cellular substrates, including members of the FoxO transcription factor family, leading to their nuclear export and inactivation. Nuclear FoxO family members regulate stress responses and lifespan in multiple organisms, including mammals. mTOR kinase is found in two distinct cellular complexes, TORC1 and TORC2. TORC1 inhibits autophagy and promotes protein translation through its downstream effectors, 4EBP1 and S6K1. Inhibition of TORC1 has been most closely linked to longevity, although TORC2 may play a role as well. (Figure prepared by David Lombard).

Building on interest in TOR signaling and its effects on protein translation, work in invertebrates and increasingly in mammals has revealed fundamental links between the maintenance of proteostasis and longevity. Proteostasis refers globally to the processes that improve the quality and function of cellular proteins, collectively termed the proteome. It includes regulation of protein translation, folding, damage repair, and degradation. Autophagy is a process by which damaged cellular proteins and even whole organelles such as mitochondria are degraded in lysosomes. In invertebrates, intact autophagy systems are required for longevity extension by essentially all interventions that increase lifespan. In mammals, autophagy function declines with age; this effect is rescued by DR. Increased expression of the autophagy protein ATG5 extends mouse lifespan, and improves neuromuscular function and glucose tolerance in old mice. Rapamycin, which extends lifespan in many different organisms, decreases translation of many cellular proteins, while promoting increased autophagic function. Collectively, these findings indicate that maintenance of proteostasis is a key requirement of longevity.

Sirtuins

As one of the most influential aging-related discoveries generated in the yeast model system, the sirtuin proteins have captured the public interest and sparked robust debate in aging circles. The sirtuins are a family of protein deacetylases that consume the metabolic cofactor NAD+ during catalysis. Cellular NAD+ levels increase under conditions of fasting or DR, in a tissue-type specific manner. In light of their NAD+ requirement, sirtuins have been implicated as energy sensors and potentially as mediators of some of the benefits of DR. In yeast, worms, and flies, sirtuin overexpression extends longevity, albeit more modestly in worms and flies than initial reports suggested. Mammals possess seven distinct sirtuins; these are a diverse protein family, from the standpoint of biochemical activity, protein targets, and localization. Mammalian sirtuins target their protein substrates via deacetylation, or removal of other posttranslational modifications, to regulate a wide range of proteins involved in gene expression, DNA repair, metabolism, and many other processes. Three sirtuins are present in the mitochondrial matrix, where they regulate intermediary metabolism and other aspects of mitochondrial function. In mammals, most studies have focused on SIRT1, the closest homolog of the yeast SIR2 protein. SIRT1 is required for certain effects induced by DR—such as increased physical activity and elevated skeletal muscle insulin sensitivity—but is not needed for many other DR-associated phenotypes.

Whole-body overexpression of SIRT1 does not increase overall lifespan in mice, although it is protective against age-associated metabolic dysfunction and certain forms of neoplasia. Overexpression of SIRT1 in the brain only, however, does extend mouse lifespan. This effect has been postulated to occur through enhanced neural function in specific hypothalamic nuclei, leading to a host of beneficial downstream effects, such as improved maintenance of skeletal muscle mitochondrial function, and improved sleep quality during aging. Of note, reducing age-associated inflammation in the hypothalamus also extends lifespan in mice, suggesting that this brain region may play an important role in pacing the rate of systemic aging. Overexpression of the sirtuin SIRT6 throughout the body also extends lifespan in male mice, potentially by improving metabolic fitness and suppressing neoplasia. SIRT6 promotes metabolic homeostasis and enhances genomic stability; it will be important to elucidate which of SIRT6's many functions are most important in its prolongevity role.

Beginning with resveratrol, a series of small molecule activators of SIRT1 have been developed. In mice, these drugs show beneficial effects, particularly in the context of dietary challenge such as high-fat feeding. At least two of these SIRT1-activating agents modestly increase mean lifespan in mice. There are continued controversies regarding these agents, particularly focused on the extent to which they target SIRT1 directly, versus exerting indirect effects through other signaling molecules. Nevertheless, these or similar agents could conceivably find utility in treating age-associated metabolic dysfunction in humans.

Stress Response

Mutations that extend lifespan in invertebrates typically render the animals resistant to multiple forms of lethal injury, whether the threat comes from oxidative agents, heat, heavy metals, or irradiation. Indeed, this stress resistance seems likely to represent a mechanism by which these mutations delay the aging process. Thus presumably much of the cellular and extracellular pathology that produces dysfunction and increases mortality risk in older animals is held in abeyance by the same, poorly defined, defenses that permit nematodes and flies to survive when exposed to external stress in an experimental setting. Genetic dissection of the relevant pathways has shown, surprisingly, that in normal, nonmutant worms, the levels of stress resistance, and thus resistance to aging, are actively diminished by inhibition of specific DNA-binding transcription factors, members of the FoxO family (**Figure 1-5**). These pathways are retained by evolutionary pressures because they provide reproductive advantages in the natural environment, in which animals

must be able to quickly take advantage of transient access to nutrients. Activation of FoxO proteins in the laboratory produces mutant animals that are not ideally suited for natural conditions, but which are resistant to many kinds of stress and which age more slowly than normal. Studies of gene expression patterns in the long-lived mutant worms have shown that the FoxO proteins can trigger transcription of over 100 genes that together protect against many different forms of cellular damage. The list includes enzymes that destroy free radicals, heat shock proteins, and other chaperones that guard against misfolded proteins, proteins that protect against infection, and chelating agents that bind toxic metal ions, among others.

The connection between induction of these stress-resistance pathways and late-life diseases has been shown by two sets of informative experiments. In the first, genetically identical worms were exposed to a brief, nonlethal heat stress, and physically separated into those that showed a strong response of chaperone proteins and those that did not. Worms with the most robust response to transient stress were found to be longer-lived than those with lower stress responses. A second approach involved worms bearing genetic variants that cause aggregation of proteins and neurodegeneration (Huntington disease) in people; neurologic dysfunction in these worms can be delayed, and in some cases prevented entirely, by augmentation of the FoxO-dependent stress-resistance pathways. Similarly, age-dependent increases in susceptibility to stress-induced cardiac arrhythmias in *Drosophila* can be significantly postponed by activation of FoxO-dependent protective pathways.

Figure 1-6 shows some of the evidence linking stress resistance to lifespan in worms, mice, and cells from longer-lived mammalian species. DR and at least some of the long-lived endocrine mutant stocks show elevated levels of enzymes with antioxidant action, heavy metal chelators, and intracellular chaperone proteins, and also have lower levels of oxidative damage to DNA, proteins, and lipids. Cells grown in tissue culture from long-lived Snell and Ames dwarf mutant mice, or from mice lacking GH receptor, are resistant to lethal injury caused by cadmium, peroxide, heat, a DNA alkylating agent, ultraviolet light, and paraquat (which induces mitochondrial damage by free radical generation). Mice prepared by CR or MR diets are resistant to liver damage induced by the oxidative hepatotoxin acetaminophen, and long-lived mutant mice are somewhat more resistant to death induced by paraquat injection. Stress resistance also seems to play a role in evolution of long-lived species. For example, cells from long-lived rodents and other mammals are resistant in culture to several forms of oxidative and nonoxidative damage. This work suggests that variations in aging rate may be due to differences in stress-resistance pathways, but many questions remain unanswered.

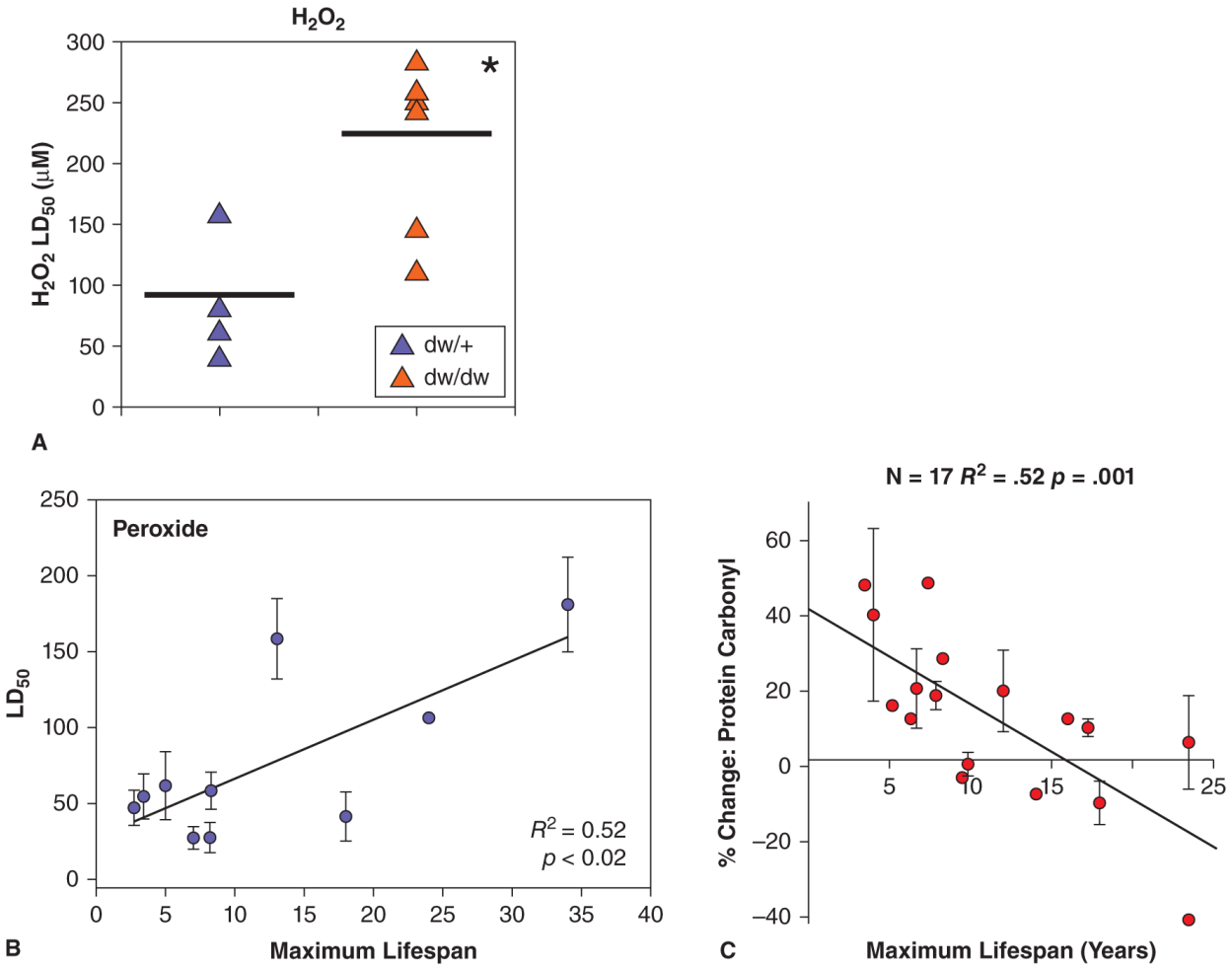


FIGURE 1-6. Links between exceptional longevity and resistance to stress. (**A**) Skin-derived fibroblasts from long-lived mutant (red symbols, dw/dw, Snell dwarf) mice are resistant to the lethal effects of hydrogen peroxide, H_2O_2. Each symbol is an individual mouse, and the Y-axis shows the amount of H_2O_2 needed to kill 50% of the cells. (Adapted from Murakami S, Salmon A, Miller RA. Multiplex stress resistance in cells from long-lived dwarf mice. *FASEB J.* 2003;17:1565–1566.) (**B**) Skin-derived fibroblasts from long-lived species are relatively resistant to lethal injury induced by H_2O_2. Each symbol represents a different rodent or bat species with the indicated maximum lifespan. Species, left to right, are laboratory mouse, wild-caught mouse, rat, red squirrel, white-footed mouse, deer mouse, fox squirrel, porcupine, beaver, and little brown bat. LD_{50} is the amount of hydrogen peroxide that kills 50% of the cells. (Reproduced with permission from Harper JM, Salmon AB, Leiser SF, Galecki AT, Miller RA. Skin-derived fibroblasts from long-lived species are resistant to some, but not all, lethal stresses and to the mitochondrial inhibitor rotenone. *Aging Cell.* 2007;6:1–13.) (**C**) Cells from long-lived rodent species are resistant to changes in oxidized proteins ("protein carbonyl" on Y-axis) induced by 1-h exposure to H_2O_2. Each symbol is a different species, with the species' lifespan indicated on the X-axis. (Reproduced with permission from Pickering AM, Lehr M, Kohler WJ, Han ML, Miller RA et al. Fibroblasts from longer lived species of primates, rodents, bats, carnivores and birds resist protein damage. *J Gerontol A Biol Sci Med*. 2015;70:791–799.)

Genome Maintenance and Reactive Oxygen Species

A long-standing model posits that chronic accumulation of unrepaired damage to nuclear and/or mitochondrial DNA contributes to the effects of aging. ROS, generated via normal cellular metabolism, have been hypothesized to represent a major source of this damage. In support of this idea, DNA lesions, mutations, and aneuploidy (incorrect chromosomal number) accumulate with age in mammalian tissues. Because such events occur stochastically on a cell-by-cell basis, in most cases it has proven difficult to rigorously identify and quantitate such events. Aging leads, in mice and humans, to increased incidence of aneuploidy, both in tissues that divide, like the spleen, and in those where cell division is rare, like the heart. Although evidence that accumulation of DNA damage contributes to aspects of aging other than neoplasia is currently modest, a recent paper has shown that elevated levels of a protein involved in repair of DNA damage can increase mouse lifespan and delay cancer, muscle loss, and glomerulosclerosis. Further work in this and similar models may help to clarify the possible role of genome maintenance in aging and nonneoplastic diseases.

The role of ROS in inducing age-associated genetic damage, or in aging more generally, remains controversial.

Resistance to many forms of stress, including oxidative injury, is a common feature of long-lived mutants, both invertebrates and mice. Moreover, across different vertebrate species, cellular stress resistance correlates with longevity. Indeed, improved stress resistance seems likely to represent one mechanism by which mutations that extend lifespan can delay the aging process. Thus presumably some of the cellular and extracellular pathology that produces dysfunction and increases mortality risk in older mammals is held in abeyance by the same, incompletely defined defenses that permit nematodes and flies to survive when exposed to external stress such as oxidative stress in an experimental setting. However, many mouse mutations that impair resistance to ROS damage have no detectable effect on lifespan and show no obvious acceleration of age-related pathology. Furthermore, administration of antioxidants to mice or people does not extend lifespan, and may under some circumstances actually increase mortality. Conversely, for the most part mouse strains with increased activity of ROS defense systems show protection from specific toxins that cause oxidative injury, but do not show extended lifespan. The only current exception is a mouse strain overexpressing the antioxidant enzyme catalase in mitochondria. These animals show increased lifespan, and, by some measures, improved health in old age. Pathogenic roles for ROS in the aging and age-associated diseases will no doubt continue to be the subject of work in aging biology. Interpretation of such studies is complicated by the fact that ROS, in addition to damaging cellular macromolecules such as DNA, also play important natural signaling roles in the cell.

Cellular Senescence, Telomeres, and Cancer

The famous observation of Hayflick that human diploid fibroblasts cease to grow in culture after a limited number of population doublings sparked a line of experimentation that continues to yield important insights into the molecular control of cell growth, differentiation, and neoplastic transformation. Human fibroblasts placed in tissue culture will divide until approximately 50 cell doublings have occurred, after which the remaining cells survive indefinitely in a healthy but nondividing state. In the 1970s and 1980s, this “clonal senescence” model seemed to be an attractive approach to study the genetics and cell biology of aging. It is now clear that growth cessation of continuously passaged human fibroblasts is caused principally by the progressive loss of telomeric DNA at the ends of each chromosome at each mitosis. The telomeres consist of repetitive regions of DNA at the distal chromosomal tips. The chemistry of DNA replication requires that duplication of the end of each DNA molecule be conducted by a specialized enzyme complex called telomerase, and telomeres therefore become shorter at each cell division, except in cells like stem cells, germ cells, and most cancers, that express telomerase. In normal cells, critically shortened telomeres induce a DNA damage response in the cell, leading to senescence or cell death. Short telomeres can influence intracellular signaling to hamper mitochondrial function, thereby impairing cellular metabolism, suggesting that damaged telomeres might exert effects even in tissues such as the liver that are largely postmitotic. Telomere-dependent clonal senescence clearly plays a critical role in the protection of humans from many forms of cancer. Telomerase is turned on, and telomere attrition prevented, in approximately 90% of malignant tumors in humans. Genomic sequencing efforts have revealed that individuals with mutations that chronically elevate telomerase activity, or increase the accessibility of telomeres to telomerase, are at increased risk for a variety of cancers. It thus seems likely that short telomeres and stringently repressed telomerase gene expression emerged during the course of human evolution to protect against fatal cancers that would otherwise arise early in life. Most cancers are clonal, and each clinically significant tumor represents the outcome of several stages of selection for rare cellular variants for independence from growth control, resistance to immune defenses, and barriers to metastasis. For this reason, evolution of large-bodied species, with a much higher number of potential target cells for neoplastic transformation, should require development of strong antitumor defenses not needed in smaller creatures. The average human has approximately 3000 times as many cells as a mouse; if each had the same annual likelihood of neoplastic transformation as a mouse cell, the annual cancer incidence in humans would be 3000 times higher than in mice. In fact, however, humans usually avoid neoplasia over a lifetime that is 30 times longer than the mouse’s lifespan; evolution has developed strategies that reduce per cell transformation rate by a factor of about 90,000 in evolving humans from shorter-lived, smaller species. These defenses may well include telomere-based clonal senescence responses, as well as improvements in repair of somatic mutations and reduction of intracellular levels of DNA-modifying agents. In tissue culture, human cells are dramatically more difficult to render immortal than rodent cells. There is no reason to believe, however, that evolved defenses against cancer in humans could not be further improved; similar considerations show that whale cells, for example, are about 10,000-fold more resistant than human cells to neoplastic transformation.

A more general, long-standing question in aging biology involves whether telomere attrition and/or cellular senescence can deliver important clues about the biology of aging. The most obvious possibility is that some of the diseases and disabilities in older individuals might represent a loss, with age, in proliferative capacities of one or more

cell types. There are some challenges to this idea. For example, telomere erosion has been postulated to contribute to dysfunction of memory T cells in older subjects; but it is hard on this ground to explain the equally poor function, in the same subjects, of naïve memory T cells, whose telomeres are similar in old age to those of memory cells found in young adults. In addition, there are many cell types, such as intestinal crypt stem cells and hematopoietic progenitor cells, that can divide many thousands of times over the course of a lifespan, but which nonetheless show age-related functional decline.

Studies of the role of telomeres and telomerase in the biology of aging in mice have produced interesting but controversial findings. Mice have much longer telomeres than humans, but live much shorter lives. The rate at which telomeres shorten, however, is more rapid in mice than in humans, and mouse strains engineered to have elevated telomerase show increased cancer rates, consistent with a role for telomere length as a contributor to malignancy in mice, as in humans. Paradoxically, elevated telomerase function may improve some aspects of health in mice carrying other alleles that block many forms of neoplasia, though with no effect on maximum lifespan, a provocative observation worth further exploration. As indicated in **Figure 1-7**, telomere erosion can, in different settings, lead to cellular senescence, changes in cell properties related to DNA damage, genomic instability, or neoplastic transformation. The potential role of these changes in late-life human disease is an area of active investigation. Genetic disruption of telomerase can also produce lines of mice with shortened telomeres. These mice are short-lived, but the spectrum of pathology, featuring skin ulceration, infertility, increased frequencies of specific forms of neoplasia, and frequently lethal gastrointestinal lesions, does not closely resemble the pattern of illnesses seen in normal aging mice or humans. Thus telomere attrition, except for its major role in oncogenesis, does not seem likely to represent a major contributor to aging in rodents.

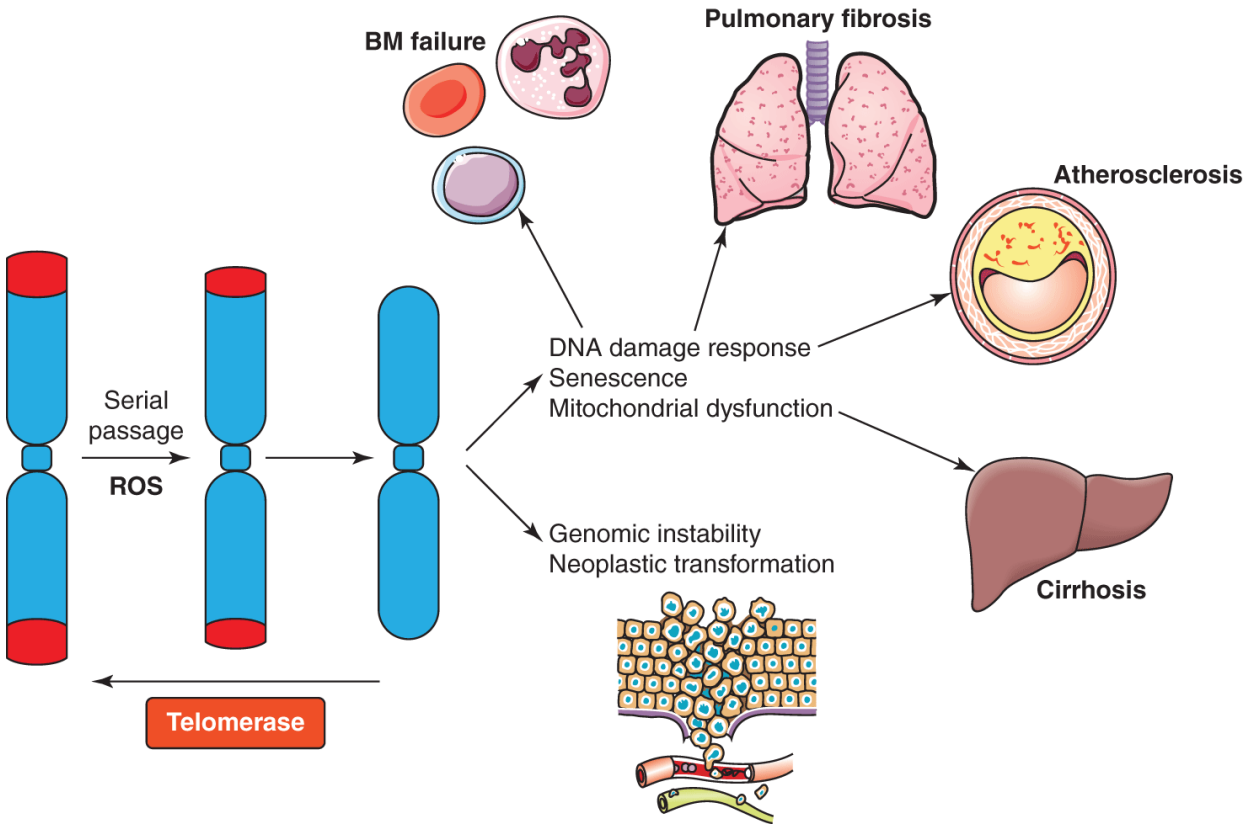


FIGURE 1-7. Telomere shortening as a tumor suppressor mechanism. The distal tips of mammalian chromosomes are "capped" by numerous copies of a hexanucleotide repeat (TTAGGG, designated in red). During serial cell division, or in response to genomic insults such as reactive oxygen species (ROS), telomeres progressively shorten. When they reach a critical threshold of attrition, loss of telomere binding proteins and telomere unfolding ("uncapping") occurs, provoking a DNA damage response and leading to permanent cell cycle arrest (*i.e.* senescence). Critically shortened telomeres can also cause mitochondrial dysfunction in vulnerable tissue types like the liver. Telomere uncapping and senescence can promote pathologies such as bone marrow (BM) failure, pulmonary fibrosis, atherosclerosis, and hepatic cirrhosis. By contrast, in cells that lack checkpoint control proteins like p53, shortened telomeres can provoke genomic instability, such as chromosomal end-to-end fusions, eventually culminating in neoplastic transformation. In stem cells and most cancer cells, telomerase is expressed and opposes telomere shortening by adding telomeric repeats back to the ends of chromosomes, thereby stabilizing telomere length. Some graphics in the figures were obtained and modified from Servier Medical Art from Servier. (http://www.servier.com/Powerpoint-image-

bank). (*Used with permission from* David Lombard).

Early work based on histologic assays suggested that senescent cells were rare (< 0.1%), even in biopsies from very old donors, although new methods for detecting other aspects of the senescent phenotype have led to upward revisions of this estimate. It remains a challenge, however, to develop and test models to explain how properties of tissues, organs, and multiorgan systems (like the brain and endocrine circuits) might be altered by the presence of a small admixture of nondividing senescent cells. Senescent cells in vitro express a suite of secreted enzymes and inflammatory cytokines that are not produced by dividing fibroblasts. By secreting such proteins, senescent fibroblasts have been shown to facilitate the growth of cancer cells, and it is possible that these may contribute to other aspects of aging at the tissue or organ level. Several research groups have now developed methods that can delete senescent cells from adult mice. It will be of great interest to see if deletion of these cells do or do not extend healthy lifespan.

Stem cell biology has suggested a key role for a specific protein, p16/INK4a, as a mediator of the balance between cancer and aging. INK4a is induced as part of the process during which cellular senescence halts cell proliferation. An increase in levels of INK4a is observed in many tissues of aging mice, but particularly in stem cells, suggesting that senescent stem cells may indeed accumulate as a consequence of normal aging and may represent an evolved mechanism to prevent early-life neoplasia. INK4a may lead, in parallel, to diminished stem cell function in the aging bone marrow, brain, and pancreas. Mice engineered to have reduced levels of INK4a retain stem cell activities at ages at which these cells proliferate poorly in normal animals, even though the same mice are somewhat more cancer-prone than normal controls. In humans, genetic polymorphisms near the *p16/INK4a* gene have been linked to age-associated conditions such as type 2 diabetes, coronary artery disease, and frailty. Interventions that prevent age-related induction of INK4a might be an attractive approach to diminishing many forms of late-life illness in parallel, if the intervention did not simultaneously increase cancer risk.

Other Genes and Processes That Influence Mouse Aging

Complementing the mechanisms of aging discussed earlier, there are many more engineered mouse strains for which increased longevity has been reported in at least one laboratory. For some mutants, lifespan extension is sex-specific, as with SIRT6 overexpression, which increases male longevity specifically. In other cases, for example, the Ames and Snell dwarf strains, extended lifespan is observed in both sexes. Long-lived mouse mutants often show protection against important classes of age-associated pathologies, such as cancer, kidney disease, cataracts, immune failure, and glucose intolerance. This finding underscores the close connection between aging and age-associated disease. As noted previously, several of these long-lived mutants show reduced GH signaling, typically with lower IGF-1 levels, and some also feature increased insulin sensitivity or alterations in insulin responses by specific cell types. Other mutants show impaired mTOR function or reduced activity of TOR's downstream effectors, although these changes are often seen in one sex only, and typically produce less increase in lifespan than alterations in GH and IGF-1 signals. Other long-lived genetically engineered mouse strains highlight particular cellular functions that are important for longevity, such as genome integrity. For example, mice overexpressing the BUBR1 mitotic checkpoint protein show improved maintenance of the proper chromosomal number (euploidy) during age, along with protection from cancer and extended longevity. Similarly, mice overexpressing the ATG5 protein show increased levels of autophagy, a cellular process for recycling damaged proteins and organelles, and increased lifespan. As a cautionary note, the majority of these studies have been performed in one laboratory, mostly in a single mouse strain. It will be important to replicate such studies in different genetic backgrounds and in multiple laboratories, to see whether the findings are reproducible and robust.

More work is needed to determine to what extent these mutations influence common pathways, to see whether they do or do not influence aging through the same mechanism. It is possible, for example, that some of these mutations diminish risk of cancer, a common cause of death in many inbred mouse strains, without effect on any other age-dependent trait, while others may modulate the effects of aging on multiple organ systems, thus diminishing mortality risk from both neoplastic and nonneoplastic diseases. In this regard, it will be useful to determine how these pathways may intersect with the DR response. In invertebrates, genetic studies have revealed that reduced mTOR signaling appears to overlap mechanistically with the response to DR. Conversely, there are hints that DR diets and the Ames dwarf gene may affect longevity by different mechanisms. Some proteins may be required only for specific aspects of the response to DR, but dispensable for others. For example, in mice, SIRT1 is required for the increased skeletal muscle insulin sensitivity that occurs during DR, but dispensable for many other DR-associated effects.

As mentioned earlier, diminution of GH or IGF-1 levels can create mice that are long-lived compared to controls. An association between IGF-1 and lifespan has also been noted using experimental designs in which individual mice

are tested for IGF-1 levels as young adults; those mice with the lowest IGF-1 levels were found to live significantly longer than those with higher IGF-1 concentrations. Similarly, mouse stocks bred by selection for slow early-life growth trajectory are smaller than controls and also longer-lived. There is also highly suggestive evidence for a similar relationship between IGF-1, body size, and lifespan in dogs and horses. For dogs, small-size breeds have greater longevity than large breeds, and there is a strong relationship between body size and life expectancy among mixed-breed (mongrel) dogs as well (**Figure 1-8**). Anecdotal and some published data suggest that pony breeds of horses are also substantially longer-lived than horses of full-sized breeds. The relationship between body size and life expectancy in humans is complicated by the strong effects of socioeconomic status on both endpoints; wealthier people tend to be both taller and longer-lived than poor people. On the whole, tall stature is associated with lower mortality risks from cardiovascular diseases, which are a major cause of mortality in developed countries. In contrast, a remarkably consistent set of studies (**Table 1-1**) show that tall stature is associated with significantly higher mortality risk from a wide range of neoplastic diseases. There is also limited data that centenarians, on average, were shorter as mature adults than those who do not attain centenarian status. Testing the idea that short midlife stature is associated with delayed or decelerated aging in humans will depend on measuring a wide range of age-dependent traits, rather than merely lifespan, on large populations of middle-aged people. Individuals with a genetic abnormality in GH receptor ("Laron dwarf mutation") in an Ecuadorian community had very low serum levels of IGF-1 and IGF-2, and were much less likely than control subjects to die of cancer or to be diagnosed with adult-onset diabetes, findings consistent with the low age-adjusted cancer incidence and excellent insulin sensitivity of the corresponding, long-lived, mutant mouse stock. It is also important to note that IGF-1 clearly exerts many beneficial effects in older adults, for example, in preventing skeletal muscle wasting.

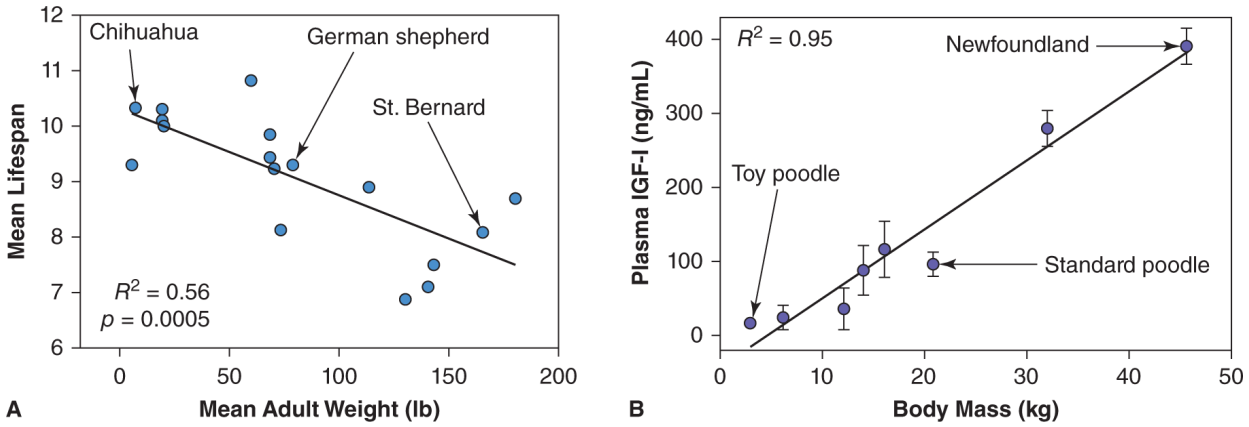


FIGURE 1-8. Longevity, size, and insulin-like growth factor 1 (IGF-1) levels among breeds of purebred dogs. Left panel (**A**) shows mean breed lifespan as a function of mean breed weight for each of 16 breeds of dogs; three breeds are indicated by arrows. (Data from Li Y, Deeb B, Pendergrass W, Wolf N. Cellular proliferative capacity and life span in small and large dogs. *J Gerontol A Biol Sci Med Sci.* 1996;51(6):B403–B408.) Right panel (**B**) shows mean plasma IGF-1 levels as a function of body mass in eight breeds of purebred dogs. (For details and citations, see Miller RA, Austad SN. Growth and aging: why do big dogs die young? In: Masoro EJ, Austad, SN, eds. *Handbook of the Biology of Aging*, 6th ed., New York, NY: Academic Press; 2006.)

TABLE 1-1 POPULATION-BASED ASSOCIATION BETWEEN SHORT STATURE AND LOWER MORTALITY RISK FOR MULTIPLE NEOPLASTIC DISEASES

TEST POPULATION	TALL PEOPLE DO BETTER	SHORT PEOPLE DO BETTER
15,000 Scots	All cause mortality Stroke Coronary disease	Colorectal, prostate, hematopoietic cancers
12,000 NHANES (United States) men		Cancers; 40%–60% effect; adjusted for race, smoking, income
NHANES women		Breast and colorectal cancer
22,000 US male physicians		Cancer; adjusted for age, BMI, exercise, smoking

570,000 Norwegian women		Breast cancer
400,000 American women		Breast cancer, postmenopause
1.1 million Norwegians		Esophageal cancer
England and Wales (by county)	All-cause mortality Ischemic heart disease	Breast, prostate, ovarian cancer

BMI, body mass index; NHANES, National Health and Nutrition Examination Survey.

For reference citations, see Miller RA, Austad, SN. Growth and aging: why do big dogs die young? In: Masoro EJ, Austad SN, eds. Handbook of the Biology of Aging. 6th ed. New York, NY: Academic Press; 2006:512–533.

Connections to Molecular Pathobiology

Integration of findings from invertebrates (including yeast cells), rodents, and cultured human cells has substantially enhanced understanding of the molecular pathogenesis of many diseases, and continues to provide the driving engine for experimental therapeutics leading to clinical trials. A similar strategy focusing on pathways that regulate the aging process, and through altered rates of aging, could lead to the coordinated postponement of the wide array of age-dependent diseases. Thus, pathways that clearly deserve deeper scrutiny have been delineated, usually because investigations in invertebrates, or, more rarely, mice, have revealed that genetic or chemical alteration of the target molecules can slow aging, preserve health, and extend maximal lifespan. Elucidation of the links between these biochemical pathways and hormonal signals, neoplastic transformation, stem cell homeostasis, and the balance between cell growth and cell death is likely to provide both rationale and direction for translational work aimed at slowing the aging process and retarding age-related disease and dysfunction.

Many of these pathways are interconnected, either within cells or through neuroendocrine connections, often making it difficult to make draw simple, unidirectional maps discriminating causes from effects. Making the leap from convenient invertebrate organisms to the added physiologic complexity of rodents and humans also poses major challenges. **Figure 1-5** illustrates connections among many of the molecular targets and intercellular pathways, potentially involved in the control of aging rate in mammals, which have attracted experimental attention and continue to be sources of controversy and new ideas. None of these has yet been proven to be a central regulator of aging and multiple age-related illnesses; none of those shown has yet been ruled out. Research in the coming decade should expand the list of interesting candidates, refine our knowledge of how these molecules control one another within the cell, and start to delineate the specific cell types, and tissues, through which these pathways influence aging rate and age-related diseases in mammals. Higher resolution in each of these dimensions, in synergy with the results of drug-screening trials in worms, flies, and mice, should provide a better foundation for development of drugs that slow aging with minimal side effects in humans.

Looking to the Future

Seminal discoveries of aging regulatory mechanisms in simple model systems repeatedly turn out to be evolutionarily conserved and applicable to mammals. Because of the time required to create mutant mice and their significantly longer lifespan, it normally it takes 5 to 10 years for initial discoveries to be repeated in vertebrate systems. Nevertheless, it is worth pondering the importance and potential impact of ideas that are currently in the "pipeline," three of which are mentioned here:

1. **Epigenetic modifications** are a group of chemical changes to DNA and histones, such as DNA methylation and histone methylation, phosphorylation, and acetylation, which are capable of regulating gene expression through chromatin remodeling without altering DNA sequence. Surprisingly, long lifespan can be inherited in worms though epigenetic modifications, that is, by changes in DNA methylation or histone modifications that do not involve changes in DNA sequences per se. This sort of epigenetic memory has been observed for other traits, such as stress resistance, obesity, and behavior; and it is susceptible to nutrition and other environmental influences. The extent to which similar processes might influence aging in other species, including mammals, is uncertain.
2. **Sensory systems** strongly modulate aging in nematodes and fruit flies, and this modulation is evolutionarily conserved. Exposure of worms or flies to food-based odorants is sufficient to reduce lifespan and limit the beneficial effects of dietary restriction, while mutations that largely abolish olfactory function result in long life. It has become clear that some sensory neurons enhance longevity while others suppress it and that even the well-known relationship between body temperature and lifespan may have a sensory component. All organisms share

similar goals: the need for food and mates, and the desire to avoid danger. While the specific smells, tastes, etc that are associated with these goals are different among species, the biological responses to what those cues represent are much the same. Flies and humans both produce insulin-like peptides when they smell food, for example, suggesting deeper biological responses to sensory input should be targets for studies of aging in mammals. Encouragingly, the first instance of sensory modulation of lifespan in mice, involving a pain-sensing TRP channel, has been described. Similarly, alterations in pain nerve sensitivity have been noted in an exceptionally long-lived (and cancer-resistant) rodent species, the naked mole rat.

3. **Interactions among tissues.** In worms and flies there is mounting evidence that the aging process of the entire organism is coordinated nonautonomously by ongoing communication among specific tissues. Signaling from the germline controls aging of nonmitotic tissues. A few sensory neurons that detect food, danger, or mates can double or halve a fly's lifespan, and a similar number control the DR response in worms. Insulin and glucagon-like hormones, dynamically produced in the brain or fat tissues, accelerate aging and functional decline throughout the animal. Similar results are emerging from rodent studies where the hypothalamus has become a focus point through its influence on global energy homeostasis and inflammation. Surgical removal of visceral fat, though not of subcutaneous fat, extends lifespan in rats, suggesting that some adipose tissue depots may modulate aging rate through metabolic or endocrine factors. Mutations that extend mouse lifespan by lowered GH/IGF-1 signals lead to reduced levels of visceral fat, with relative sparing of subcutaneous fat depots. It seems likely that this coordinated and distributed control is adaptive, allowing the organism to detect and evaluate a range of environmental signals and modulate appropriate timing of feeding, reproduction, and survival. Inducible genetic recombination systems can now knock out genes in specific tissues and at specific times. These tools, together with the ability to activate or inhibit specific neurons with lasers, will likely permit delineation of cell- and tissue-specific control of aging as a major focus of mammalian studies in the coming years.

DRUGS THAT EXTEND LIFESPAN IN MODEL SYSTEMS

Characterizing genetic mutants with increased lifespan is one means to elucidate pathways important in regulating longevity. A different, complementary strategy is to identify small molecules that extend lifespan. Work in this direction is being carried out by a consortium of three laboratories, funded by the US National Institute on Aging as the Interventions Testing Program (ITP). The ITP consortium evaluates three to six new drugs or nutritional supplements each year for possible benefits to mouse lifespan, using a genetically heterogeneous mouse stock to diminish the chances of detecting, or missing, results that would apply only in mice carrying a single, potentially idiosyncratic, genotype. There is now evidence that at least three drugs—rapamycin, acarbose, and 17-α-estradiol—can improve survival and increase maximal longevity in mice. Rapamycin, an inhibitor of the intracellular enzyme mTOR, increases lifespan in both males and females, with increases exceeding 23% at the highest dose so far tested. Acarbose, which slows the intestinal digestion of starches to sugars and thus blunts postprandial surges in blood glucose, increases male lifespan by 22%, and has smaller, though still significant, effects in females. 17-α-Estradiol, a nonfeminizing isoform of estrogen (17-β-estradiol) increases lifespan of male mice by 19%, but does not extend lifespan in females. A fourth agent, nordihydroguaiaretic acid (NDGA), which has both antioxidant and anti-inflammatory actions, improves lifespan of male mice only, and a significant survival benefit was also reported for male mice given a very low dose of aspirin. **Figure 1-9** illustrates lifespan extension in mice given rapamycin or acarbose, and shows the delay in several forms of midlife pathology in rapamycin-treated mice.

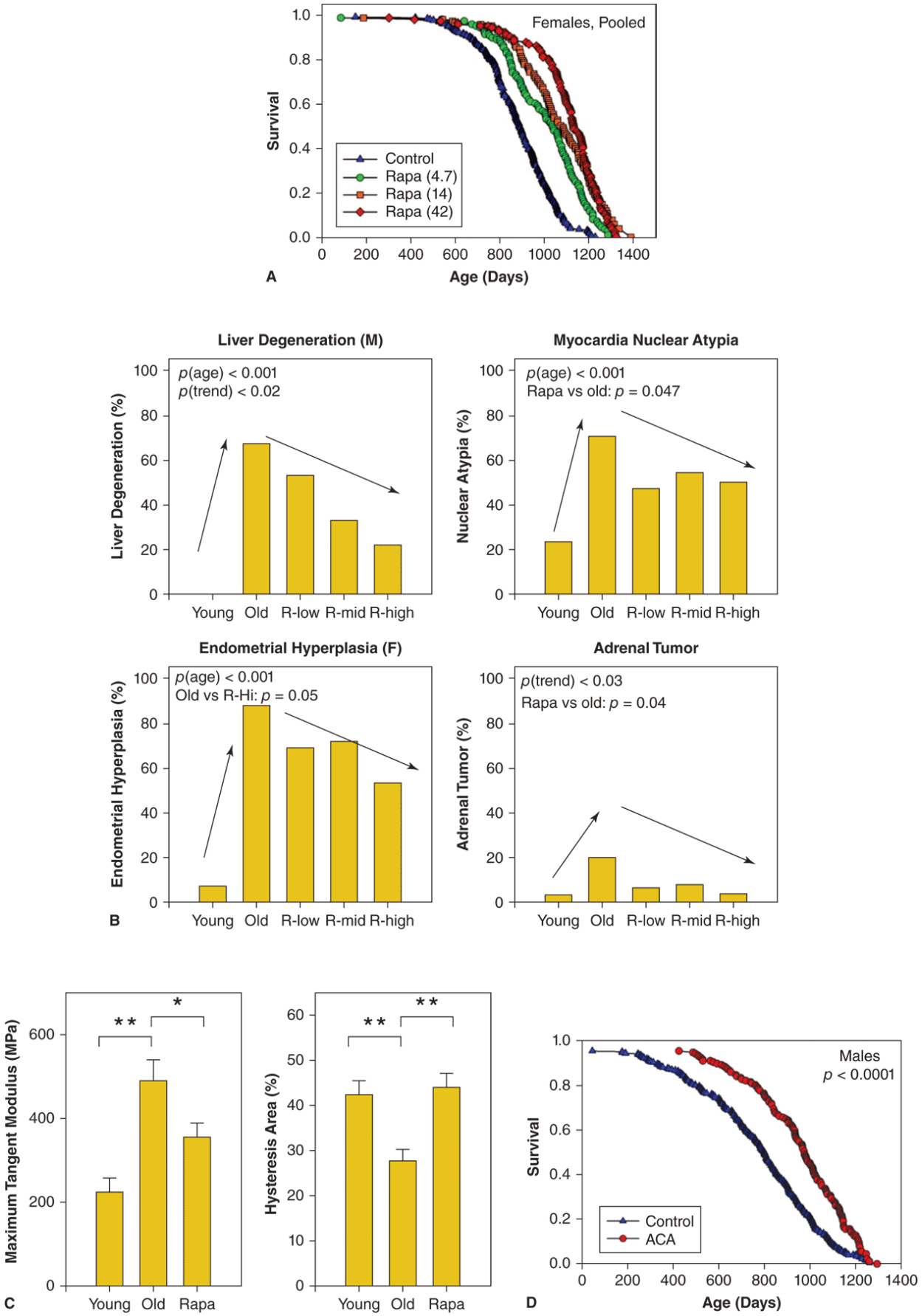


FIGURE 1-9. Increased lifespan and improved late-life health in mice treated with rapamycin or acarbose. (**A**) Increased mean and maximal lifespan in female mice exposed to varying doses of rapamycin (4.7, 14, or 42 mg drug per kg food) from 9 months of age. (Adapted from Miller RA, Harrison DE, Astle CM, et al. Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction. *Aging Cell.* 2014;13:468–477, Figure 1, lower panel.) (**B**) Four forms of age-related pathology seen in 22-month-old

mice that are less frequent in mice treated with rapamycin. (Adapted from Wilkinson JE, Burmeister L, Brooks SV, et al. Rapamycin slows aging in mice. *Aging Cell.* 2012;11: 675–682, Figure 1.) (**C**) Rapamycin treatment delays the effects of aging on the properties of an extracellular tissue, in this case elasticity of collagen fibers from the tail tendon. (Adapted from Wilkinson JE, Burmeister L, Brooks SV, et al. Rapamycin slows aging in mice. *Aging Cell.* 2012;11:675–682, Figure 3.) (**D**) Extension of lifespan in male mice treated with acarbose (1000 mg per kg food) from 4 months of age. (Adapted from Harrison DE, Strong R, Allison DB, et al. Acarbose, 17-α-estradiol, and nordihydroguaiaretic acid extend mouse lifespan preferentially in males. *Aging Cell.* 2014;13:273–282, Figure 1A.)

Studies of this kind serve a variety of purposes. First, they establish, as proof of principle, that drugs added to food can increase mammalian lifespan. From this perspective they help support the evidence from studies of diets and single-gene mutations that the aging process in mammals can be delayed or decelerated sufficiently to have an important effect on survival, and overall health, at older ages. **Figure 1-10** compares the extent of lifespan extension achieved, so far, in drug-treated mice, in parallel to effects produced by single-gene mutations, both spontaneous and targeted.

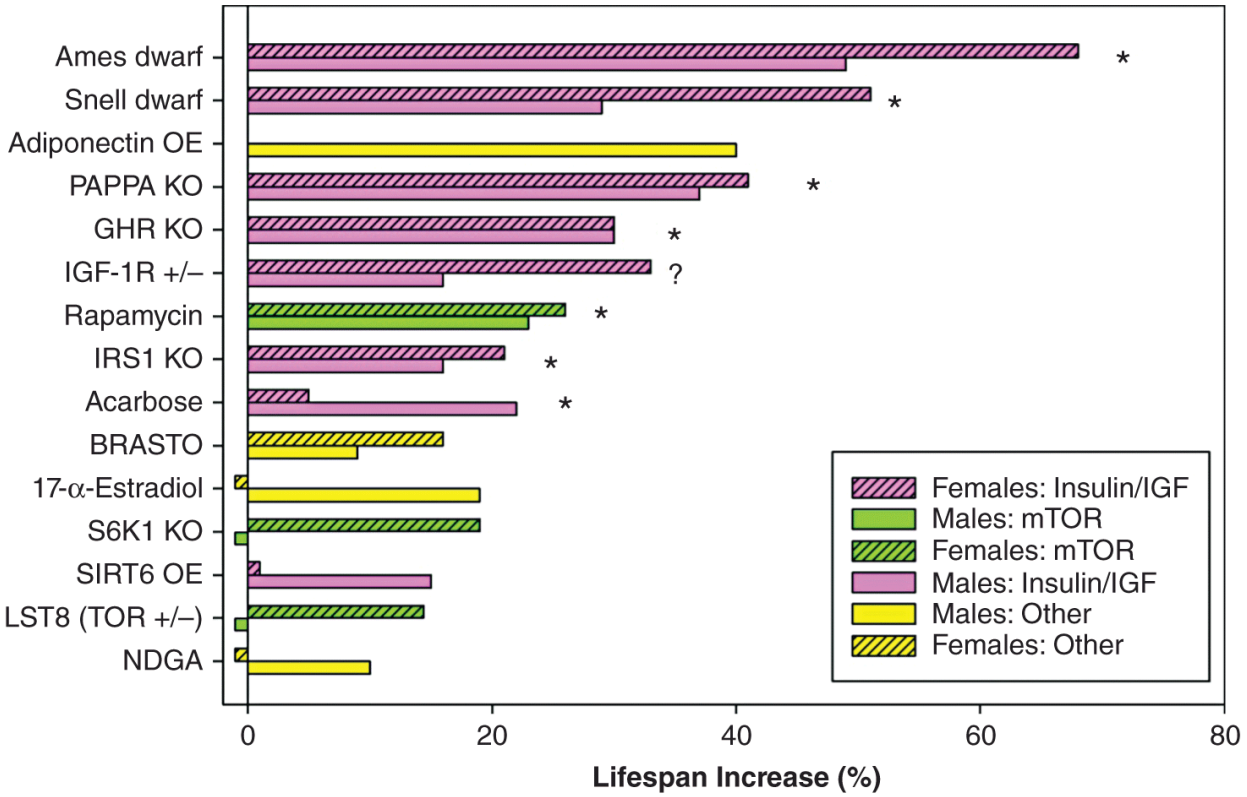


FIGURE 1-10. Selected reports for mouse lifespan extension mediated by mutations or drugs. Colors indicate functional groupings: pink for alteration of GH, insulin, or IGF-1, green for mTOR, yellow for unknown or other pathways. (*) indicates confirming reports from at least one other laboratory group and/or in at least two independent cohorts. (?) indicates that substantially smaller results were obtained in another laboratory. Effects that were reported as "zero" are illustrated, as a convention, at −1 to allow the bar to be visible. BRASTO: brain-specific SIRT1-overexpressing; IRS1: insulin receptor substrate 1; KO: knockout; LST8: lethal with SEC13 protein 8; OE: overexpressor; PAPP-A: Pregnancy-Associated Plasma Protein A; s6K1: S6 Kinase 1. (*Used with permission from* David Lombard and Richard A. Miller.)

Second, they point to specific drugs, and classes of drugs, that might deserve further, more intensive analysis, as tools to learn more about the biology of aging and late-life diseases. Studies in invertebrates had suggested an important role for mTOR, the target of rapamycin, and the subsequent demonstration that rapamycin itself could extend mouse lifespan helped to focus renewed attention to the role of mTOR in aging and late-life diseases. The benefits of rapamycin on lifespan seem to be equivalent whether the drug is initiated in young adult mice or in mice already more than half the age of median survival, suggesting that inhibition of TOR function may be beneficial even if started at relatively late ages. Moreover, this result hints that mTOR signaling may increase in older individuals, and contribute to the degenerative effects of aging. Work examining mTOR signaling in aging mouse models supports this idea. Strikingly, pharmacologic mTOR inhibition in older adult humans improves responses to influenza vaccination, hinting that drugs identified as having beneficial effects on lifespan and late-life health in rodents may have similar effects in humans.

The striking acarbose results should prompt additional studies of the role of transient glucose surges in the control of aging rate. Although the effects of acarbose on peak glucose levels make it a useful tool for the treatment of

diabetes in humans, it is noteworthy that diabetes is quite rare in the mouse stock used by the ITP, and that most of the ITP mice die because of some form of neoplasia. More work will be needed to discover how acarbose slows cancer progression, whether or not it slows the pace of other age-related changes, such as cataracts, sarcopenia, immunosenescence, and cognitive decline, and to determine why the lifespan benefit is so much stronger in male than in female mice. The male-specific benefits of 17-α-estradiol will prompt new work on the routes by which steroids can modulate cancer and other late-life diseases. This agent is nonfeminizing and does not require the presence of the classical estrogen receptors for its cellular effects, suggesting new avenues for exploration of steroid influences on late-life illnesses. Obstacles related to translation of these experimental results into clinical trials are discussed later.

GENETIC APPROACHES TO ANALYSIS OF AGING IN HUMANS

Attempts to find genetic variations that influence aging in humans have been plagued with practical and conceptual problems in addition to the obvious difficulty that selection of mating partners is not amenable to experimental control. For one thing, heritability calculations show that roughly 15% to 20% of the variation in lifespan among humans can be attributed to genetic factors. However, the magnitude of the influence of genetics on longevity may rise with increasing age. Furthermore, an unknown but potentially large fraction of this genetic variation probably reflects genetic variants that influence susceptibility to diseases of childhood, infectious agents, and specific common illnesses of old age. For example, genetic variants that cause Huntington disease or type 1 diabetes or which triple the normal risk of myocardial infarction by the age of 50 would all contribute to the measured heritability of lifespan, but do so by altering mortality risks from a specific form of illness rather than by alteration of aging with its effects on multiple late-life traits. Thus genetic variants that mold lifespan by effects on aging per se, if they exist at all, are likely to influence only a small fraction of variation in how long people live.

Formal analyses of the genetics of human aging have so far relied mostly on candidate gene approaches, in which long-lived and control populations are evaluated for variations at one or a small number of genetic loci selected on theoretical grounds as most likely to be involved in aging or disease processes. In such studies, polymorphisms near the *FOXO3A*, *APOE*, and *SIRT3* genes have been identified as enriched in long-lived individuals. The FOXO3A transcription factor is a FoxO protein, modulated by insulin and IGFs. Apolipoprotein E (*APOE*) polymorphisms are well known to affect the risk of developing cardiovascular disease and Alzheimer dementia. SIRT3 is a sirtuin family member; this protein resides in mitochondria, where it regulates multiple metabolic processes. An alternative approach is whole genome screening of large populations for association of longevity with hundreds of thousands of genetic variants. Thus far, only *APOE* polymorphisms have been identified in multiple studies, while other potential genetic associations have proven difficult to replicate. There are several possible explanations for these discrepancies, including lack of a consistent definition of longevity between studies, different ethnic backgrounds of study populations, inadequate sample sizes leading to insufficient statistical power, differing living conditions, lack of ideal control populations, and other confounding factors.

A major problem with all these approaches, from the perspective of biological gerontology, is the lack of a defensible phenotype: a measure of aging better than lifespan. There are now several dozen reports of candidate loci at which particular alleles are overrepresented among centenarians or near-centenarians, and advocates of this strategy hope that among this collection are some loci that control aging rate. But skeptics note that alleles that increase risk of cardiac disease, Alzheimer disease, stroke, various common forms of cancer, or severe osteoporosis are likely to have contributed to disease and death before the age of 90 or 100, and thus to have been eliminated or greatly reduced among very old people. Thus it should be assumed that a collection of genetic loci whose frequency discriminates very old people from others of the same birth cohort will include many genes with influence over common forms of lethal illnesses rather than genes that modulate aging per se. This problem is not one that can be solved by technological innovation or larger numbers of tested subjects; it requires development of a phenotype that provides more information about health in old age than merely a record of the age at death. For example, a genetic allele that identified, among 70-year-old people, those most likely to have excellent eyesight and hearing, no history of cancer, angina, diabetes, or arthritis, above-average responses to vaccination, and retention of baseline levels of cognition and muscle strength would be a much stronger candidate for an authentic “antiaging” gene than one that predicted survival to the age of 100.

MODELS OF ACCELERATED AGING

There are a small number of rare inherited diseases, of which Werner syndrome (WS) and Hutchinson-Gilford syndrome (HGPS) are the most celebrated, that have been mooted as possible examples of "accelerated" aging (see Chapter 2 for more details). Some of the physical features and symptoms of these diseases do resemble, at least superficially, some of the changes that typically affect older people, including in particular changes in skin, connective tissues, and the vasculature. HGPS, sometimes called "progeria," is now known to be caused in most patients by mutations in the gene encoding Lamin A, a component of the nuclear membrane. WS patients usually have mutations in an enzyme (WRN) that functions as a DNA helicase (unwinding coiled DNA) and as an endonuclease. Patients with HGPS typically survive to their early teens, when they usually succumb to dramatically accelerated atherosclerotic disease. WS patients frequently survive into their mid-forties, about 10 years after the age of typical diagnosis, and usually succumb to cancer or coronary artery disease.

It is debated whether either of these diseases provides strong clues about the molecular or cellular basis for age-related changes in normal individuals. WS patients do resemble older people in some ways: they frequently suffer from cataracts and premature graying of the hair, and by their early thirties often develop osteoporosis, diabetes, and atherosclerosis. On the other hand, many features of normal aging are not seen in WS patients and many features of WS are not seen in normal old individuals. WS patients, for example, do not show signs of Alzheimer disease or other amyloidoses, hypertension, or immune failure. Mesenchymal tumors, which are rare in normal people, are about 100-fold more frequent in WS patients, but the epithelial and hematopoietic tumors characteristic of normal aging are not seen in these individuals. Furthermore, WS patients exhibit many features that are not seen in normal aging, including subcutaneous calcifications, altered fat distribution, vocal changes, flat feet, malleolar ulcerations, high levels of urinary hyaluronic acid, and a number of other idiosyncrasies not seen commonly in older adults. Mice with mutations in the *WRN* gene live a normal lifespan and do not show signs of premature senescence. However, mice lacking *WRN* that also possess genetically engineered defects in telomere maintenance show a spectrum of effects very similar to those observed in WS patients, implying that the WRN protein plays important roles at the telomeres, functions required for maintenance of organismal health.

It seems possible that investigation of the pathogenesis of WS, HGPS, and related diseases may provide key clues to the mechanisms of some age-related pathologies. But it seems at least equally plausible that the *WRN* mutation, perhaps through alteration of cells responsible for connective tissue maintenance, induces multiorgan failure through processes distinct from the changes that impair some of the same organs in normal aging.

AGING RESEARCH AND PREVENTIVE MEDICINE

The central rationale for biological gerontology is the hope that discoveries in this field will lead to innovations in preventive medicine. Mice subject to DR, or with genetic manipulations that increase lifespan, show protection from a wide away of diverse age-associated pathologies, and there is growing evidence that multiple signs of aging occur more slowly in mice treated with rapamycin. An authentic antiaging drug that produced the same demographic changes in humans seen in rodents on DR or MR diets would yield about 10-fold greater improvement in mean life expectancy than would the complete elimination of cancer or of myocardial infarction (**Figure 1-11**). A detailed understanding of the molecular pathways that lead to coordinated stress resistance in cells of dwarf mice, or of the adjustments that render DR rats resistant to autoimmune, neoplastic, and degenerative diseases, or of the evolutionary changes that permit large animals to survive cancer-free and cataract-free for many decades should in principle suggest avenues to preventive medical care that could dramatically postpone disability and lethal illnesses.

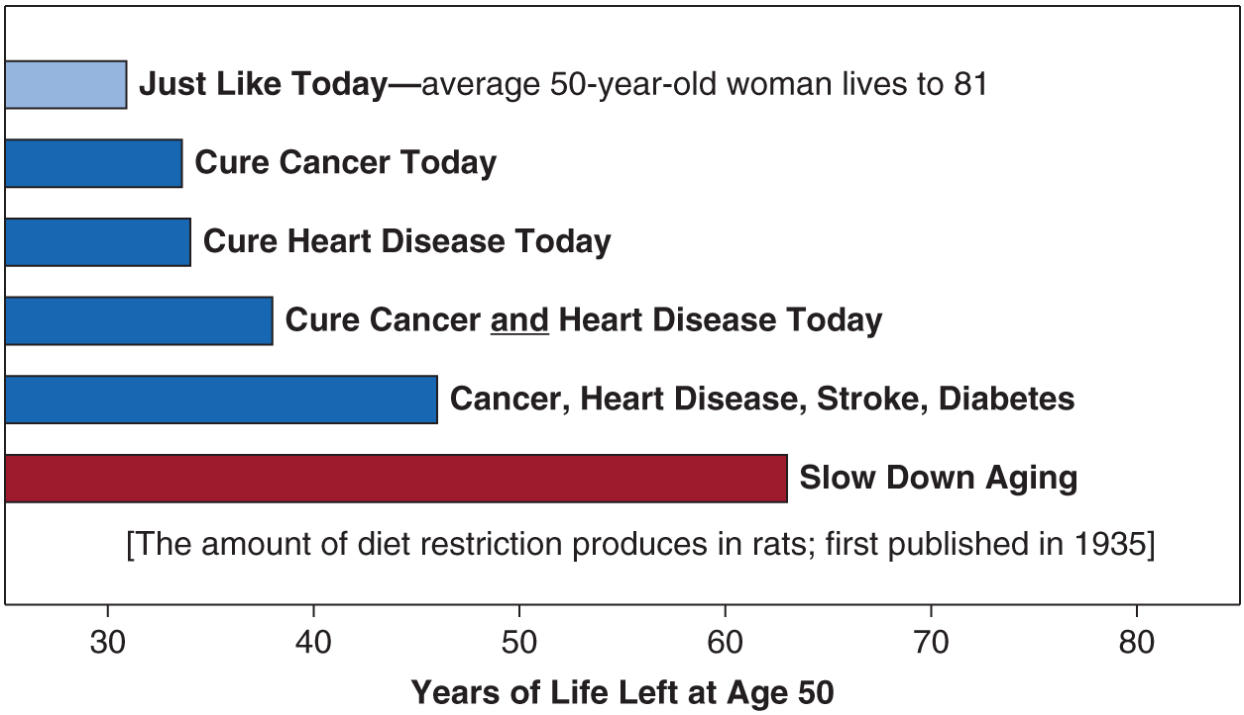


FIGURE 1-11. Theoretical remaining life expectancy of a 50-year-old white woman in the United States under a variety of demographic assumptions. The top bar shows remaining life expectancy with disease-specific mortality rates that prevailed in 1985. The four middle bars show projected life expectancy under the assumption that mortality risks for the indicated diseases were in fact zero. (Data from Olshansky SJ, Carnes BA, Cassel C. In search of Methuselah: estimating the upper limits to human longevity. *Science*. 1990;250:634.) The bottom line shows projected longevity if it were possible to retard human aging to the same degree that is obtained in the typical study of caloric restriction in rats or mice. (*Data* from Miller RA. Extending life: scientific prospects and political obstacles. *Milbank Q.* 2002;80:155–174.)

But the pathway connecting discovery in this area of basic science to intervention is strewn with obstacles, some scientific, but others political, economic, and legal. Even if research in mice or rats were to demonstrate a dramatic effect of a specific agent on the aging process, producing, for example, a 40% increase in mean and maximal lifespan, showing that the agent was able to safely extend human lifespan would require vast resources and treatment of young or middle-aged adult subjects for many decades. Pharmaceutical firms have little commercial incentive for embarking on expensive tests that might (or might not) demonstrate safety and efficacy of an agent many decades in the future, and governmental agencies, already strained by limited resources and competition among medical researchers with alternate priorities, are also unlikely to be able to support such an ambitious long-term undertaking. Nor are many scientists eager to devote their careers to an experiment whose conclusions are unlikely to emerge until the time of their own retirement. A hypothetical agent that is active in those already old could, in principle, be tested with a relative short follow-up, that is, over a period of 5 to 10 years. Such agents might be evaluated in the context of discrete age-associated pathologies, rather than in lifespan extension. In this regard, the demonstration that an mTOR inhibitor enhances the response to the influenza vaccine in older individuals represents a significant step forward. A few of the interventions tested so far in mice, including rapamycin and a diet low in methionine, lead to lifespan extension even when initiated in mice already well into the second third of their lifespan, and provide some hope that interventions that slow aging could in principle be effective when administered to middle-aged people as well.

Introduction of authentic antiaging compounds into the practice of health care is thus likely to involve relatively unconventional pathways. The public has shown an unbridled appetite for consumption of compounds and mixtures, labeled as “nutritional supplements,” which are exempt from laws that govern prescription and nonprescription drugs, and are purported to oppose the effects of aging. Thus far, there is no evidence that any of the agents so touted, including melatonin, dehydroepiandrosterone, homeopathic remedies, and many others, can retard, delay, or reverse aging in humans or animal models. However, it seems possible that agents that did prove, in animal studies, to have the ability to delay or decelerate aging might make their way into human use, or into clinical trials. Studies of these interventions in pet dogs might prove to be economically feasible, socially acceptable, and scientifically valuable, and evidence that a drug extended healthy lifespan in dogs could help to shape the discussion about ways to introduce such interventions into preventive medicine. If a promising agent can be shown through typical short-term clinical tests to be useful for the treatment or prevention of a specific disease or condition, further study of broader disease prevention and enhanced survival may ensue.

ANTIAGING RESEARCH: SOCIAL OBSTACLES AND ETHICAL CONCERNS

Serious research into the basic biology of aging, and proposed translational research to turn gerontological discoveries into antiaging medicines have long been hobbled by pessimism, specifically the assumption that aging is immutable, and by stigma, arising from claims made for allegedly effective antiaging potions promoted unscrupulously for commercial gain. For these reasons, many political and scientific leaders have been understandably shy of lending support for research efforts whose goal is to develop antiaging interventions for human use. Journalists, who are often aware of promising discoveries in biological gerontology, are nonetheless often drawn ineluctably toward promotion of extreme claims, which, while entertaining, go well beyond scientific evidence and thus further impair the credibility of the antiaging research enterprise. Although several decades of evidence has now clearly refuted the common assumption that the aging process is too complex or too stable to be altered, the attitudes and expectations of opinion leaders and the lay public greatly undermine and complicate efforts to attract support for this research agenda.

A related concern is often posed as a question of ethics: if the goal of antiaging research is to help keep people alive and healthy for several decades beyond their current "natural" lifespan, would not realization of this goal greatly complicate efforts to solve the current set of Malthusian dilemmas? In a world where resource depletion, food shortages, and environmental degradation already consign billions to great suffering, would not methods that delay aging and death lead to unacceptable exacerbations of these and related problems? Arguments along these lines are often influenced by the unstated assumption that old people are typically ill, unhappy, and unproductive, and by a desire to avoid creating a society in which an ever-increasing proportion of the population has the problems that can afflict people at the very end of life.

This concern that development of antiaging medicines would be unethical is widespread, but easy to refute. Most of modern medical research is designed to help prevent or treat diseases with a high risk of mortality and thus to increase the likelihood that patients will enjoy additional years or decades of good health. Efforts to develop vaccines for influenza, or to eradicate residual tumor burden by adjuvant chemotherapy, or to correct arrhythmias, or the symptoms of diabetes or gall stones are all designed to allow patients to remain healthy and active as long as possible. These research efforts are appropriately considered ethical and indeed heroic, even though patients so treated are quite likely to encounter additional illnesses, often associated with suffering, at later ages. A similar motivation and justification underlies translational research in biological gerontology. Clearly, there is no pressing need for agents that merely prolong life in people who are in the final stages of a dementing illness or nearing death in great pain, and developing drugs that extend lifespan without improvements in health would not be an attractive goal. Fortunately, each of the dietary and genetic manipulations shown in rodent models to extend longevity does so by an increase in the length of healthy lifespan; postponement of death goes hand in hand (and is almost certainly caused by) postponement of a very wide range of diseases and forms of disabilities.

A society in which many people remain active and productive at ages of 80 to 100 or so would indeed require economic adjustments and alterations of assumptions about retirement ages and family structure, just as adjustments of this kind have been required as societies have experienced reductions in infant and childhood mortality that greatly increase the proportion of newborns that reach the ages of 20 to 50. Such adjustments are not trivial, but such fears have not raised concerns about the ethical merit of insulin therapy, vaccination programs, smoking cessation clinics, or adjuvant chemotherapy. From this perspective it is hard to understand why success in antiaging research should be considered pernicious.

There is, however, a serious ethical concern about antiaging interventions that deserves attention. There is some basis for believing that agents that decelerate aging, either by alteration of IGF-1 signals or through the still undiscovered mechanisms of CR and MR diets, might be more effective if imposed early in life, perhaps as early as the childhood years. In such a case, decisions about use of such preventive treatments might have to be made by parents on behalf of their young children. If such agents had side effects, such as postponement of puberty, or permanent short stature, would parents be acting ethically to impose these side effects on their children in order to provide them with additional decades of excellent health in adult life? Conversely, would parents be acting ethically to deny their children additional decades of healthy life just to allow them to grow to what is now considered "normal" height? Questions of this kind are harder to answer than concerns about whether postponement of late-life illnesses is or is not desirable on its own merits.

ACKNOWLEDGMENTS

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Chapter 2

Genetics of Age-Dependent Human Disease

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Learning Objectives

- To provide the genetic background for diseases associated with aging
- To review the current available genetic tools and properties to study the complex phenotypes of aging
- To appreciate the important role played by genes in age-associated diseases

Key Clinical Points

1. **Genetic screening for genetic predisposition is justified if the disease (ie, age-associated diseases) is clearly clinically defined. The greater the differences between healthy subjects and disease carriers, the greater is the chance to find a genetic link.**
2. **Genetic tests for age-associated diseases are important, especially in families with history of such diseases.**
3. **Carriers of a mutation associated with disease may be at higher risk to develop the disease; however, many carriers may not ever develop the disease.**
4. **Positive genetic test results may provoke anxiety and distress. Nevertheless, they allow positive action such as early treatment and preclinical screening to reduce risk.**

INTRODUCTION

Aging can be characterized as a multisystem decline in healthy performance with time. This phenomenon has been observed across the animal kingdom, and analogous processes occur in the plant kingdom. Do we start aging at the moment we stop growing (at about 25 years old), or is there a period of maintenance/latency? In females, a period of maintenance appears to exist until the menopause (which is followed by a steep decline in some aspects of health). In males physical attrition may start earlier, is more gradual, and lasts longer. The dramatic increased prevalence of common diseases with age is discussed in detail in Chapter 5. For most diseases, there is a low incidence between 20 and 50 years of age, and a manifold increase afterward. Such events suggest that during the adult period there are enough biological resources (the biological system is still “in shape” and is moving from growing to maintenance) to buffer deleterious biological effects of preaging processes and thus maintain age-associated diseases on a “low flame.” When these resources are exhausted, the body can no longer cope with the harmful aging processes and thus serves as a Petri dish for the occurrence of diseases.

The questions that we ask are (a) Does the profound multisystem performance decline with age promote disease occurrence? or (b) Is genetic predisposition the main cause of the decline? or (c) Does a combination of the two enhance the accumulation and progression of diseases?

Failure of body systems with age contributes to frailty (see Chapter 46) which can result in more severe diseases leading to death. Our first question is supported by this example. However, in this chapter we will list a group of age-associated diseases and organ failures that are a result of an increased prevalence of deleterious genetic predispositions with age and the mechanisms of their effects. These examples support our second question. That said, we presume that the answer is more complex and is a result of the two initial listed hypotheses. On one hand a combination of the two

decreases life expectancy; on the other hand each one of them can promote early mortality. The picture becomes less clear when successful aging is present—exceptionally long-lived individuals who survive, delay, or avoid major age-associated diseases probably due to underlying mechanisms that protect them from further age-related decline. Thus, having a protector allele may block or delay the comorbid condition and the deleterious predisposition, and lead to successful aging. Identifying the deleterious alleles and the mechanisms of their effects (which is the effort of this chapter) should be done in parallel with the hunt for longevity-associated alleles to spur drug development, maintaining a focus on the underlying genetic mechanisms of aging rather than on the physiologic decline with age.

CANCER

Cancer arises from one single cell. The transformation from a normal cell into a tumor cell is a multistage process, typically a progression from a precancerous lesion to malignant tumors. These changes are the result of the interaction between a person's genetic factors and environmental factors such as physical, chemical, and biological agents. The rise in cancer development as age advances affects both sexes and every type of cancer studied, although particularly breast cancer in women (see Chapter 97) and prostate cancer (see Chapter 98) in men.

Cancer genetics is comprised of two main subfields: genetic susceptibility and somatic cell genetics. Genetic susceptibility focuses on inherited (constitutional or germline) genetic variation in cancer susceptibility genes, and the effects of that inherited variation on an individual's lifetime cancer risk. In contrast, somatic cell genetics focuses on mutations that arise in an individual's cells during their lifetime and the role that those mutations play during tumor initiation and progression.

Underlining the common biological basis of the substantial gene mutations involved in cancer initiation and progression, several biological characteristics consistent with tumor growth and metastasis were termed "hallmarks." Those are six common traits that direct the transformation of normal cells to malignant cells. They include (1) growth stimulation, (2) evasion of growth suppressors, (3) resistance to apoptosis, (4) replicative immortality, (5) induction of angiogenesis, and (6) activation of invasion and metastasis. To these features, other key hallmarks were added: abnormal metabolic pathways and evasion of the immune system along with genome instability and tumor-promoting inflammation.

The best-known example of the mechanism involved in cancer is the TP53 tumor suppressor protein in which a mutation leads to inhibition of this gene activity and enables the survival of cancerous cells through resistance to programmed cell death.

IMMUNOSENESCENCE

An emerging consensus suggests that maintenance of appropriate immunity is necessary for exceptional longevity and, by implication, also for "normal" longevity. While all components of innate and acquired immunity experience changes with age, the scientific impact of these changes is not clear, and mechanisms of and markers for immunosenescence (see Chapter 3) are controversial.

One of the mechanisms suggested for immunosenescence has to do with murine Zizimin2, a guanine nucleotide exchange factor (GEF) for Cdc42 and one of the major Rho GTPases. The expression pattern of Zizimin2 was previously shown to be restricted in immune tissues (spleen, thymus, and lymph nodes). Thus, researchers expected Zimizin2 to be associated with immune responses. Zimizin2 expression levels in immune tissues are reduced with aging in mice, suggesting that its expression is associated with the mechanisms responsible for immunosenescence.

CARDIOVASCULAR DISEASES

Aging cardiovascular tissues are characterized by pathologic alterations including hypertrophy, altered left ventricular (LV) diastolic function, diminished LV systolic reverse capacity, increased arterial stiffness, and impaired endothelial function. The risk of cumulative exposure to traditional cardiovascular risk factors like smoking, diabetes, and a sedentary lifestyle can be viewed as an age effect on cardiovascular diseases (CVDs). Therefore, the interaction between cumulative exposures (aging), cardiovascular risk factors, and genetic factors is the reason for the observed increase in CVDs in older people (see Chapter 75).

In most CVD cases, the risk of disease is conferred by variants of hereditary components. Disease and other factors

such as subtype of disease and the age of onset are determining factors for the exact scale of the role inheritance plays. Some forms of CVD display a simple model of inheritance suggestive of a single causal gene with a great effect on phenotype. Examples include families with mendelian inheritance of early coronary artery disease, mendelian forms of hypertension, and several forms of congenital heart disease. However, most CVD traits, such as myocardial infarction or concentration of plasma low-density lipoprotein (LDL) cholesterol, show complex inheritance, indicative of an interaction between multiple genes and nongenetic factors. Many genes and their linked pathways have been assessed in different model organisms for their role in regulating longevity as well as CVD including SIR2, a key component of the longevity network that has a number of effects on cardiovascular health demonstrated in mice but by which the molecular mechanism is not fully understood; and insulin-like growth factor 1 (*IGF1*), one of the initial genes to be identified as a longevity gene with a significant role for its pathway that has been defined in regulating cardiovascular health.

FOXOs are downstream effectors of the IGF1 signaling cascade and play a role in regulating expression of genes involved in longevity. Even though deletion of *FOXO* genes in mice leads to deficient vascular and cardiac growth, the interaction of the FOXO factors with the longevity network in cardiovascular tissues is yet to be understood. Adenosine monophosphate-activated protein kinase (AMPK) affects the longevity network by regulating mammalian target of rapamycin (mTOR) and modulating the IGF1 pathway through the extracellular signal-regulated kinase (ERK) cascade. AMPK is cardioprotective during ischemia and reperfusion, and its inhibition abolishes the cardioprotection. Another example of such activity (longevity through cardioprotection) is p66sch, a redox enzyme-modulating mitochondrial reactive oxygen species (ROS). In the cardiovascular system, loss of the *p66sch* gene blocks the decline in cardiac progenitor cell senescence and preserves LV volume and function, thus reducing heart failure. Catalase converts one of the major ROS, hydrogen peroxide, into water and oxygen. Targeting the peroxisomal catalase to the mitochondria leads to an approximately 20% increase in lifespan. In addition, the transgenic mouse model in which catalase is overexpressed and targeted to mitochondria is also protected from angiotensin II–induced cardiac hypertrophy.

Another example of an aging genotype associated with CVD is the BubR1, a serine/threonine protein kinase and an inhibitor of the anaphase-promoting complex, regulating the mitotic spindle assembly checkpoint. Mice with near-deficient levels of BubR1 develop premature aging phenotypes and have a shortened lifespan. BubR1 hypomorphic mice exhibit arrhythmias, thought to be the primary mechanism leading to their death. Further studies are needed to elucidate the molecular mechanisms by which these genes regulate longevity and/or various CVDs.

DIABETES

Type 2 diabetes (see Chapter 110) is an age-related disease caused by complex interactions between adverse environmental factors and certain genetic factors. During the last decade, enormous effort has revealed more than 153 genetic variants in 120 loci (**Table 2-1**) associated with type 2 diabetes and its related phenotype. However, the contribution of these variants to the phenotypic variance of the disease was only close to 20%. Initial linkage analysis and a candidate gene approach had resulted in only four genes associated with type 2 diabetes: CAPN10, a cysteine protease with functions in glucose metabolism; TCF7L2, a transcription factor that plays a key role in the Wnt signaling pathway; PPARG, a key regulator of adipocyte differentiation and glucose homeostasis; and KCNJ11, which codes for four subunits of the ATP-sensitive potassium (K-ATP) channel. This small list of genes grew dramatically following the completion of the Human Genome Project, which provided a cheap genomic screening tool with millions of genetic variants to search for, in association with a given trait. These methods, termed GWAS and metaanalysis, require statistical thresholds that necessitate the use of tens of thousands of cases versus control subjects. These methods have identified broader lists of candidate genes. This genomic screening provides a powerful tool for candidate loci detection; however, most of the newly identified genomic loci have been in noncoding areas (see **Table 2-1**). Future intrinsic studies of the new revealed candidates may lead to identification of functional elements that have important ramifications to the understanding of the disease pathology which may lead to drug design and tailored treatment to cure or cope with diabetes.

TABLE 2-1 CANDIDATE GENES ASSOCIATED WITH TYPE 2 DIABETES

GENE LOCATION (# OF VARIANTS)	GENE/NEAREST GENE (# OF VARIANTS)
Coding (1)	*MACF1*

Coding missense (9)	*COBLL1, THADA, PPARG, WFS1, C6orf57, KCNK16, SLC30A8, KCNJ11(2)*
Intergenic (57)	*TLE4, CDC123, TSPAN8, PROX1, BCL11A(2), GRB14(2), IRS1, RND3, TMEM163, FAM148B, LPP, PPARG, PSMD6, SFRS10, UBE2E2, TMEM154, ANKRD55, HLA-B, DGKB, DGKB/TMEM195, GCC1-PAX4, GCK, KLF14, CDKN2A/2B(5), CDKN2B, TLE1, ADRA2A, CDC123/CAMK1D(2), HHEX, HHEX/IDE, CENTD2, HCCA2, MTNR1B, BCDIN3D/FAIM2, CCND2, DCD, HNF1A, KLHDC5, SPRY2, C2CD4A/B, HMG20A(2), VPS13C/C2CD4A/B, ZFAND6, BCAR1, MC4R(2), GIPR, FITM2-R3HDML-HNF4A, DUSP9*
Intron (75)	*RBMS1/ITGB6, GATAD2A/CILP2, FAF1, NOTCH2, CAPN10(2), G6PC2/ABCB11, GCKR, KIAA1486/IRS1, THADA, TMEM163, ADAMTS9-AS2(2), ADCY5(2), IGF2BP2(2), PPARG(2), ST6GAL1, MAEA(2), WFS1(2), ARL15, ZBED3, CDKAL1(6), SSR1-RREB1, ZFAND3, JAZF1(3), ANK1(2), TP53INP1, GLIS3(3), PTPRD, GRK5, TCF7L2(2), ZMIZ1, CRY2, FADS1, INS-IGF2, KCNQ1(4), MADD, MTNR1B, HMGA2(2), MPHOSPH9, OASL/TCF1/HNF1A, SGCG, PRC1, RASGRP1, FTO(3), HNF1B(2), SRR, LAMA1, PEPD, SUGP1/CILP2, HNF4A, FAM58A*
Intronic/promoter (1)	*TCF7L2*
Near gene (4)	*WFS1, POU5F1-TCF19, IGF1, SRR*
3’-UTR (5)	*SLC30A8(2), ADRA2A, VPS26A, AP3S2*
5’-UTR (1)	*ARAP1*

KIDNEY

Kidney diseases place a global public health burden, especially among older people, with increased morbidity and premature death. While the environment has a large effect on the occurrence and expression of kidney diseases, genetic predisposition has a clear role in determination, prevention, and cure. Understanding the structural and functional changes modulated by genetic factors and leading to kidney diseases of aging can promote drug discovery and tailored treatment (see Chapter 86).

Large candidate gene approaches resulted in only one candidate, CUBN, involved in age-related albuminuria. The genomic approach (genome-wide association study [GWAS]) initially found two more candidates: UMOD (associated with age-related albuminuria via a defect in tubular reabsorption) and SHROOM3 (may play an important role in renal aging by inducing fibrosis). However, follow-up efforts using the same strategy resulted in additional candidates. Defects in the *SLC7A9* gene are associated with stone formation in the urinary tract, tubular necrosis, and chronic interstitial nephritis. An *SLC34A1* variant causes nephrolithiasis. Mutations in *ALMS1* lead to age-dependent ciliopathies in the kidney. The association of *DAB2* with kidney disease was demonstrated in African Americans. Deleterious VEGFA variants have an impact on the number of nephrons. GCKR, with its neighboring *IFT172* gene, has a role in the formation of primary cilia. *PRKAG2* variants present with renal tubular dysfunction. A genetic network including DACH1, SIX, and EYA mutations lead to branchiootorenal syndrome. *LASS2* mutants are implicated in ceramide synthesis dysfunction causing aging kidney diseases. A few more candidate genes *TFDP2*, *PIP5K1B*, *UBE2Q2*, and *ATXN2* for kidney diseases have as yet no clear biological connection to renal function. eQTL mapping highlighted *MMP20* as a factor in aging kidney disease.

Thus, genetic studies using genomic tools highlight the role of specific genes in renal diseases. Future understanding of renal aging and its association with the genetic changes in both animal models and humans will take us closer to developing a multisystem drug or treatment program to cure or prevent renal diseases.

THYROID

Autoimmune thyroid disorders (AITD) are particularly common in older adults and may lead to either hypothyroidism or hyperthyroidism (see Chapter 109). AITD arise from the same genetic pathways; however, with a combination of unique genes, they manifest in opposite phenotypes. Both hypo- and hyperthyroidism share a mutated *HLA-DR* gene and segregate via interactions with different cells of the immune system. The different cells can induce apoptosis of

thyroid cells (leading to hypothyroidism) or cause overactivation of the thyroid-stimulating hormone receptor (TSHR) (leading to hyperthyroidism). Both conditions are characterized by a lymphocytic infiltration of the thyroid and production of thyroid autoantibodies. Thyroid peroxidase (TPO) and thyroglobulin (Tg) are the major autoantigens in hypothyroidism, but TPO-Ab and Tg-Ab are also observed in about 70% of patients with hyperthyroidism. On the other hand, the TSHR is the major autoantigen in hyperthyroidism, but TSHR antibodies have also been documented in some patients with hypothyroidism. Furthermore, some of the contributing genes are located on the X-chromosome, supporting the observation of higher prevalence of thyroid disorders in females. Alongside the genetic risk factors, there is interplay between genes and environment in the development of AITD. Environmental factors such as diet (especially iodine consumption), smoking, alcohol, drugs, stress, and inflammation can all provide triggers to the development of AITD.

There is also a positive genetic predisposition regarding the thyroid. Carriers of two distinct single nucleotide polymorphisms (SNPs) in the TSHR are more likely to have reduced thyroid activity with age, leading to a lower metabolic rate and increased lifespan. Genetic predisposition to elevated serum thyrotropin is also associated with exceptional longevity.

GENOME MAINTENANCE AND STOCHASTIC EVENTS IN AGING

Genomic structure stability relies on an intricate system of DNA damage repair (DDR) and maintenance. During the course of life of an organism, the somatic cells fend off a variety of DNA damage compromising the integrity and stability of the genome. The DDR system is able to overcome most of those threats while the cells are still undergoing mitosis; however, there is a decrease in DDR activity with the induction of cellular senescence in the postmitotic phase of the somatic cell. During this phase the DNA begins to accumulate sporadic mutations, single-strand breaks (SSB), double-strand breaks (DSB), and interstrand crosslinks (ICL) alongside shortened telomere length, all of which lead to genomic instability. Stochastic mutations can occur in significant locations affecting gene expression and leading to detrimental outcomes. This process coincides with the aging phenotype observed in aging individuals, potentially affecting their health and lifespan (**Figure 2-1**).

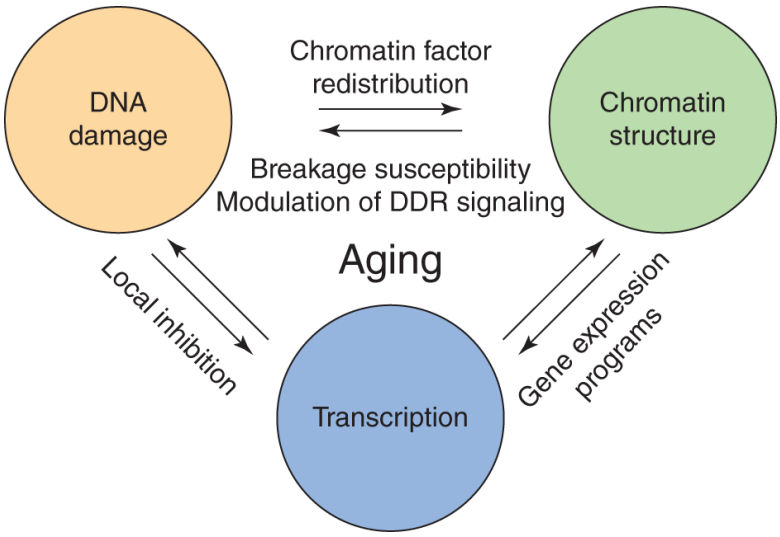


FIGURE 2-1 The tripod interaction of DNA damage, chromatin, and transcription in aging. (Adapted from Burgess RC, Misteli T, Oberdoerffer P. DNA damage, chromatin, and transcription: the trinity of aging. *Curr Opin Cell Biol*. 2012;24:724–730.)

The genetics of genome maintenance is complex and involves many different genes and pathways. Abnormalities of some of these genes result in genetic progeroid syndromes, such as Werner syndrome and Cockayne syndrome. These syndromes are characterized by early onset of aging (among other symptoms). As summarized in **Table 2-2**, some of those genes include *ATM*, *p53*, *NBS1*, *RAD50*, *WRN*, *UVSSA*, *LMNA*, and *ZMPSTE24*, mutations in which interfere with different genome maintenance pathways, promoting the early aging that is characteristic of those syndromes. Most syndromes presented in **Table 2-2** present with a progeroid phenotype with the exception of Li-Fraumeni syndrome and xeroderma pigmentosum. Most of them share an enhanced cancer susceptibility which is also

associated with age (as discussed earlier). These syndromes have shed light on the function of different genes in the genome maintenance network and have elucidated their functions in the process of aging. The different mutated genes are involved in various DDR pathways: DSB repair, nucleotide excision repair (NER), ICL repair, nuclear structure maintenance, and helicase function. It is clear that genome maintenance is a key process in an organism's healthy lifespan, and normal function of each and every cell depends on genomic stability.

TABLE 2-2 HUMAN GENOME MAINTENANCE DISORDERS

DISORDER	GENE(s) MUTATED	MUTATION	ANIMAL MODEL	PATHWAY IMPAIRED
Ataxia telangiectasia	*ATM*	Several—all resulting in loss of function	ATM disrupted/deficient mice	DSB repair
Ataxia telangiectasia–like disorder	*MRE11*	Several nonsynonymous	*MRE11* mutated mice	DSB repair
Atypical Werner syndrome	*WRN*	Several deletions—all resulting in truncated protein	*WRN* and *TERC* mutated mice	Nuclear structure
Bloom syndrome	*BLM*	Three INDELs and one nonsynonymous substitution, all resulting in malfunctioning gene product	*BLM* null embryonic mice and *BLM* mutated B-cells mice	Recombination Q (RECQ) helicase
Cockayne syndrome	*CSA*	Several deletions and substitutions all resulting in truncated protein	$Ercc^{null}$ mice exhibiting Cockayne syndrome-like symptoms	TC-NER
Cockayne syndrome type II	*CSB*	Several INDELS and substitutions all resulting in truncated protein	Few mouse models all with $Ercc6^{null}$ mutations	TC-NER
Dyskeratosis congenital X-linked	*DKC1*	Several nonsynonymous mutations all resulting in nonfunctioning protein	*DKC1* mutant mice	Telomere maintenance
Fanconi anemia	*FANCA*	Several deletions all resulting in truncated or nonfunctioning protein	*FANCA* mutated mice	ICL repair
Hutchinson-Gilford progeria syndrome	*LMNA*	Most documented—silent mutation causing alternative splicing and resulting in nonfunctioning protein	Few mouse models with mutated *LMNA*	Nuclear structure
Li-Fraumeni syndrome	*p53*	Several nonsynonymous mutations in various places along the gene	$P53^{null}$ mice crossed with CE/J mice	Many (p53 tumor suppressor inactivation)
Mandibuloacral dysplasia	*LMNA*	Several nonsynonymous mutations in various places along the gene	None	Nuclear structure
Nijmegen breakage syndrome	*NBS1*	90% of patients are homozygous for a 5bp deletion resulting in truncated protein	Few mouse models all with inactivation of *NBS1*	DSB repair
Restrictive dermopathy	*ZMPSTE24*	Several deletions and duplications all resulting in truncated protein	Four mouse models for two genes—*FST* and *SLC27A4*	Nuclear structure
Rothmund-Thomson syndrome	*RECQL4*	Several deletions resulting in truncated or alternatively spliced protein	*RECQ14* mutated mice	RECQ helicase

UV-sensitive syndrome	*UVSSA*	Different mutations all resulting in nonfunctioning protein	Mouse Kps3 cell line	NER
Werner syndrome	*WRN*	Mostly INDELs leading to truncated protein	*WRN* mutated mice	RECQ helicase, influencing nuclear structure, DSB repair, ICL repair, MMR, BER, TLS
Xeroderma pigmentosum	*XPA*	Several substitutions leading to alternative splicing and truncated protein	*XPA*-deficient mice	NER

From the genetic point of view, it is easy to postulate that genome maintenance deterioration could very possibly be the main reason for aging. Once maintenance subsides, there are more opportunities for stochastic mutations to undergo genomic preservation, hence having a lasting effect on a cell. Decrease of genome maintenance is also a signal for induction of cellular senescence or apoptosis (programmed cell death). The depletion of cells (as a cause of enhanced apoptosis) and the cessation of mitosis in a tissue are both characteristic of the aging process and are both direct outcomes of a decrease in genome maintenance.

NEURODEGENERATIVE DISEASES

Neurodegenerative diseases are a group of diseases affecting the nervous cells throughout the body, and especially in the brain. As a group, they are defined by deterioration of the nerves and their complete loss of function. Since most nerve cells are postmitotic, there is very little regeneration in those tissues leading to detrimental consequences of cell loss. The genetic pathways involved in the different diseases are complex and not fully elucidated yet. Age is the main risk factor for most of the neurodegenerative diseases. We will further discuss the genetic factors involved in three types of neurodegenerative diseases: Parkinson disease (PD), Alzheimer disease (AD), and dementia.

Parkinson Disease

The exact genetic background for PD is not yet completely elucidated. GWAS studies have identified 28 loci that could potentially be associated with PD; however, the information deducted from those studies remains limited. Some genetic pathways have been identified as harboring key candidate genes that may account for PD: mitochondrial damage-related genes, oxidative stress response genes, mitochondrial quality control genes, several ubiquitination pathway genes, and cellular stress response genes. All those have in common the fact that they cause aggregation of damaged proteins within the neurons (called Lewy bodies) which in turn brings on an apoptotic response or malfunction of the cell in question. To date, there are no validated genes known to be directly linked to PD. Age is the main risk factor for PD. The few patients with early-onset PD show increasing severity of the disorder with age. In addition, the prevalence of PD dramatically increases with age.

Alzheimer Disease

The genetics of AD is extremely complex and elusive and seems to be multigenic (see Chapter 66). At least 10 loci have been identified and confirmed as contributors to disease risk (APOE, PICALM, CLU, CR1, BIN1, CD2AP, EPHA1, MS4A4A, CD33, and ABCA7), yet these do not elucidate in full the genetic pathways involved in the process of AD. In addition to these loci, it is known that the amyloid plaques are a result of the cleavage of a mutated amyloid precursor protein (APP) by β- and γ-secretases (a pathogenic proteolytic process) which results in the formation of β-amyloid that aggregates extracellularly. This aggregation is the main mechanism underlying AD development. ADAM10, PSEN1, and PSEN2 have recently been identified as contributors to the β-amyloid accumulation. Those proteins are part of the APP protein-processing pathway and when mutated cause pathologic protein trafficking and cleavage. The intracellular neurofibrillary tangles are formed by hyperphosphorylated tau protein aggregates, a process that follows the accumulation of the extracellular β-amyloid plaques.

Other Dementias

Dementias, other than AD, are also directly caused by neurodegeneration. These forms of dementia are characterized

by relentlessly progressive cognitive impairment and loss of ability for independence. Genes interplay with lifestyle and environment in the course leading to dementia with recent advances in genetics shedding some light on risk factors. All of these types of dementia share a common mechanism of protein misfolding that causes accumulation of plaques in different regions of the brain. Two such major proteins are encoded by the tau and β-amyloid genes. Each type of dementia is associated with a different characteristic misfolded protein aggregate. Not all dementias are associated with age (eg, Huntington disease or early-onset PD); however, most of the common forms of dementia are positively and strongly correlated to age. Lewy body dementia has been found to be affected by the following genes: *GBA*, *SNCA*, *MAPT*, and *LRRK2*.

ADIPOSE TISSUE, LIPID METABOLISM IN AGING

Aging influences both fat mass (FM) and adipose tissue (AT) with a significant age-related increase in FM that normally peaks at about age 65 in men and later in women. The genetic links between lipid biology and aging have largely emerged from *Caenorhabditis elegans* studies. One particular treatment that extends lifespan is the removal of the germline by laser ablation of gonad precursor cells or by genetic means. These interventions are thought to act by removing a germline-derived signal that promotes aging.

Several different mechanisms have been identified by which removal of the germline affects lipid metabolism in a manner that extends lifespan. First, loss of the germline causes a reduction in TOR expression, which induces lipase and autophagy expression via the two factors DAF-16 and PHA-4. In addition, germline loss also increases expression of the FAT-6 desaturase, which produces oleic acid from stearic acid. This suggests that germline loss induces a healthier lipid status, leading to increased longevity. However, how changes in lipid status affect longevity is unknown.

THE GH/IGF1 AXIS IN AGING

It is well established that during human normal aging there are declines in synthesis and secretion of growth hormone (GH) and, consequently, that of IGF1 levels. This phenomenon is sometimes referred to as somatopause and is also seen in other mammals (see Chapter 110).

The reduction in the GH/IGF1 axis is correlated with increased percentage of total body and visceral fat, decreased muscle mass, decreased physical fitness, decreased immune function, and physiologic declines in estrogen and androgen concentrations. A meta-analysis on recombinant human GH (rhGH) use in older adults indicated that it has minor benefits on body composition but also has risks, such as the development of diabetes mellitus.

By contrast, abnormally high levels of GH, as in acromegaly, increase the incidence of heart problems, diabetes, morbidity, and mortality in both rodent models and humans. Caloric restriction, which decreases GH/IGF1 signaling and has many other effects, extends longevity in a wide variety of species including worms, fruit flies, yeast, and mice.

Animal knockout experiments have considerably increased our knowledge on the role of the GH-IGF1 axis in growth and development throughout life. Long-lived models share a decrease in IGF1 activity but different mechanisms lead to the reduction:

a. Multiple pituitary hormone deficiencies: Snell mice, Ames mice
b. Decreased GH action: Ghr–/– mice, Lit/Lit mice, rat GH antisense transgenic
c. Increasing IGF1 resistance: IGF1R+/– mice
d. Inhibiting IGF1 signaling: p66Shc –/–, Klotho transgenics, IRS1 –/– mice

There are no consistent phenotypic outcomes shared by all models with increased lifespan, and there are even disparate results with the same mutant. Several long-lived mouse strains with reduced activity of the GH/IGF1 axis have a dwarf phenotype, increased size of the subcutaneous adipose tissue depot, and improved insulin sensitivity. However, other mouse strains are normal-sized, lean, and even insulin-resistant but still display increased lifespan. Most of the strains showed resistance to tumors and to stress, which may play an important role in longevity effects.

Reports of patients with genetic defects in GH-IGF1 axis also support these conclusions. GH resistance, also known as Laron syndrome, is caused by homozygous mutations in GHR or GH-induced intracellular signaling molecules. Two cohorts expressing this syndrome have been studied. Mediterranean patients may show impaired glucose metabolism and even overt diabetes mellitus. Large-scale longevity data are still not available for this cohort,

given that many patients have been treated with rhIGF1, and most patients are still alive. Patients from Loja, Ecuador, are obese and short without higher prevalence of age-associated diseases. Remarkably, to date, only one case of (nonlethal) cancer has been reported in both Laron syndrome cohorts, and the prevalence of long-lived individuals among these cohorts is increased. Likewise, Ashkenazi Jewish centenarians demonstrated higher prevalence of two heterozygous *IGF1R* gene mutations, Ala37Thr, and Arg407His. These mutations suppress IGF1 signaling and decrease transcription of target genes.

On the contrary, individuals who suffer from GH signaling deficiency, like in the Itabaianinha cohort (homozygous GHRHR mutations), the Sindh cohort (homozygous GHRHR mutations) and a Swiss cohort (homozygous 6.7-kb deletion mutation that spanned the *GH1* gene) usually show dwarfism and reduced mean lifespan.

CONCLUSION

In summary, this chapter has comprehensively detailed the genetic variants linked with a number of age-associated diseases. We have tried to make the reader appreciate the important roles played by these genes. Through this overview we have listed candidate variants that can serve for future genetic test development for older people in general and specifically for those with a history of diseases in the family. Positive genetic test results may provoke anxiety and distress. Nevertheless, they will allow positive action such as early treatment and preclinical screening in order to reduce risk. Finally, the environment crosstalk with genetics (epigenetic) is another complex layer of possible effects on age-associated diseases. However, epigenetic effects were not discussed in this chapter, as this area of work is still in its infancy. The scientific world has made remarkable progress in the understanding of the pathophysiology of age-associated diseases and their genetic components. These efforts are likely to result in tailored drug treatments that may increase lifespan and promote aging with grace.

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Chapter 3

Immunology of Aging

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Learning Objectives

- Recognize the relationship of immunosenescence with impaired vaccine responses and increased risk of infections such as zoster and influenza.

Key Clinical Points

1. **Immunosenescence—the cumulative effect of aging on immune function—affects all cell types and many molecular pathways at all levels of the immune response. The resulting general phenotype is one of low-level inflammation at baseline, but impaired innate and adaptive immune responses to an acute stimulus. Responses to naïve antigens are often more impaired than memory responses.**
2. **Increased levels of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), acute-phase reactants such as C-reactive protein (CRP), and clotting factors are found in the plasma of older adults, compared to young adults, a phenomenon termed "inflammaging," and, though causal links have not yet been demonstrated, inflammaging is associated with cardiovascular events, Alzheimer disease, decreased muscle mass/strength, and mortality risk in cohorts of older adults.**
3. **Cumulative immune changes render many vaccines less effective in seniors. Specific changes in vaccine formulation (eg, high-dose influenza vaccine, conjugated pneumococcal vaccine) attempt to address this concern, and clinical efficacy trials demonstrate benefit versus standard vaccines in some (eg, high-dose influenza).**

OVERVIEW OF IMMUNOSENESCENCE

Immunosenescence refers to changes in the immune system that occur with aging. These changes affect virtually all cell lineages of the immune system, and result in alterations in diverse innate immune responses mediating the earliest interactions of the immune system with pathogens or vaccines, as well as slower onset, highly specific adaptive immune responses in B cells and T cells. Indeed, these changes extend to hematopoietic stem cells in the bone marrow that give rise to all cell lineages of the immune system. Age-related immunologic alterations are manifested by changes in cellular signal transduction or function that may arise from intrinsic mechanisms with a genetic component, but also reflect the complex interactions of the aged immune system with factors such as chronic or repetitive infection (such as with herpesvirus family reactivation or HIV), hormonal changes, and endogenous cellular damage as a potential result of chronic medical conditions. Immunosenescence has profound clinical consequences in older adults, who are at increased risk for morbidity and mortality from infectious diseases. For example, older adults more often develop reactivation tuberculosis and varicella zoster virus (VZV) infection than young adults; age is also an independent risk factor for mortality and impaired functional outcome from sepsis. Immune system aging also contributes to impaired responses to vaccines against influenza and other pathogens. The protean manifestations of immunosenescence provide insights into clinically important problems that disproportionately affect older adults and potential interventions to improve immunologic responses. Here, we provide an overview of aging of the human immune system.

EFFECTS OF AGING ON HEMATOPOIESIS

Hematopoietic stem cells (HSC) in the bone marrow give rise to all blood cell lineages (**Figure 3-1**) and as a result must maintain their ability to both differentiate and self-renew so that hematopoiesis can continue throughout life. The effects of aging on HSCs are complex; for example, HSC numbers appear to increase with age, rather than the decrease that might be expected. Aging is associated with impaired differentiation and repopulation of blood cell lineages upon transplantation; this has been most clearly demonstrated in model mouse systems, although the substantial effect of donor age on outcomes from hematopoietic stem cell transplantation suggests a similar effect in humans. Notably, there appears to be a significant bias favoring development of progenitor stem cells for the myeloid lineage (which give rise to granulocytes, monocytes, macrophages, erythrocytes, and platelets) and diminished numbers of lymphoid progenitors responsible for B- and T-lymphocyte development. This likely contributes to the impairment in B- and T-cell development found in older adults, and it is attractive to speculate that increases in myeloid progenitors could contribute to age-associated myeloproliferative disorders. The mechanisms underlying these alterations in hematopoiesis remain incompletely understood, but current concepts are outlined in Chapter 103.

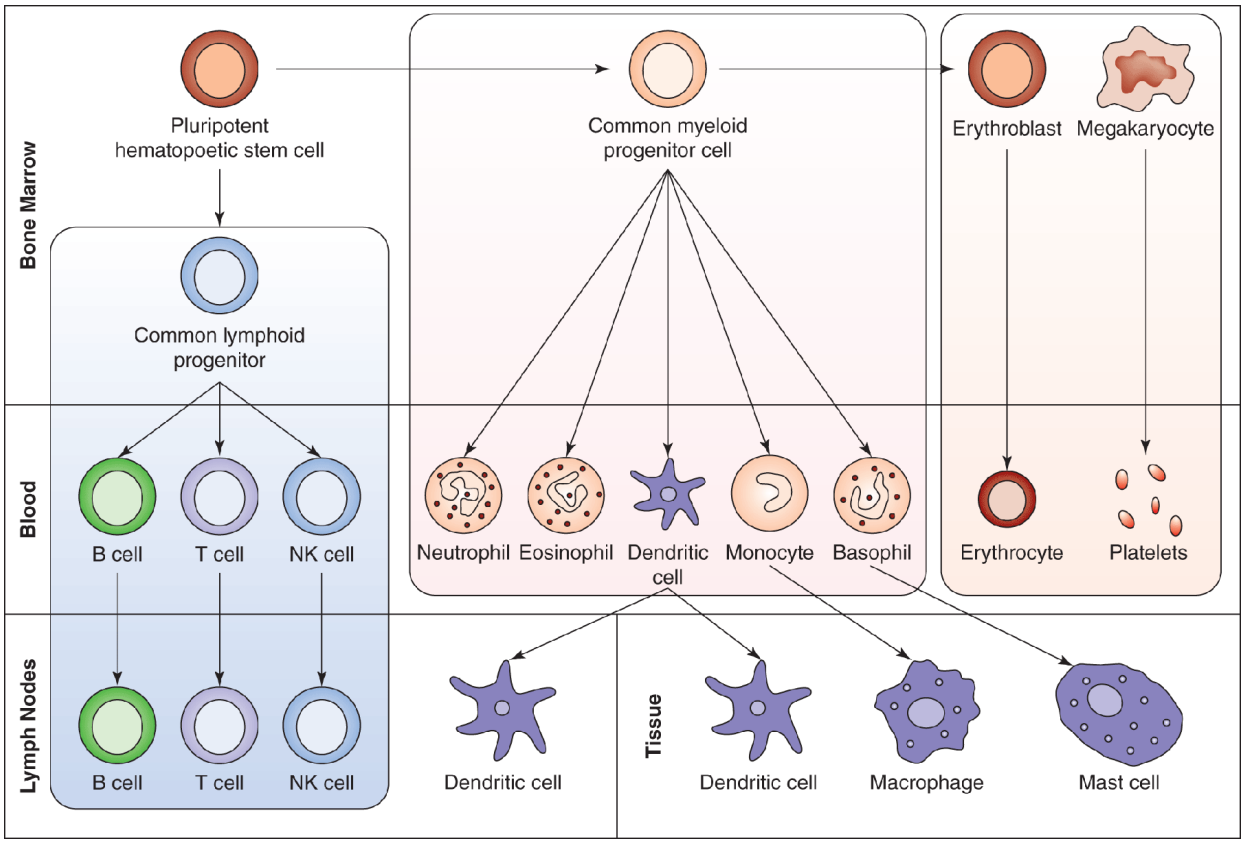


FIGURE 3-1. Schematic representation of hematopoiesis. Hematopoietic stem cells (HSCs) differentiate into lymphoid progenitors in the bone marrow that give rise to T cells (which develop in the thymus) and B cells, and myeloid progenitors that differentiate to monocytes, dendritic cells, neutrophils, basophils, eosinophils, as well as erythroid and megakaryocytic lineages. Aging is associated with impaired HSC differentiation and repopulation function, and with a bias toward myeloid at the expense of lymphoid progenitors.

OVERVIEW OF THE INNATE IMMUNE SYSTEM

The earliest-onset responses to pathogens or vaccines are mediated by the innate immune system. Innate immune responses are mediated by a network of cells including epithelial cells, neutrophils, monocytes, dendritic cells, natural killer (NK) cells, basophils, and eosinophils, and by biochemical factors including complement, antimicrobial peptides (eg, defensins), proinflammatory cytokines, and antiviral interferon responses (**Table 3-1**). Such responses include pathogen clearance via intracellular killing (in neutrophils and macrophages/monocytes), killing of virus-infected or

malignant cells (by NK cells), and complement fixation and lysis of extracellular organisms.

TABLE 3-1 COMPONENTS AND FUNCTIONS OF THE INNATE IMMUNE SYSTEM

COMPONENT	FUNCTION
Epithelial barriers of skin, mucus membranes	Prevent entry of microbes, mucosal immunity (mucociliary clearance)
Complement	Opsonization of microbes, killing of microbes, activation of leukocytes
Cytokines	Recruit phagocytic cells to site of infection, inflammation
Neutrophils	Phagocytosis, killing of pathogens
Eosinophils	Killing of antibody-coated parasites
Mast cells and basophils	Release of granules containing histamine and active agents, induction of inflammation and tissue responses
Macrophages	Phagocytosis, killing of pathogens, cytokine release, antigen presentation
Dendritic cells	"Professional" APCs, immunity to foreign antigens
Natural killer cells	Destroy tumor cells and virus-infected cells, antibody-dependent cellular cytotoxicity

Pattern Recognition Receptors of the Innate Immune System

Another crucial function of the innate immune system is to activate proinflammatory cytokine and chemokine production, particularly in cells such as dendritic cells or monocytes which present peptides derived from pathogens in conjunction with a host major histocompatibility antigen for recognition by T-cell antigen receptors. Activation of such antigen-presenting cells (APCs) results in the expression of costimulatory molecules such as CD80 and CD86—proteins that interact with a ligand on the surface of T cells to provide a critical additional signal (in conjunction with that provided by engagement of the T-cell receptor) for T-cell activation. This innate proinflammatory response and upregulation of costimulatory protein expression are mediated by a series of invariant innate immune pattern recognition receptors (PRRs). Toll-like receptors (TLRs) are one family of PRRs that are associated with either extracellular or intracellular membranes and recognize highly conserved, so-called pathogen-associated molecular patterns (PAMPs) found in bacteria, mycobacteria, fungi, and viruses. Examples of PAMPs recognized by TLRs include lipopolysaccharide (LPS) and flagellin on gram-negative bacteria (TLR4 and TLR5, respectively), and lipopeptides found in bacteria, mycobacteria, and yeasts (recognized by the TLR1/2 and TLR2/6 heterodimers). While these TLRs are expressed as membrane-associated receptors on the cell surface, other TLRs recognizing nucleic acids are localized to intracellular endosomal plasma membranes; such TLRs are activated by single-stranded RNA (TLR7 and TLR8) and double-stranded RNA (TLR3) produced during viral infections, as well as unmethylated CG-rich DNA (TLR9). Activation of TLRs on APCs engages signal transduction pathways employing myeloid differentiation primary response gene 88 (*MyD88*) or a pathway including the TIR (Toll-Interleukin-1 Receptor)-domain-containing adapter-inducing interferon-β (TRIF) protein and TRIF-related adaptor molecule (TRAM), resulting in not only upregulation of costimulatory proteins but also production of proinflammatory cytokines such as IL-6 and TNF (Tumor Necrosis Factor)-α via activation of the NF-κB transcription factor, or production of type I interferons via interferon regulatory factor (IRF) engagement (eg, IRF3 and IRF7). By activating APCs presenting antigen to T cells, such TLR signaling links the innate immune response to adaptive immunity (**Figure 3-2**).

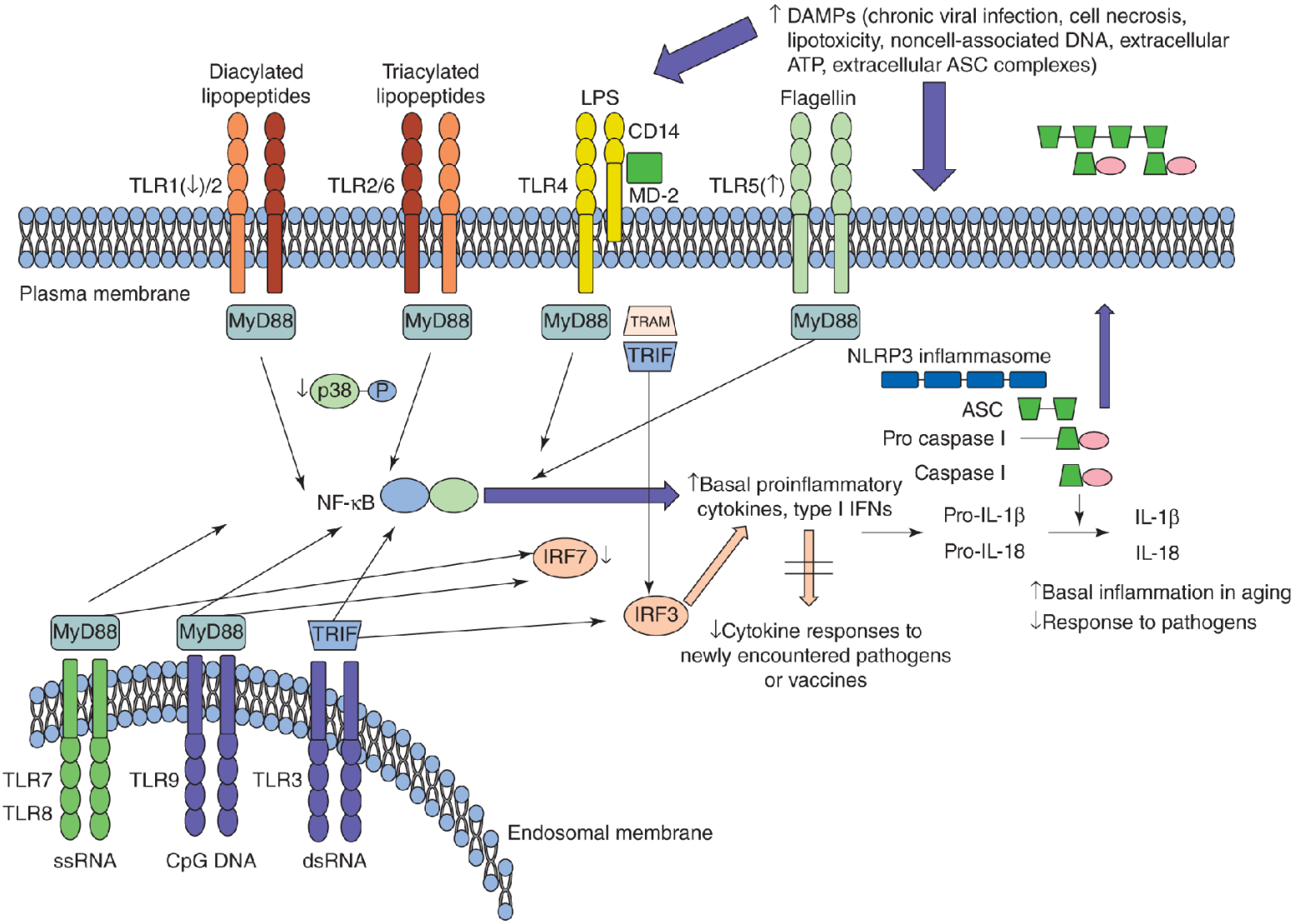


FIGURE 3-2. Depiction of pattern recognition receptors (PRRs) of the innate immune system, including TLRs that are associated with the plasma membrane (eg, recognizing lipopeptides, LPS, or flagellin) or endosomal membranes (for recognition of single- or double-stranded RNA or unmethylated CG-rich DNA). The NLRP3 inflammasome, activated by endogenous and exogenous damage-associated molecular patterns (DAMPs), is also depicted. TLR-dependent activation of NF-κB–dependent signaling resulting in proinflammatory cytokine production (blue arrows) and of type I interferon signaling (orange arrows) is indicated. Findings of age-associated dysregulation of PRR function are indicated.

Recent studies have also identified families of PRRs localized to the cytoplasm (in contrast to the membrane localization of TLRs), also including receptors recognizing viral RNAs (retinoic acid–inducible gene-1 [*RIG-1*] and melanoma differentiation antigen-5 [*MDA-5*]) that are particularly important for antiviral interferon responses. A member of the nucleotide-binding oligomerization domain (NOD)-like receptor family, NLRP3, has emerged as an example of an innate immune PRR that responds to not only bacterial and viral motifs but also so-called damage-associated molecular patterns (DAMPs). NLRP3 activation results in assembly of a multiprotein complex termed the inflammasome, a multiprotein complex containing the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD [caspase activation and recruitment domain]) polymerized into helical filaments that can be visualized using immunofluorescence as a protein "speck" within cells. The CARD domains of these multimerized ASC proteins then mediate the activation of caspase-1 and the consequent proteolytic processing of immature forms of proinflammatory cytokines such as IL-1β and IL-18 to their mature, active forms. DAMPs activating NLRP3 include exogenous factors such as silica and asbestos, and endogenous factors such as uric acid, extracellular ATP, and necrotic cells. The activation of innate immune inflammatory responses by such endogenous DAMPs is hypothesized to be a contributing factor to the increased levels of inflammation found in older adults, as discussed below.

A Heightened Proinflammatory Environment in Older Adults

The effects of age on innate immunity are complex, and reflect the diversity of innate immune responses. Increased levels of proinflammatory cytokines such as IL-6 and TNF-α, acute-phase reactants such as CRP, and clotting factors are found in the plasma of older adults, compared to young adults, a phenomenon termed "inflammaging." Inflammaging, as manifested by such elevated cytokine levels, is associated with mortality risk in cohorts of older adults, and is also correlated with decreased muscle mass and strength. In this regard, it is also notable that several diseases of aging, such as cardiovascular disease, Alzheimer disease, and osteoporosis, are reported to have an inflammatory component that contributes to pathogenesis. The mechanisms underlying inflammaging remain incompletely understood, but are hypothesized to include activation of innate immune PRRs by PAMPs arising from chronic infections (such as viral infections with herpesvirus family members, or HIV infection, which is associated with increased inflammatory parameters even in individuals with nondetectable viral loads) and DAMPs such as urate crystals, extracellular ATP, amyloid, hyaluronan, and noncell-associated nucleic acids resulting from tissue damage. The inflammatory environment in older adults can also be influenced by additional factors; for example, both testosterone and estrogen suppress IL-6 production, with reduced sex hormone levels of menopause and andropause associated with increased cytokine levels. Finally, dysregulated mitochondrial function with aging and associated uncoupling of oxidative phosphorylation could result in increased levels of reactive oxygen species that may also increase proinflammatory cytokine production (see **Figure 3-2**).

Age-Associated Alterations in Innate Immune Cell Function

Neutrophil function in older adults In cells of the innate immune system, age-associated changes include both impaired responses and inappropriate persistence of inflammation that may result from alterations in signal transduction (**Table 3-2**). For example, neutrophils from older adults show diminished signaling via the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor that usually mediates antiapoptotic cell survival. Impaired age-associated signaling via the triggering receptor expressed on myeloid cells-1 (TREM-1) may also contribute to functional alterations in cytokine or reactive oxygen species (ROS) production. Human neutrophils show an age-associated decline in migration toward a chemical stimulus (chemotaxis), and in phagocytosis and intracellular killing of engulfed pathogens. In addition, the release of neutrophil extracellular traps (NETs), complexes of DNA, histones, antimicrobial proteins released from the neutrophil that facilitate pathogen capture and killing, is also decreased in neutrophils from older, compared to young adults. While alterations in specific signaling pathways as discussed above have been linked to some of these findings, how age influences these functions remains unclear, particularly in view of the short lifespan of human neutrophils in vivo (approximately 5 days). It should be noted that alterations in function such as chemotaxis that may influence migration to sites of infection or injury could result in not only impaired migration to sites of infection or wound healing, but also impaired egress of neutrophils from these sites, potentially resulting in an inappropriate prolongation of the inflammatory response.

TABLE 3-2 AGE-RELATED CHANGES IN INNATE IMMUNE CELLS

	AGE-RELATED DECREASE	AGE-RELATED INCREASE
Neutrophils	Phagocytosis and intracellular bacterial killing NET formation Chemotaxis Signal transduction (eg, via GM-CSF, TREM-1)	
Monocytes	TLR 1/2-induced cytokine production	
	Expression of TLR-1	LPS-induced cytokine production by CD14+ CD16+ monocytes
	TLR-induced costimulatory molecule expression TNF production (skin macrophages)	
NK cells	Cytotoxic killing	CD56low population (cytotoxic activity)
	CD56hi population (cytokine production)	
	Secretion of proinflammatory cytokines	
	Recruitment of perforin to the cell membrane	

Dendritic cells	TLR-induced cytokine production (myeloid and plasmacytoid DCs)	Basal cytokine production
	Type I interferon production following viral infection (monocyte-derived DCs and plasmacytoid DCs)	LPS and self-DNA induced cytokine production (monocyte-derived DCs)

NK cell function in aging Age-associated decline in function has also been reported for NK cells, a class of innate immune lymphocyte sensitive to cytokine activation which plays an important role in killing virus-infected cells and in immunosurveillance against malignant cells. Critical proteins for the killing function of NK cells include proteases known as granzymes (for their storage in cytoplasmic granules), and perforin, a protein which forms a pore or channel in the target cell through which granzymes may be introduced. Inhibitory NK cell surface receptors recognize host class I major histocompatibility complex (MHC) protein expression and prevent apoptosis, but with loss of MHC class I expression—as frequently occurs on tumor cells to facilitate evasion of antitumor T-cell responses—NK-dependent killing via apoptosis of target cells ensues. NK cells also express surface receptors recognizing the so-called Fc constant region of antibodies, and may thereby also mediate killing of targets bound to immunoglobulin (Ig), a process termed antibody-dependent cytotoxicity. With age, the proportion of NK cells specialized for cytotoxicity (as assessed by low expression of the surface CD56 adhesion protein) increases at the expense of NK cells specialized for cytokine production (which express high levels of CD56). However, the cytotoxic function of aged NK cells is decreased on a per cell basis, likely in part resulting from diminished recruiting of perforin to the target cell. Studies of NK cell function in the context of aging are likely to have future clinical impact; notably, NK cell counts and measures of NK function have been associated with mortality from sepsis and other critical illness, and with increased infection and mortality rates in older nursing home residents.

Age-associated alterations in PRR function The effects of aging on human innate immune PRR function such as TLRs show evidence for an age-associated impairment in TLR-dependent expression of costimulatory proteins on monocytes, likely influencing the ability of these cells to serve as APCs that can maximally engage T cells. In addition, TLR-induced production of proinflammatory cytokines such as IL-6 and TNF-α in APCs such as monocytes and dendritic cells is also diminished in cells from older adults. In particular, TLR1/2-induced cytokine production (in response to triacylated lipopeptides such as those found in many gram-positive organisms) appears diminished in monocytes from older, compared to young adults. TLR function has also been evaluated in human dendritic cell (DC) populations, which may be predominantly divided into myeloid DCs, which express a wide range of TLRs and mediate production of IL-12 for activation of T-cell immunity, and plasmacytoid DCs, which express a more narrow range of TLRs but are particularly adept at type I interferon production in response to viral infection. For both of these DC subtypes, a generalized age-associated decrease in TLR-induced cytokine production has been observed. At the same time, it is important to recognize that these studies largely represent in vitro assessments of TLR function. In vivo tissue context is likely to be an important factor; for example, evaluation of TLR function in monocyte-derived DCs showed an age-associated increase in cytokine production; such DCs are derived from monocytes using growth factors and cytokines (GM-CSF and IL-4), and could model DCs generated in the context of inflammation. LPS (recognized by TLR4)-induced cytokine production also appears increased in so-called CD14+CD16+ monocytes (as opposed to CD14+CD16− conventional monocytes) that arise in the setting of inflammation-associated conditions such as sepsis, HIV infection, and myocardial infarction. As a final example, TNF-α production by macrophages in human skin was diminished in the setting of a delayed-type hypersensitivity response to purified protein derivative (PPD), yet TNF-α production in vitro by such macrophages was preserved, arguing for the importance of local factors (such as the potential influence of regulatory T cells in the skin of older adults, in this case) in assessing innate immune function.

The mechanisms underlying these age-related changes remain incompletely understood; some changes in expression of specific TLRs have been reported in APCs (including an age-associated decrease in surface TLR1 in monocytes), but such decreases in protein expression alone do not appear sufficient to explain the observed findings and it is likely that both transcriptional (ie, gene expression) and posttranscriptional (eg, protein stability, modification, localization or damage) mechanisms contribute. Moreover, these effects are not uniform for all cell types and must be reconciled with age-related increases in circulating cytokine levels. In this regard, there is evidence for increased basal cytokine production, for example in dendritic cells in the absence of in vitro TLR stimulation. Thus, age-associated impairment in cytokine production could reflect inflammatory dysregulation and an inability to further increase cytokine levels beyond a basal level in response to a newly encountered antigen (such as a PAMP from a pathogen or

vaccine). In addition, the wide range of TLR expression on nonblood-derived cells—including cells of epithelial, endothelial, and neuronal origin—represents an additional, largely unexplored source of complexity in the integration of TLR activity in older adults. The function of cytoplasmic PRRs in older adults remains to be definitively evaluated; however, the recent demonstration that "specks" of multimerized ASC and inflammasome components can be released from the cell, where they may cause extracellular inflammatory activation and activate inflammation in neighboring cells, suggests a potential source for endogenous immune activation that could contribute to an age-related inflammatory environment.

OVERVIEW OF ADAPTIVE IMMUNITY

The term adaptive immunity refers to highly specific immune responses mediated by lymphocyte-specific antigen receptors. In B cells, immunoglobulins (Ig) or antibodies—which are both membrane-bound as the B-cell antigen receptor (BCR) and secreted—control so-called humoral immunity; and in T cells, the exclusively membrane-associated T-cell receptor (TCR) mediates cell-mediated immunity. Humoral and cell-mediated immunity are examples of immunologic memory, in which the response to previously encountered antigens is enhanced in both speed and antigen recognition affinity upon repeat exposure.

Both the BCR and TCR are comprised of two polypeptide chains. The BCR contains two antigen-binding sites, each comprised of one Ig heavy chain and one Ig light chain; the TCR contains a single α chain complexed with a β chain that recognizes a host MHC protein bound to a peptide derived from enzymatic processing of a protein antigen on the surface of an APC (such as a monocyte, macrophage, dendritic cell, or even in some cases a B cell) (**Figure 3-3**). The specificity of the humoral or cell-mediated immune response results from a highly diverse repertoire of BCRs on B cells and TCRs on T cells, respectively, that can recognize millions of different antigenic specificities. This diversity results from a lymphocyte-specific gene rearrangement program that acts on the genetic loci for Ig heavy chains or the β TCR subunit, which contain clusters of variable (V regions), diversity (D regions), and joining (J regions); or V and J regions only for Ig light chains or the α TCR subunit. All BCR or TCR chains contain a constant or invariant region (C region). For the BCR Ig heavy chain, several different C regions are present which denote the Ig isotype and functional implications, such as the Cμ region found in IgM, Cγ1-Cγ4 regions found in IgG subclasses, Cα found in IgA secreted at mucosal surfaces, and Cε denoting IgE, a critical component for allergic responses. The BCR light chain locus contains two C regions, encoding sequences specific for either the κ or λ light chains.

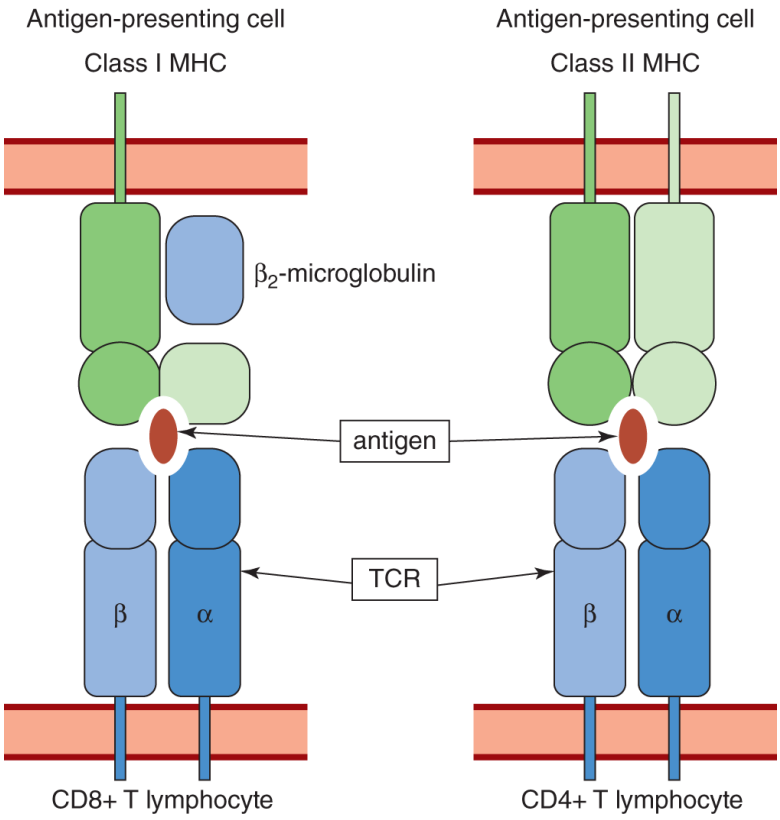


FIGURE 3-3. Depiction of presentation of a peptide (red) resulting from proteolytic processing of a protein antigen in antigen-presenting cells (APCs) such as monocytes, dendritic cells, or B cells. The peptide is bound to host major histocompatibility complex (MHC) protein, and this combination of peptide and class I or peptide and class II MHC is recognized by T-cell receptors (TCR) on CD8+ cytotoxic or CD4+ helper T cells, respectively.

The state of BCR or TCR gene rearrangement denotes specific maturation stages of B- or T-lymphocyte development, respectively. A rearranged Ig heavy chain or β TCR locus contains a single V, D, and J region linked together to form the variable region of the heavy chain or β TCR protein, while VJ gene rearrangement is found for the Ig light chain and α TCR loci. To accomplish this, the lymphocyte-specific recombinase activating genes (*RAG*) mediate site-specific DNA cleavage at unrearranged V, D, and J regions. The subsequent joining of these gene segments to form a rearranged antigen receptor gene utilizes proteins responsible for DNA repair (nonhomologous end joining) that are generally expressed in all cell types as part of the response to DNA damage of any kind; such proteins include Ku70, Ku80, DNA-dependent protein kinase (DNA-PK), Artemis nuclease, X-ray repair cross-complementing protein 4 (XRCC4), DNA ligase IV, and others. Recombinatorial gene rearrangement of V regions to a more limited number of D and/or J segments, combined with imprecision in the rejoining of cleaved gene segments, results in the tremendous antigenic diversity found in B and T lymphocytes at birth (**Figure 3-4**). Substantial changes in this diversity occur with age, as described below.

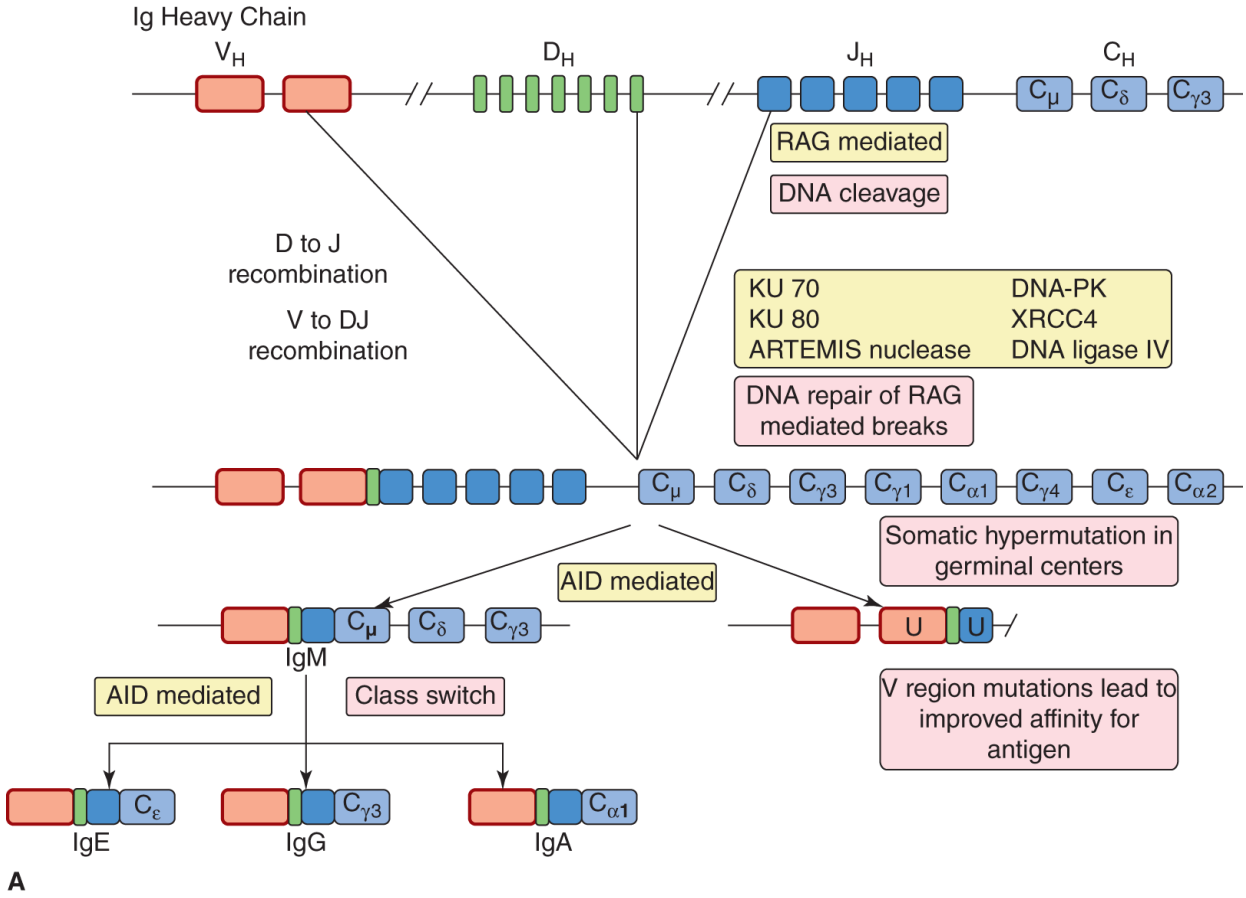


FIGURE 3-4A. Depiction of DNA rearrangement events occurring in B cells. The immunoglobulin (Ig) heavy chain locus is shown. VDJ recombination is initiated by lymphocyte-specific recombinase-activating gene (*RAG1* and *RAG2*)-induced breaks at specific sequences upstream of V, D, and J gene segments, with joining of breaks using generally expressed DNA nonhomologous end-joining repair proteins. D to J gene rearrangement occurs first, followed by a V to DJ gene rearrangement to yield the complete heavy chain variable region gene recognizing antigen. A similar process occurs at the Ig light chain loci. IgM (expressing the μ constant region gene) is first expressed during an initial antibody response, with subsequent expression of additional Ig isotypes such as IgG subtypes, IgE and IgA resulting from class switch recombination that deletes previously expressed constant region genes in mature B cells. Somatic hypermutation also occurs in mature B cells, a process where the Ig V region undergoes mutation to enhance affinity of antigen recognition. Both class switch recombination and somatic hypermutation require the B-cell–specific protein activation-induced cytidine deaminase (AID), as well as generally expressed DNA repair proteins.

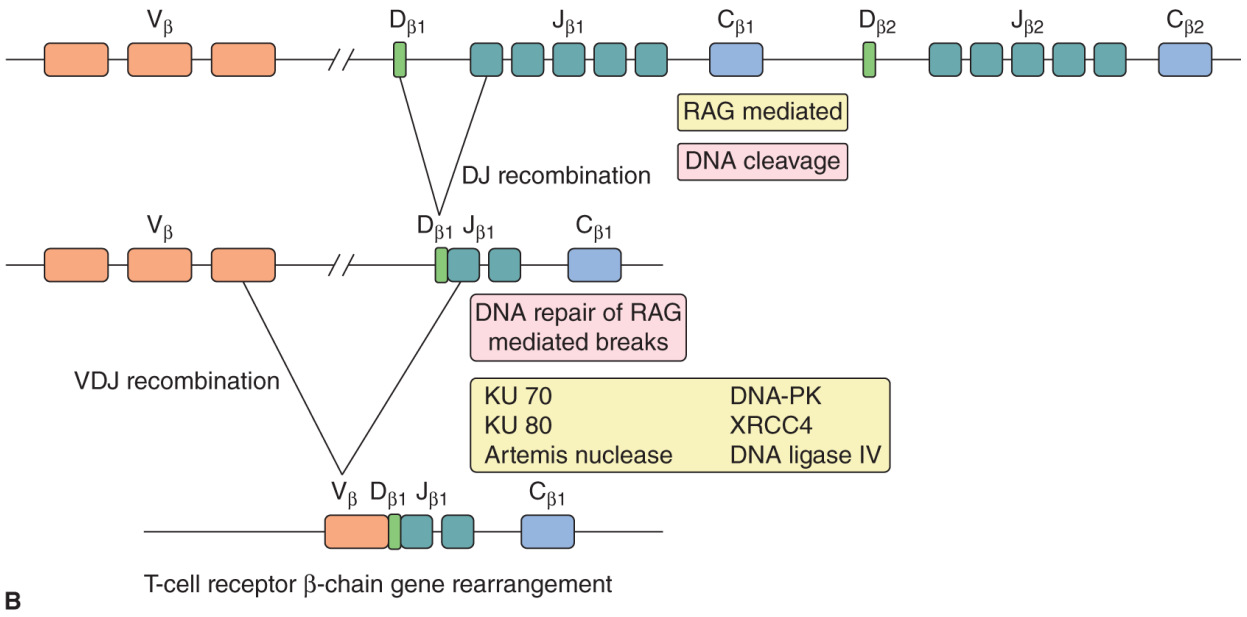


FIGURE 3-4B. Depiction of T-cell receptor (TCR) gene rearrangement. The TCR β-chain genetic locus is shown. As in the immunoglobulin loci, RAG1- and RAG2-dependent cleavage occurs at specific sequences upstream of TCR β V, D, and J segments, with D to J gene rearrangement occurring first, followed by V to DJ gene rearrangement. Joining of DNA breaks is accomplished by DNA nonhomologous end-joining repair proteins.

In B cells, additional genetic steps are required for the evolution of a humoral immune response. Following gene rearrangement, an IgM BCR is generated (with surface IgM on B cells that can differentiate to secrete IgM with the same antigenic specificity), since the Cμ constant region is most proximal to the rearranged VDJ region. Following initial VDJ gene rearrangement and expression of a mature IgM BCR containing the Cμ constant region, a B-cell–specific process known as heavy chain class switching results in the replacement of the C region exon with that of another isotype, with deletion of the intervening DNA (in this case, containing the previous Cμ region) and preservation of the rearranged variable region. This process is the mechanism by which evolution of the humoral immune response occurs, from initial expression of IgM early in infection to subsequent expression of IgG and other isotypes. A B-cell–specific protein, activation-induced cytidine deaminase (AID), is essential for heavy chain class switching. The mechanism of heavy chain class switching is still a subject of active investigation, but is facilitated by transcription at highly repetitive regions of DNA found upstream of each C region exon, termed switch regions. Current models suggest that AID targets single-stranded regions of DNA exposed by transcription of the opposite DNA strand, and deaminates cytosine DNA residues to induce a mutation to uracil residues. These mutations are then subjected to generally expressed DNA excision repair proteins to generate double-stranded DNA breaks, which are then repaired by similar nonhomologous end-joining repair mechanisms utilized for VDJ recombination. The ability of AID to induce C to U mutations that are resolved by DNA repair processes also plays an essential role in another function critical to the memory B-cell response—somatic hypermutation, the process by which rearranged variable region genes in mature B cells undergo additional mutation, resulting in improved affinity of the encoded immunoglobulin molecule for antigen 9 (**Figure 3-4A**). Clearly, mechanisms associated with maintaining the integrity of genomic DNA such as DNA repair pathways—which are likely affected by aging—play crucial roles in these fundamental processes in adaptive immunity.

Overview of T-Cell Development and Function

The generation of mature T cells occurs in the thymus, a bilobed organ located in the anterior mediastinum (**Figure 3-5**). Each lobe is comprised of a capsule, a cortex with abundant numbers of developing T cells just beneath the capsule, and a deeper medulla region with sparser quantities of lymphocytes. In addition to developing T cells, several other cell types are present in the thymus to carry out crucial functions related to selection of T cells and clearance of apoptotic cells resulting from thymic selection processes (described below), such as cells of the thymic epithelium, dendritic cells, and macrophages. The thymic cortex is colonized by early thymic progenitor cells originating from the bone marrow. Subsequent developmental steps are driven by rearrangement of *TCR* genes **(Figure 3-4B)** and are linked to specific regions of the thymus; in general, more mature T-cell subsets are found in deeper layers of the cortex, with the most mature cells occupying the medulla. The TCR β–chain locus is the first to undergo

rearrangement, with subsequent incorporation of the β–chain protein in a pre-TCR complex that signals for survival of precursors with a successful β–chain gene rearrangement. Subsequent rearrangement of the TCR α–chain genes corresponds to upregulation of both CD4 and CD8 expression (such CD4+ CD8+ cells are referred to as "double-positive" thymocytes), and if a productive gene rearrangement occurs (ie, one able to encode for an α–chain protein), the mature αβ TCR is expressed. These developing cells subsequently undergo so-called positive selection, in which cells bearing TCRs that recognize host class MHC class I or class II proteins survive, while those that do not undergo apoptosis. This step coincides with differentiation to "single-positive" CD4+ cells recognizing MHC class II proteins, and cytotoxic CD8+ T cells recognizing MHC class I. Another process of negative selection eliminates those T cells carrying αβ TCRs with high affinity for self-peptide/MHC complexes that could result in autoimmunity. Additional lineage specification for development of regulatory T cells (Treg), which inhibit T-cell activation, and γδ T cells expressing two distinct classes of TCR proteins that may play a role in the recognition of lipid antigens, also occurs in the thymus (**Figure 3-6**).

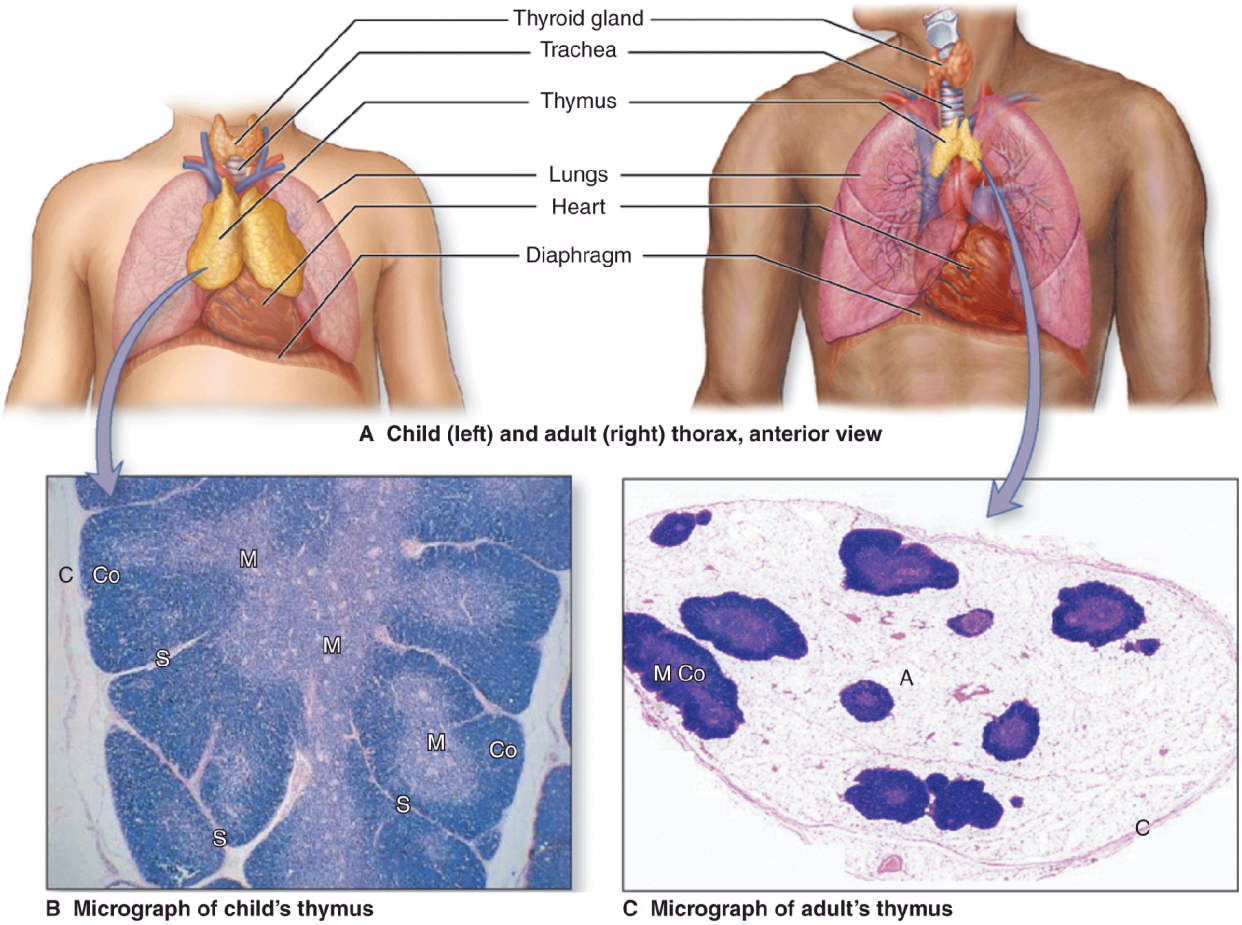


FIGURE 3-5. Histologic examination of the thymus in a child (left) and adult (right). The thymic capsule (C) is indicated, with the thymic cortex (Co) (which is initially colonized by T-cell progenitors originating in the bone marrow) and medulla (M) (containing mature T-cell subsets) indicated. With age, marked thymic involution occurs, with increased replacement of thymic epithelium with adipose tissue (A). (From Mescher AL. *Junqueira's Basic Histology*, 13th ed. New York, NY: McGraw-Hill; 2013, Figure 14-8.)

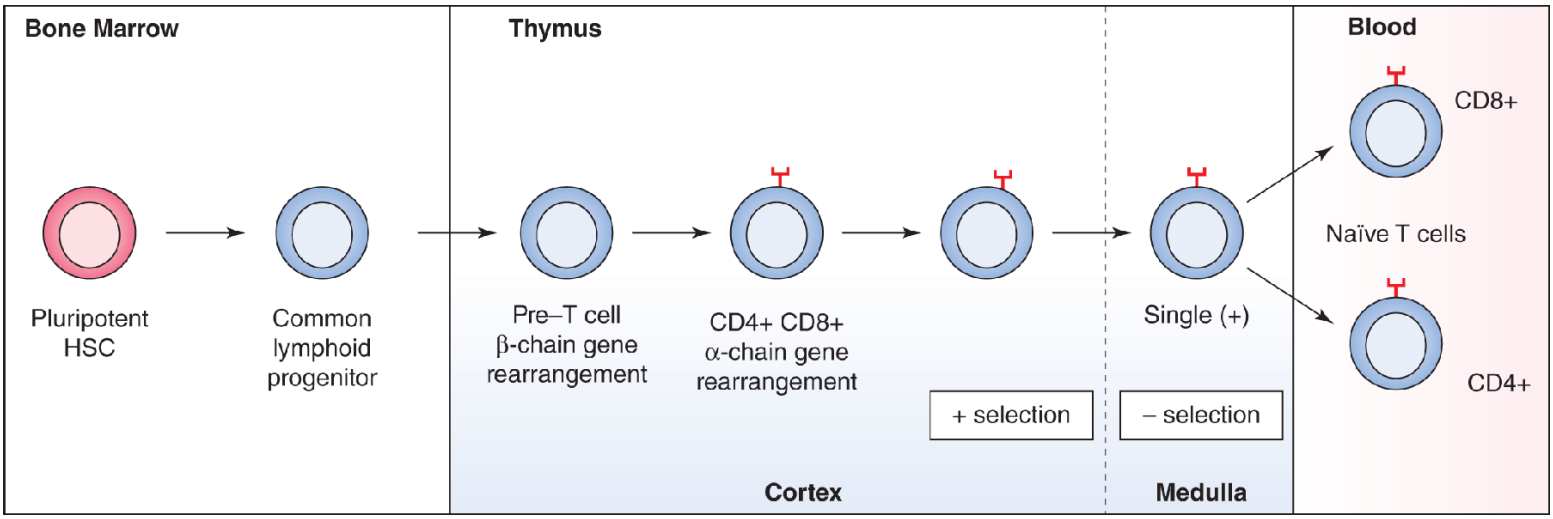


FIGURE 3-6. Overview of T-cell development. T lymphopoiesis is closely linked to the state of T-cell receptor gene rearrangement in the thymus, with initial β–chain gene rearrangement followed by TCR α–chain gene rearrangement in T-cell precursors expressing both CD4 and CD8 ("double-positive" T cells). Following expression of a TCR on the cell surface (indicated in red), positive selection (+ selection), which selects for survival of T cells bearing TCRs that recognize host MHC class I or class II, and negative selection (− selection), which deletes potentially autoreactive T cells, occur in single-positive T cells (single [+]) expressing CD4 or CD8.

Aging and T-Cell Development and Function

Thymic involution The human thymus is at its maximal size in infancy, and begins to decrease in size and cellularity in childhood. The thymic epithelium begins to diminish, particularly after puberty, and is replaced by adipose tissue that may be a source of cytokines and chemokines that interfere with thymopoiesis (see **Figure 3-5**). The T-cell generation capacity of the thymus is substantially diminished by young adulthood, to around 10% of the capacity seen in infancy (**Table 3-3**). T-cell lifespan can be assessed by in vivo metabolic labeling, and the generation of new T cells may be measured via the detection of T-cell receptor excision circles (TRECs), the excised products of VDJ recombination of DNA that are only detectable in recently matured T cells, since they cannot undergo replication and are diluted by cell division. Such analyses have revealed minimal thymic activity in older adults, and indicate that maintenance of the T-cell pool occurs instead via cell division and expansion of preexisting T cells. Not surprisingly, this absent thymic activity results in decreased numbers and proportion of naïve (CD45RA+) T cells in peripheral blood, with an increase in T lymphocytes with a memory phenotype (CD45RO+). In this regard, it is notable that a similar T-cell phenotype resembling that seen in aged adults was found in young adults who had undergone thymectomy in childhood. The mechanisms underlying thymic involution remain a subject of active study; alterations in thymic epithelial cells that facilitate the developmental expansion and selection steps of T-cell development, such as changes in expression of the master transcriptional regulator FoxN1, are thought to play an important role. There is interest in developing interventions that can stabilize or reverse thymic involution and thereby improve T-cell production in older adults. However, the widespread conservation of thymic involution in most mammals raises the speculative question of whether it might represent an evolutionary adaptation, perhaps protecting the host from lymphocytic malignancies in older age.

TABLE 3-3 ■ AGE-RELATED CHANGES IN THE ADAPTIVE IMMUNE SYSTEM

	AGE-RELATED DECREASES	AGE-RELATED INCREASES
T cells	T-cell lymphopoiesis (thymic involution) Naïve T cells Mitogen-associated proliferation Signal transduction Diversity of T-cell repertoire Expression of CD28 on CD8+ T cells	Memory T cells
	Antibody response (eg, to vaccine)	Autoantibody titer (eg, rheumatoid factor)

B cells	Antibody-secreting cells (eg, responding to vaccination) Class switch recombination Expression of AID Diversity of B-cell repertoire	Monoclonal gammopathy

Influence of CMV infection on T-cell repertoire The lack of generation of new (naïve) T cells in older adults as a result of thymic involution also results in marked changes in the diversity of the TCR repertoire, which decreases substantially with age. Notably, cytomegalovirus (CMV) infection is associated with such profound alterations in diversity (**Figure 3-7**). Like other herpesviruses, following primary infection CMV establishes a state of latency in the host, with reactivation to productive infection throughout life, often in the setting of stress or non-CMV–associated illness; reactivations are usually asymptomatic and not associated with CMV-dependent end-organ disease. However, such reactivations result in marked expansion of CMV-specific CD4+ and CD8+ memory T-cell populations, and resultant decreases in TCR diversity with expansion of nonmalignant T-cell clones, many of which recognize CMV peptides. Such oligoclonal T-cell expansions may comprise a large proportion (even in some cases the majority) of CD4+ or CD8+ T cells, and are also found in CMV seronegative older adults; in such individuals, it is likely that other herpesviruses associated with latent infection, such as Epstein-Barr virus (EBV) or human herpes virus-6 (HHV-6), other viruses such as hepatitis C virus, or other sources of chronic immune system activation may contribute to loss of repertoire diversity. Notably, the extent of diversity loss has been linked to decreased lifespan in older adults, though the underlying mechanisms and associated factors remain incompletely understood.

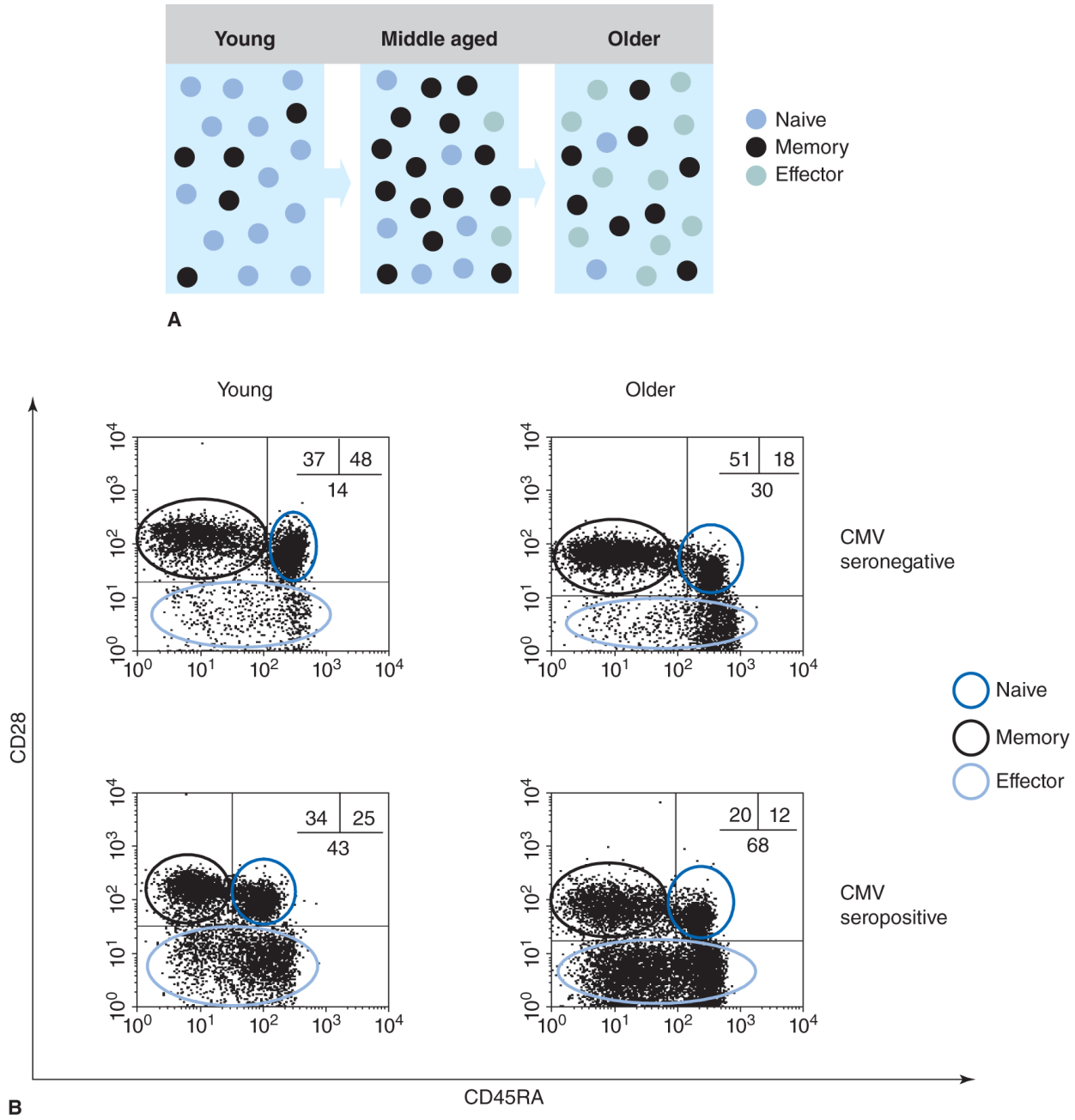


FIGURE 3-7. (**A**) Graphical depiction of age-associated decrease in naïve T cells (blue) and increased proportion of memory (black) and effector (light blue) T cells, reflecting thymic involution and proliferative expansion of preexisting T cells. (**B**) Flow cytometric plots of CD28 expression (Y-axes) vs expression of CD45RA (a marker of naïve T cells) in CD8+ T cells from representative young and older subjects stratified by CMV seroreactivity, with percentages of the indicated cell populations indicated in the upper right of each graph. Note the increased proportion of CD8+ T cells expressing low or absent levels of CD28, increased proportion of effector cells and decreased proportion of CD45RA expressing naïve T cells in older adults; these changes are enhanced in CMV-seropositive older adults. (Reprinted with modifications from Almanzar G, et al. Long-term cytomegalovirus infection leads to significant changes in the composition of the CD8+ T cell repertoire, which may be the basis for an imbalance in the cytokine production profile in elderly persons *J Virol.* 2005;79:3675. With permission from the American Society for Microbiology.)

Aging and alterations in T-cell phenotype and signal transduction The age-related increase in memory phenotype T cells, with decreased naïve T cells, is also associated with several additional findings. For example, aged human T cells show a substantial loss of expression of the costimulatory protein CD28 from the surface of CD8+ cytotoxic T cells (**Figure 3-7**). CD4+ T cells show a much lesser degree of CD28 loss with aging, although marked increases in CD4+ CD28− cells can be found in adults with rheumatologic disease. CD28 associates with costimulatory ligands (CD80 and CD86) on the surface of APCs such as activated macrophages or dendritic cells, and this interaction provides a second signal, in addition to that provided by the TCR interaction with peptide bound to host MHC, that is critical for optimal T-cell activation. Thus, this loss of CD28 would be expected to influence T-cell

activation in CD8+ T cells.

In this regard, signal transduction by the TCR is also diminished in the context of aging—in general, nonreceptor tyrosine kinase–dependent pathways downstream of the TCR are inhibited in T cells from older adults, with potential mechanisms for impaired signaling including increased expression of phosphatases that are negative regulators of mitogen-activated protein (MAP) kinase-dependent signaling. Though the mechanisms underlying diminished signaling in human T cells remain incompletely understood, both cell-intrinsic mechanisms, such as mitochondrial dysfunction in T cells resulting in increased levels of reactive oxygen species (ROS), and cell-extrinsic mechanisms, such as the inhibition of TCR signaling and engagement of inhibitory cytokine signaling pathways (such as the suppressor of cytokine signaling [SOCS] proteins) resulting from increased systemic levels of TNF-α and other cytokines, appear to be important contributing factors.

It is likely that such signaling alterations may differ among different T-cell populations and lineages to extend beyond the dichotomy of CD8+ and CD4+ T cells to CD4+ T-cell subtypes. These include T_{H1} helper T cells that develop in response to IL-12 produced by activated APCs and the transcriptional regulator T-bet to produce interferon-γ and facilitate intracellular immunity against bacteria, viruses, and fungi; T_{H2} helper cells developing in response to the GATA3 transcription factor that produce IL-4, IL-5, and IL-13 and mediate allergic and antiparasitic T-cell responses; T_{H17} cells, a heterogeneous lineage in humans that are named for their production of IL-17 and are associated with inflammatory responses in the context of bacterial and fungal infections, autoimmunity and malignancy; follicular helper T cells found in lymphoid follicles of lymph nodes and other secondary lymphoid organs that provide crucial interactions with B cells in the generation of B cell memory responses; regulatory T cells (Treg) expressing the FoxP3 transcription factor that inhibit immune responses; and resident memory (T_{RM}) T cells present in specific tissues or organs such as lung, skin, or gut that do not recirculate and appear critical for rapid responses to pathogens (both Treg and T_{RM} cells may be either CD4+ or CD8+ single positive). The functional consequences of aging on these human T-cell subsets remain incompletely understood, but are likely to be complex; for example, current evidence suggests that human CD4+ and CD8+ Treg cells are found in increased numbers in the blood of older, compared to young adults, but the ability to induce Treg cell development (particularly CD8+ Treg cells) with cytokine treatment is diminished with age. The consequences of these opposing effects on the regulation of T-cell responses remain to be determined.

OVERVIEW OF B-CELL DEVELOPMENT

In contrast to T lymphopoiesis, where T-cell progenitors migrate from the bone marrow to the thymus, B cells arise from hematopoietic stem cells that differentiate to a common lymphoid progenitor. However, as with the T-cell lineage, antigen receptor gene rearrangement (in this case, Ig heavy and light chain genes) is intimately linked to B-cell development, with Ig heavy chain gene rearrangement occurring in early B-cell progenitors (pro-B cells). The Ig heavy chain protein in conjunction with an invariant surrogate light chain protein forms the pre–B-cell receptor complex that links to signal transduction pathways to mediate expansion and progression to the pre–B-cell stage, when light chain gene rearrangement occurs to generate the mature Ig B-cell antigen receptor (BCR) (**Figure 3-8**). Through this process, a library of B cells is developed with a repertoire of millions of specificities. Notably, an incompletely understood mechanism of negative selection occurs in the B-cell lineage (as in the T-cell lineage) by which B cells expressing potentially autoreactive BCRs are deleted both in the bone marrow and in peripheral lymphoid tissues.

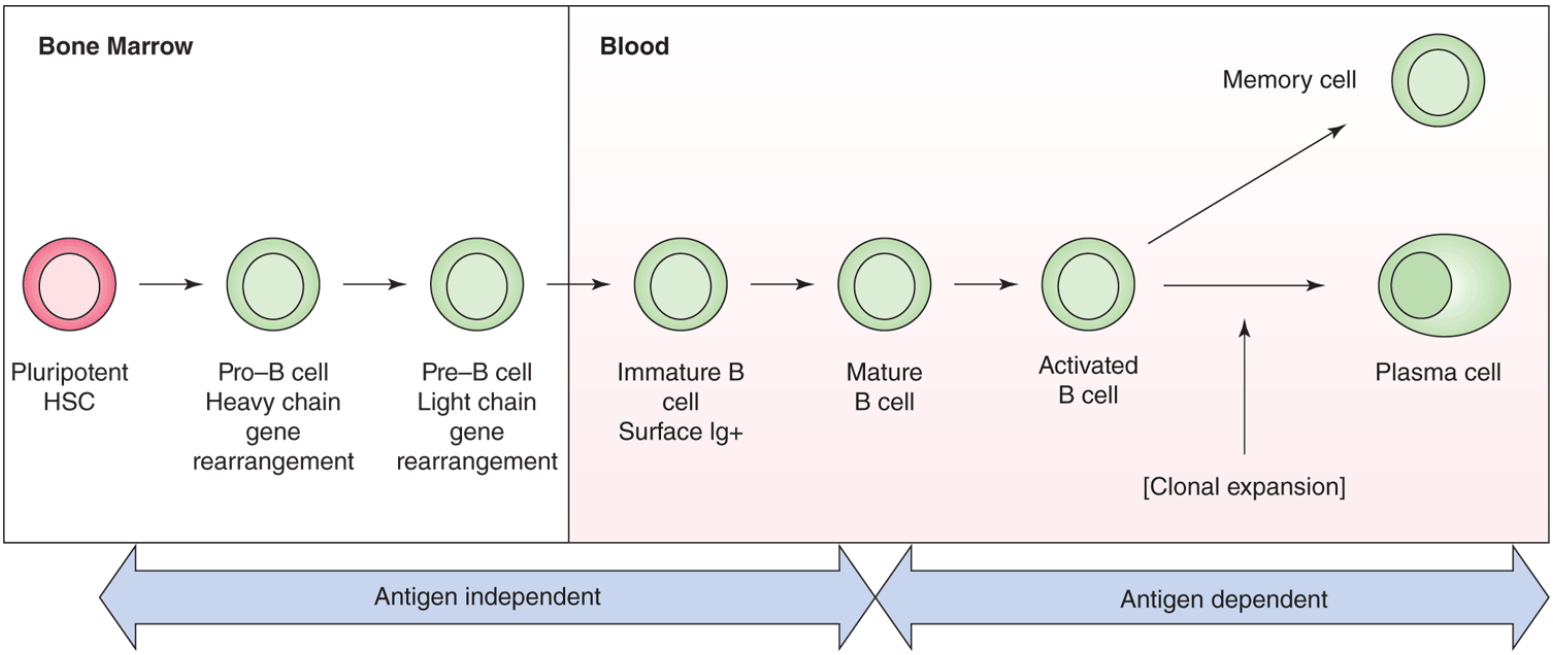


FIGURE 3-8. Depiction of B-cell development. Immunoglobulin gene rearrangement (first of the heavy chain genes, followed by light chain gene rearrangement) is crucial to B lymphopoiesis, resulting in generation of a library of mature B cells collectively expressing a highly diverse repertoire of surface immunoglobulin (the B-cell antigen receptor). Encounter with a specific antigen results in expansion of a clone of B cells recognizing that antigen, and generation of memory B cells and plasma cells secreting immunoglobulin of the same specificity.

Effects of Aging on B-Cell Development and Function

Dramatic effects of aging on B-cell development are found in mouse models; however, human B lymphopoiesis in the bone marrow appears generally preserved with age, although the total number and percentage of B cells diminish in the blood of older, compared to young adults (**Table 3-3**). However, B-cell production of antibodies in response to infection or vaccination is impaired with age, and is associated with diminished production of antibody secreting B cells termed plasmablasts, which generally appear approximately 7 days following immunization. In part because of the use of varying definitions of B-cell subsets, it has proven difficult to determine whether, as in the T-cell lineage, memory B cells are expanded with age. Notably, the proportion and number of memory B cells that have undergone heavy chain class switching does decrease with age; it is likely that age-associated alterations in T-cell function contribute to such differences, since B-cell responses are intimately associated with helper T-cell activity. However, B-cell–intrinsic changes have been identified in older adults, such as the decreased expression of AID (essential for heavy chain class switching—see **Figure 3-4A**) in B cells from older adults linked to decreased levels of the E47 transcription factor. Though age-related developmental changes in the B-cell lineage remain incompletely understood, functional alterations are manifested, for example, by the age-associated increase in monoclonal gammopathy, which has been estimated to affect as many as 3% of adults over age 50 and 5% of adults over age 70. In addition, titers of autoantibodies such as rheumatoid factor are generally increased with age, suggesting additional dysregulation and in particular, possible alterations in the negative selection steps mediating deletion of autoreactive B-cell clones. The persistence of autoreactive B-cell clones may also be reflected in age-related changes in the B-cell repertoire. Notably, repertoire diversity appears to be diminished with age, with marked increases in nonmalignant clonal expansions of B cells. As with T cells, there is evidence that such expansions could be associated with the control of reactivation of chronic herpesvirus infections with CMV or EBV. In addition, profound loss of B-cell repertoire diversity has been associated with alterations in health or functional status, such as frailty; the effects of functional alterations or multimorbidity on the immune system in older adults is an emerging area of significant research and clinical interest.

EFFECTS OF AGE ON VACCINE RESPONSES

Impaired responses to vaccines represent perhaps the clearest examples of the consequences of immunosenescence, and have important clinical consequences reflected in the increased susceptibility to infectious diseases found in older adults. Mechanisms discussed in this chapter contribute to this impaired response, but multiple additional host factors

including gender, age-associated changes in body composition (eg, changes in adipose tissue), and associated comorbid medical conditions or medication use all contribute. Here, we provide an overview of three vaccines—against influenza, VZV, and *Streptococcus pneumoniae*—currently recommended for older adults.

Influenza Vaccine

Over 90% of the approximately 30,000 annual deaths from influenza in the United States occurs in adults over age 65, and older adults are at increased risk for morbidity arising from complications of influenza, such as viral pneumonia or bacterial superinfection. The seasonal vaccine in wide use is an inactivated vaccine containing defined doses of the hemagglutinin (HA) protein, one of the surface glycoproteins of the influenza virus; anti-HA antibodies are associated with protection against disease. However, because of a high mutation rate in the HA protein, the composition of viral strains in the vaccine is adjusted annually based on surveillance of circulating strains. Either three (trivalent) or four (quadrivalent) influenza strains are present in the vaccine, with two influenza A strains (typically one H1N1 and one H3N2 subtype) and either one or two B strains.

The efficacy of the standard dose seasonal influenza vaccine in older adults has been estimated at approximately 40% for the prevention of an influenza-like illness, and approximately 60% for confirmed influenza, and is lower in older individuals with increased comorbid conditions (such as residents in long-term care facilities). Demonstration of a mortality benefit for influenza vaccination has proven to be difficult; it has been hypothesized that many studies may be influenced by selection bias in which a subset of frail adults who are undervaccinated because of poor health disproportionately contribute to mortality from influenza. However, a history of revaccination, as opposed to first vaccination against influenza, has been associated with decreased mortality in at least one study.

Evidence for poor vaccine efficacy, combined with the demonstration of impaired antibody responses to vaccination reflected in decreased levels of antibody producing cells following influenza immunization have led to interest in alterative vaccine formats to improve response in older adults. Both the live attenuated influenza vaccine, which uses a cold-adapted virus that replicates in nasal mucosal tissues (at lower temperature than in the lungs) to establish immunity, and an intradermal influenza vaccine which utilizes the immunologic milieu of the skin (containing APCs including Langerhans cells) that is bypassed by intramuscular vaccination, have shown efficacy in older adults; in fact, antibody titers to influenza viral vaccine strains were higher in older adults given the intradermal preparation versus standard intramuscular vaccine in at least one study. However, at present, these formats are not approved for adults age 65 and older. A high-dose trivalent influenza vaccine containing four times the dose of HA protein for each vaccine strain has been approved for adults ≥ age 65 years since 2009. Several studies have shown equivalent or increased antibody titers to vaccine viral strains compared to standard dose vaccine in studies enrolling older adults, and a randomized comparing standard to high-dose vaccine in nearly 32,000 older adults revealed a modest benefit for the high-dose vaccine (with a 24% relative efficacy for prevention of influenza-like illness compared to standard dose vaccine). With demonstration of improved protection against disease as well as increased antibody titers, the high-dose vaccine should see increased use in older adults. Ongoing work to further improve influenza vaccines includes the use of adjuvants such as TLR agonists to boost immune responses (note that the seasonal inactivated vaccines discussed above are unadjuvanted); for example, the TLR5 agonist flagellin has been used successfully in experimental influenza vaccines in older adults. Other adjuvants such as MF59, a squalene derivative that appears to enhance antigen presentation through still unclear mechanisms, are already in clinical use in influenza vaccines in Europe, where they appear effective in older adults. An additional research direction is the development of a “universal” influenza vaccine, which would use a highly conserved viral antigen and would obviate the need for annual revision of the vaccine. At present, such universal vaccine antigens all appear to be weakly immunogenic, perhaps raising the likelihood that adjuvanted universal vaccines will prove to be effective. Finally, biochemical pathways implicated in vaccine response may be pharmacologically modulated to enhance vaccine protection. A recent example of this possibility came from the demonstration in a placebo-controlled trial that low doses of the immunosuppressive agent rapamycin-enhanced antibody response to influenza vaccination by about 20% in older adults. This study implicated the mechanistic target of rapamycin (mTOR) pathway, which is inhibited by rapamycin, in vaccine response. Notably, in addition to its effects on T-cell signal transduction (relevant particularly for prevention of transplant rejection), rapamycin administration to mice late in life resulted in significant lifespan extension (14% for female and 9% extension for male mice). The role of mTOR in metabolic regulation, including modulation of amino acid, lipid, and nucleotide synthesis, and regulation by insulin receptor signaling may be critical for lifespan extension, as well as salutary effects of rapamycin on processes such as hematopoietic stem cell function in mice or vaccine response in mice and humans. Future mechanistic studies, and the development and testing of new

mTOR inhibitors that, for example, lack the immunosuppressive effects of rapamycin, could provide additional insights with implications for not only vaccine response but also age-related conditions or functional alterations.

Varicella Zoster Vaccine

Herpes zoster (shingles), resulting from reactivation of varicella zoster virus, frequently affects older adults, usually manifesting as a painful cutaneous vesicular eruption in a dermatomal distribution that could also present as multidermatomal or disseminated zoster in the setting of immunosuppression or malignancy. The incidence of herpes zoster increases markedly with age, and the CDC estimates that approximately one-third of Americans will have an episode of zoster infection during their lifetime. Studies in immunosuppressed adults have established that defects in T-cell immunity, like those associated with aging, are essential for maintaining VZV in a state of latency in ganglia associated with peripheral and cranial nerves, although the precise mechanisms involved in maintaining VZV latency remain incompletely understood. Notably, studies to quantify VZV-specific CD4+ T cells have revealed that approximately 30% to 40% of adults over age 55 have no detectable CD4+ VZV responses, a potential correlate for the increased risk of older adults for zoster infection; the currently available zoster vaccine seeks to boost this defective cell-mediated immunity. The vaccine is a live attenuated preparation containing approximately 10- to 40-fold more plaque forming units of virus compared to the childhood vaccine given for the prevention of primary varicella infection. A large placebo-controlled vaccine efficacy trial enrolling over 38,000 adults of 60 years and over revealed that the vaccine was associated with a 51% reduction in the incidence of zoster infection, and a 67% reduction in postherpetic neuralgia. Despite these results, it is notable that vaccine efficacy still appears to decrease substantially in adults of 70 years and older. Currently, there are no recommendations regarding the timing of revaccination, and approaches to improve immunogenicity of the vaccine, particularly in adults over age 70 include increased vaccine dose, addition of adjuvants, and different vaccine delivery formats (such as intradermal vaccine).

Pneumococcal Vaccine

Older adults over age 65 and children under age 2 are at greatest risk for the development of invasive pneumococcal disease (eg, bacteremia, endocarditis, meningitis), but the highest mortality rates (of 15%–20%) are found in adults over 65. For decades, vaccination against *S pneumoniae* utilized the 23-valent polysaccharide vaccine, which contains purified pneumococcal capsular polysaccharides from 23 (of at least 90) strains that are commonly associated with infection in the United States. In most studies, this polysaccharide vaccine appears to reduce the risk for invasive pneumococcal disease, but at the same time most studies have not shown a benefit in prevention of noninvasive disease (such as pneumococcal pneumonia) or all-cause pneumonia in older adults. From an immunologic perspective, the polysaccharide vaccine is a so-called “T-independent” vaccine, as the pneumococcal polysaccharides stimulate B cells directly, inducing activation and differentiation to antibody secreting cells. Because of this mechanism, no T cell–dependent immunologic memory response is generated—a potential limitation given the importance of the memory response in facilitating more rapid responses mediated by higher-affinity antigen receptors resulting from processes such as somatic hypermutation in B cells.

For this reason, pneumococcal conjugate vaccine offered the possibility of improved efficacy, since in these vaccines polysaccharides are conjugated to a carrier protein, CRM197—a nontoxic mutant of diphtheria toxin. This step allows the polysaccharide conjugate to undergo antigen processing for presentation in the context of host MHC to T cells, allowing a full memory response to be generated (with the resulting generation of memory B and T cells). While T-cell function and memory responses are clearly diminished in older adults (as discussed above), there is biological plausibility to the hypothesis that immunologic memory, even diminished, is preferable to a complete absence of memory. The recently completed CAPiTA study specifically evaluated the 13-valent conjugate pneumococcal vaccine in a randomized, placebo-controlled trial of more than 80,000 adults over age 65 in the Netherlands who had never previously received a pneumococcal vaccine. The conjugate vaccine was found to diminish the risks of both noninvasive and invasive pneumococcal infection arising from vaccine-related strains, and the protective effect extended for the duration of the study (~ 4 years). Whether these studies will show a similar benefit in older adults in the United States remains to be determined. Because the CAPiTA trial began in the Netherlands prior to the general use of conjugate vaccine in Dutch children, it has been speculated that the benefits of vaccination may be less clear in the United States, where the general use of conjugate vaccine in children has led to a substantial decrease in invasive disease in older adults. Nonetheless, these and other studies have resulted in a recent shift in recommendations for pneumococcal vaccination in adults over age 65. The 13-valent conjugate vaccine is now recommended to be given first in adults greater than or equal to 65 without a previous history of vaccination, followed

by the 23-valent polysaccharide vaccine 6 to 12 months later. Methodologic limitations currently limit the total number of pneumococcal polysaccharide strains that can be conjugated with CRM197, and so the 23-valent T-independent vaccine remains recommended to extend coverage to as many strains as possible (despite the lack of immunologic memory for some strains). However, some increased valency of the conjugate vaccine should be expected in future versions of this vaccine.

FUTURE PERSPECTIVES

Understanding of the mechanisms underlying age-associated immune dysfunction has implications not only for morbidity and mortality from infectious diseases and vaccine response, but also for the age-related increase in malignancy (perhaps reflecting age-related changes in tumor surveillance and DNA repair or genome stability) and for emerging fields of research such as wound healing and organ transplantation. Studies of immune system aging have begun to utilize multidimensional data from whole genome analyses of gene expression, including evaluation of small microRNAs whose expression has been implicated in the regulation of many genes. The analysis of age-related epigenetic changes, such as methylation or histone modification, that are linked to the regulation of gene expression has also advanced, and will soon be routinely done at the single-cell level. In addition, the emerging interface of immunity and metabolism, as manifested for example by mitochondrial alterations or engagement of the mTOR pathway, suggests the utility of metabolic pathway analyses (metabolomics) using mass spectroscopy platforms. Immunologic studies increasingly will also include high dimensional data from mass cytometry (CyTOF) platforms that should be able to substantially exceed the number of analytic channels available using conventional flow cytometry. An additional area of ongoing research will evaluate the components of intestinal commensal organisms (the intestinal microbiome) or those at other tissue sites, and their interaction with the immune system in modulating inflammation, metabolic activity, and other parameters; initial studies have already found age-related differences in content of the intestinal microbiome that are associated with factors such as nutritional status, diet, and functional status such as frailty. In view of the high degree of heterogeneity found in older adults, encompassing medical comorbidities, medication use, as well as gender and race, future research on the aged immune system should provide new biological insights into how this heterogeneity is translated into changes in functional status, with the hope of identifying methods to improve quality of life in older adults.

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Chapter 4

Chronic Inflammation

Jeremy D. Walston

Learning Objectives

- Understand the concept, definitions, and etiologies of chronic inflammation in older adults.
- Understand how chronic inflammation drives systemic changes that increase risk for adverse outcomes in older adults.
- Understand present strategies and future research agendas to prevent and treat chronic inflammation and related adverse health outcomes in older adults.

Key Clinical Points

1. **Chronic inflammation is increasingly understood as a driver of many adverse health outcomes in older adults, including functional decline, frailty, and early mortality.**
2. **Many chronic disease states including congestive heart failure, diabetes, and chronic obstructive pulmonary disease (COPD) activate chronic inflammation in older adults.**
3. **Although interventions with mild anti-inflammatory interventions are being studied, exercise interventions are to date the most effective way to reduce chronic inflammation.**

INTRODUCTION

Over the past two decades, it has become increasingly clear that low-grade elevations in serum levels of inflammatory mediators are strongly associated with a host of adverse health outcomes in older adults, including mobility disability, frailty, worsening chronic disease states, and early mortality. Hundreds of epidemiologic studies of older adults from populations around the world have helped to confirm and extend these findings. Although these epidemiologic studies do not prove causality, more recent basic biological studies suggest that at least some chronic inflammatory cytokines have a direct pathophysiologic impact on organs, tissues, and physiologic systems that ultimately weaken the organism, especially in the setting of aging. These pathophysiologic changes in turn contribute to the older adult's vulnerability to adverse health outcomes.

Given the increasing recognition of the clinical relevance of chronic inflammation in disease processes and functional declines that greatly impact older adults, the ongoing study of etiologic, diagnostic, mechanistic, and potential treatments represents an important new and rapidly evolving area of investigation in geriatric medicine. Given the emerging relevance of chronic inflammation to those who care for older adults, this chapter will (1) describe evolving definitions, demographics, and measures of chronic inflammation used in the context of aging research and clinical practice, (2) review the biology that underlies chronic inflammation, (3) identify its many possible etiologies in older adults, (4) characterize the relationships between inflammatory pathway activation, multisystem decline, and the biological vulnerability observed in older adults, and (5) highlight the current and potential future interventions that may suppress chronic inflammation and reduce related adverse outcomes in older adults.

DEFINITION OF CHRONIC INFLAMMATION IN OLDER ADULTS

The activation of the innate immune system is often referred to as inflammation (**Figure 4-1**). It is a complex and critically important physiologic response to external threats. The activation of this system propagates a vast array of intra- and extracellular mediators that quickly act to fight acute infections and repair injuries. Activation of the immune system functions throughout the lifespan to attenuate or eliminate countless infections and injuries and prevents them from becoming life-threatening events. The process is in general self-limiting in that it ends when the infection or injury is resolved and the local and systemic inflammatory pathways return to a state of inactivation. In most cases, these small (local) or large (systemic) innate immune system responses are regulated by negative feedback mechanisms and by the resolution of initial injury or infection. However, substantial and growing evidence from population studies of older adults suggests that many older individuals who have no obvious injury or infection have ongoing low-grade activation of inflammatory processes as measured by modest elevations of serum levels of inflammatory signaling proteins. These proteins include C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) and its receptors, and interleukin 1 receptor antagonist (IL-1RA). The low-grade chronic elevation of these and other measurements has evolved to be named "chronic inflammation" by investigators and more recently by clinicians. Importantly, these elevations are often present in chronic disease states, but also when no active disease processes are noted in a subset of older adults. This chronic low-grade elevation often stands in contrast to the more widely recognized condition of "acute" inflammation, which is usually associated with an abscess or the onset of an acute illness such as pneumonia. In addition, acute exacerbations of chronic diseases such as congestive heart failure or COPD are also often associated with acute elevations in mediators.

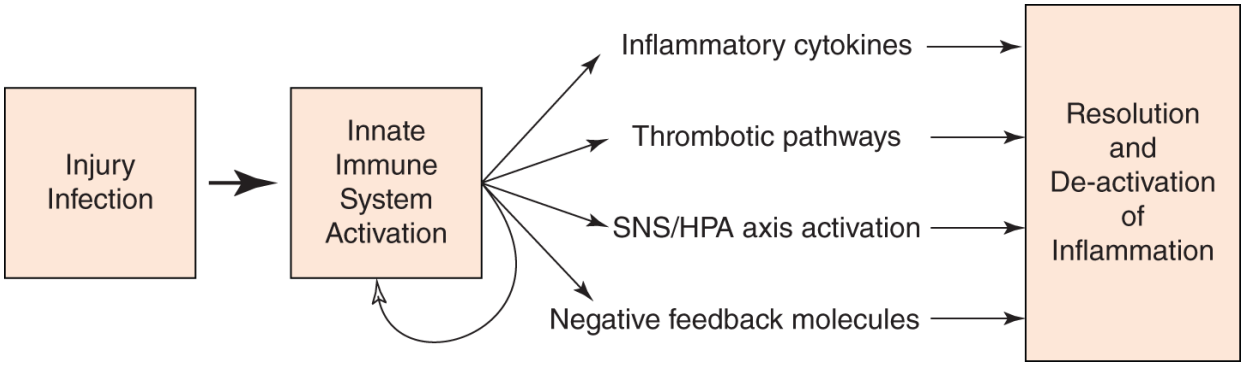


FIGURE 4-1. Traditional model of inflammation via innate immune system. Ongoing unique aging-related triggering mechanisms and failure to resolve injury or illness lead to long-term activation of this pathway and pathophysiologic change associated with chronic inflammation.

Association Between Chronic Inflammation and Adverse Outcomes

Over the past 20 years, it has been recognized that serum levels of inflammatory markers increase with age, independently of medical conditions such as diabetes and congestive heart failure that may be expected to increase inflammatory signaling in older adults. Further, dozens, if not hundreds, of well-performed association studies have identified significant inverse relationships between chronic inflammation and almost every common adverse health outcome measured in older adults, including disability, cognitive decline, frailty, sarcopenia, and early mortality. Beyond these outcomes, chronic inflammation in older adults is highly associated with disease states, including cardiovascular disease, vascular dementia, cardiovascular events such as myocardial infarction (MI), and some types of cancer. Although many of these relationships were first identified in cross-sectional studies, subsequent longitudinal studies have also demonstrated similar relationships between inflammation and adverse outcomes, further suggesting causality.

The strength of these relationships varies widely by inflammatory measures, outcomes, and populations, which limits their activity in clinical practice. Examples of the noteworthy associative studies are described below. An early study by Ferrucci et al. demonstrated a 76% increased risk of developing mobility disability over 4 years in previously nondisabled participants of the Established Populations for Epidemiologic Studies of the Elderly who were in the highest tertile of IL-6 compared to those in the lowest tertile. This study identified a serum IL-6 level of 2.5 pg/mL as an important threshold point beyond which the risk for developing disability rose exponentially. In the Cardiovascular Health Study, investigators identified an odds ratio for being frail of 2.80 in those older adults with a CRP level above 5.77 μg/mL even after excluding those participants with cardiovascular disease and diabetes. Puts et al. identified an odds ratio of 1.69 for incident frailty in older adults with a CRP level between 3 and 10 mg/mL. Other investigators

have identified strong inverse relationships between inflammatory mediators and mortality in older adults. In the Study of Osteoporotic Fractures, Tice et al. identified an eightfold risk for cardiovascular mortality over 6 years in those with CRP levels above 3.0 mg/mL. Harris et al. identified a 1.9-fold increased relative risk for death over 4.6 years in those participants in the Iowa 65+ Rural Health Study with IL-6 levels greater than 3.19 pg/mL compared to those with low IL-6 levels. Similarly, CRP levels over 2.78 mg/mL also predicted a relative risk for death of 1.6 over the same period of time. Importantly, combining IL-6 and CRP in the analysis increased the sensitivity of identifying those at increased risk of all-cause mortality by identifying a 2.6-fold risk of dying over the same period if both inflammatory markers were elevated compared to the group with neither elevated.

As mentioned above, chronic inflammation has mostly been measured by serum levels of IL-6. Indeed, Ershler et al. called IL-6 a "cytokine for geriatricians" given his early observations of strong relationships between this marker and adverse outcomes in older adults. Beyond IL-6, CRP is probably the most commonly measured inflammatory marker published in chronic inflammation studies. Although no gold standard of measurement has yet emerged, Varadhan et al. recently published a manuscript that attempted to clarify which of 15 inflammatory markers was the most related to adverse outcomes. In this study, 15 cytokines were first measured in a population of older adults; IL-6, TNFR1, CRP, IL1RA, and interleukin 18 (IL-18) were found to best predict 10-year mortality. In further model development, TNFR1 and IL-6 were found to be the two best single predictive measures for 10-year mortality. Importantly, an aggregate model that combined IL-6 and TNFR1 in a simple index substantially improved the predictive ability for mortality compared to any single measure. The biological reasons that these two cytokines performed the best may have to do with their specific biological activity as described in more detail below.

Molecular Biology of Chronic Inflammation

Although triggers for inflammation may vary, the key gateway molecular signal transduction system for chronic inflammation centers around the nuclear transcription factor nuclear factor kappa B (NFκB) (**Figure 4-2**). NFκB, when activated by specific stress or inflammatory signals, facilitates the expression of inflammatory mediators and in general leads to a cascade of molecular messages, some of which can in part be measured in the serum.

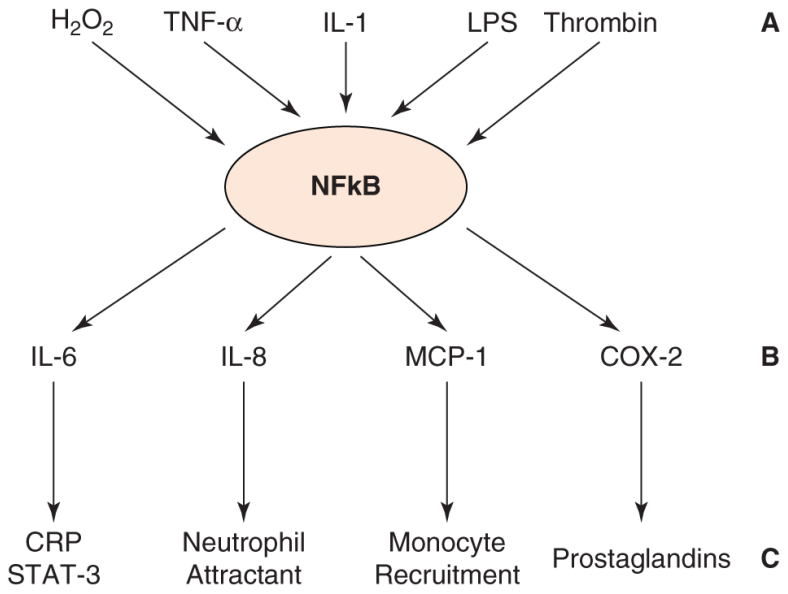


FIGURE 4-2. Schematic of the inflammatory gateway nuclear transcription factor NFκB (center circle), along with inflammatory triggers (Row A), and inflammatory outflow (Rows B and C). Row A shows specific inflammatory stimuli that lead to NFκB activation via specific cell receptors and signal transduction pathways (not shown). Activated subunits of NFκB (center circle) in turn lead to the expression of proteins that provide negative feedback for inflammation (not shown) or that propagate inflammatory message (Row B) and influence the activation of other components of the inflammatory response, including cellular components, thrombosis, prostaglandin expression, and apoptosis.

A set of cell surface receptors (**Figure 4-2A**) act through cell signal transduction pathways to activate NFκB. This links the message of "stress" to the cell nucleus, where inflammatory mediators are in turn generated (**Figure 4-2**, Row B). One of the more important triggers of NFκB-induced inflammatory pathway activators is TNF-α. TNF-α is secreted very early in the inflammatory process, usually from immune system cells in response to infections.

Originally discovered as a serum factor related to cancer, TNF-α is also secreted in high amounts from connective tissue surrounding malignancies, and from adipocytes. There are several specific TNF-α receptor subtypes that act to transmit the message of inflammation, which in turn activates NFκB and leads to the expression of a host of inflammatory mediators (**Figure 4-2**). IL-1 is most often secreted in response to infections, injury, and disease, and activates and amplifies inflammatory signaling through its own cell surface receptor. In addition, IL-1 has recently been identified as a major cytokine that is secreted from senescent cells, providing support that may play an important role in late life activation of inflammatory pathways. IL-1 along with IL-18 are considered important products of inflammasome assembly, which is an early response to inflammatory triggers. In addition to these early inflammatory cytokine signals, the bacterial surface antigen lipopolysaccharide (LPS) and some viral particles bind to a family of toll-like receptors (TLR), which in turn set off a separate signal transduction pathway that in turn amplifies NFκB-related inflammatory signaling. This pathway to inflammatory activation is certainly crucial for the protection of the organism against acute infections, and likely also helps in organized defense against chronic infections. Recent evidence also suggests that the clotting protein thrombin may also activate inflammatory pathways through its own receptor. This observation provides evidence for a link between injury and inflammation. Finally, and potentially very important for aging-related activation of inflammatory systems, the free radicals superoxide and hydrogen peroxide activate inflammatory pathways via signal transduction pathways that lead to NFκB-mediated inflammatory gene production (**Figure 4-2**, Row A). In sum, TNF-α, IL-1, LPS, thrombin, and free radicals activate complex intracellular signal transduction pathways via cell surface receptors, and transmit an inflammation activation message to the nucleus of the cell where NFκB-related activity induces the expression of inflammatory mediators that act to either amplify the inflammatory message or exert negative feedback that brakes inflammatory signaling as described below (**Figure 4-2**). Variations in signal and coactivating factors play a role in modulating both inflammatory message and negative feedback.

The molecules generated by inflammatory signaling give specificity to the inflammatory message (**Figure 4-2**, Rows B and C). The complexity of these pathways and the limited understanding of what drives inflammatory specificity, limits the following discussion to a general overview relevant to previously published aging studies. The molecules that are most known for being elevated and associated with adverse outcomes in older adults that make up the most easily measurable systemic inflammatory response include IL-6 and CRP. IL-6 is a pleiotropic cytokine that in combination with cell-bound and circulating IL-6 receptor plays a crucial role in both inflammatory and anti-inflammatory signaling in acute inflammation. Chronic IL-6 production also leads to the expression of CRP, a commonly measured inflammatory mediator that functions at the interface between inflammation and thrombosis and is an important marker of cardiovascular disease risk. Other potent inflammatory mediators produced by NFκB activation include: (1) cyclooxygenase 2 (Cox-2), best known for its role in joint inflammation and its key role in prostaglandin production, (2) IL-8, a potent neutrophil attractant factor, and (3) monocyte chemo-attractant protein 1 (MCP-1), a protein that amplifies monocyte inflammatory response. Each of these factors, and multiple others known to be stimulated by NFκB-related activation, serve to amplify inflammatory signaling both locally and systemically, and provide some specificity in response. In addition to these inflammation-specific functions, NFκB signaling also leads to the expression of proteins that provide negative feedback to NFκB.

Emerging evidence suggests that NFκB-related signaling may impact aging phenotypes well beyond the influence of inflammatory mediators. NFκB-related signal transduction also plays an important role at the interface between inflammatory signaling, apoptosis, and the development of cellular senescence. The recent discovery that TNFR1 is strongly associated with mortality and other adverse health outcomes in aging and disease states highlights this potential importance given the role that TNFR1 plays in transducing apoptotic signaling. Although the details of these pathways are still emerging and are beyond the scope of this chapter, more detailed understanding of the balance between chronic inflammation, apoptosis, and cell senescence may help elucidate the most relevant pathways that drive late life decline in multiple physiologic systems.

ETIOLOGIES OF CHRONIC INFLAMMATION

As detailed above, several NFκB pathway triggering mechanisms related to aging likely drive the production of inflammatory mediators including: (1) increased numbers of dysfunctional, cytokine secreting senescent cells of all types, (2) increases in TNF-α and IL-6 producing adipocytes related to increased body fat in older adults, (3) age-related increases in free radicals of oxygen, which directly trigger NFκB activity and lead to the increased generation of inflammatory mediators, (4) age-related declines in levels of hormones such as estrogen known to attenuate NFκB

activity, and (5) most chronic disease states. Many of these aging-related etiologies are aggregate and perhaps synergistic, which in turn triggers chronic inflammatory signaling with many pathophysiologic consequences (**Figure 4-3**).

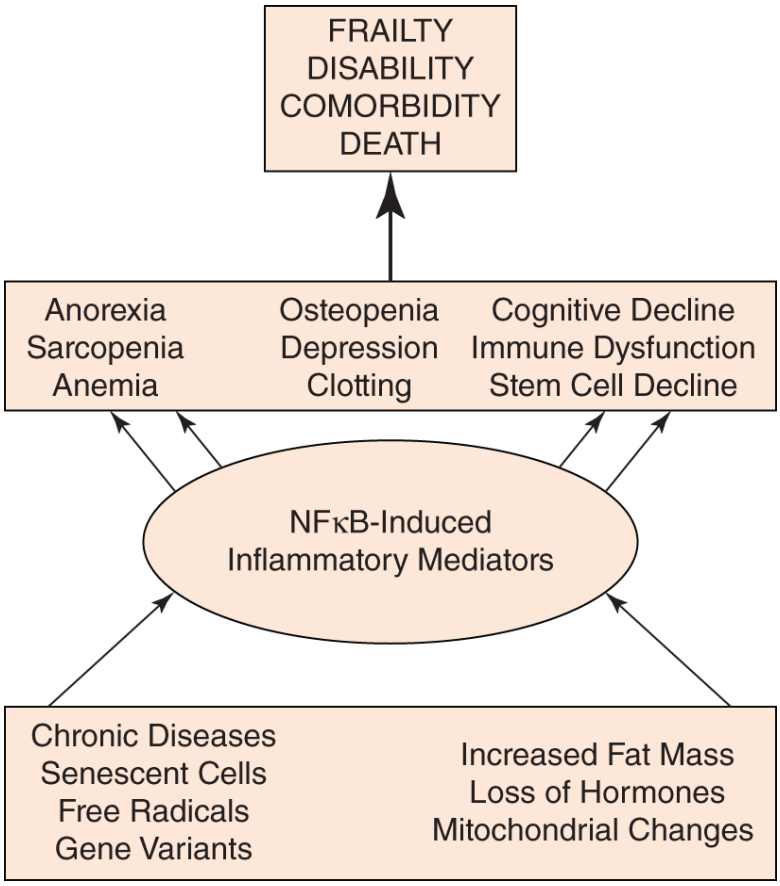


FIGURE 4-3. Platform of vulnerability related to chronic inflammation in older adults demonstrating etiologies of activation of chronic inflammation in older adults driving expression of NFκB-induced mediators, which in turn drive subclinical and clinical changes that put some older adults with chronic inflammation at higher risk for adverse health outcomes.

With increasing age and increasing numbers of cell cycle passage, many cell types take on senescent characteristics that include inability to undergo apoptosis or reproduction, altered gene expression that results in altered cell function (or dysfunction), and increased tendency to secrete inflammatory cytokines. These senescent characteristics have been observed in multiple cell types, including endothelial cells, adipocytes, fibroblasts, and immune system cells. Next, body composition changes associated with aging are also likely to contribute to increased cytokine production, especially related to the increase in the less metabolically active adipocytes that take the place of metabolically active muscle tissue. These fat cells secrete both TNF-α and IL-6, both of which amplify inflammatory signaling. Tissue levels of free radicals of oxygen also tend to rise with increasing age, which is caused by both age-related declines in enzymes that quench free radicals and increased production. This is ultimately due to mitochondrial dysfunction and lack of clearance by mitophagy/autophagy. Free radical molecules, including hydrogen peroxide and superoxide, are potent stimulators of the NFκB signal transduction cascade, leading to production of inflammatory mediators such as IL-6. Age-related declines of DHEA-S, testosterone, and estrogen also play an important role in the activation of inflammation. DHEA-S works in part by blocking NFκB activation, while the sex steroids normally bind gene transcription sites for inflammatory cytokines such as IL-6. This hormonal “braking action” gradually declines as levels of these hormones subside with increasing age.

Although chronic disease states are not necessarily intrinsic to the aging process, most are closely related to aging. Chronic diseases known to activate inflammation include rheumatoid arthritis, polymyalgia rheumatica, and most types of cancer. In addition, many common chronic disease states not traditionally categorized as inflammatory diseases, including renal failure, congestive heart failure, diabetes, and COPD, trigger the production of NFκB-related inflammatory mediators. This is especially evident during disease exacerbations. These conditions, in combination with the aging-related alterations in cell-type and oxidative stress, are important drivers of the elevated levels of

inflammatory mediators detectable in the serum of many older adults. Finally, variations in genes that code for inflammatory mediators and inflammatory signal transduction have been shown to be increasingly relevant late in life. For example, specific gene variants present at birth are often most relevant in the face of disease states that trigger inflammatory mediators. At least two studies have now demonstrated that older men with both MI and an IL-6 gene promoter variant were much more likely to die of MI-related complications than those without the promoter variant, likely due to failure of recovery from ongoing inflammatory activation.

THE CONTRIBUTION OF CHRONIC INFLAMMATION TO PATHOPHYSIOLOGIC CHANGE AND CHRONIC DISEASE

Although multiple studies now demonstrate strong associations between the activation of inflammatory pathways, chronic disease states, and adverse health care outcomes, there is no single mechanism that connects inflammation to the vulnerability to adverse health outcomes frequently observed in older adults with chronic activation of inflammatory pathways. Recent evidence from molecular biological studies suggests that inflammatory mediators found to be associated with adverse health outcomes in older adults actually contribute directly to the decline in multiple physiological systems, and declines in the structure and viability of specific tissues such as skeletal muscle. Evidence for inflammatory activation playing a role in multiple system decline in late life comes from association studies in populations of older adults and from molecular studies. For example, one of the most critical physiologic systems for preserving function and well-being in older adults is skeletal muscle. Aging-related declines in skeletal muscle mass and strength, often termed sarcopenia, is an important contributor to disability and frailty, and is strongly associated with elevated inflammatory markers. Older Dutch participants in a longitudinal study on aging had a two to threefold increased risk of losing 40% of their grip strength over 3 years if their IL-6 level was greater than 5.0 pg/mL and their CRP was greater than 6 mg/mL. Cesari et al. demonstrated a significant decline in strength over 3 years in older CHIANTI participants with the highest levels of IL-6, CRP, and IL-1RA. IL-1 RA production is stimulated by IL-6, and it is utilized as a surrogate measure for the strongly proinflammatory cytokine IL-1. For molecular evidence, consider a study of IL-$6^{-/-}$ mice injected with IL-6, where marked gastrocnemius muscle atrophy and protein degradation by cathepsin L and B was demonstrated. Other molecular studies directly link NFκB activation to the downregulation of MyoD, a critical factor in skeletal muscle differentiation and repair. Beyond actual muscle decline, inflammatory cytokines and related activation of TGF-β stimulate fibrotic and fat tissue in place of muscle, leading to further weakening of this tissue crucial to functionality in older adults.

Beyond sarcopenia, chronic exposure to inflammatory mediators influences many other critical physiologic systems that in turn drive late life vulnerability to adverse outcomes. The adaptive immune system is altered over time in response to low-grade inflammatory stimulation, with slowed T-cell maturation, T-cell dysfunction, and progenitor cell exhaustion all likely making individuals with chronic inflammation more rather than less vulnerable to infections. One in vivo study performed in young rhesus monkeys demonstrates the multisystemic and pleiotropic influence of inflammatory cytokines. These monkeys were injected with low doses of human recombinant the IL-6 for 30 days. During this period, those injected lost 10% lean body mass, developed depression, mild anemia, osteopenia, and increased levels of CRP. Bone tissue loss is driven in part by chronic inflammation given that osteoclasts, cells that are important in resorption of bone, are directly upregulated by IL-6. Neurologic damage in Alzheimer disease and other neurodegenerative conditions have been directly linked to both Cox-2 and IL-6 expression. Further, TNF-α and IL-6 have been demonstrated to alter iron absorption and utilization in red blood cells, which in turn decreases red blood cell production. Chronic IL-6 expression also stimulates the anorexic proteins including leptin, neuropeptide Y, melanocortin, and orexin that suppress hunger. These studies and many others provide substantial evidence that NFκB pathway activation and the downstream products of chronic inflammation can induce profound tissue changes and ultimately facilitate many of the pathophysiologic processes that are associated with aging.

Beyond the evidence that supports chronic inflammation as a driver of many components of the aging phenotype per se, there is increasing evidence that chronic inflammation exacerbates preexisting disease states, and perhaps even triggers the onset of new disease states. Substantial evidence suggests that chronic inflammation is an integral part of the development of both vascular lesions that lead to chronic blockages in blood vessels, to the acute process that results in infarctions through activation of thrombotic pathways, and to the remodeling in alveoli that accompanies COPD. Chronic elevations in inflammatory mediators likely drive worsening glucose control in diabetics and obese individuals. Recent laboratory evidence demonstrates that NFκB-related inflammatory mediators contribute directly to malignancy promotion in prostate and liver cancer, and likely in many others. In sum, these studies strongly support

that chronic activation of inflammatory pathways and the resulting bioactive molecules not only drive tissue and organ changes normally attributed to aging per se, but they also exacerbate and trigger chronic disease states. This combination in turn puts the older individual at much higher risk of adverse health outcomes.

CLINICAL UTILITY OF INFLAMMATORY MARKERS AND ANTI-INFLAMMATORY INTERVENTIONS IN OLDER ADULTS

As evidence emerges that chronic inflammation contributes to pathophysiologic changes that increase risk for adverse health outcomes in older adults, attention has turned to the need for improved diagnostic tools and novel preventive and intervention strategies. Although CRP measurement has been suggested as an additional risk factor for cardiovascular disease, and it has been used to monitor treatment progress in chronic infections such as osteomyelitis, no markers of chronic inflammation have been recommended for implementation into the clinical management of older adults. There are likely two reasons for this. First, at this point, there is no gold standard measurement of chronic inflammation in older adults. Although CRP is utilized in clinical practice as mentioned above, it is in general not as predictive of adverse outcomes as is IL-6 and even TNFR1. While these markers solely and in the aggregate are most predictive across a broad range of outcomes, they are at present used almost exclusively in the research setting. Future studies in human subjects that better define population norm values for these cytokines will be important in the development of an optimal clinical assay for the diagnosis of chronic inflammation in older adults. Second, and most importantly, to date there are very few, if any, recommendations for managing those older adults with higher levels of inflammatory markers beyond disease-focused treatments, making routine monitoring of chronic inflammation not clinically useful at present. When measurement of individual inflammatory mediators become more standardized and feasible, as more specificity is assigned to these markers, and as specific, targeted, and safe interventions targeting inflammatory pathways are developed, serum inflammatory markers will likely evolve into a more useful clinical tool that can both identify the most vulnerable older adults and guide targeted therapeutic or preventive interventions.

To date, the safest and most effective intervention for chronic inflammation in older adults is increased levels of physical activity. In one study of community dwelling older adults, serum IL-6 levels were significantly reduced after a 12-month period of moderate-intensity physical activity intervention. This association held after adjustment for weight loss, and was especially evident in older adults that started with higher levels of IL-6. Other studies of activity intervention in obese older adults have demonstrated similar significant reduction in serum IL-6 and CRP. The use of pharmaceutical agents targeting chronic inflammation in older adults has to date been mostly for research purposes. One major concern expressed by clinicians regarding the potential treatment of chronic inflammation per se is that suppression of inflammatory signaling may unleash worsening disease states that are being kept in check. Exceptions include the use of known anti-inflammatory agents that have mostly been used as over the counter pain medications, including aspirin (ASA) and nonsteroidal antiinflammatory drugs (NSAIDs). Although ASA has been shown to reduce the incidence of vascular diseases with a clotting component, including MIs and stroke, through the reduction in clotting, the exact impact on chronic inflammation and related outcomes are not yet known. Recent epidemiological evidence that ASA helps to prevent colon cancer and all-cause mortality, suggest that some of its health-related benefits may be derived from its known anti-inflammatory properties. As to the role of NSAIDs, epidemiologic studies in chronic disease states have shown mixed evidence related to long-term impact on slowing cognitive decline. Despite their use in arthritic conditions for disease treatment and pain management, a substantial side effect profile in older adults will likely prevent their widespread use as agents useful in chronic inflammation in older adults.

Over the past several years, many other more specific anti-inflammatory medications have been utilized to treat other geriatric conditions such as anorexia and weight loss, usually in a specific disease state rather than aging or frailty per se. Thalidomide, a repurposed drug that degrades TNF-α RNA and hence blocks inflammatory signal propagation, has shown some promise. In clinical trials, it appears to be well tolerated and positively influences weight gain in HIV and in pancreatic cancer, despite the fact that it offered no survival advantage. Megestrol, a hormonal agent known to block IL-6 transcription, has also been shown to be beneficial in HIV- and cancer-related cachexia. It has been tolerated with minimal side effects, and is probably safe but not clearly effective at stimulating appetite in most geriatric populations. More recently, the anti-inflammatory agent methotrexate is being tested in lower doses to target chronic inflammation and cardiovascular disease in older adults.

Although more cytokine-specific blocking agents such as IL-6 and TNF-α receptor blockers are available for the treatment of autoimmune conditions, there is no indication for the use of these agents in older adults without these specific disease states. Indeed, extreme caution must be taken when using these agents in older populations given the

increased risk of life-threatening infections that is inherent in agents that effectively block key components of the inflammatory cascade such as TNF-α or IL-6.

Future development efforts should be aimed at safely modulating or attenuating chronic inflammatory signaling. For example, targeting sources of inflammatory signaling such as a permeable gastrointestinal track, augmenting removal of mitochondria that are a source of oxidative stress, or clearing senescent cells may be safer and more specific than blocking a crucial inflammatory pathway.

DOES CHRONIC INFLAMMATION CONTRIBUTE TO AN ALTERED BIOLOGICAL PLATFORM FOR LATE LIFE VULNERABILITY?

Chronic inflammation in older adults drives many pathophysiologic processes that end in adverse health outcomes. Mounting evidence suggests that aging itself, in combination with a number of chronic disease states, drives the activation of chronic inflammation through the gateway nuclear receptor NFκB. The products of that chronic activation, including molecules such as IL-6 and TNFR1, drive further pathophysiologic changes in organs, tissues, and disease states, leaving the older adult more vulnerable to a host of adverse health outcomes. Developed with this background in mind, **Figure 4-3** illustrates a comprehensive model of chronic inflammation that connects etiologies with inflammatory triggers, pathophysiologic changes, and ultimately adverse health outcomes observed in older adults. Future studies that improve the understanding of etiologies, the interface between molecular change and disease development, and how interventions may attenuate inflammation without triggering adverse outcomes are key to improving health outcomes in older adults.

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Chapter 5

Demography and Epidemiology

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Learning Objectives

- Describe the changing demographic characteristics and longevity of the aging population in the United States and worldwide.
- Identify the leading causes of death and common diseases affecting older adults.
- Gain understanding of the occurrence, determinants, and consequences of disability in the older population.

Key Clinical Points

1. **Improvements in survival over the last century have resulted in a population with a large proportion of individuals who will survive to advanced old age.**
2. **Although there is much useful information gained by observing individual diseases responsible for mortality and disability, a full picture of disease status in the older population should include consideration of co-occurring diseases.**
3. **Disability status measures are the best predictors of adverse health outcome, as disability measures capture the impact of the presence and severity of multiple pathologies, as well as the potential synergistic effects of these conditions, on overall health status.**

INTRODUCTION

Over the past century there have been truly remarkable changes in the numbers and characteristics of older persons throughout the world. The growth of the older population has resulted from a general increase in the overall population size but has been particularly affected by major declines in several of the leading causes of mortality. The increased survival of older persons has also been accompanied by declining birth rates, so the proportion of the population aged 65 and older has increased dramatically and will continue to increase for the next 50 years. These demographic transformations have an effect on society that reverberates well beyond the increased medical care needs associated with an older population.

As more people live to advanced old age, it is important to gain a greater understanding of more than just the individual diseases that affect them. It is critical to appreciate the global picture of older persons who may have multiple chronic conditions, decrements in functional abilities, and social and psychological problems that may have an impact on many facets of their health and quality of life. In contrast to the previous stereotype, older people become more heterogeneous, not more alike, as they age, and understanding this process is one of the key challenges of geriatric medicine. Adding to the clinical perspective on single patients or small samples of patients, geriatric epidemiology has provided a useful tool with which to approach these challenges by studying representative populations of older persons. Going beyond the demographic focus of counting and projecting the number of older people in the population, epidemiology has made additional contributions to our understanding of the health status and functional trajectory of the older population. In the past 25 years, epidemiologic researchers either have utilized previously initiated cohort studies that include persons who have aged during the study or have begun new cohorts focusing on older people. These epidemiologic studies have assessed the distribution and determinants of specific

diseases and have evaluated issues of relevance to an aging population, such as quality of life, geriatric syndromes, comorbidity, functional status, and end-of-life issues. Many of the chapters in this book refer to epidemiologic research on specific diseases and conditions. This chapter focuses on the more general or "geriatric" outcomes, particularly disability, that have also been the subject of much epidemiologic investigation.

The chapter begins by documenting the rapid growth and impressive increases in the number of older persons in the United States and other countries. It then examines improvements in survival and life expectancy. Selected demographic characteristics are then considered, including living situation and labor force participation across many developed countries.

The second section, on mortality, depicts current causes of death in the older population in the United States and considers the change in death rates with increasing age. Data on overall and disease-specific changes in mortality rates from 1950 through 2004 show the dramatic changes in these rates. The third section addresses chronic disease in the older population by using data from national surveys on self-reporting of chronic conditions, ambulatory medical visits, and hospital discharges. Data are then presented for cancer, dementia, obesity, and sensory impairments, as examples of conditions where the use of only mortality data would provide an incomplete picture. The fourth section presents epidemiologic data on disability in older persons. This section describes the prevalence of disability, its causes and consequences, individual transitions in functional status, population changes in disability prevalence, and measurement issues. Finally, the chapter provides a description of important behavioral risk factors for chronic disease, injury, and disability and the prevalence rates of these risk factors in the older population.

DEMOGRAPHICS

Aging of the Population in the United States

One-hundred-fifty years of aging in America is summarized in **Table 5-1**, beginning with 1900 and including projections through 2050. This table demonstrates how the older population has grown, as well as how the oldest segment of the older population has grown even more rapidly. In 1900 only 4.1% of the 76 million persons in the United States were aged 65 and older, and among those in this age group only 3.3% were aged 85 and older. By 1950 more than 8% of the total population was aged 65 and older, and by 2000 this percentage had increased to 12.4. The US Census Bureau creates several alternative mortality scenarios when developing population projections, and according to their middle mortality assumption, there will be 84 million persons aged 65 and older in the United States in 2050. If mortality declines faster than projected under this assumption, the number of older people will be even higher. In 2050 one in five Americans will be aged 65 or older. The growth of the 85 and older population, termed by some the oldest old, will be even more dramatic. By 2050, when the current baby boom generation will be in this age group, it is projected that 18 million persons, representing nearly a quarter of all persons aged 65 and older, will be 85 years and older. There will be more than 4 times as many people in the 85 years and older age group as there are now, and almost 200 times as many as there were in 1900. Thus, the numbers of older people are growing dramatically, the proportion of the total population aged 65 and older is increasing, and the older population itself is getting older, with increasing proportions in the 85 years and older subgroup.

TABLE 5-1 ACTUAL AND PROJECTED GROWTH OF THE OLDER US POPULATION, 1900 TO 2050 (MILLIONS)

		65 YEARS AND OLDER		85 YEARS AND OLDER	
	TOTAL POPULATION (ALL AGES)	NUMBER	% OF TOTAL	NUMBER	% OF ≥ 65
1900	76.0	3.1	4.1	0.1	3.3
1950	150.7	12.3	8.1	0.6	4.9
2000	281.4	35.0	12.4	4.2	12.0
2050	399.8	83.7	20.9	18.0	21.5

Data from Population Division, US Census Bureau, Washington, DC, 20233.

Aging of the Population and Life Expectancy

Population aging is taking place throughout the world. **Figure 5-1** presents data on the current and projected percentage of the population aged 65 and older for six regions of the world. Change in the proportion of a population that is older age depends on changes both in the survival of older persons and in the birthrate. Improved survival at older ages and a low birthrate have resulted in European countries having the oldest populations in the world. In fact, the Population Reference Bureau estimates that of the world's 25 countries with the oldest populations (not including small island countries), 24 are in Europe. In both Italy and Germany approximately 21% of the population is 65 years or older, the oldest populations in Europe and the second and third oldest in the world. Sometime around 2004 Japan surpassed Italy to become the oldest major country in the world, with 26% of its population being 65 years or older. Japan remains the only major country not in Europe on the list of the oldest 25 populations. Considering countries of all sizes, the tiny country of Monaco is second to Japan, with approximately 24% of the population being 65 years or older. Europe will continue to have the oldest populations in the world in the twenty-first century, with almost one in four Europeans projected to be aged 65 or older by 2030. The current percentage aged 65 years and older in Latin America, the Caribbean, Asia, the Near East, and North Africa is low, ranging from about 4% to 7%. However, growth of the older population will be rapid in these countries. It is projected that in 2030 the proportion of their population in this age range will double. Sub-Saharan Africa has few older persons, and it is expected that the percentage of older people in the general population will not grow substantially in the future.

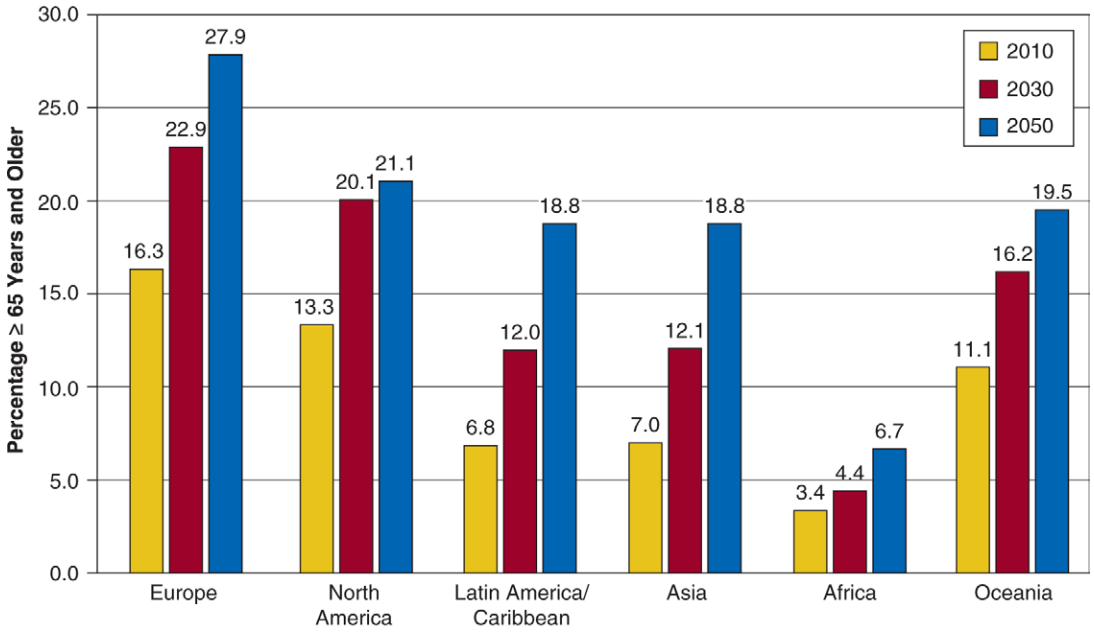


FIGURE 5-1. Percentage of population age 65 years and older in 2010 and projected for 2030 and 2050. (Data from US Census Bureau, International Data Base. http://www.census.gov/compendia/statab/2012/tables/12s1329.pdf. Accessed January 15, 2015.)

Populations have aged at different speeds and during different time periods throughout the world. **Figure 5-2** shows the number of years it took, or is projected to take, for specific countries to progress from having 7% of the population aged 65 and older to having 14% of the population in this age range. The United States reached 14% in 2013 and took 69 years to make the transition. Sweden and the United Kingdom reached the 14% level in 1975, with Sweden taking 85 years to go from 7% to 14% and the United Kingdom taking about half of that time. Japan has already reached the 14% mark and took only 26 years to do so.

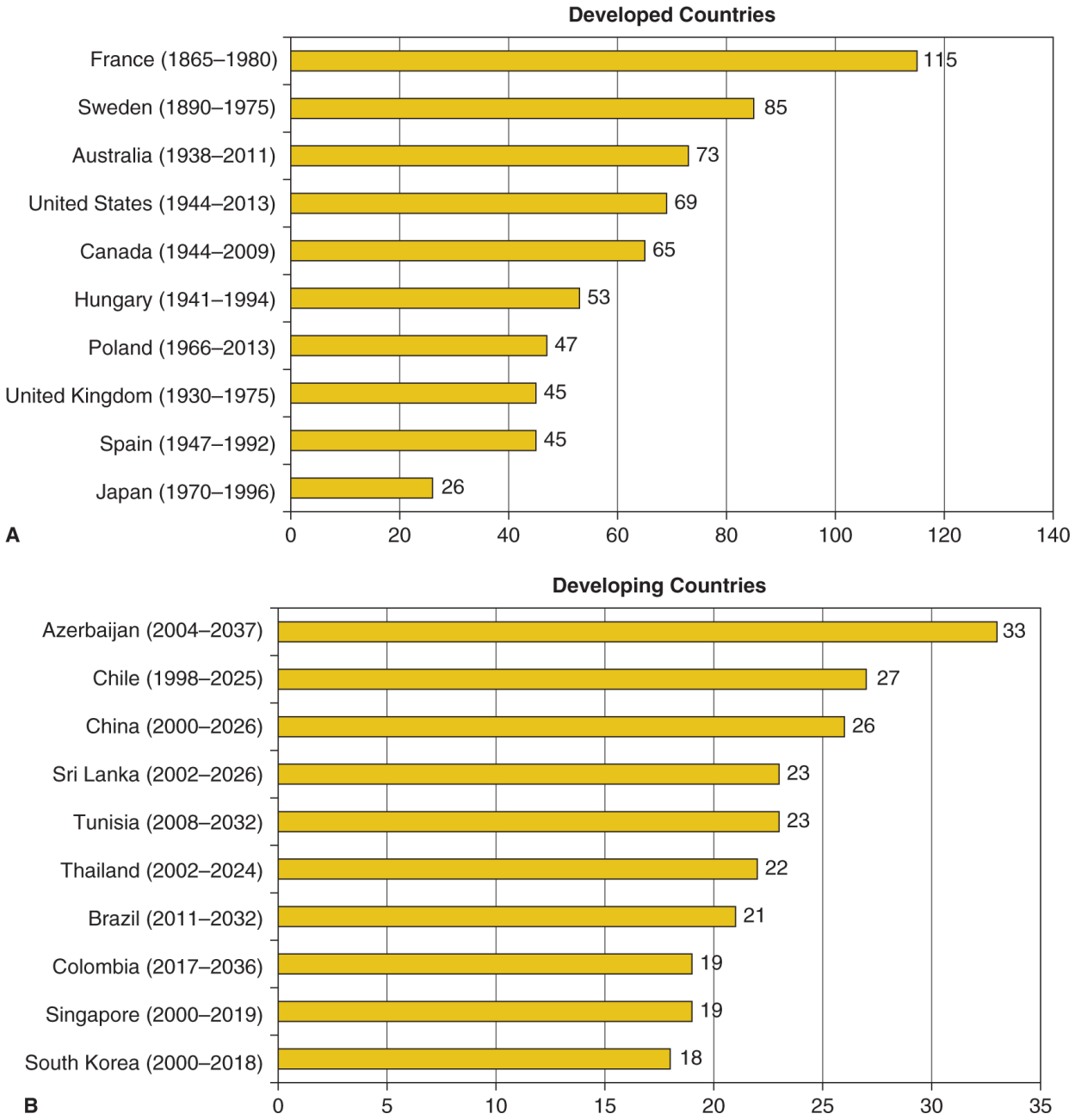


FIGURE 5-2. Speed of aging: number of years and time period in which percent of population aged 65 and over doubled or will double from 7% to 14%. (Data from Kinsela K, He W. *An Aging World: 2008. US Census Bureau, Series P95/9–1*. Washington, DC: US Government Printing Office; 2009. Figure 2-6. http://www.census.gov/prod/2009pubs/p95-09-1.pdf.)

A particularly clear message about the speed of aging in developing countries is presented in **Figure 5-2**. Although the developing countries shown will generally not reach the 14% mark until the third decade of this century, most will have spent less than 27 years making the transition. The rapid aging of these countries will certainly have a large societal impact, with less ability to adapt than in countries that have aged more slowly.

Life Expectancy at Different Ages

Better survival at all ages has had a major impact on the size and age distribution of the older population. **Figure 5-3** depicts survival curves for the total US population over the course of the twentieth century and into the twenty-first century. In 1900 there was substantial mortality in infancy and early childhood, with the survival curve in midlife being somewhat steeper than at the end of the twentieth century. By 1950 a large proportion of early-life mortality had been removed, although survival in this age range was still improving by the end of the century. By 2000 a large proportion of persons were living to age 60 years, and only at age 70 years did the survival curve start to fall rapidly. The survival curve continued to shift to the right through 2009. The change observed in the shape of survival curves has been termed the rectangularization of survival, and it has been proposed that at some point full rectangularization will be

reached, with no further increases in life expectancy. When this will occur is not yet clear, but the US Census Bureau and Social Security Administration are projecting continued increases in survival for at least the next 50 years.

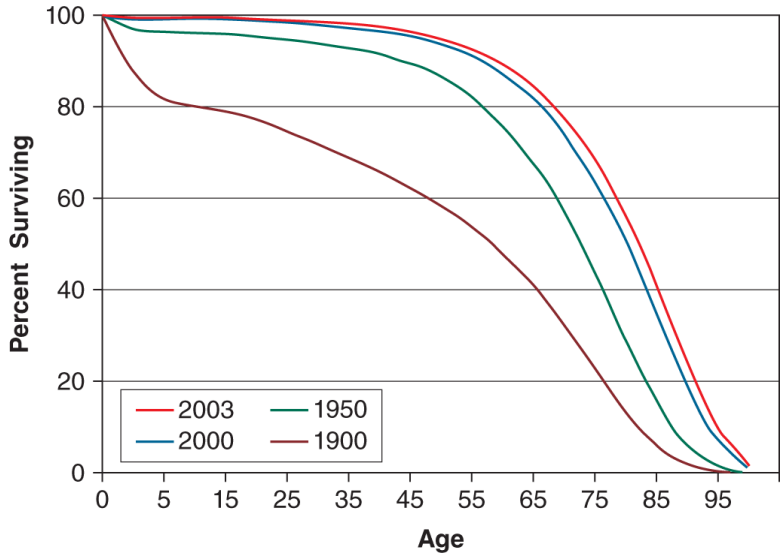


FIGURE 5-3. Survival curves for US population. (Data from Arias E. *United States Life Tables, 2009. National Vital Statistics Reports, Vol. 62, No. 7.* Hyattsville, MD: National Center for Health Statistics; 2014. Table 20. http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_07.pdf.)

Life expectancy at age *x* is defined as the average number of years remaining to be lived by a member of a survivorship group who is exactly age *x*. Most life expectancy estimates use current life tables, meaning that they use the age-specific mortality experience of the current population. With this approach, life expectancy at birth gives an estimate of the average length of life of a cohort of children who are born now and then experience today's age-specific mortality rates as they proceed through life. This is an artificial construct, but it provides a way to represent the overall mortality experience of a current population and allows us to compare this experience across countries and over time. If mortality rates continue to decline, as is expected, the average child born today will live considerably longer than the estimate shown on a current life table. Given these caveats, it is nonetheless useful to examine changes in life expectancy over the last century and life expectancy at specific ages. Life expectancy at birth was only 47.3 years in 1900 and rose to 68.2 years by 1950, affected to a large extent by improvements in infant and child mortality. Life expectancy continued to rise through the second half of the twentieth century, driven mainly by increases in survival in middle and old age. **Table 5-2** shows life expectancy at birth and at ages 65, 75, and 85 years for the year 2009. At all ages females have a higher life expectancy than males, with the differential at birth being 4.9 years. The gender differential for blacks (6.5 years) is greater than for whites (4.8 years). Blacks have a lower life expectancy than whites through age 75 and then have a higher life expectancy at age 85. The observations of importance to geriatric medicine in these estimates are that the average 75-year-old man will live about 10 more years and the average 75-year-old woman will live more than 12 additional years. At age 85, the average person can still expect to live another 6 to 7 years.

TABLE 5-2 LIFE EXPECTANCY IN 2009 (YEARS)

	MALE			FEMALE		
AGE	ALL	WHITE	BLACK	ALL	WHITE	BLACK
At birth	76.0	76.4	71.1	80.9	81.2	77.6
At 65 years	17.6	17.7	15.8	20.3	20.3	19.3
At 75 years	11.0	11.0	10.3	12.9	12.9	12.6
At 85 years	5.9	5.8	5.9	7.0	7.0	7.2

Data from Arias E. United States life tables, 2009. National Vital Statistics Reports, Vol 62, No 7. Hyattsville, MD: National Center for Health Statistics; 2014. http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_07.pdf. Accessed January 15, 2015.

The estimates shown in **Table 5-2** do not include Hispanics. Although the National Center for Health Statistics does publish data on Hispanic mortality rates, these data come with warnings of problems associated with their accuracy. The denominator for Hispanic rates comes from the US Census, where Hispanic ethnicity is self-reported. At the time of death, Hispanic ethnicity is reported by the person completing the death certificate, and there is likely a large amount of underreporting. It is also known that Hispanic persons often return to their native countries to spend the last years of their lives, and so their deaths are not enumerated as deaths in the United States. Thus, there is substantial under-ascertainment of the numerator for Hispanic death rate calculations, leading to an underestimation of the true rates.

The improvements in survival over the last century are relevant to the field of geriatric medicine, as the decline in mortality rates throughout life has resulted in a population with a large proportion of individuals who will survive to advanced old age. This point is made compellingly by the data shown in **Figure 5-4**. This figure was generated using data from 1900, 1950, 2000, and 2009 life tables and illustrates the proportion of 50-year-old men and women who can expect to live to age 90 or older. Only about 3% of 50-year-olds could expect to live to this age in 1900. By 1950 this proportion had risen to 5% in men and nearly 10% in women. The large decreases in old-age mortality in the second half of the century led to large changes by 2000, when over 16% of 50-year-old men and more than 28% of 50-year-old women could expect to reach the age of 90 or older. By 2009 this proportion increased to almost 19% of 50-year-old men and 30% for women. All these estimates are derived from current life tables; so if mortality continues to decline, these percentages will be even higher in the current cohort of 50-year-olds. The consequence of these changes is that an unprecedented proportion of the current middle-aged population will live to very old age.

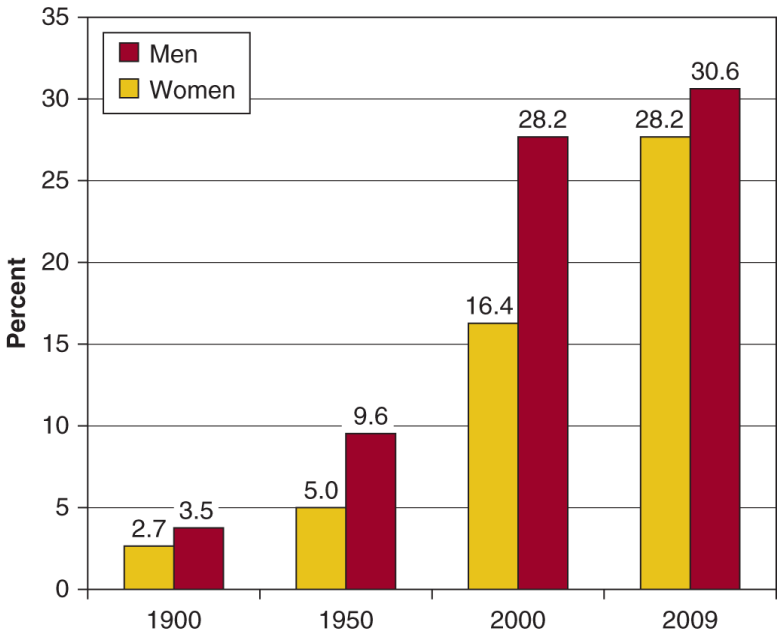


FIGURE 5-4. Percentage of 50-year-olds living to 90, 1900 to 2009. (Data from US life tables in Arias E. *United States life tables, 2009. National Vital Statistics Reports, Vol. 62, No. 7.* Hyattsville, MD: National Center for Health Statistics; 2014. Table 20. http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_07.pdf.)

Extreme Longevity

Despite great popular interest in extreme longevity, the demographics of very long life have been formally studied only in recent years. Examples of persons that lived to 100 years are mentioned at the time of Imperial Rome and, although these reports cannot be directly validated, there is no reason to believe that a few rare individuals might not reach extreme longevity. However, as the percentage of centenarians has risen, especially in the last century, centenarians are no longer rare and virtually all geriatricians have dealt with a centenarian patient. Studying centenarians provides a magnified view of the aging process, but the study of long-lived individuals can also provide results that are important in geriatric practice. In fact, little is known about the factors that predict decline in health status, disability and mortality in individuals in their nineties.

Previous claims for the world record for longevity were often unsubstantiated, and pockets of the world where claims were made for general high longevity usually turned out to have no different longevity than other parts of the

world. However, data from places like Sardinia, Italy, have identified areas of increased longevity that have been meticulously validated. There is currently no solid explanation about why centenarians are concentrated in such geographic areas.

Better age documentation has made it possible to be more confident about the numbers of centenarians and changes in these numbers. It has been estimated that the number of centenarians in western Europe has doubled every decade since 1950, and estimates for the United States also show a doubling between 1980 and 1990 and again from 1990 to 2000, when the total number of centenarians rose from 28,000 to more that 50,000 (**Figure 5-5**). In 2000, the Unites States had approximately 50,000 centenarians, more than any other country in the world and about 12% of the estimated living world centenarians. In comparison, the population of the United States represents only 4.6% of the world population. However, future increases will be spectacular. It has been estimated that between 2000 and 2050, the number of centenarians will increase more than eightfold, with a projected 442,000 centenarians in the United States in 2050. In 1990, 78% of US centenarians were non-Hispanic whites. However, since then, the Hispanic and Black populations have expanded much faster than the White population. Thus, centenarians in the future are expected to be much more ethnically diverse. In all reported series, with the single exception of Sardinia, there are fewer male than female centenarians. However, men reaching this age are considerably less likely to have significant mental and cognitive disability than women.

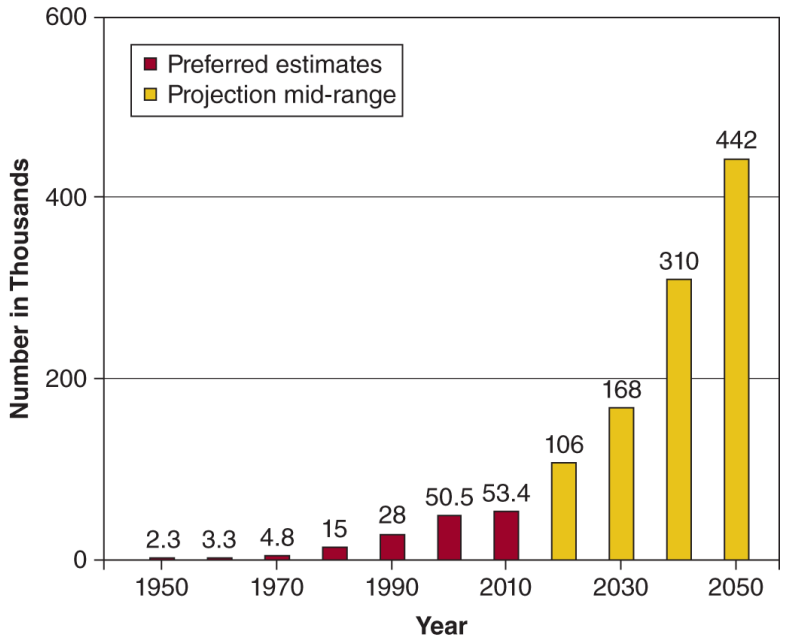


FIGURE 5-5. Number (thousands) of centenarians in the United States using preferred estimates (1950–2010) and mid-range projections (2010–2050). (Projected numbers adapted from 2012 National Population Projections: Summary Tables, US Bureau of the Census. https://www.census.gov/population/projections/data/national/2012/summarytables.html. Preferred estimates for 1950–1990 acquired from Krach, CS, Velkoff VA. "Centenarians in the United States," Current Population Reports P23-199RV (1999). https://www.census.gov/prod/99pubs/p23-199.pdf. Preferred estimated for 2000–2010 acquired from Me2010SR-03. Meyer J. "Centenarians: 2010," 2010 Census Special Reports C2010sr-03 (2012). http://www.census.gov/prod/cen2010/reports/c2010sr-03.pdf.)

Although family and twin studies suggest a strong genetic predisposition to extreme longevity and candidate genes have been described, the full mechanism is not understood. The secret is probably a lucky combination of favorable genetic background and environmental factors that exert their influence in critical periods over the lifespan. In fact, many centenarians report that they were completely independent in self-care activities of daily living and free of disabling condition up to their late nineties. In addition, a sizable proportion of centenarian "escapers" are totally independent and free of major medical conditions. Supercentenarians, individuals of 110 years or older, appeared around 200 years ago and their number is currently estimated at about 300 to 400. However, age has been validated in less than 100 of these people. In spite of many claims, only two persons have been clearly documented to have lived to 120 years.

Centenarians are becoming more and more frequent. There is probably at least one in all US towns with more than 10,000 inhabitants. Soon there will be a centenarian in each neighborhood and then in each family. The traditional wish "May you live to 100 years," which is popular in many countries, will be soon losing its traditional meaning.

Demographic Characteristics of the Aging Population

Further demographic characteristics relevant to the social environment in which older persons find themselves living are shown in **Figures 5-6** and **5-7**. In **Figure 5-6**, the elderly ratio, defined as the number of persons aged 65 and older divided by the number of persons aged 20 to 64, multiplied by 100, is shown for the total population from 1940 and projected to 2050. With the faster growth of the older population and the less rapid increase in the younger population, this ratio will rise dramatically in the future. Currently there are about 21 older people for every 100 persons aged 20 to 64. By 2050 there will be 36 older people for every 100 persons in the younger age group, the group often called on to care for older parents and grandparents and whose Social Security payments will be used to provide for retirees. Now and in the future the elderly ratio is highest in whites. Blacks currently have a higher ratio than Hispanics, but by 2050 there will be about 26 blacks, Hispanics, and persons of other races over age 64 for every 100 people aged 20 to 64 years.

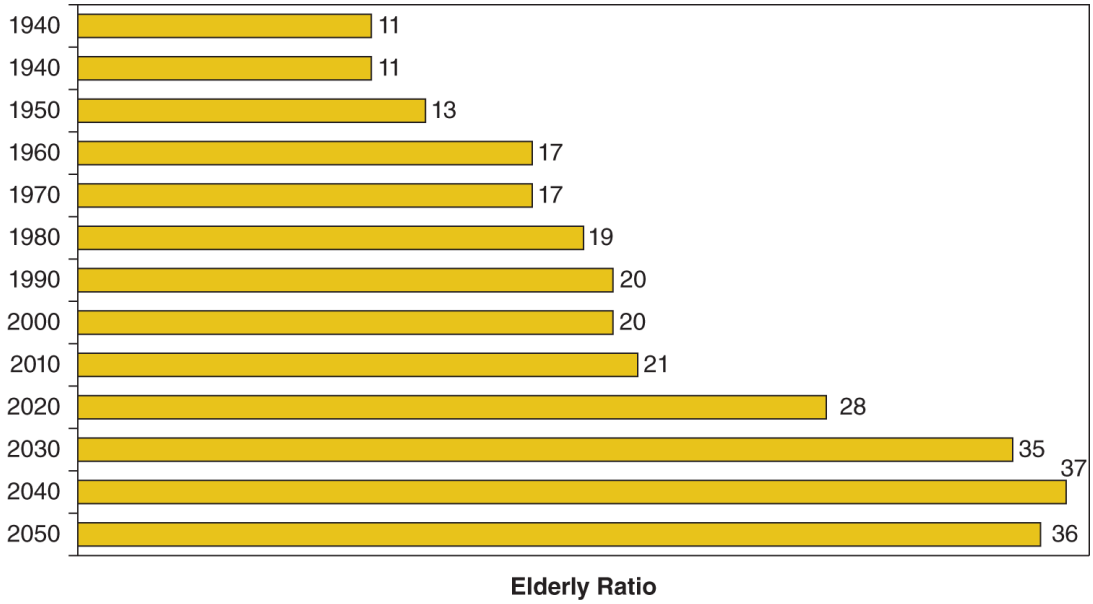


FIGURE 5-6. Elderly ratio: number of persons aged 65 years and older divided by number of persons aged 20 to 64, times 100. (Data from He W, Sungupta M, Velkoff VA, DeBarros KA. *U.S. Census Bureau, Current Population Reports, P23-209, 65+ in the United States, 2005.* Washington, DC: US Government Printing Office; 2005. Figure 5. http://www.census.gov/prod/2014pubs/p25-1140.pdf.)

Living situation is determined by health, financial factors, and widowhood and varies considerably by gender and age, as seen in **Figure 5-7**. Among community-living persons in the United States, women are much more likely to live alone, with almost 60% of women aged 85 and older living alone. A large proportion of men live with their spouses. Women are more likely to outlive their husbands not only because they live longer but also because they tend to marry older men. Modest percentages of older persons live with other relatives and a very small proportion live with nonrelatives.

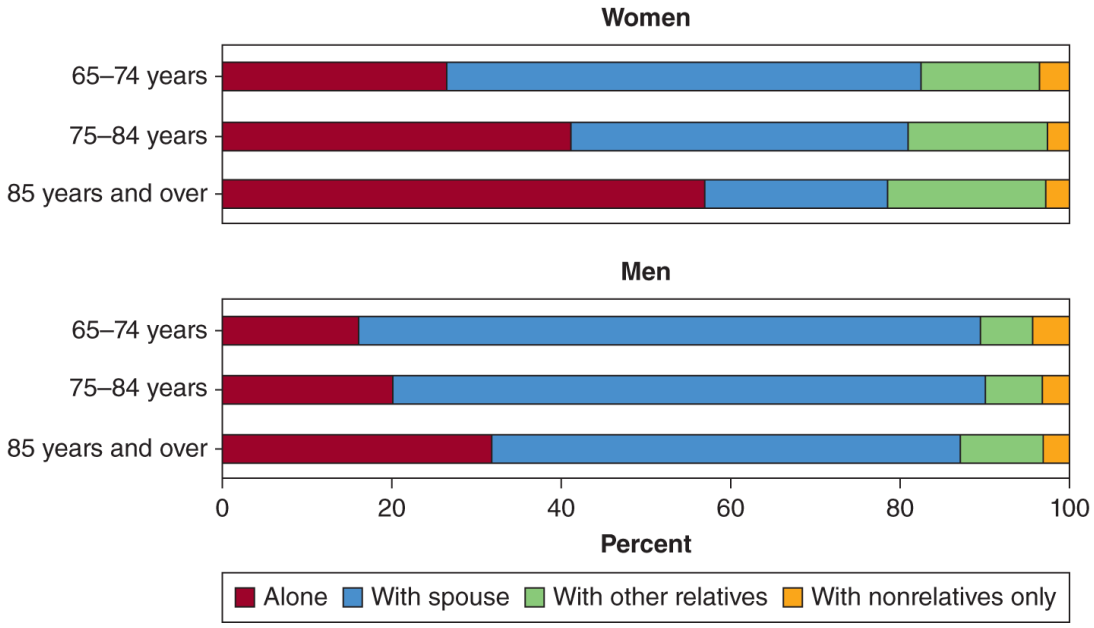


FIGURE 5-7. Living arrangements of community-dwelling persons 65 years and over, United States, 2010. (Data from West LA, Cole S, He W. *U.S. Census Bureau, Current Population Reports, Table 5-3, P131, 65+ in the United States: 2010.* Washington, DC: US Government Printing Office; 2012. http://www.census.gov/content/dam/Census/library/publications/2014/demo/p23-212.pdf.)

TABLE 5-3 LEADING CAUSES OF DEATH AMONG PERSONS 65 YEARS AND OLDER IN 2010

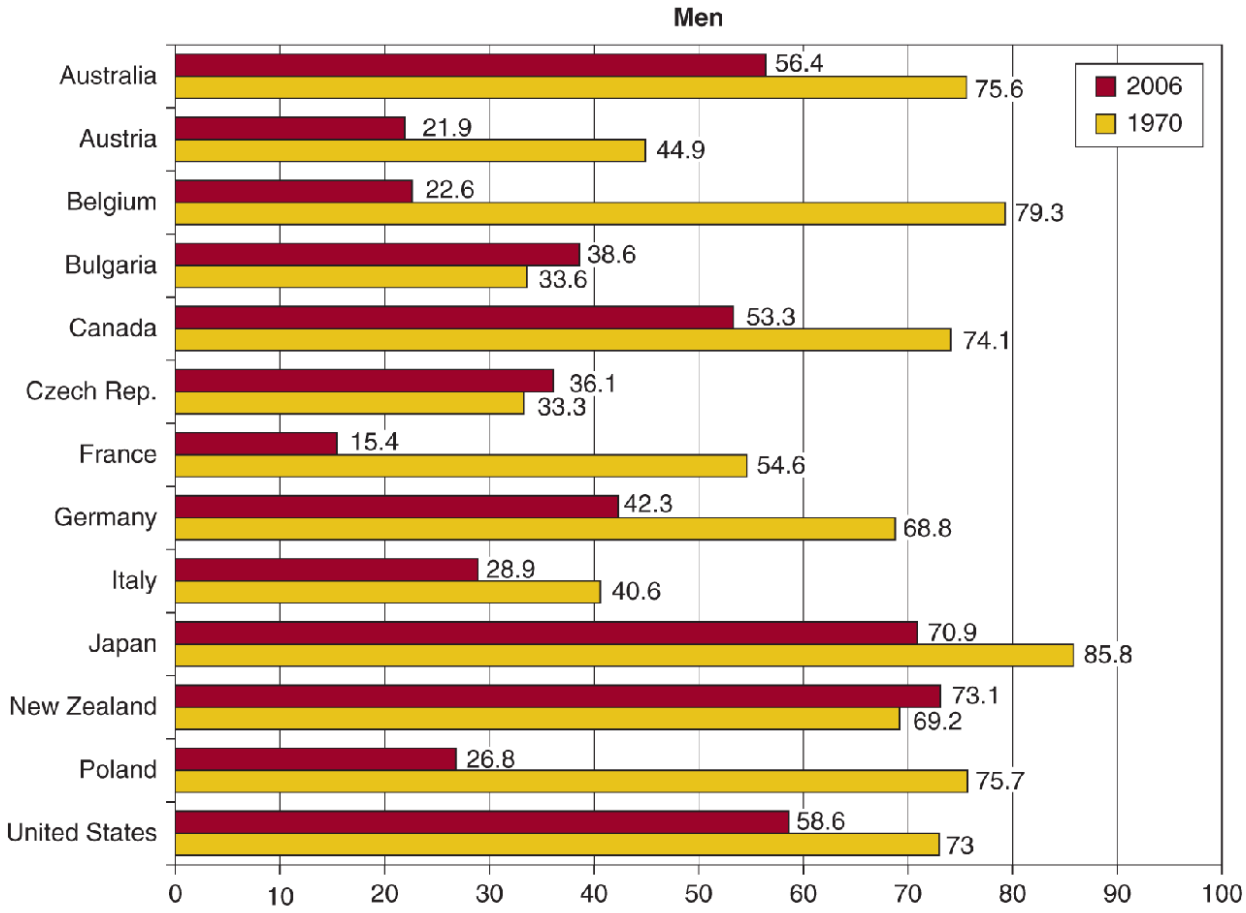
CAUSE OF DEATH	NUMBER OF DEATHS	DEATH RATE (PER 100,000 POPULATION)	% OF ALL DEATHS IN PERSONS ≥ 65 YEARS
Heart disease	477,338	1185.4	26.5
Malignant neoplasms	396,670	985.1	22.1
Chronic lower respiratory disease	118,031	293.1	6.6
Cerebrovascular disease	109,990	273.1	6.1
Alzheimer disease	82,616	205.2	4.6
Diabetes mellitus	49,191	122.2	2.7
Influenza and pneumonia	42,846	122.2	2.7
Nephritis, nephrotic syndrome, and nephrosis	41,994	104.3	2.3
Unintentional injuries	41,300	102.6	2.3
Septicemia	26,310	65.3	1.5
All other causes (residual)	411,990	1023.1	22.9
Total	**1,798,276**	**4465.8**	**100.0**

Data from Heron M. Deaths: leading causes for 2010. National Vital Statistics Reports, Vol 62, No 6. Hyattsville, MD: National Center for Health Statistics; 2013. http://www.cdc.gov/nchs/data/nvsr/nvsr62/nvsr62_06.pdf. Accessed January 15, 2015.

Employment

In recent years, the percentage of older men who work and the average age of retirement have fallen throughout the developed countries. In **Figure 5-8** the percentage of persons working is shown for the early 1970s and the mid- 2000s for the 60- to 64-year age group, the group that was traditionally preretirement. Overall, women work less than men, but in a few countries, including the United States, the percentage of women in this age group who were working rose during this time. In many countries, there have been extremely large declines in the percentage of men in this age group who work. For example, the percentage of men 60 to 64 years old who were employed declined over this 25-year period from 76% to 56% in Australia, from 79% to 23% in Belgium, from 55% to 15% in France, and from 69%

to 42% in Germany. An increase in societal wealth has been the main driving force for decreased workforce participation, but other factors include obsolescence of the skills of older workers, pressure for older workers to leave their jobs to make room for younger workers in countries with high unemployment, and the growth of financial incentives for early retirement. The percentage of men in the 65 years and older age group who work has also declined. For example, in the United States the percentage of men in this age group who work dropped from 24.8% in the early 1970s to 20.3% in the mid-2000s. The corresponding percentages for men in Germany were 16% and 5%, in France 10.7% and 1.6%, and in Japan 54.5% and 29.3%. With earlier retirement and longer life expectancy, the number of years people alive after retirement has increased greatly. The Organization for Economic Cooperation and Development (OECD) has estimated that in 1960 men in developed countries could expect to spend 46 years in the labor force and a little more than 1 year in retirement. By 1995 years in the labor force had decreased to 37, whereas years in retirement had increased to 12.



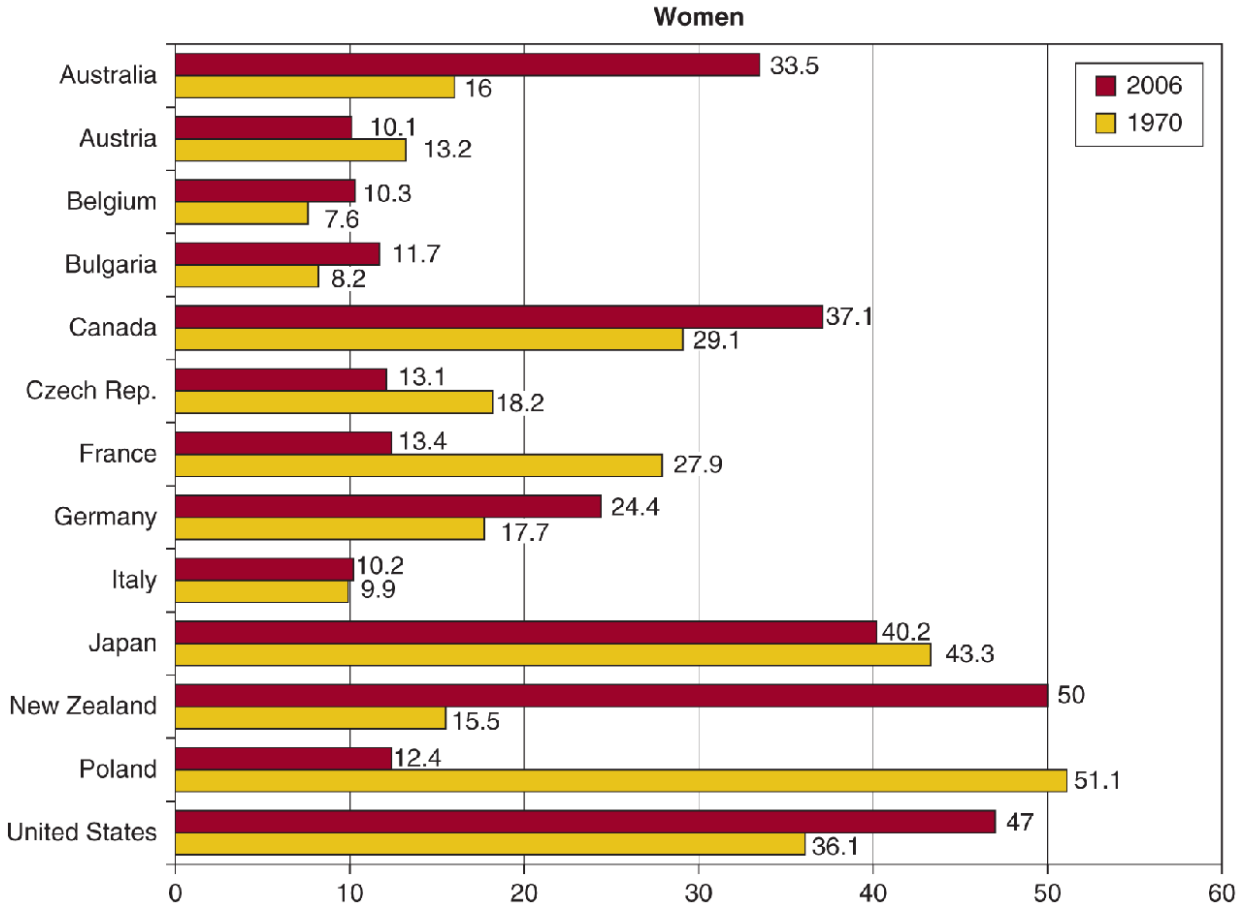


FIGURE 5-8. Labor force participation rates for men and women aged 60–64 in developed countries, early 1970s and mid- 2000s. (Data from Kinsella K, He W. *An Aging World: 2008. US Census Bureau, Series P95/09–1.* Washington, DC: US Government Printing Office;

2009. Figure 2-4. http://www.census.gov/prod/2009pubs/p95-09-1.pdf.)

MORTALITY

Leading Causes of Death

The increasingly greater life expectancy of the population has been driven in part by reduced mortality at older ages. It is instructive to review the US vital statistics data on causes of death in the older population, changes in these rates with increasing age, and trends in overall and disease-specific mortality over time. **Table 5-3** lists the leading causes of death in the population age 65 and older in 2010. It employs the ICD-10 classification system, which was first used for national data in 1999. As in younger individuals, heart disease is by far the most common cause of death, followed by cancer. The five leading causes of death—heart disease, cancer, chronic lower respiratory tract disease, stroke, and Alzheimer disease account for 65.9% of all deaths. Alzheimer disease, which in the past was rarely assigned as the underlying cause of death and was not on the list of leading causes of death, was the seventh leading cause of death in older persons in 2000 and by 2010 rose to the fifth leading cause of death, responsible for 4.6% of deaths. This is still likely a gross underestimation, and the contribution of Alzheimer disease in the future will probably grow substantially. However, assigning a single underlying cause of death is fraught with problems when an older individual dies and has multiple chronic conditions. What is surprising is that despite this difficulty the distribution of causes of death in the United States remains quite stable from year to year.

Age-specific mortality rates for selected leading causes of death are depicted in **Figure 5-9**. On this logarithmic scale a straight-line increase indicates an exponential increase in mortality rate with age. Increases are seen for heart disease, cerebrovascular disease, and pneumonia and influenza. The exponential rise with age for Alzheimer disease mortality is substantially steeper. The mortality rates for cancer and lower respiratory tract disease do not maintain as steep a rise with increasing age, perhaps because the people who contribute in large part to these categories are smokers, who die at younger ages and are less represented in the oldest segment of the population. Diabetes mortality rates also do not show an exponential increase with advancing age, again because diabetic patients may die disproportionately at younger ages. The one condition in this figure for which the mortality rate slope becomes steeper with advancing age is accidents. Although motor vehicle accidents are an issue of real concern in older persons, there are four times as many deaths from other types of accidents as from motor vehicle accidents.

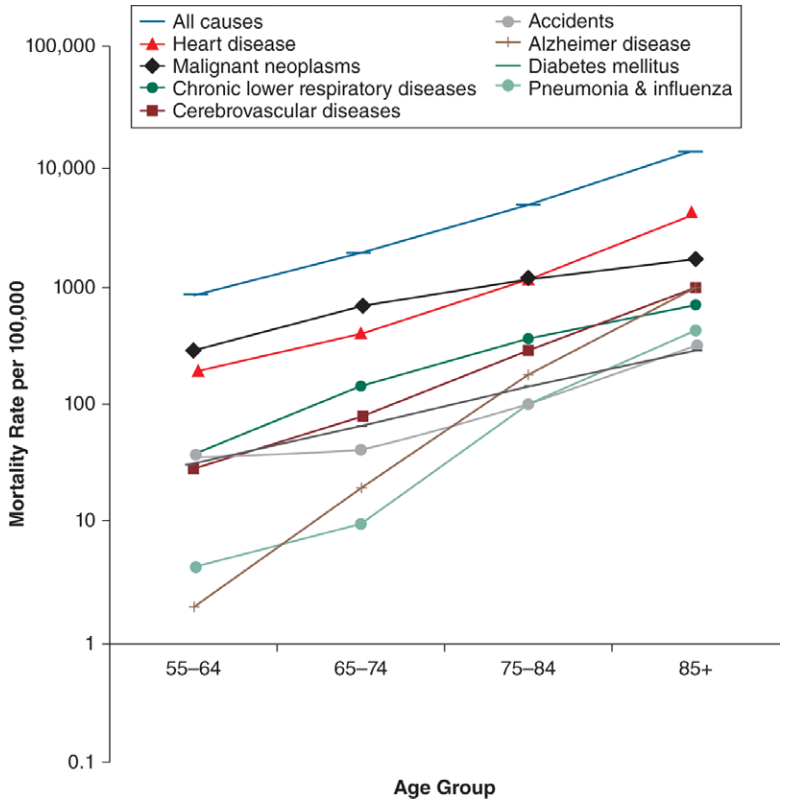


FIGURE 5-9. Age-specific death rates for leading cause of death in the older population, United States, 2010. (Data from Murphy SL, Xu J, Kochanek KD. *Deaths: Final Data for 2010. National Vital Statistics Report. Vol. 61, No. 4.* Hyattsville, MD: National Center for Health Statistics; 2014. Table 9. http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf.)

Mortality Rates

The graph of the exponential rise in mortality with increasing age, which has been described for many species, has been termed the Gompertz curve. It has been difficult to evaluate whether the exponential increase is maintained to the very end of life, as the numbers of extremely old individuals available for study have traditionally been quite small. More recently, larger populations of very old humans and other species have been evaluated to examine whether the Gompertz curve continues to describe mortality rates at advanced old age. The conclusion from these studies is that the force of mortality declines somewhat in individuals who survive to very old age, although the causes of this phenomenon remain unclear.

The first half of the twentieth century saw large declines in mortality in infants and children, but in the second half of the century there were unprecedented declines in mortality in the older segment of the population. In the total population of all ages, mortality rates between 1935 and 2010 fell by 60% (**Figure 5-10**). It is notable that this magnitude of decline was also seen in the 65- to 74- and 75- to 84-year-old age groups. Even for people 85 years and older, there was a mortality rate decline that exceeded 30%.

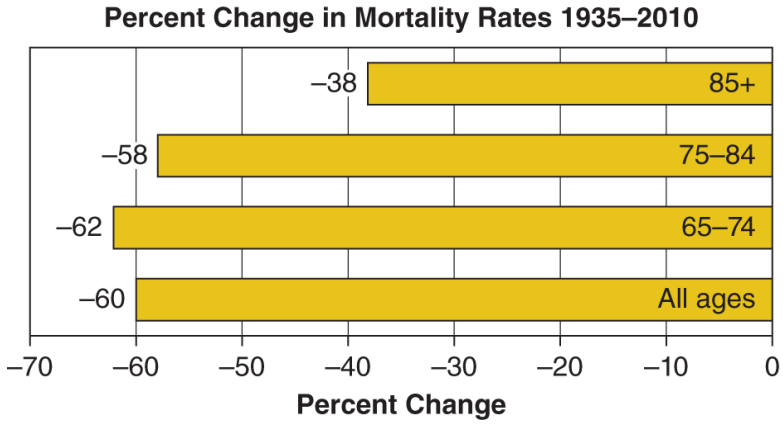


FIGURE 5-10. Percent change in mortality rates, United States, 1935–2010, for all ages (age-adjusted using year 2000 standard population) and for older age groups. (Calculated from data in National Center for Health Statistics. *Health, United States, 2013 with Special Feature on Prescription Drugs.* Hyattsville, MD: National Center for Health Statistics; 2014. http://www.cdc.gov/nchs/data/hus/hus13.pdf.)

Mortality change over this time period is further explored in **Table 5-4**, which lists 1950 and 2010 death rates and percentage changes in these rates for heart disease, stroke, and cancer, diseases that account for 60% of deaths in older adults. For the total population, heart disease mortality declined more than 60%, and stroke mortality dropped more than 70%, a truly remarkable decline in these diseases that reflects major advances both in prevention and treatment, as well as a secular trend that is not fully understood. For both these diseases, the declines in the 65- to 74- and 75- to 85-year-old age groups generally exceeded the percentage decline seen for the total population. In persons aged 85 and older, heart disease mortality declined by more than 50%, with stroke mortality dropping by more than 70% in men and more than 60% in women, impressive declines in this very old segment of the population. Unfortunately, the declines in mortality seen for heart disease and stroke were not as large for cancer. In women, there was a 19.5% decline in cancer mortality at all ages, with those 65 to 84 showing more modest declines and those 85+ having an increase. Cancer mortality rates rose in older men, with increases of 14% in men 75 to 84 years and 47% in men 85 years and older. Heavy cigarette smoking in the cohort of men who were in the older age groups at the end of the last century was probably a major contributing factor to this increase in cancer rates. **Figure 5-11** depicts change in mortality from cancers of the lung, trachea, and bronchus over the past half century. Mortality in men was much higher than in women and rose very steeply in men 75 to 84 years and 85 years and older until the early 1990s, when it leveled off and began to decline. Cancer mortality rose less steeply in men 65 to 74 years, leveled off in the late 1980s and is now showing a downturn. Mortality from cancer of the lung, trachea, and bronchus in older women rose slowly after 1960, with a slightly steeper rise in those 75 to 84 years beginning in the 1980s.

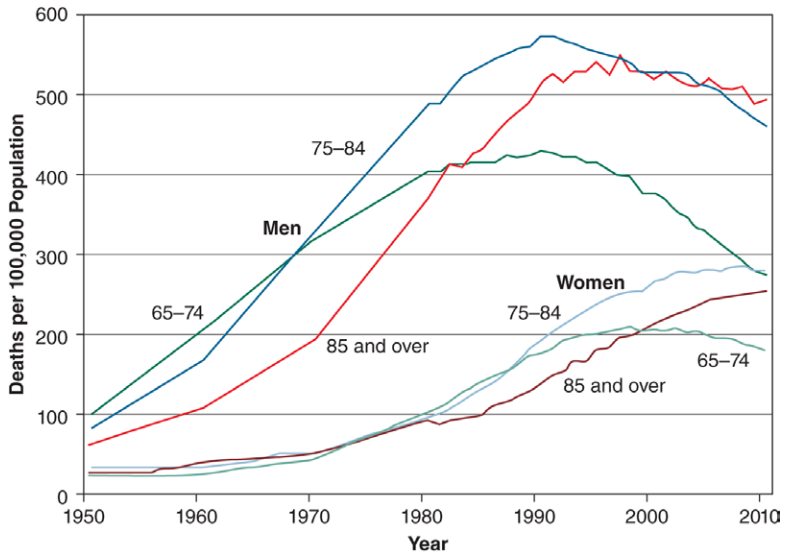


FIGURE 5-11. Mortality rate for malignant neoplasms of the trachea, bronchus, and lung by age, sex, and year: United States, 1950–2010. (Data from *Health, United States, 2013 with Special Feature on Prescription Drugs*. Table 29. Hyattsville, MD: National Center for Health Statistics; 2014. http://www.cdc.gov/nchs/data/hus/hus13.pdf#listfigures.)

TABLE 5-4 ■ AGE-ADJUSTED[a] AND AGE-SPECIFIC MORTALITY, UNITED STATES, 1950 AND 2010, AND PERCENT CHANGE

		1950	2010	CHANGE
DISEASES OF THE HEART				
Males				
	All ages	699.0	225.1	−67.8
	65–74	2310.2	553.0	−76.1
	75–84	4825.8	1475.7	−69.4
	85+	9661.4	4833.6	−50.0
Females				
	All ages	486.6	143.3	−70.6
	65–74	1434.9	284.2	−80.2
	75–84	3873.0	952.7	−75.4
	85+	8798.1	4020.3	−54.3
CEREBROVASCULAR DISEASE				
Males				
	All ages	186.4	39.3	−78.9
	65–74	589.6	92.0	84.3
	75–84	1543.6	295.2	−80.9
	85+	3048.6	892.0	−70.7
Females				
	All ages	175.8	38.3	−78.2
	65–74	522.1	72.8	−86.0
	75–84	1461.1	283.4	−80.6
	85+	2949.4	1043.0	−64.6
MALIGNANT NEOPLASMS				

Males				
	All ages	208.1	209.9	1.0
	65–74	791.5	789.2	−0.3
	75–84	1332.6	1514.2	13.6
	85+	1668.3	2452.6	47.0
Females				
	All ages	182.3	146.7	−19.5
	65–74	612.3	559.1	−8.7
	75–84	1007.7	977.0	−3.0
	85+	1299.7	1380.1	6.2

[a]Data for "all ages" is age-adjusted using the US 2000 standard population.

Data from National Center for Health Statistics. Health, United States, 2013 with Chartbook on Trends in the Health of Americans. Hyattsville, MD; 2014. http://www.cdc.gov/nchs/data/hus/hus13.pdf#044. Accessed January 15, 2015.

Mortality from AIDS has had a small but not insubstantial impact on older persons compared to the younger population. **Figure 5-12** shows trends in age groups beginning at age 45. The steep rise and then fall in AIDS mortality in the 45- to 54-years age group is reflected in similar but increasingly less pronounced patterns in each succeeding age group.

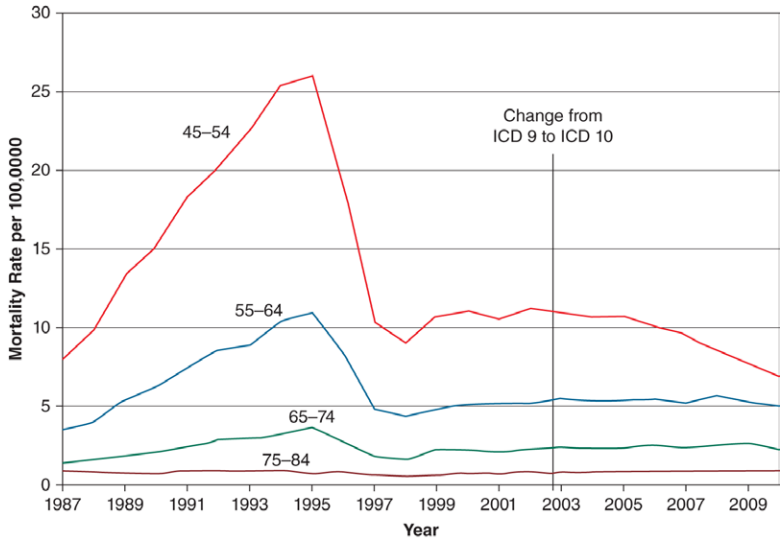


FIGURE 5-12. Mortality rate for HIV/AIDS by age and year in the United States, 1987–2010. (Data from *Health, United States, 2013 with Special Feature on Prescription Drugs.* Table 31. Hyattsville, MD: National Center for Health Statistics; 2014. http://www.cdc.gov/nchs/data/hus/hus13.pdf#listfigures.)

DISEASE STATUS

Prevalence of Common Diseases

A number of ascertainment approaches that work well to characterize morbidity in the general population are used here to give an overview of important diseases prevalent in older persons. This overview is not meant to provide a comprehensive epidemiology of all medical conditions that often develop with aging but to show data that allow for a comparison of rates across the major conditions.

Multiple sources of data can be used for epidemiologic analyses of disease status. When a medical history is obtained, a clinician begins to construct a profile of disease status from self-reporting by the patient. The resulting data, from Medicare beneficiary claims, for example, can provide insight on the disease diagnoses in older adults. In extending this approach to surveys of large, representative samples of older persons, self-reporting works quite well for

most diseases.

The most common chronic conditions among Medicare beneficiaries aged 65 and older in the United States are listed in **Table 5-5**. Hypertension is present in over half of Medicare beneficiaries, and is the most common chronic condition in adults 65 years and older. High cholesterol (hyperlipidemia) is the second most common condition, followed by ischemic heart disease and arthritis. The prevalence of these chronic conditions differed by sex. Men were 1.3 times more likely to have heart disease, but women were 1.7 times more likely to have arthritis and depression. Arthritis is diagnosed in almost 30% of older persons and, like many of the conditions on the list, has a large impact on overall health and quality of life but does not appear on the list of the most common conditions causing death.

TABLE 5-5 MOST COMMON CHRONIC CONDITIONS PER 100 MEDICARE BENEFICIARIES 65 YEARS AND OLDER IN 2012

CONDITION	MALE	FEMALE
Hypertension	54	61
Hyperlipidemia	44	46
Ischemic heart disease	36	27
Arthritis	22	35
Diabetes	29	27
Heart failure	16	16
Chronic kidney disease	16	14
Depression	10	17
Chronic obstructive pulmonary disease	12	11
Alzheimer disease	9	13
Atrial fibrillation	9	7
Cancer	9	7
Osteoporosis	0	11
Asthma	3	6
Stroke	4	4

Data from chronic conditions among Medicare beneficiaries. 2012. http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Downloads/2012Chartbook.pdf. Accessed January 15, 2015.

There are some differences in the prevalence rates of chronic conditions according to race and ethnicity. For example, data from the National Health Interview Survey indicate that in persons aged 70 years and older, diabetes is more common in non-Hispanic black and Hispanic persons than in non-Hispanic whites. Non-Hispanic blacks have 1½ times as much hypertension as non-Hispanic whites. Non-Hispanic white men report more heart disease than Hispanic whites or non-Hispanic blacks, whereas non-Hispanic black women report more stroke than non-Hispanic whites or Hispanics.

Co-Occurrence of Multiple Chronic Conditions

An important aspect of disease status that distinguishes the older population from the younger population is the high rate of the co-occurrence of multiple chronic conditions, termed comorbidity. Because the risk of developing most diseases increases progressively with age, the increased prevalence and severity of comorbidity is not surprising. However, the observed prevalence of comorbidity is higher than the prevalence expected based on the rates of individual diseases, implying a clustering of diseases in certain individuals. The concept of comorbidity is a useful one in considering the burden of disease in older people. However, the operationalization of a definition for comorbidity depends on the number of conditions being ascertained and the intensity of the diagnostic effort to identify prevalent diseases. The longer the list of conditions and the harder one works to find prevalent diseases, the greater the prevalence of comorbidity. In the United States, two thirds of Medicare beneficiaries have two or more chronic conditions. This estimate increases with age, as 63% of 65- to 74-year-olds have two or more chronic conditions, 87%

of those 75 to 84 years, and 83% of those 85 year and older. Women are also more likely to have multiple chronic conditions than men; 72% of female and 65% of male Medicare beneficiaries have two or more chronic conditions. Although comorbidity is a characteristic of older patients that is dealt with regularly by clinicians, there has been a limited amount of research on the classification of specific patterns of comorbidity and on the impact of comorbidity. In particular, certain combinations of conditions seem to occur at a higher rate than would be expected by chance alone, and certain pairs of conditions may have a synergistic effect on functional loss.

Health Care Utilization

Physician and ambulatory visits Data on the number and frequency of physician visits and hospitalizations can also provide insight into the disease status of older people. **Table 5-6** shows data on medical visits and hospitalizations in 2010 for the full age spectrum. With increasing age the number of physician visits increases steadily, and persons aged 75 years and older make over 52 visits per 100 persons per year. The proportion of each age group's visits that are for new problems and for chronic problems are shown separately, and there is a clear trend in both, with new problems decreasing steadily with increasing age and chronic problems rising with age and accounting for almost 60% of office visits in persons aged 75 and older. Data on prescription drug use is shown in **Figure 5-13**. The number of prescription drugs used increases with age. Half of adults 65 years and older use one to four drugs, and 40% of this age group uses five or more.

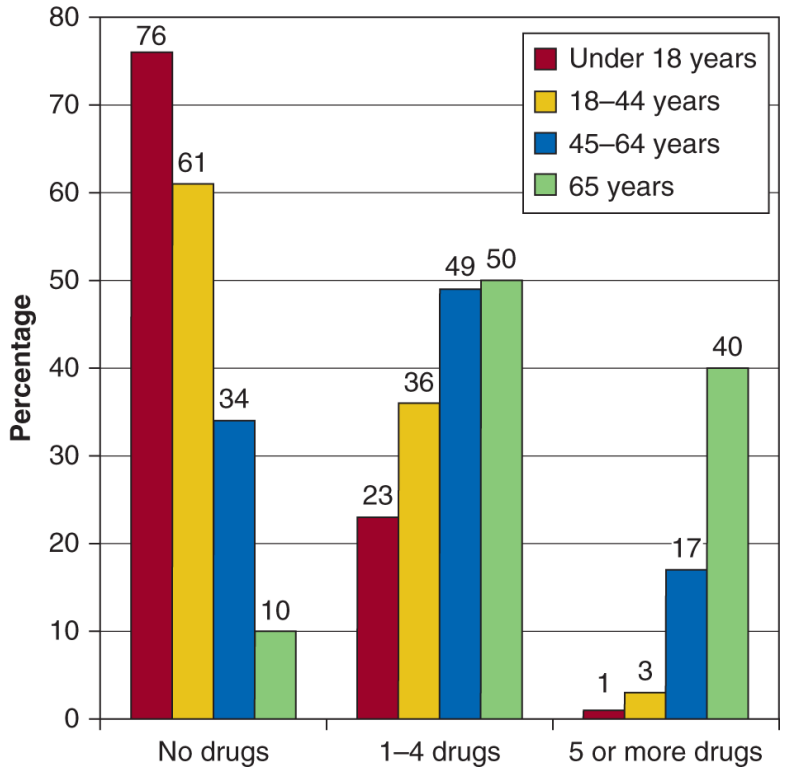


FIGURE 5-13. Prescription medication use in the past 30 days by age, United States: 2007–2010. (Data from *Health, United States, 2013 with Special Feature on Prescription Drugs.* Figure 20. Hyattsville, MD: National Center for Health Statistics; 2014. http://www.cdc.gov/nchs/data/hus/hus13.pdf#listfigures.)

TABLE 5-6 OUTPATIENT MEDICAL VISITS, REASONS FOR THE VISIT[a] AND DRUG PRESCRIPTION ACCORDING TO AGE GROUP, AND HOSPITAL DISCHARGES BY AGE GROUP, UNITED STATES, 2010

AGE GROUP	NUMBER OF VISITS PER 100 PERSONS PER YEAR[b]	PERCENT VISITS FOR NEW PROBLEMS	PERCENT VISITS FOR CHRONIC PROBLEMS (ROUTINE OR FLARE-UP)
< 15	34.1	42.5	28.4
15–24	24.9	34.9	48.3

25–44	26.6	33.5	33.9
45–64	34.7	27.7	51.1
65–74	50.4	23.4	56.5
75+	52.2	25.1	57.9

[a]Table does not account for pre- or postsurgery/injury follow-up, nonillness care, or unknown reason for visit.
[b]Per person estimates utilizing 2010 census numbers.
Data from National Hospital Ambulatory Medical Care Survey: 2010 Outpatient Department Summary Tables. http://www.cdc.gov/nchs/data/ahcd/nhamcs_outpatient/2010_opd_web_tables.pdf. Accessed January 15, 2015.

Table 5-7 demonstrates data from the National Ambulatory Medical Care Survey on the reasons for ambulatory visits to physicians' offices in 2010. This table shows that the likelihood of having a chronic condition increases with age. The three most common chronic conditions present at these visits were hypertension, hyperlipidemia, and arthritis. For almost all listed chronic conditions, the presence of these diseases at office visits increased with age, and even increased in persons 75 years and older as compared to those 65 to 74 years. The only exceptions were depression, obesity, and asthma, which were less commonly reported at office visits in those 75 years and older.

TABLE 5-7 PRESENCE OF CHRONIC CONDITIONS AT PHYSICIAN OFFICE VISITS BY AGE IN THE UNITED STATES, 2010

	PERCENTAGE OF PHYSICIAN OFFICE VISITS[a]				
	ALL AGES COMBINED	UNDER 45 YEARS	45 TO 64 YEARS	65 TO 74 YEARS	75+ YEARS
Hypertension	26.0	5.9	35.4	48.9	52.5
Hyperlipidemia	15.7	3.9	22.3	30.2	27.5
Arthritis	13.4	4.3	18.4	21.4	25.9
Diabetes	11.2	3.1	15.3	21.7	19.7
Depression	8.5	7.0	12.1	7.6	6.5
Obesity	7.1	5.9	10.7	6.8	3.2
Asthma	6.8	8.0	6.2	6.3	4.9
Cancer	6.2	1.0	7.3	12.7	15.9
Chronic obstructive pulmonary disease	3.9	1.0	4.0	8.0	10.0
Ischemic heart disease	3.5	0.2	3.4	8.1	10.6
Osteoporosis	2.4	[b]	2.5	5.6	7.0
Congestive heart failure	1.4	[b]	1.3	2.3	5.6
Chronic renal failure	1.4	[b]	1.6	2.7	4.5
Cerebrovascular disease	1.3	[b]	1.1	3.1	4.3

[a]Percentage of visits exceeds 100% because more than one chronic condition may be reported per visit.
[b]Estimate has poor reliability or precision.
Data from National Ambulatory Medical Care Survey, 2010 data. Table 14. http://www.cdc.gov/nchs/data/ahcd/namcs_summary/2010_namcs_web_tables.pdf. Accessed January 15, 2015.

Causes of hospitalization The actual causes of hospitalization in persons aged 65 and older are represented in **Table 5-8**, which uses data from the National Hospital Discharge Survey. Heart disease is the most important cause of hospitalization by far, with congestive heart failure a slightly more common cause of hospitalization than other manifestations of heart disease. Other diseases that are frequent causes of death in older adults (pneumonia, stroke, and cancer) are also common reasons for hospitalization, but so are diseases not as strongly associated with mortality, including fractures, osteoarthritis, chronic bronchitis, and psychosis. The presence of septicemia and volume depletion on this list of the leading causes of hospitalization reflects the fact that a portion of the older population is frail and at

high risk for these kinds of illnesses.

TABLE 5-8 THE 10 LEADING CAUSES OF HOSPITALIZATION IN PERSONS AGED 65 AND OLDER, FIRST LISTED DIAGNOSIS IN UNITED STATES, 2010

	DISCHARGE RATE PER 10,000 POPULATION
1. Heart disease	581.9
Acute myocardial infarction	87.4
Coronary atherosclerosis	92.1
Other ischemic heart disease	11.4
Cardiac dysrhythmias	124.4
Congestive heart failure	177.7
2. Pneumonia	153.1
3. Cerebrovascular disease	163.6
4. Malignant neoplasms	145.5
5. Fractures, all sites	144.6
Fractures, neck of femur	63.6
6. Osteoarthrosis and allied disorders	140.5
7. Septicemia	129.2
8. Urinary tract infection	103.7
9. Chronic bronchitis	98.3
10. Psychoses	51.6

Data from National Hospital Discharge Survey: 2010 annual summary with detailed diagnosis and pocedure data. National Center for Health Statistics. Vital Health Stat. 2012;13(151). http://www.cdc.gov/nchs/data/nhds/3firstlisted/2010first3_rateage.pdf. Accessed January 15, 2015.

Cancer

Cancer mortality rates do not always reflect the incidence rates of newly diagnosed cancers. The latter data are available from the Surveillance, Epidemiology, and End Results (SEER) survey of the National Cancer Institute and other cancer registries. **Figure 5-14** depicts the age-specific incidence of the most common cancers that affect men and women. The highest incidence rates in men are seen for prostate, lung, colon and rectum, and bladder cancers, and in women for breast, colon and rectum, lung, and uterine cancers. The incidence of most of these cancers rises steadily with increasing age, but several, including prostate, breast, and lung cancers, begin to drop in incidence at the oldest ages (see Chapter 96 for more details).

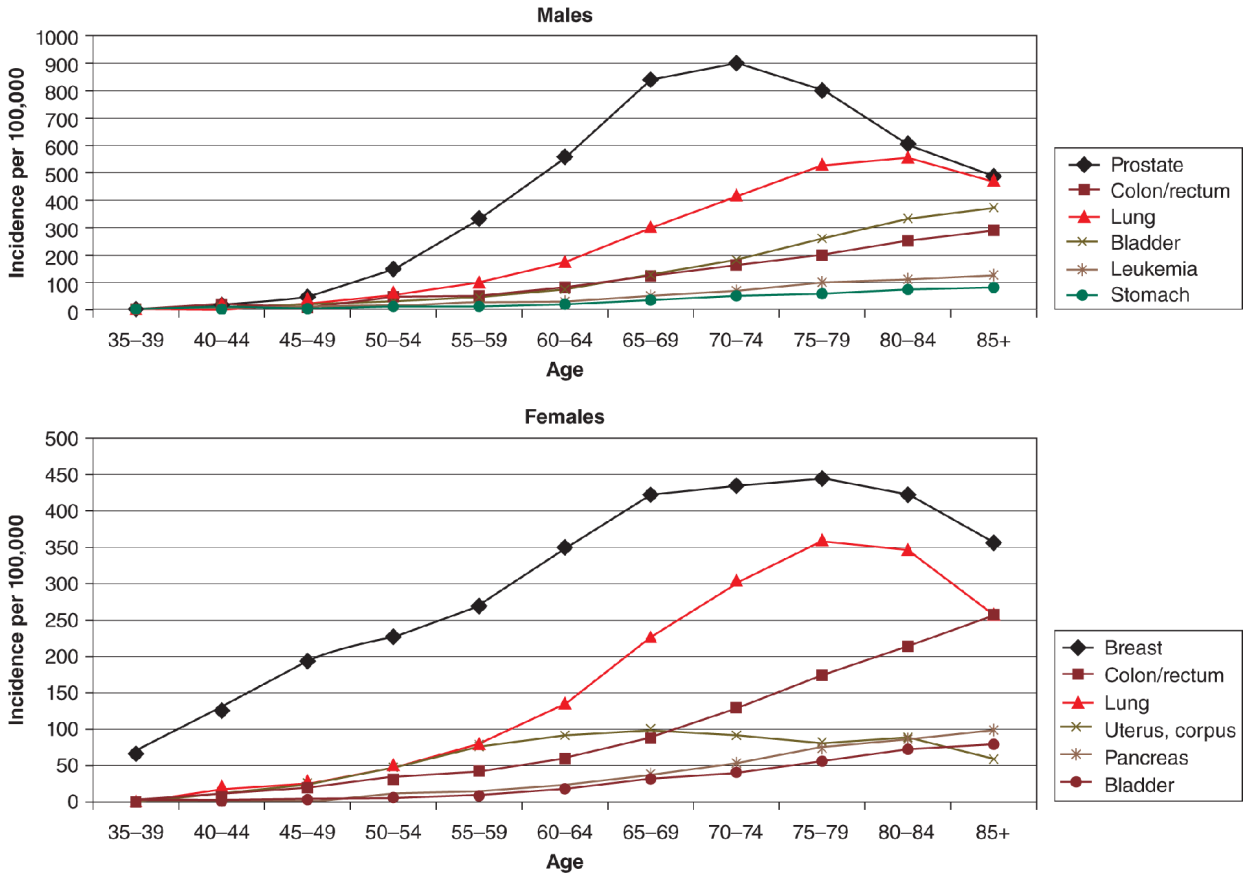


FIGURE 5-14. Incidence rates of specific cancers in men (top panel) and women (bottom panel) by age. (Data from SEER Cancer Statistics Review 1973–1998. Surveillance, Epidemiology and End Results Program, National Cancer Institute. http://seer.cancer.gov/csr/1973_1998/.)

Dementia

Dementia is a condition of aging for which prevalence and incidence rates cannot be validly obtained from either national survey data or registries. Because of the complexities of diagnosing dementia, data on the occurrence of the condition must rely on well-designed epidemiologic studies in local geographic areas. A network of dementia studies in Europe used comparable diagnostic techniques, which allowed for the aggregation of data on both prevalence and incidence (**Figure 5-15**). These pooled results show that both incidence and prevalence increase with age, with a steep rise in prevalence after age 80, when the prevalence in women becomes somewhat higher than in men. The incidence data show a clear rise in women to age 90 and older, but some leveling off in men after age 85 years. The incidence rates are about 15% to 30% of the prevalence rates. In a condition such as dementia, which cannot be cured, this relationship between incidence and prevalence indicates that mortality occurs about 3 to 5 years after diagnosis. An even larger collection of studies on dementia incidence from around the world supported an exponential increase in dementia with age and demonstrated that rates tend to be lower in East Asia than in Europe and the United States (see Chapter 66 for more details).

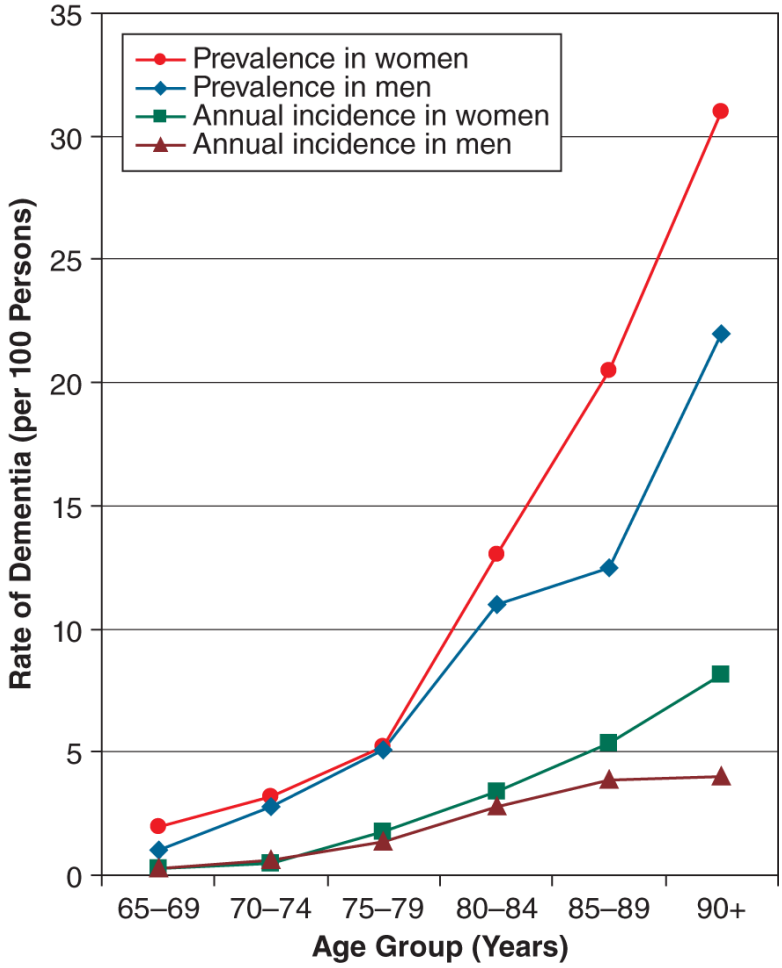


FIGURE 5-15. Age- and gender-specific prevalence and annual incidence of dementia in persons aged 65 and older. Data from pooled analyses of 11 studies carried out in 8 European countries (prevalence) and in 8 studies in 7 countries (incidence). (Adapted with permission from Lobo A, Launer LJ, Fratiglioni L, et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. *Neurology.* 2000;54[suppl 5]:S4; Fratiglioni L, Launer LJ, Lobo A, et al. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. *Neurology.* 2000;54[suppl 5]:S10.)

Sensory Impairments

Sensory impairments, including impaired vision, impaired hearing, loss of feeling in the feet, and impaired postural balance, are common among older adults. In the National Health and Nutrition Examination Survey among adults 70 years and older, over 75% have a postural balance impairment, 27% have loss of feeling in the feet, 26% have a hearing impairment, and 15% have a vision impairment (**Figure 5-16**). The prevalence of these impairments increases with age. In adults 70 to 79 years, 69% have balance impairment, 24% have loss of feeling in the feet, 17% have a hearing impairment, and 11% have vision impairment. These estimates increase to 89%, 34%, 45%, and 25%, respectively, among those 80 years and older. While some sensory loss is irreversible, an estimated 57% of older adults with vision impairment could benefit from proper lens correction, and using a hearing aid may help up to 72% of those with a hearing impairment. Sensory impairments in older adults have significant impacts on morbidity, quality of life, the ability to live independently, and functional limitations. Therefore efforts aimed at minimizing sensory impairments are particularly important to the health of older adults.

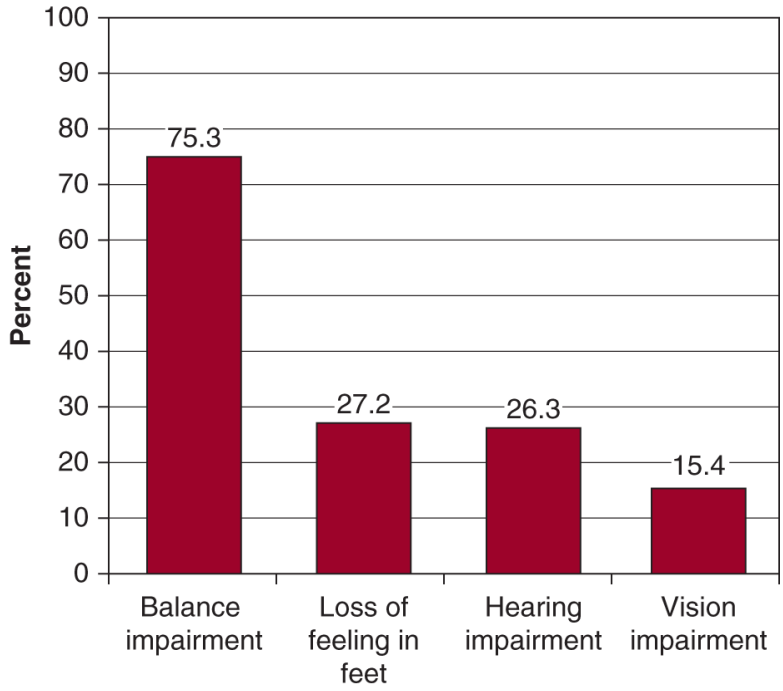


FIGURE 5-16. Prevalence of sensory impairments among adults 70 years and older, United States, 1999–2006. (Data from Dillion CF, Gu Q, Hoffman HJ, Ko CW. *Vision, Hearing, Balance, and Sensory Impairment in Americans Aged 70 Years and Over: United States, 1999–2006.* NCHS Data Brief. No 31. April 2010. Figure 1. http://www.cdc.gov/nchs/data/databriefs/db31.pdf.)

DISABILITY

A hallmark of geriatrics is emphasis on the functional ability of older patients. This subject is discussed from a clinical point of view in several chapters in this book. This approach recognizes that although individual diseases are important and that our system of modern medicine is oriented toward the diagnosis and treatment of specific diseases, the consequences of single and multiple diseases can be understood best by evaluating the functional status of the patient. A large body of epidemiologic work undertaken over the past two decades has treated disability as a condition that can be studied in much the same way as if it were a well-defined chronic disease by using epidemiologic tools to assess prevalence, incidence, and a wide range of risk factors. This work has led to a greater understanding of the occurrence, determinants, and consequences of disability in the older population and has provided insights into strategies for the prevention of disability.

Measures of Function and Disability

Measures of disability were originally developed for use in the clinical setting and were aimed at quantifying the impact of severe medical conditions such as stroke on physical and mental functioning, obtaining standard information on the rate and degree of recovery from these conditions, and assessing work ability and the need for formal and informal care. These assessment tools were gradually applied in clinical research and population-based studies, and almost all research studies in older populations now assess disability status. Federal data collection efforts did not include very old populations as recently as 30 years ago, but these surveys now have no upper age limit and include various instruments to assess disability. This type of assessment is illustrated in **Figure 5-17**, which is based on data from the Medicare Current Beneficiary Survey. Activities of daily living (ADLs) are basic self-care tasks. Instrumental ADL (IADLs) are tasks that are physically and cognitively somewhat more complicated and difficult than self-care tasks and are necessary for independent living in the community. ADLs and IADLs are measures of disability and reflect how an individual's limitations interact with the demands of the environment. With increasing age the prevalence of ADL disability increases rapidly, and the proportion of persons with no limitations decreases to under 30% in persons 85 years and older. Additionally, the prevalence of disability is higher in women compared to men of the same age.

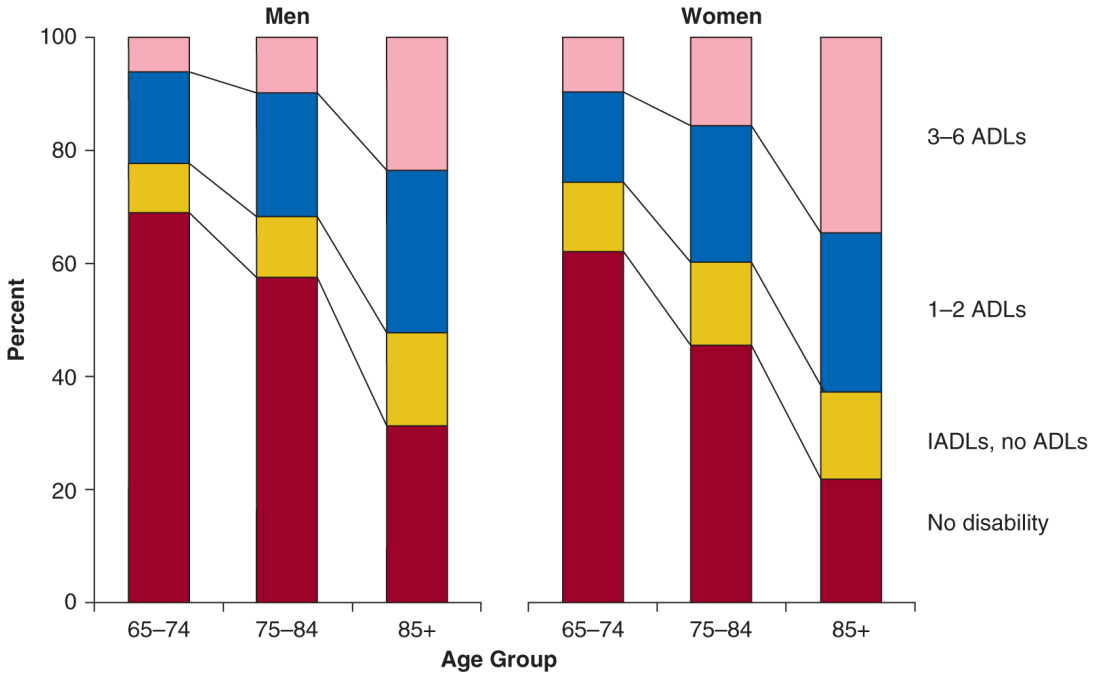


FIGURE 5-17. Physical limitations and disability according to age and sex, United States, 2004. Instrumental activities of daily living (IADLs) are defined as any difficulty doing one or more of the following: using the telephone, doing light housework, doing heavy housework, preparing meals, shopping, and managing money. Activities of daily living (ADLs) are defined as any difficulty doing one or more of the following: bathing or showering, dressing, eating, getting in or out of bed or chair, walking across a room, and using the toilet. (Data from Functional limitations of Medicare beneficiaries by age, residence, sex, race and ethnicity from the Medicare Current Beneficiary Survey, 2011. Murgolog M. The Characteristics and Perceptions of the Medicare Population. Centers for Medicare and Medicaid Services. Table 2.1. http://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/Data-Tables-.)

Disability has been assessed with a wide variety of instruments, and even when instruments contain the same items, they may differ in how they assess specific aspects of performing the task or the severity of limitation in performing the task. For example, it is debatable whether it is better to ask people whether they actually perform a specific task or whether they should be asked to judge whether they could perform the task even if they have not done it for long time. The former approach gives more concrete information, but respondents could be classified as disabled simply because they have chosen not to do a task that they are perfectly capable of performing. The latter approach allows for classification of people regardless of whether or not they have actually done the task recently but is limited because respondents who have not done the task are required to speculate as to their ability. For this and other issues in disability assessment, there is no single best way to perform an assessment, and there is therefore no single instrument that is ideal. The lack of standardization that results from the use of multiple competing instruments makes it difficult to compare rates of disability across studies, as differences in prevalence rates result from different methods of assessment. Disability classified as having any difficulty performing a task has a higher prevalence than disability classified as requiring human assistance or being unable to perform. Disability classified as requiring human help or help from an assistive device has a higher prevalence rate than disability requiring human help only and is similar in prevalence to the classification using difficulty. In one study of individual ADL, the assessments that relied on difficulty produced estimates of disability 1.2 to 5.0 times greater than assessments that used human assistance as the criterion for disability. Thus, in evaluating research that reports on disability rates, it is critical to examine the way questions are asked and how responses are used to determine the presence of disability.

Disability as an Indicator of Health Status and Prognosis

Disability status is one of the most potent of all health status indicators in predicting adverse outcomes. This is probably because disability measures are able to capture the impact of the presence and severity of multiple pathologies, including physical, cognitive, and psychological conditions, as well as the potential synergistic effects of these conditions on overall health status. The hierarchy of disability statuses are defined as independent in ADL, independent but reporting some difficulty with ADL, and dependent on personal assistance for ADL. For these three groups, the cumulative probabilities over a 4-year follow-up period of being admitted to a nursing home and mortality are greater for individuals classified as dependent and least for individuals who are independent. These results support

the discussion in the previous paragraph that different disability criteria can identify population subgroups with different prognoses. They also support the validity of disability measurement, with level of disability being highly predictive of two important outcomes.

Prevalence of Disability

The higher prevalence rate of disability in women shown in **Figure 5-18** has been repeatedly demonstrated and is consistent across a variety of measures and in studies using both self-reporting and objective assessments. Indeed, the fact that women live longer than men in spite of their worse health and higher rate of disability at all ages is one of the most interesting paradoxes in the epidemiology of aging. Another valuable measure of disability that has received increasing attention is mobility disability and is usually evaluated using questions related to walking and climbing stairs. **Figure 5-18A** shows that mobility disability, defined as the inability to walk 1/2 mi or climb stairs, increases with age and has a higher prevalence in women than in men at all ages after 65 years. The dynamics of this difference in prevalence are highly instructive. Prevalence is a snapshot at a single point in time and is a function of the flow into and out of the condition being assessed. In the case of mobility disability, women have a higher incidence (new occurrence) of disability (**Figure 5-18B**) and are less likely to exit from the disabled state than men because they have lower mortality than men when they are disabled (**Figure 5-18C**) and because they are less likely to recover from disability than men (**Figure 5-18D**). Thus, the prevention of disability and better treatment of women who have become disabled are likely to have a beneficial effect in lowering the disability rates of women to the level of those of men. Reduction in mortality in disabled men would also contribute to reducing gender differences in disability prevalence.

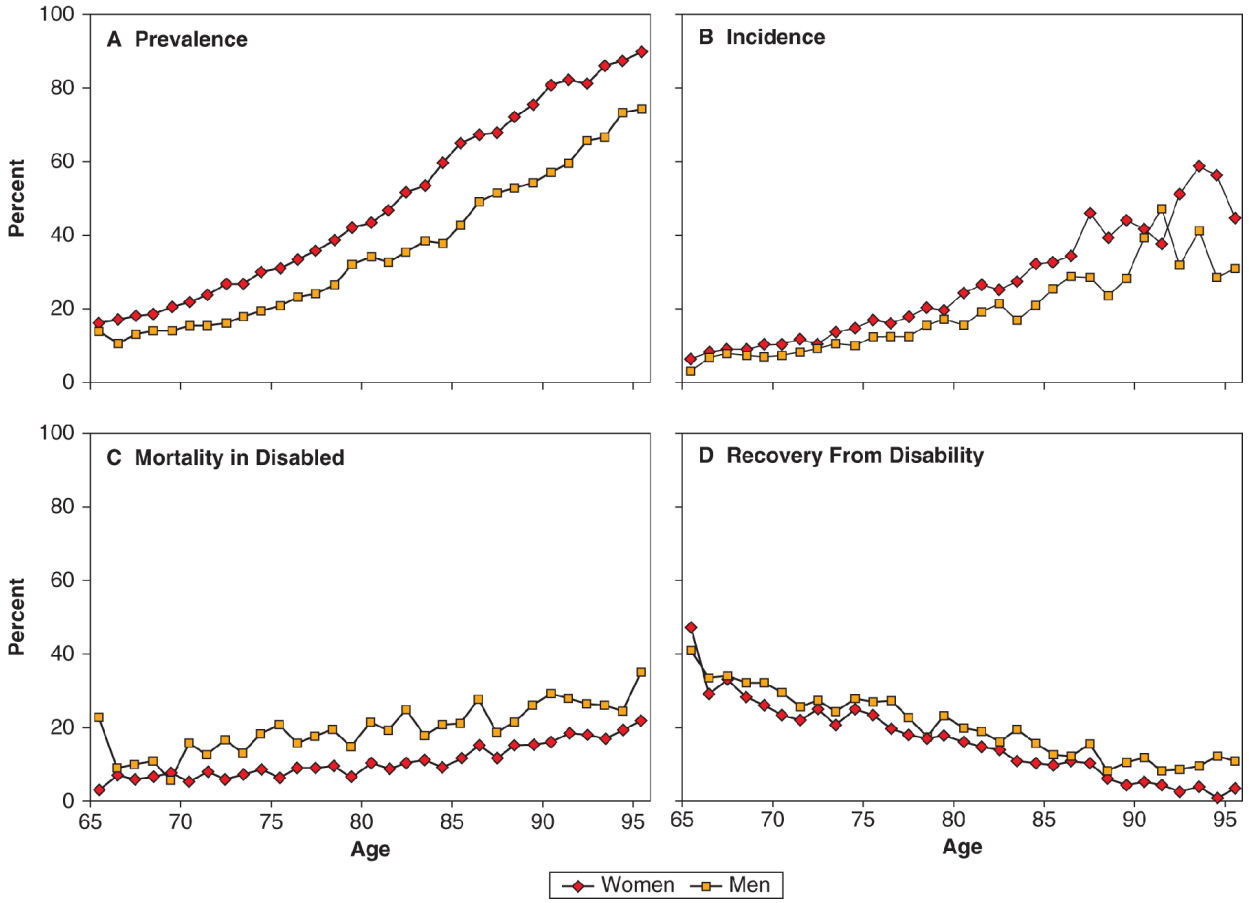


FIGURE 5-18. Women's and men's prevalence of mobility disability (**A**), 1-year incidence among nondisabled persons (**B**), and 1-year mortality (**C**) and recovery (**D**) among disabled persons, by age. Established populations for the epidemiologic study of older persons. (Reprinted with permission from Leveille SG, Penninx BW, Melzer D, Izmirlian G, Guralnik JM. Sex differences in the prevalence of mobility disability in old age: the dynamics of incidence, recovery, and mortality. *J Gerontol Soc Sci.* 2000;55:S41.)

Risk Factors for Disability

In addition to gender, there is a wide array of risk factors for disability in older populations. The relative risk of disability for many risk factors is consistent across different disability definitions, providing strong support for the importance of these risk factors. The most commonly and consistently reported risk factors for disability are listed in **Table 5-9**, which comes from a review of 78 community-based longitudinal studies that assessed factors related to decline in functional status in older persons. Risk factors are divided into two sections: behavioral factors and individual characteristics, and specific chronic conditions. There is a great deal of interdependence between these risk factors. Behavioral risk factors such as physical inactivity and smoking can promote the development of a variety of diseases, which can then go on to cause disability. These behavioral risk factors may also have direct effects of their own. For example, physical inactivity may be a risk factor for the onset of specific diseases, and it also may have a direct negative impact on muscle, bone, and the central and peripheral nervous systems. These changes can move an individual closer to the physiologic and functional threshold beyond which functioning is impaired to the point that disability occurs. **Figure 5-19** shows the relative contributions of specific conditions to disability according to age group. These data were obtained by asking persons who reported a limitation in their activities (work limitation or need for assistance in ADLs or IADLs) to specify the health condition that was responsible for that limitation. Arthritis and heart or other circulatory diseases make by far the largest contributions to physical limitations, but it is notable that sensory limitations are also reported to make large contributions. Dementia is reported by proxies to be a substantial contributor to activity limitations in those age 85 and older.

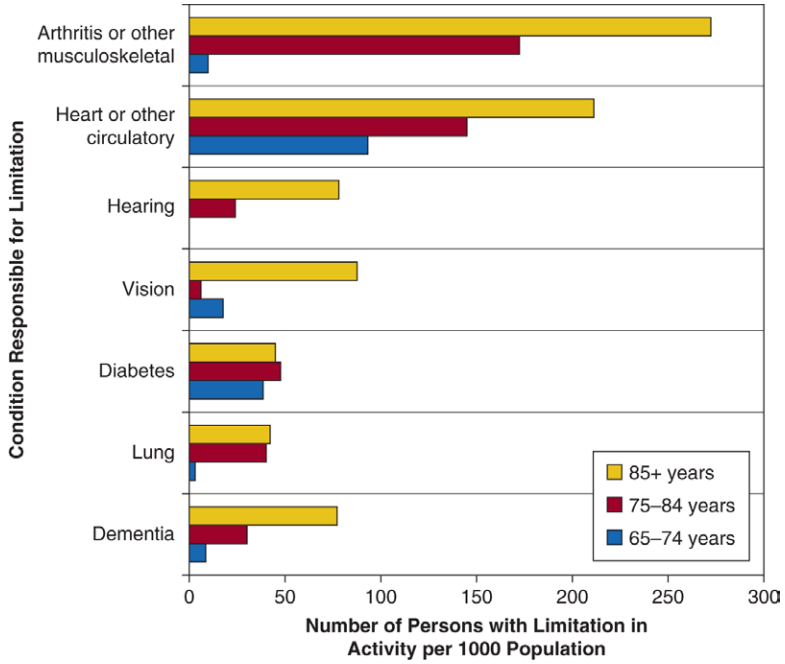


FIGURE 5-19. Reported chronic conditions responsible for self-reported activity limitation by age group: NHIS, 2005–2006. Activity limitation defined as work limitations or need for assistance with ADLs (eating, bathing, dressing, and getting around inside the home) or IADLs (household chores, doing necessary business, and shopping or running errands). If any limitations are identified, the respondent is asked to specify the health condition(s) causing the limitation(s) and indicate how long he or she has had each specified condition. (Data from US Census Bureau 2004. *Health, United States, 2008 with Special Feature on the Health of Young Adults.* Hyattsville, MD: National Center for Health Statistics; 2009. Figure 13. http://www.cdc.gov/nchs/data/hus/hus08.pdf.)

TABLE 5-9 ■ RISK FACTORS FOR FUNCTIONAL STATUS DECLINE

Behavioral Risk Factors and Individual Characteristics
Low physical activity
Smoking
High and low body mass index, weight loss
Heavy and no alcohol consumption
Increased age
Lower socioeconomic status (income, education)

High medication use
Poor self-rated health
Reduced social contacts
Chronic Conditions
Cardiovascular disease
Hypertension
Coronary heart disease
Myocardial infarction
Angina pectoris
Congestive heart failure
Stroke
Intermittent claudication
Osteoarthritis
Hip fracture
Diabetes
Chronic obstructive pulmonary disease
Cancer
Visual impairment
Depression
Cognitive impairment
Comorbidity

Data from Stuck AE, Walthert JM, Nikolaus T, Büla CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. Soc Sci Med. 1999;48:445–469.

The role that cognitive impairment plays in physical disability has been generally underappreciated. For clinicians attending to severely disabled persons in nursing homes, however, it is evident that dementia itself prevents these individuals from being independent. **Figure 5-20**, based on data from population-based studies in Tuscany, Italy, shows estimates of the numbers of men and women with ADL disability in 1999 according to age. It also separates these people into those with and without dementia. There is an overall increase in the number of disabled persons through the mid-eighties in men and through the late eighties in women, with a drop-off in the numbers after that because of the decline in the total number of persons in the population at these advanced ages. The obvious gap in these otherwise smooth curves is a result of the low birthrate during and just after World War I, which translated into a smaller population 80 years later. In both men and women, most ADL disability before age 75 is not associated with dementia. From age 75 to 90 about half of ADL disability is accompanied by dementia, and after age 90 the majority of persons with ADL disability have dementia. These data do not prove that dementia is what caused the disability in these individuals. Serious physical impairments and diseases co-occur with dementia, and it may not be possible to always understand just what the cause of disability is. Nevertheless, it is impressive that such a large proportion of disabled persons have dementia, and it is clear that cognitive functioning must be considered when developing interventions to prevent or treat disability.

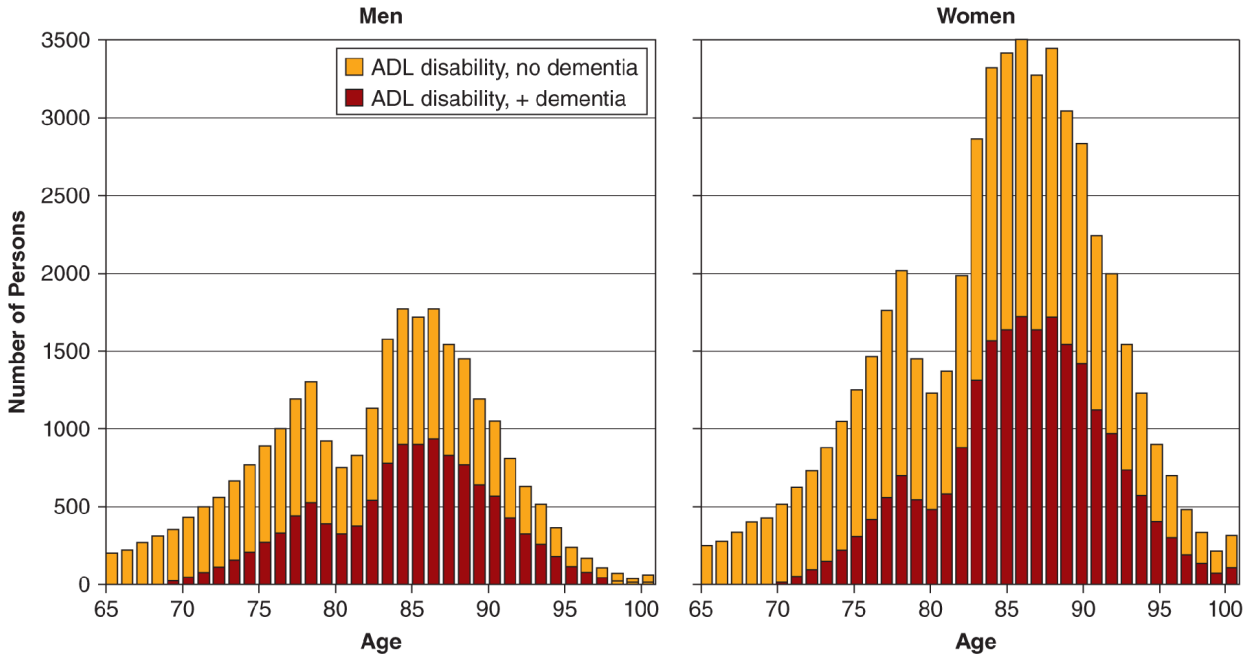


FIGURE 5-20. Estimated number of men and women with activities of daily living (ADLs) disability (need for help of another person) with and without an additional diagnosis of dementia according to age, Tuscany, Italy, 1999. (The figure was obtained by applying estimates from three large population-based epidemiologic studies in the Tuscany population, the Italian Longitudinal Study on Aging, JCARE Dicomano, and InCHIANTI. The original analyses and population estimates are from Istituto Nazionale di Statistica: National Statistical Institute of Italy, 1999, www.istat.it.)

Recovery From Disability

Longitudinal epidemiologic studies have revealed much about the dynamics of disability onset and progression. Contrary to previous belief, a substantial proportion of individuals who are disabled report improvement on subsequent assessments. In effect, disability is a product of the disease or diseases from which an individual suffers, sedentary lifestyle or disuse, and physiologic declines that may be the result of aging or pathologic processes that are not specific diseases but result from factors such as inflammation or endocrine changes. As these predisposing conditions change, they have an impact on the initiation of disability and on changes in the status of already established disability. Among community-dwelling persons age 70, recovery rates were high and long-term recovery was quite common among those with any disability. Recovery rates were also high in persons who had disability reported for 2 or more consecutive months (persistent disability) and 3 or more consecutive months (chronic disability). Other studies have observed high rates of improvement in disability status over intervals, ranging from 1 to 3 years despite missing transient improvement due to long time intervals between assessments. Observed improvement in function could result from inaccurate self-reporting of disability over time (unreliability of instrument), a true change in disability status, or both. In fact, both these explanations play a role, but a certain amount of real improvement in disability is consistently found. Age less than 85, good cognitive function, remaining physically mobile, absence of depression, and good social support have all been associated with a greater probability of recovery.

Types of Disability Progression

In understanding the dynamics of disability progression it is useful to consider the pace at which disability develops. The terms “progressive disability” and “catastrophic disability” have been used, indicating a slow downhill course or a very rapid decline, respectively. Progressive disability results from one or more ongoing chronic conditions and causes disability over months or years, whereas catastrophic disability can occur in moments as a result of a stroke or a hip fracture. The prevalence of both progressive and catastrophic severe ADL disability (defined as needing help with three or more ADLs) increases with increasing age, although progressive disability rises faster than catastrophic disability. Among older persons with severe ADL disability, the proportion that has catastrophic ADL disability is much higher at younger ages, and the proportion that has progressive ADL disability is much higher at the oldest ages (**Figure 5-21**). A similar age pattern has been found for onset of severe mobility disability (inability to walk across a room), which is much more common in people who have three or more chronic conditions.

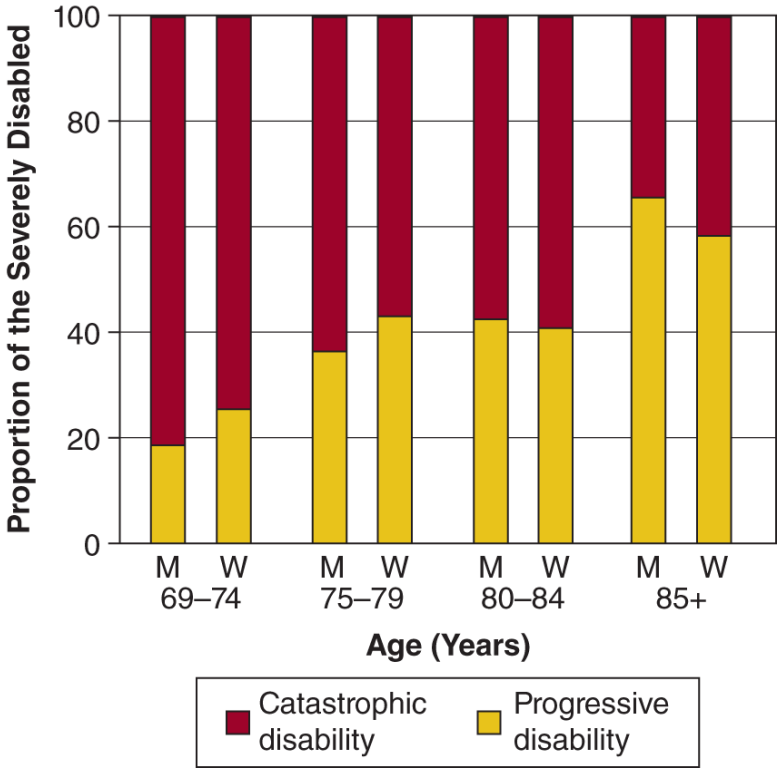


FIGURE 5-21 Proportion of population needing help with three or more activities of daily living (ADLs) who have catastrophic disability (no ADL disability in preceding year) and progressive disability (need for help with one or two ADLs in previous year), by age and gender. (Reprinted with permission from Ferrucci L, Guralnik JM, Simonsick E, Salive ME, Corti C, Langlois J. Progressive versus catastrophic disability: a longitudinal view of the disablement process. *J Gerontol Med Sci.* 1996;51:M123.)

The dynamics of disability can also be approached by studying the pathologic changes that precede its onset. Most disability results from disease, and different theoretical pathways have been proposed to describe the changes that occur as a person proceeds from disease to disability. The theoretical pathway that has received substantial empirical support in aging research is that proposed by Nagi and endorsed by the Institute of Medicine. In this pathway, two intermediate steps, impairment and functional limitation, follow disease and lead to disability (see Verbrugge and Jette, 1994). Impairment describes the dysfunction and structural abnormalities in specific body systems that result from pathology. Functional limitation describes restrictions in basic physical and mental actions that result from impairments. Functional limitations are the basic building blocks of functioning, and the interaction of these components of functioning with environmental demands faced by an individual determines whether that person is disabled (see Guralnik and Ferrucci, 2003). Conventional study of the consequences of disease describes the physiologic organ impairments that result from specific conditions. More recent work in aging has gone on to describe further steps in the pathway. Impairments such as poor balance, muscle weakness, and visual deficits have a clear impact on functional limitations and disability. Furthermore, the relationship between functional limitations, such as reduced gait speed, and subsequent disability also supports the pathway.

Physical Performance Measures

Objective measures of physical performance have received increasing attention as assessments that can measure functioning in a standardized manner in both the research and clinical settings. These measures can be used to represent impairments, functional limitations, or actual disability, but most are indicators of functional limitations. A short, standardized battery of performance tests was administered to a large number of participants in the Established Populations for the Epidemiologic Study of the Elderly (EPESE). This battery, which included gait speed, time required to rise from a chair and sit down five times, and hierarchic measures of balance, was used to create a summary score of lower extremity performance that ranges from 0 to 12. This measure, the short physical performance battery (SPPB), predicts mortality, the need for nursing home admission, and health care utilization in the overall older population. Furthermore, in a population that had no disability at the time the SPPB was administered, the score was highly predictive of who developed ADL and mobility disability 1 and 4 years later. These findings indicate that there is a state of preclinical disability, expressed as impairments and functional limitations, that indicates a high risk of

proceeding to full-blown disability. This approach could identify high-risk older persons for whom preventive interventions may be highly effective.

Objective performance measures also provide a means of comparing functional status over time or across countries or cultures, where disability measures may lose comparability because of environmental differences or differential access to assistive devices. **Figure 5-22** shows results from the English Longitudinal Study on Aging, a nationally representative sample of older persons in England. It demonstrates the prevalence according to age and sex of poor physical performance, documented as an SPPB score of less than or equal to 8 and gait speed of less than 0.5 m/s. Performance below these cut points is strongly associated with multiple adverse outcomes. Poor performance affects only about 10% of persons in their 60s but the prevalence rises rapidly in the 70s and attains very high levels in persons above 80. Women have higher rates of poor performance than men at all ages.

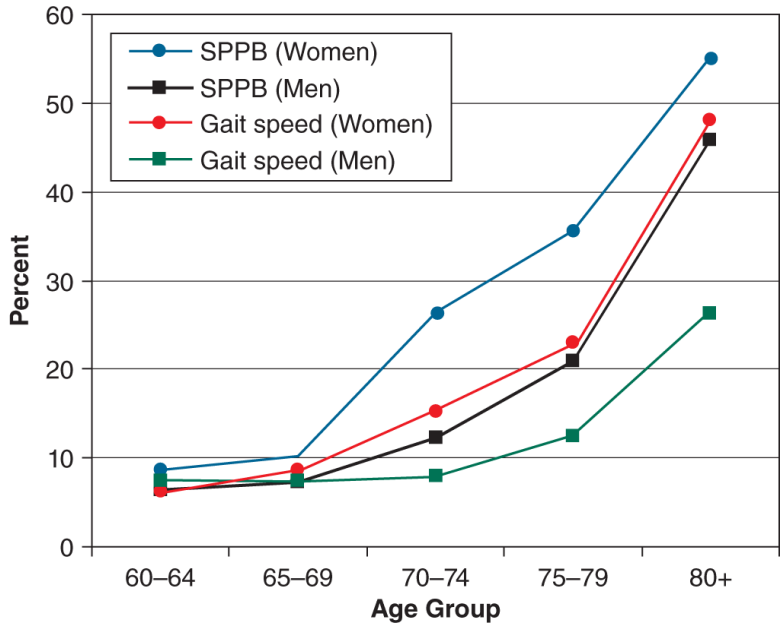


FIGURE 5-22. Percent of men and women with short physical performance battery score ≤ 8 and gait speed ≤ 0.5 m/s: England, 2002–2003. (Data from Institute for Fiscal Studies. Retirement, health and relationships of the older population in England. The 2004 English Longitudinal Study of Aging [Wave 2]. Tunbridge Well: Petersons; 2006. http://www.ifs.org.uk/elsa/report06/elsa_w2.pdf.)

Trends in Disability

Because disability status is a good way of representing overall health status in older persons with complex patterns of disease, and because disability also has direct implications for the long-term care needs of an older person, there has been much interest in evaluating disability trends over time. Although a number of national surveys now assess disability, uniform disability assessment done over time has been available only since the mid-1980s in just a few studies with nationally representative samples. Although these studies use different assessment instruments, a decline in age- and gender-specific rates of disability was observed from the mid-1980s through the 1990s. The National Long Term Care Survey has similar assessments of ADL and IADL disability available from 1982 to 2005, and indicates that the decline in disability observed for the first 12 years of the study continued and actually accelerated from 1994 to 2005 (see Manton et al., 2006). In another study that utilized reports of functional limitations, including lifting and carrying 10 lb, climbing stairs, walking 1/4 mi, and seeing words in a newspaper, changes in prevalence were evaluated between 1984 and 1993. Declines were seen in the ability to perform all four of these tasks in the 65 years and older population over this period as well as the 80 years and older population. The functional limitations evaluated in this study, which assess more basic tasks than disability, are an excellent way to follow trends over time because they are influenced less by changing roles that can affect disability assessment (more men cooking in more recent surveys and more women managing money).

However, there is mounting evidence that the decline in disability prevalence among older adults is reversing. Analyses comparing two periods of NHANES data (1988–1994 vs 1999–2004) indicate that the prevalence of ADL, IALD, and mobility disability increased among those 60 to 69 years (see Seeman et al., 2010). For those 70 to 79 years, a similar pattern was reported, although the decline was not significant. The oldest group, those 80 years and

older, were the only group to show a trend of declining disability, but only for functional limitations. Additionally, the change in disability prevalence was varied by race/ethnicity. Non-Hispanic blacks had a greater increase in ADL disability among those 60 to 69 years and in functional limitations for those 70 to 79 years over this period than among non-Hispanic whites of the same age groups. For those 80 years and older, the observed decline in disability did not differ by race/ethnicity, but women had a greater reduction in functional limitations over this period than did men. The reasons for the increase in disability among those aged 60 to 69 years remain unclear. However, it is suggested that this increase may be a byproduct of the rapidly growing number of overweight and obese Americans. In the analyses by Seeman et al., overweight and obese 60- to 69-year-olds reported greater increases in IADL disability than those of normal body weight in the same age group. Reciprocally, among those 80 years and older, those of normal weight were less likely to report mobility disability over this time period. The increase in disability is particularly concerning, as it appears to be occurring among the fastest-growing subgroups of older adults, those 60 years and older, non whites, and those overweight and obese. The increasing burden of disability among older adults is of public health significance for all ages. The impact of this increase could be far-reaching and negatively affect both the US health care system and economy.

There is an interplay among time of disability onset, duration of disability, and time of death that determines the number of years that older individuals live in the disability-free state, termed active life expectancy, and the number of years spent in the disabled state. Life table approaches have been used to calculate active and disabled life expectancy, utilizing data from population-based longitudinal studies on transitions from the nondisabled state to disability and death and from the disabled state to nondisability and death. Using this approach may provide insight into the mechanisms and risk factors that affect the quality of aging and suggest potential targets for intervention. In EPESE low education (< 12 years) was associated with shorter total life expectancy and shorter active life expectancy in both black and white women and men. However, when comparing persons with the same educational status, there were only small differences between blacks and whites. Alternative methods have been developed to estimate active life expectancy that utilize mortality data and prevalence of disability, which is easier to obtain in a national survey than 1-year transition probabilities. As more data become available to estimate both active and disabled life expectancy, we will gain more insight into the prospects for a compression of morbidity, which is the reduction in disabled life expectancy that results from compressing chronic disease and disability into a smaller number of years between disease and/or disability onset and mortality.

Aging of Individuals With Life-Long Disabilities

In addition to the large number of persons who will develop disabilities in old age, there is a smaller cohort of persons with life-long disabilities who will enter old age with these disabilities. Persons with developmental disabilities are a heterogeneous population with varying abilities, and their disabilities may result from a variety of conditions such as cerebral palsy, mental retardation, learning disorders, autism, and epilepsy. It is estimated that in 2000 there were over 600,000 people in the United States with mental retardation and other developmental disabilities. Their numbers will double to 1.2 million by 2030 when all of the post–World War II “baby boom” generation will be in their sixties. Life expectancy of many persons with mental retardation and developmental disabilities has risen dramatically, and many people with these disorders will live into advanced old age. Down syndrome is an exception, however, with signs of accelerated aging and development of Alzheimer disease at early ages. A further consideration related to the growing number of older persons with developmental disabilities is the continuation of their care when their own parents reach old age. Nearly two-thirds of persons with developmental disabilities live with their families, and in one-quarter of these households the primary caregiver is 60 years or older. Over the next 30 years, there will be a considerable increase in the number of families where parents more than 80 years old are caring for an older child with a developmental disability.

BEHAVIORAL RISK FACTORS

An important role for epidemiology is to elucidate risk factors for disease, injury, and disability which can have a large impact in older persons. Although certain risk factors that are potent predictors of major diseases in middle age may have less or no impact at old age, most behavioral risk factors continue to be important throughout old age. Cigarette smoking, for example, continues to predict mortality even in smokers who have survived past age 65 years, and stopping smoking even in old age is associated with better outcomes. The Centers for Disease Control and Prevention perform national surveys on a wide range of behavioral risk factors and include the older population in these

assessments. **Table 5-10** demonstrates the prevalence of risk factors and protective factors across four age groups, from 25 to 44 years through 65 years and older. For almost all these health practices, older persons have similar or somewhat better rates than younger individuals.

TABLE 5-10 BEHAVIORAL RISK FACTORS IN MIDDLE-AGED AND OLDER PERSONS, UNITED STATES, 2011

	PERCENTAGE OF AGE GROUP		
	25–44	45–64	65+
Alcoholic beverages			
≥ 1 drink within the past 30 days	62.3	54.9	40.7
Men > 2/d Women > 1/d	7.1	6.3	3.9
5+ at one time	25.4	14.1	4.3
Cholesterol check			
Past 5 y	66.9	87.4	94.8
Never	28.4	8.7	3.7
BMI			
Overweight (25.0–29.9)	35.5	37.8	39.5
Obese (≥ 30.0)	27.9	32.8	25.3
Physical activities			
0 min/wk	25.3	28.9	35.6
1 to < 150 min/wk	25.0	20.2	12.0
150+ min/wk	49.7	50.9	52.4
Smoking status			
Everyday	16.8	15.8	6.5
Some days	7.3	5.3	2.3
Former	17.9	28.7	43.5
Never	58.1	50.3	47.7
Immunization			
Flu in past year	28.0	38.1	60.2
Pneumonia ever	17.0	24.8	69.0
Use of seatbelts			
Always	85.7	88.8	89.7
Nearly always	7.5	5.9	5.0
Sometimes	3.2	2.5	2.2
Seldom	1.4	1.0	0.9
Never	1.9	1.5	1.6
Length of time since last routine checkup			
Past 12 mo	57.4	70.5	86.0
1–2 y ago	16.8	12.5	7.1
2–5 y ago	11.7	7.8	3.2
> 5 y ago	12.3	8.1	3.1

Never	2.0	1.0	0.6

Data from Centers for Disease Control and Prevention (CDC). Behavioral Risk Factor Surveillance System Survey Data. Atlanta, GA: U.S. Department of Health and Human Services. http://apps.nccd.cdc.gov/s_broker/WEATSQL.exe/weat/freq_analysis.hsql?survey_year=2011. Accessed January 15, 2015.

These results are compatible with findings that adherence to physicians' recommendations and medication schedules is better in older than in younger persons. Thus, this is a population that faces increasing risk of disease and disability with increasing age but one that cares about its health, has a positive risk factor profile, and is willing to comply with interventions to prevent or improve adverse health outcomes. Applying what has been learned in epidemiologic studies on older populations so that effective prevention and treatment strategies will be available to older persons is a continuing challenge for the field.

ACKNOWLEDGMENT

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Chapter 6

International Gerontology and Geriatric Medicine

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Learning Objectives

- What is the nature of population aging worldwide?
- What are the implications of population aging among the world's nations?
- How are the world's nations responding to population aging?
- What is the role of geriatric medicine, and how is it organized among the world's nations?
- To what extent do older people receive consistent health care even among nations with similar economic circumstances?

IMPLICATIONS OF GLOBAL POPULATION AGING FOR HEALTH AND HEALTH CARE

Overview

Population aging is a pervasive, unprecedented global phenomenon. The trend toward population aging is expected to continue well into the twenty-first century. The older population is itself aging; the fastest growing age group is the oldest-old, those aged 80 years or older.

The chapter begins by highlighting the consequences and implications of the global population aging. In the economic area, population aging will have an impact on economic growth, savings, investments, consumption, labor markets, pensions, and taxation. This phenomenon will also have a direct bearing on the intergenerational and intragenerational equity and solidarity that are the foundations of our societies. In the social sphere, population aging will affect health and health care, family composition and living arrangements, housing, and migration. Some of the inadequacies of health professional education and health care delivery systems in meeting the chronic health care needs of aging populations around the world are discussed.

Geriatric medicine is an important ingredient in the delivery of health care to older people, particularly those with physical or cognitive functional limitations. The place of geriatric medicine across the world's nations is reviewed.

The second section of the chapter describes how health care systems around the world are preparing to deal with patients with multiple chronic, degenerative diseases. Information is provided about developed countries in four continents including Canada and the United States of America for North America; Brazil for South America; France, Iceland, Italy, and the United Kingdom for Europe; China, India, and Japan for Asia; and Australia for Oceania. The current situations in Brazil, China, and India provide examples of emerging nations with significant challenges associated with rapid population aging without a substantial legacy of aged care systems or a geriatric medicine workforce. For each country, the following information is presented: the principal characteristics of the health care system; the organizational approaches and the services available for older adults; the current status of geriatric medical practice; and unique features that might be instructive to other nations. Each nation's profile concludes with a description of how the prevailing "system" would respond to a hypothetical example of an 87-year-old widow hoping

to return home after suffering a stroke with motor and speech deficits.

The third section of the chapter provides a brief example of how a systems approach to assessment of older people might not only enhance clinical care, but also improve the efficiency and equity of service administration through derivative quality and casemix systems.

Finally, the chapter discusses the evidence that the unprecedented demographic changes, which had their origins in the nineteenth and twentieth centuries, are continuing well into the twenty-first century. The number of older persons has tripled over the last 50 years, and will more than triple again over the next 50 years. In contrast with the slow process of population aging experienced by the more developed countries, the aging process in most of the less developed countries is taking place in a much shorter period of time, and is occurring in a larger population. Such rapid growth will require far-reaching economic and social adjustments in most countries. Effective and efficient health care for the chronic health problems facing this growing population of older adults will be a daunting challenge for all countries.

Global Population Aging (See Also Chapter 5)

Notwithstanding some heterogeneity, life expectancy is increasing across the globe. In most industrialized countries, this increase in life expectancy has mostly occurred over the last century. However, in the most recent decades, its pace has progressed at an unprecedented speed, reaching estimates far beyond those predicted by most international organizations such as the United Nations. The increase in life expectancy, seen in many countries throughout the world, does not seem to be leveling off (**Figure 6-1**). This phenomenon is also apparent in developing nations, where the rate of change (and hence the need for adaptation) appears to be greatest. Previously, growth in average life expectancy has been fuelled by dramatic reductions in infant and mid-life mortality. More recently, dramatic changes have been observed in mortality rates among older individuals (aged over 60 years), particularly among men in wealthier nations. This phenomenon is now contributing substantially to the growth in average life expectancy worldwide, which, for the first time, in 2011, exceeded 80 years.

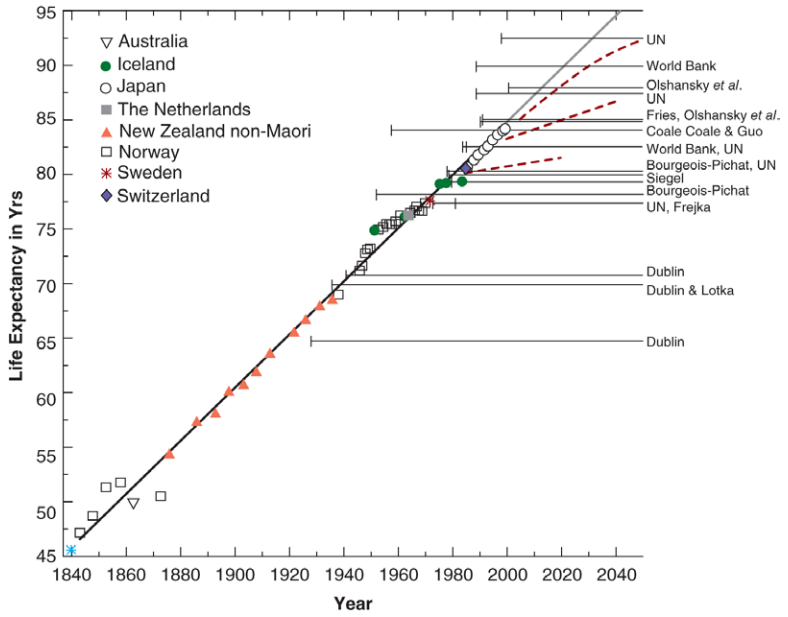


FIGURE 6-1. Increase in female life expectancy (in years) observed in selected countries since 1840 (solid lines) and extrapolated to 2040 (dashed lines). The horizontal black lines show asserted ceilings on life expectancy, with a short vertical line indicating the year of publication. (Reprinted with permission from Oeppen J, Vaupel JW. *Science.* 2002;296:1029–1031.)

The increase in life expectancy has resulted in increased proportion of individuals reaching the eighth and ninth decades of life. Individuals 80 years and older are consistently found to be the fastest growing segment of the population. Similarly, there is an unprecedented and increasing appearance of centenarians and supercentenarians (**Figure 6-2**).

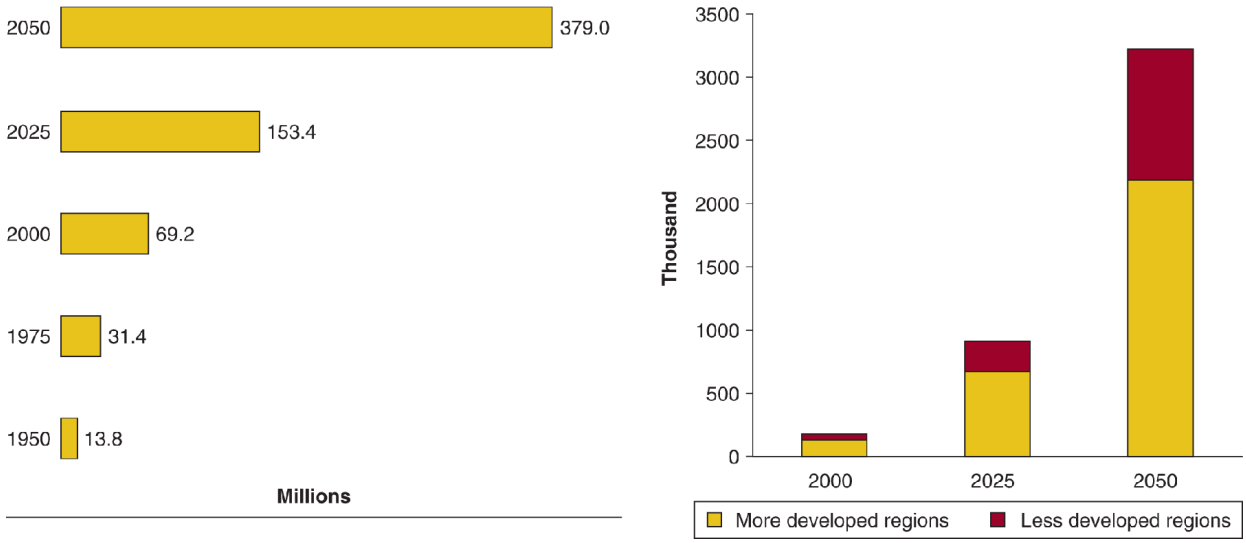


FIGURE 6-2. Population aged 80 y or older (in millions) in the period 1950 to 2050 (left panel). Distribution of world centenarians by development regions (2000–2050) (right panel). (Reprinted with permission from World Population Aging 1950–2050. United Nations.)

The disproportionate life advantage favoring women over men has created a progressive feminization of the older population. Among individuals 85+ years, there are, on average, 55 men for every 100 women.

The increase in life expectancy has been paralleled—especially in the western world—by declining fertility rates. In most countries, the fertility rate is much below the mortality rate and below what it is considered the minimum for population replacement and conservation. The concomitance of an increased life expectancy with a reduced fertility rate has produced profound effects on the labor market, the financial resources, and other societal factors. One example is the potential support ratio, that is, the number of persons aged 15 to 64 years per one older person aged 65 years and over. Between 1950 and 2000, the potential support ratio fell from 12 to 9 people per each person 65 years or older. By midcentury, the potential support ratio is projected to fall to four working-age persons for each person 65 years or older. Potential support ratios have important implications for social security schemes, particularly traditional systems in which current workers pay for the benefits of current retirees (**Figure 6-3**).

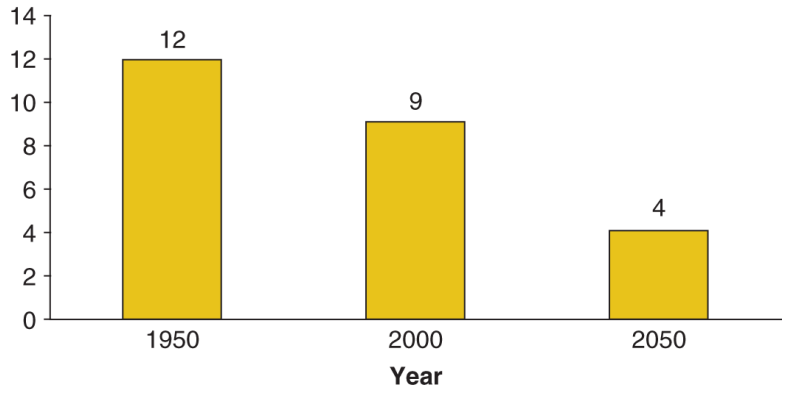


FIGURE 6-3. Potential support ratio: world, 1950–2050. (Reprinted with permission from World Population Aging 1950–2050. United Nations.)

Effect of Population Aging on Health and Health Care

Epidemiologic evidence shows that as age increases, there is a progressive, exponential increase in the occurrence of most chronic, degenerative, and progressive diseases, including cardiovascular disease, cancer, chronic obstructive pulmonary disease, dementia, and other degenerative conditions. Furthermore, there is an increase in the co-occurrence of these diseases, resulting in comorbidity.

Health care systems around the world have been based on a disease model. Diagnosis and treatment is focused on eliminating or ameliorating the underlying pathology; health outcomes are determined by the disease. Also, functional impairment and quality of life are assumed to be improved by treating the “causative” disease. The disease model has resulted in the creation of health systems centered on acute care hospitals and disease (or organ)-based specialists. This

model has informed the way we have developed and accrued knowledge. For example, evidence-based medicine (EBM) has been promoted as the best approach to improving health and health care. The randomized controlled trials on which EBM recommendations are based typically provide evidence of modest reductions in the relative risk of the disease-specific outcomes that are associated with the use of various interventions such as medications. Older patients and patients with multiple health conditions and therapies are excluded from the majority evidence-generating randomized, controlled trials. Arguments have been made for extrapolating the evidence from such trials to subpopulations of older patients, but the generalizability of the results to these patients remains unknown.

Consequently, physicians and health personnel are facing a "new" type of patient who presents with an array of concomitant clinical conditions. These combinations of conditions result in varying degrees of functional deficits, cognitive deterioration, nutritional problems, and geriatric syndromes (delirium, falls, incontinence), often in the face of inadequate social support and financial resources.

This "new" older patient presents a degree of complexity not previously considered by the traditional understanding of medicine and its role. The traditionally envisioned health care system, whether operating under universal coverage or private mechanisms, is challenged by this complex patient.

The response to the challenge of the complex older patient has been heterogeneous around over the world; differences in resource availability and economical and cultural issues have resulted in different organizations of health care systems. In addition, the methodological approaches adopted by systems to evaluate the needs of such complex patients have been highly variable and not standardized. In particular, the organization of services to care for geriatric patients, including geriatric assessment and management, remains highly variable. This variation is seen among nurses, physicians, therapists, nursing homes, home care services, and health systems.

The Contribution of Geriatric Medicine

Geriatric medicine emerged as a medical specialty in the mid-twentieth century—somewhat later than the majority of organ- and procedure-oriented specialties. Initially inspired by the realization that among older people living in institutions there was a substantial prevalence of diagnoses and functional impairment that could be resolved by careful diagnostic review and implementation of rehabilitation techniques, ultimately geriatric medicine approaches were found relevant to all older people, regardless of the care setting. In addition, there was a growing body of evidence that disease presentations and responses to treatment may differ among very old people compared to middle-aged adults. As this awareness was applied to patients in hospital and older people living in the community, there was an appreciation that the social and physical context of older people also influences functional status and outcomes.

In spite of a growing body of knowledge pertaining to illness in old age, and a strong evidence base for its practice, the specialty has not been uniformly adopted across, or even within, nations. Moreover, even where it is established, practice is often restricted to particular settings—hospitals, nursing homes, or ambulatory clinics. This may be a product of the overall configuration of specialty practice, funding and financial incentives, lack of leadership, or perceived lack of need at professional or government level. In many jurisdictions, geriatric medical specialist presence is restricted to large academic or metropolitan settings. In developing nations, the discipline may not exist at all.

Within hospitals, a variety of practice models have emerged. Acute geriatric units, supervised by geriatricians, may admit acutely ill patients direct from the emergency department or community. Alternatively, geriatric medicine may be restricted to postacute units, where patients are transferred after initial assessment and triaging in an acute unit. These "postacute" services may be based within acute hospitals, on a separate "subacute" precinct, or collocated with a long-term care facility.

Outside of hospitals, geriatric medicine may have a presence in long-term care, where geriatricians might act as the primary medical workforce. In other jurisdictions, they act only as specialists, consulting patients who are referred by primary care practitioners.

In most jurisdictions, there is perceived to be a shortage of geriatricians. Even where the specialty is firmly entrenched and available in a particular setting, there may be inadequate availability in other care settings. Situations where a geriatrician is available to consult patients across the entire care spectrum are probably relatively rare.

Geriatric medical practice and its availability should reflect the needs of the oldest members of a society. As such, with near universal population aging, it would be reasonable to anticipate that geriatric medicine should emerge progressively throughout the present century. In the following section, the role of geriatric medicine is described across 11 nations. In some, geriatric medicine is in an advanced stage of development. In others, it is just beginning to emerge. The wide variation of availability and service presence is reflected in these descriptions.

INTERNATIONAL COMPARISONS

In order to illustrate the way countries in the more developed world have prepared to cope with population aging we have selected 11 countries in five continents, including Canada and the United States for North America; Brazil for South America; France, Iceland, Italy, and the United Kingdom for Europe; China, India, and Japan for Asia; and Australia for Oceania.

The majority of these countries have among the highest life expectancy at birth, well over 80 years for all but the United States and United Kingdom. The percentage of the population aged 65 years and older ranges from 6% in India to approximately 21% in Italy and Japan (**Table 6-1**). In the next 50 years, the percentage of older adults will almost double in each country, estimated to reach over a third of the population in Italy and Japan (**Table 6-2**).

TABLE 6-1 TOTAL POPULATION, PERCENTAGE OF POPULATION AT LEAST 65 YEARS OLD, LIFE EXPECTANCY AT BIRTH, AND PERCENTAGE OF GROSS DOMESTIC PRODUCT SPENT ON HEALTH EXPENDITURES ACROSS 10 COUNTRIES

North America—Canada
- Population—35.2 million
- Proportion 65+—15.3%
- Life expectancy at birth—82 y
- Health expenditures—10.9% of GDP

North America—United States
- Population—316.1 million
- Proportion 65+—14.1%
- Life expectancy at birth—79 y
- Health expenditures—16.9% of GDP

South America—Brazil
- Population—201.5 million
- Proportion 65+—8.9%
- Life expectancy at birth—74 y
- Health expenditures—9.3%

Europe—France
- Population—63.5 million
- Proportion 65+—17.5%
- Life expectancy at birth—82 y
- Health expenditures—11.6% of GDP

Europe—Iceland
- Population—0.3 million
- Proportion 65+—13.1%
- Life expectancy at birth—82 y
- Health expenditures—9.0% of GDP

Europe—Italy
- Population—60.7 million
- Proportion 65+—20.8%
- Life expectancy at birth—83 y
- Health expenditures—9.2% of GDP

Europe—United Kingdom
- Population—62.6 million
- Proportion 65+—17.0
- Life expectancy at birth—81 y
- Health expenditures—9.3% of GDP

Asia—China
- Population—1385.6 million
- Proportion 65+—8%
- Life expectancy at birth—75 y

- Health expenditures—5.4% of GDP

Asia—India
- Population—1252.1 million
- Proportion 65+—5.8%
- Life expectancy at birth—66 y
- Health expenditures—4.0%

Asia—Japan
- Population—128 million
- Proportion 65+—25.1%
- Life expectancy at birth—84 y
- Health expenditures—10.3% of GDP

Oceania—Australia
- Population—23.1 million
- Proportion 65+—14.4%
- Life expectancy at birth—83 y
- Health expenditures—9.1% of GDP

TABLE 6-2 ■ POPULATION AGED 65 YEARS AND OLDER, PERCENTAGE OF THE TOTAL POPULATION 2000–2050

COUNTRY	2000	2005	2010	2020	2030	2040	2050
OECD	13.0	13.8	14.7	17.8	21.3	23.9	25.5
Canada	12.6	13.1	14.1	18.2	23.1	25.0	26.3
United States	12.4	12.4	13.0	16.3	19.6	20.4	20.6
France	16.1	16.4	16.7	20.3	23.4	25.6	26.2
Iceland	11.6	11.7	12.4	15.5	19.2	20.9	21.5
Italy	18.3	19.6	20.6	23.3	27.3	32.3	33.7
UK	15.8	16.0	16.7	19.5	22.5	24.7	27.9
Japan	17.4	20.0	23.1	29.2	31.8	36.5	39.6
Australia	12.4	13.1	14.3	18.3	22.2	24.5	25.7

OECD, Organization for Economic Cooperation and Development.

More alarming, the dependency ratio (ratio of inactive population aged 65 years and older to the labor force) is projected to be close to 50% in France, Italy, and Japan by 2020. This means that, for every older adult, there will be only two persons in the labor force. Iceland will be characterized by the lowest dependency ratio. Regardless, all countries will experience a further increase in the dependency ratio over the period 2020 to 2050. By that time in Italy, for every retired older adult, there will only one person in the labor force (**Figure 6-4**).

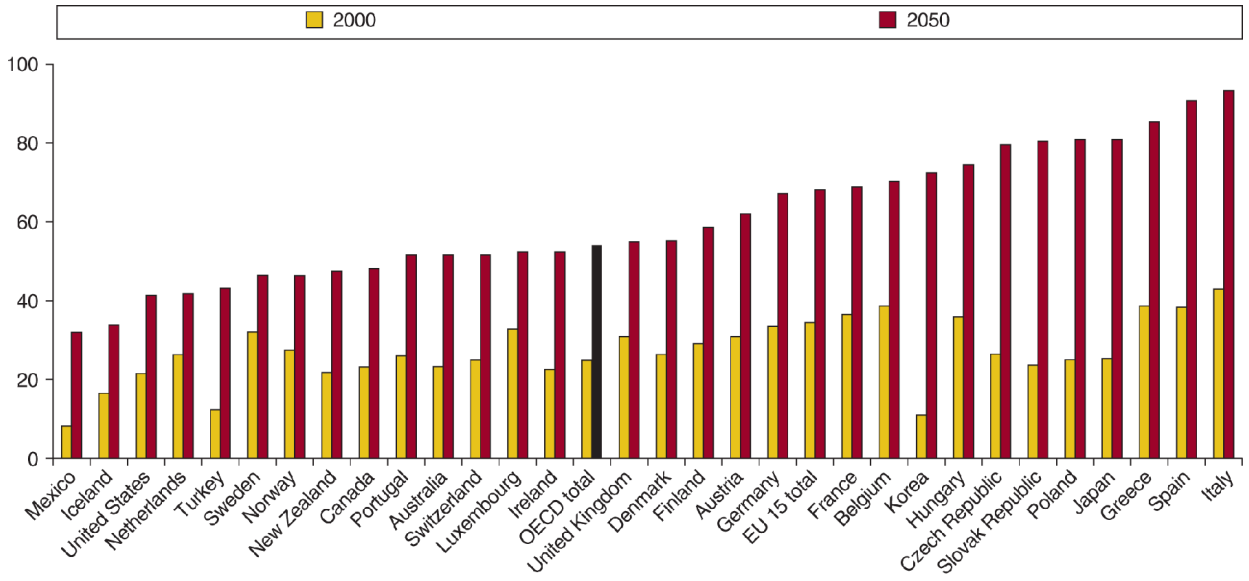


FIGURE 6-4. Ratio (percentage) of the retired population aged 65 y and older to the labor force, 2000–2050. (Adapted from *OECD Factbook 2007: Economic, Environmental and Social Statistics*.)

In most Organization for Economic Cooperation and Development (OECD) countries, expenditures on health are a large and growing share of both public and private expenditures (see **Table 6-1**). The level of health spending varies widely across countries, reflecting different market and social factors as well as the different financing and organizational structures of the health system in each country. In terms of total health spending per capita, the United States is well ahead of the next highest spending countries and well over double the unweighted average of all OECD countries (**Figure 6-5**).

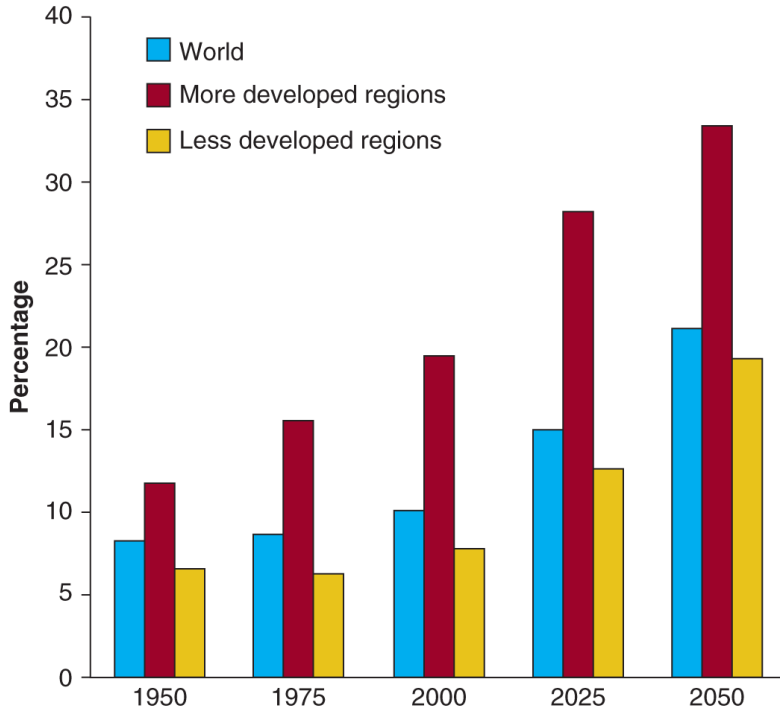


FIGURE 6-5. Proportion of population aged 60 y or older: world and development regions, 1950–2050. (Reprinted with permission from World Population Aging 1950–2050. United Nations.)

Since 1990, health spending has grown faster than gross domestic product in every OECD country except Finland, although this growth has not been constant. In most OECD countries, the bulk of health care costs are financed through taxes, with 73% of health spending, on average, being publicly funded in 2004.

The strategy and the organizational approach to deal with complex patients with multiple chronic conditions differ substantially across countries. In part, these differences are historical, cultural, demographic, financial, and societal. For

each country, we present key characteristics of the health care system and organizational approaches and services available for older adults.

North America: Canada

Canada has a population of 35 million people, of whom 15% are aged over 65 years. Life expectancy at birth is currently 82 years.

The health care system Health care in Canada is a joint federal–provincial responsibility. It is delivered and managed at the provincial–territorial level, with the majority of funding provided by provinces. The federal government transfers funds to the provinces and territories to pay for a portion of public expenditures in health care, and sets national standards that govern the delivery of hospital and physician services. The federal government is also responsible for health protection related to product safety and pharmaceuticals, and it provides funding for research and health promotion at the national level.

Hospital and physician services have been publicly funded under a "single-payer" system in Canada since the 1957 Hospital Insurance and Diagnostic Services Act and the 1966 Medical Care Act established a shared approach to payment between the two layers of government. The Canada Health Act (CHA) of 1984 represented a major development in defining health care in Canada, by establishing five principles that would govern the delivery of hospital care and physician services:

1. Public administration—provincial health care insurance must be operated and administered publicly on a not-for-profit basis.
2. Universality—all citizens must be covered equally with the same benefits and entitlements, irrespective of ability to pay.
3. Accessibility—no financial or other barriers (e.g., user fees) are permitted to ensure equity of access among citizens.
4. Portability—provides funding for Canadians visiting or moving to other parts of the country or traveling outside of Canada.
5. Comprehensiveness—ensures full coverage for "medically necessary services" provided by physicians or in hospitals (including dental surgery).

Following a protracted debate between federal and provincial governments, the Romanow Commission on the Future of Health Care in Canada was assembled to address issues such as the share of federal contributions to health expenditures and the scope of the Canada Health Act. The Commission's 2002 report made numerous recommendations, but two that had the potential for a direct impact on the older persons were (1) expansion of the Canada Health Act to include home care and (2) addition of "accountability" to the Canada Health Act as a new principle governing health care in Canada. Ultimately, neither recommendation was implemented, but there has been a modest overall expansion of home care expenditures in the last decade in order to support older persons in the community as an alternative to institutional care.

In addition, many provinces have launched their own accountability initiatives, but there is no national consensus on what should be done to ensure quality, appropriateness, and cost-effectiveness of health care. The Canadian Institute for Health Information (CIHI) has begun to publicly report on quality indicators for all health care settings, but its mandate does not include a capacity to drive quality improvement initiatives.

Another major feature of the Canadian health care system is the regional management of some aspects of planning and health service delivery. Provincial governments have played a diminishing role in the actual delivery of health care, with most organizational decision-making and resource allocation made at the local levels. The role of many provincial ministries of health has changed to a stewardship function instead of direct management and oversight. While this model may mean that health care is delivered and managed in a way that is tailored to needs at the local level, it is increasingly difficult to speak of a "Canadian" health care system. The Canada Health Act provides national standards for physician and hospital services, but these standards do not apply to nursing home care, home care, or social services for older people. There are many commonalities in models of care between provinces, but the specific services available and the terms under which they are provided vary substantially between numerous health authorities managing services in 10 provinces and three territories.

Overall organization and services available for older adults As noted above, there is no singular model of

Canadian health care. Rather, health policy and service delivery in Canada are best understood as multiple variants on a set of common, high-level principles. Health care for older adults in Canada involves several common services and care settings—home care, nursing homes, and hospitals are the constants across provinces, but the precise function of these services, payment systems, and eligibility criteria vary from province to province.

Hospital Geriatric Services Older adults are estimated to account for 40% of hospital days in Canada even though they comprise only about 14% of the population. There has been a growing trend toward adding specialized acute geriatric units to general hospitals across Canada. However, these units are generally located in teaching hospitals or larger community hospitals, and the majority of older persons do not receive hospital care in those units.

As in other countries, acute hospitals in some Canadian provinces have employed a Diagnosis Related Groups (DRG)-like system to manage hospital resources. Over several decades, this has resulted in dramatic reductions in average length of stay. In many provinces, a persistent concern has arisen with respect to alternative level of care (ALC) patients—those who no longer have acute care needs and are now in the hospital awaiting placement in a less intensive care setting. Frail older adults make up the vast majority of ALC patients in acute hospitals. The size of this population has grown with the ongoing pressures to reduce hospital length of stay and the limited availability of long-term care beds or supportive housing options.

Long-Term Institutional Care Definitional problems make it difficult to estimate rates of nursing home utilization in Canada. It is estimated that 6.3% of Canadians reside in nursing homes, representing a modest decline since the 1980s. However, the provincial rates range from a low of under 6% in British Columbia to over 8% in Quebec. That said, different provinces refer to nursing homes with different names and there is substantial variation across Canada in how nursing home stays are paid. Several provinces employ a copayment system where the resident pays a share of the costs of the stay, while other provinces require the person to pay for all costs of nursing home care until they have spent down their income and assets.

An important change that has occurred in Canada is the introduction of assisted living as a lower cost alternative to nursing home care for a population with lighter care needs. However, in some provinces, the movement toward assisted living appeared to be driven mainly by an interest in replacing regulated nursing home care with unregulated care.

Community Care There is no exact estimate of the size of the home care population in Canada, again because there are widely divergent definitions of home care. If one considers services such as nursing, personal support, home health aides, and rehabilitation, it is estimated that the rates of home care use range between 10% of persons aged 65 to 74 and 45% of those 85 years of age and older. However, this value will generally be higher if one expands the definition to include services such as transportation, meals-on-wheels, and other community supports offered by social service agencies.

A distinctive feature of home care in many provinces is the use of the case management approach to assessing needs, allocating resources, and managing community-based services for frail older adults. For example, in Ontario, Community Care Access Centres (CCACs) use care coordinators to complete an assessment of home care clients. They use the assessment information to prioritize clients for access to community- and facility-based services and to establish a care plan based on the clinical findings of the assessment. They then contract with home care companies (both for-profit and not-for-profit) to provide the services needed by the client. Typical services include nursing for wound care and intravenous management, personal support for bathing and homemaking, and physical or occupational therapy; social work, speech language pathology, nutrition, and mental health services are only provided infrequently. There are considerable practice pattern variations within and between provinces, with some provinces adjusting service intensity according to need indicators and others providing a relatively fixed set of services that varies little across need levels.

Home care services often exclude persons with severe mental illness. Instead, these individuals receive support from community mental health agencies that may or may not work in concert with home care. In addition, community mental health agencies often provide consultation services to nursing homes to assist them in meeting the needs of residents with complex psychiatric issues or high levels of behavior disturbance. However, it is not uncommon for nursing homes to discharge residents with frequent and severe behavior disturbance to inpatient geriatric psychiatry units because they do not have the expertise or resources to cope with these residents. Hence, there is a growing awareness in Canada of the need to find more cost-effective methods to respond to the mental health needs of nursing home residents.

Geriatric Medicine There is a notable shortage of geriatricians in Canada, with an estimate of about 240 geriatricians for a population of about five million older Canadians. In addition, geriatricians tend to practice in large urban settings making it difficult for older persons in rural settings to access their services. They generally work in hospital settings, but occasionally provide consultation services to family physicians caring for older persons in primary care or nursing home settings. In fact, the bulk of medical care for older Canadians is provided without the involvement of geriatricians.

Unique features About 80% of the population lives in urban settings, mainly in the southern regions of the country near the US border. However, the rest of the population lives in rural settings, sometimes covering vast geographic areas that make it difficult to offer home care programs or nearby primary care services. About one-third (12.2 million) of the population of Canada lives in the province of Ontario. Toronto (the capital city of the province) has about three million residents living in a 630 km^2 area with a population density of 3972 persons/km^2. In contrast, the 10,000 residents of Yukon Territory who live outside its capital city (Whitehorse) in the northwest region of Canada are dispersed over a 474,000 km^2 area with a density of 0.1 persons per km^2.

An important development for care of olders in Canada has been the move toward a national standard for assessment systems in home care and nursing homes. Ten Canadian territories/provinces have adopted the interRAI suite of assessment instruments as their mandatory assessments for those sectors. Canada Health Infoway designated 10 interRAI assessments as Canadian Approved Standards for the electronic medical record and CIHI manages three national reporting systems (continuing care facilities, home care, mental health) based on these instruments. These instruments are used to support need determination and care planning at the person-level, as well as performance measurement and casemix-based funding at the population level.

A case study An 87-year-old widow with an acute stroke and few comorbidities would typically receive care in a general medical ward of an acute care hospital. Few acute hospitals have a dedicated stroke unit. Rehabilitation in the postacute phase may be provided in a rehabilitation hospital or unit, or in a complex continuing care hospital (Ontario only). Depending on the patient's functional ability, medical condition, and access to informal support (in this case probably children), she may be transferred home with home care. Rehabilitation may be provided by the home care program or by community-based clinics. The home care program will also offer personal care, homemaking services, and nursing, if needed. If the patient's medical needs exceed the ability of family members to provide adequate support, then she may be placed in a long-term care home or an assisted-living setting depending on the severity of impairment.

The United States of America

The United States has a population of 316 million people, of whom 14% are aged over 65 years. Life expectancy at birth is currently 79 years.

The health care system The United States does not have universal health care. In 2010, the Affordable Care Act was passed, extending health coverage to millions of Americans who previously lacked such coverage, mostly through an expansion of coverage through the Medicaid program. Most of the remaining uninsured, approximately 40 million, in the United States are in low-income working families. Nonetheless almost the entire older population is covered for some health care services under a federal insurance program known as Medicare.

Overall organization and services available for older persons To be eligible to receive benefits, either the individual or the person's spouse must have worked for 10 years or more in a Medicare-covered capacity and be at least 65 years of age and a citizen or a legal resident of the country. Under most circumstances, enrollment in the program is automatic at age 65 years. Medicare Part A pays for most acute hospital level care services and many postacute care inpatient services for a limited period of time as well as some skilled home care and hospice services. For individuals who meet economic criteria, nonskilled home care services are provided by the states, using either Medicaid or state funds; their availability and level of coverage differs dramatically across the states.

Unlike Part A, the older person must request and pay for Medicare Part B insurance. This is the major payer for most physician services as well as ambulatory care. The Part B premium cost varies by income. In 2015, it cost most individuals about $105 per month, the exact amount being determined by their income.

Medicare Part D is an elective insurance plan that pays for pharmaceuticals. The individual desiring this insurance program usually must choose from among a large number of plans offered by different insurance companies, each of which may cost a different amount and have a somewhat different formulary.

Long-Term Institutional Care Long-term care is not covered under Medicare. Multiple plans are offered by the insurance industry, each of which may differ with respect to the cost, waiting period for eligibility, and types and duration of coverage. However, less than 8% of Americans have insurance for long-term care. Medicaid provides for long-term institutional care and many other health care services for the indigent population and for those who become indigent by virtue of spending down their assets on long-term care services. However, the eligibility requirements and the exact services available vary significantly from state to state as Medicaid is a joint federal and state program of insurance.

In 2012 there were 15,643 nursing homes in the United States. Overall, the number of residential nursing homes in the United States has decreased since 2003. Between 2008 and 2012, not-for-profit nursing homes have decreased in number by 7.1%, while the number of for-profit nursing homes (which now constitute 69% of all nursing homes and 71% of nursing home beds) has increased by 1.9%. There are now more long-term care beds than there are acute care beds in the country.

Assisted-living facilities provide long-term services and supports to people with functional or cognitive impairments who do not need nursing facility care, and generally offer more independence, choice, and home-like environments than nursing homes. In 2010, there were 31,100 such facilities with almost 972,000 beds. Assisted living is generally a self-pay model and there is significant heterogeneity across facilities.

An entirely separate health care system is provided by the Veterans Administration for military veterans who have limited assets. It has its own hospitals and ambulatory settings and employs its own physicians. Many of these facilities are attached to a varying degree to academic institutions.

Geriatric Medicine There have been some important developments in the availability of physician services for older adults in the last 25 years. In 1988, geriatric medicine was recognized as an area of "Added Competence" by both the American Board of Internal Medicine and the American Board of Family Medicine. Training programs in geriatric medicine for graduates of these two primary boards were designed and approved by the national accrediting body, the Accrediting Council for Graduate Medical Education. Similarly, geriatric psychiatry programs were established. In 2006, the American Board of Internal Medicine "upgraded" the field by making geriatric medicine a full specialty equivalent to, for example, cardiology and gastroenterology.

Nonetheless in the United States, geriatric medicine has recruited few physicians to its ranks, with perhaps as few as 200 physicians entering the specialty annually. Likely, in no small part, this is a consequence of the marked difference in reimbursement for different types of services. For example, a comprehensive assessment (CGA) of an older person is reimbursed at a far lesser amount than most any procedure that lasts half an hour or more.

In the United States, most medical students have a limited geriatric experience, perhaps in part because of the inability of medical schools to be able to recruit sufficient numbers of faculty. In addition, older adults usually have multiple chronic conditions, whereas the traditional emphasis in the medical curriculum has been on acute medical issues in a hospital setting, and more recently but still to a lesser extent, on ambulatory medicine. Most medical students have little or no exposure to such concepts as functional status or to such sites of care as the home or the nursing home. Efforts are underway to encourage specialists who care for large numbers of older adults, such as gynecologists and urologists, to have exposure to geriatrics.

The perception remains that the care of older people is not viewed as glamorously by either the public or the health profession as most other medical specialties. As older people tend to have multiple chronic conditions, multiple consultations may be viewed as necessary with the geriatrician serving in a lesser role, merely orchestrating the visits to specialists.

Unique features The extraordinary cost of the health care system in the United States, as compared to other developed nations, has become increasingly visible to American industry (which traditionally funds health care insurance programs for its workers), to the American people, and to politicians. Yet large numbers of citizens remain uninsured; the aging population is likely to need more care, increasing the per capita costs in the years ahead.

The health care system in the United States is changing under the provisions of the landmark Affordable Care Act. There is an increasing emphasis and beginnings of a cultural shift from a medical system that pays for the volume of services provided to one that seeks to pay for the value of care provided. Within the fee-for-service sector of the Medicare program Accountable Care Organizations, which assume financial risk for the health and health care costs of a population of patients, are created incentivized to attend to the health care needs of a population over the long term. Medicare managed care, by so-called "Medicare Advantage plans" provide health care services on a capitated basis to Medicare beneficiaries who choose to enroll in them, and are thus incentivized to provide high-value care.

Approximately 30% of Medicare beneficiaries are enrolled in Medicare Advantage plans.

Pay-for-performance programs of various types in the Medicare program have begun to offer financial incentives to improve the quality of medical care. Incentives at first focus on conditions such as an acute myocardial infarction and pneumonia in the hospital setting. Symptoms and geriatric syndromes, rather than discrete diseases, however, are often the most concerning health problems for older adults in many settings. Functional deficits have not yet been a focus of pay-for-performance efforts. Only recently has there been an interest in beginning to consider quality in other settings, such as ambulatory care and postacute nursing home care. The Centers for Medicare and Medicaid Services (CMS) has at its disposal a wide variety of quality indicators that could be applied to persons in postacute and nursing home settings.

A case study An 87-year-old widow who was living at home independently and presented to an emergency department with signs of an acute stroke would be evaluated immediately. If seen quickly relative to the onset of symptoms, she would undergo brain imaging. If there was a thrombosis and if the elder did not have a contraindication, she might be treated with a thrombolytic agent.

If no immediate intervention was indicated, she would be managed at an acute level of care for about 3 or 4 days. She would be evaluated by a physical therapist, and an occupational therapist. She might also be evaluated for speech deficits and aphasia and may undergo a swallowing evaluation.

Most such individuals would then be transferred to an acute rehabilitation facility or perhaps to a subacute level of care for rehabilitation, depending on the ability of the patient to engage in skilled therapies and her deficits. If the individual was transferred to a subacute facility, she would first have had to spend 3 days (ie, midnights) at an acute level of care before Medicare would pay for the service.

If the woman wished to return home and had no informal support, it would be necessary to determine her functional status. If it was felt that she could manage at home independently, then she would return to her home. However no long-term support services, such as assistance with bathing, shopping, or house cleaning, would be available unless the individual paid for them herself or was indigent and eligible for Medicaid. There are charitable organizations in some locations, but not all, that might offer to provide a very limited degree of support. But in all likelihood, these could not be counted on when arranging for discharge from a facility.

If she could not manage reasonably independently at home, it would be necessary for her to go to a long-stay nursing facility or, if she had a significant measure of functional ability, to an assisted-living facility. Both would be quite expensive, and only the former would be paid for by Medicaid if she had insufficient assets of her own.

South America: Brazil

Brazil has a population of 202 million people, of whom 9% are aged over 65 years. Life expectancy at birth is currently 74 years.

The health care system Brazil is the largest country (3.288 million sq. miles) in the Latin American region, the world's seventh largest economy, and the fifth most populous country in the world. It is composed of 27 federative units: 26 states and one federal district with an estimated multiethnic population of 203 million (in 2014), 26.3 million above 60 years, and nearly 3.5 million above 80 years.

Health care in Brazil is a constitutional right, universal and free for everyone (as of the Federal Constitution of 1988). Health care expenditure is about US $1120.56 year/per capita, or 8.9% of the GDP.

The Unified Health System (*Sistema Único de Saúde—SUS*) was implemented in 1990. The Health Minister administers national health policy; primary health care remains the responsibility of the federal government and the operation of hospitals is overseen by individual states. Since 1996, federal and state governments have been seeking to shift responsibility for administration of the SUS to municipal governments, with technical and financial cooperation (funding through *Piso de Atenção Básica*).

The SUS was designed to assist people close to their homes and refer to more distant health facilities only when necessary. Easy access is based on decentralized services, with basic health units (primary care) near home to offer initial levels of service. If necessary, the patient can then be referred for more complex health services.

There is also an important program called Family Health Program (*Programa de Saúde da Família—PSF*) designed to "deliver" health services in the home by community health agents. The PSF focuses on medical needs, on health promotion, and on attention to the social determinants of health. The PSF is still being implemented and recently had registered 62% of the Brazilian population.

Unfortunately, due to social and economic problems, the SUS cannot fully meet all the needs of the population.

Those who can pay individually for care can pay all costs to have access to private medical/hospital services or can purchase health insurance (about 23% of Brazilian population).

Private health plans and health insurance are concentrated in the southeast region of Brazil, where most private health companies are based. In the private sector, care is of the highest quality and uses cutting-edge technology. World class hospitals, services, and professionals are located in cities like São Paulo. This exceptional quality has led to international patients coming to Brazil in search of technology and qualified professionals—so-called Health Tourism.

Overall organization and services for older persons The federal government has been focusing on primary care and quality of life improvement. The Statute of the Older Person of 2003 provides health care and cash assistance for seniors at or below the poverty line, preferential treatment for older people in the SUS, free distribution of medication for chronic conditions, and a companion during hospitalization. The Pact for Life, 2006, explicitly addressed aging as a health care issue. In 2011, a health information system dedicated to the aging (SISAP-Idoso) was established to guide health professionals' and managers' decision-making and planning. The National Health Plan for 2012 to 2015 renewed the commitment to maintain and improve the health of older Brazilians and added a focus on training health care professionals through distance learning.

In Brazil, a national influenza immunization campaign that targets individuals 60 years of age and older has been conducted since 1999 and has included pneumococcal *and tetanus* vaccines since 2009. Although 15 million older people are immunized, there are some cities where coverage is under 80%.

With Brazilians dying at older ages, there is still little organized palliative and end-of-life care.

About 70% of older adults depend on the public health system. Since this system cannot meet all needs, there are incentives for the insurance industry to develop policies that offer more comprehensive coverage. Thus, for the minority of older people who can pay for health insurance, there is home care assistance for the disabled, specialized hospital units, multidisciplinary teams, and many other facilities.

Hospital Geriatric Services There are a few geriatric hospitals in Brazil, and all are funded through private insurance. Geriatric wards in general hospitals are increasingly common, in both public and private hospitals. In those wards, a health team with training in geriatrics attends to the special needs of older adults. These settings can also offer inpatient rehabilitation. Length of stay is often protracted as there are no transitions of care units, even in the private sector.

Long-Term Institutional Care In 2011, there were only 218 public long-term care institutions in the nation, and 71% of all municipalities had none. According to the 2011 World Bank Report, "Growing Old in an Older Brazil: Implications of Population Aging on Growth, Poverty, Public Finance, and Service Delivery," "The 2003 Elders' Bill of Rights stresses that institutional care is regarded as an option only upon evidence of lack of family, poverty or abandonment." There is no consensus in Brazil on what defines a residential institution, but the perception remains that they are places of last resort. Shelter for indigent older adults has traditionally been the province of Christian philanthropy, so most Brazilian long-term care institutions for the poor are charities. Private institutions receive no public funding.

Community Care Health agents perform home visits as a part of the Family Health Program. This is an example of a public scheme to assist disabled older people who cannot travel to primary care centers. A home care system called "Better at Home" (*Melhor em Casa*) ensures free multidisciplinary home care to older and disabled persons and provides family support.

There are others initiatives, such as "Gyms for Older People," also called "Outdoor Gyms," promoted by the federal Ministry of Health and implemented by municipalities; Community Centers and Geriatric Reference Centers for older people offer a range of health promotion activities and an ambulatory secondary care center with assessment by a multiprofessional team.

Geriatric Medicine Geriatrics in Brazil has been increasing in recent years. More and more health systems seek a geriatrician's experience in the management of older and chronically ill people. This has led to an expansion of demand for geriatrics training through formal fellowship. The geriatrics fellowship recognized by the Ministry of Education (MEC), lasts 2 years, with 2880 class-hours per year and a required completion of a 2-year residency in internal medicine. The government pays the salary of fellows and residents during their training.

There is increased support for geriatric training of all health care professionals. Geriatric medicine is now included in the medical school curriculum. There are public health messages related to care for older adults. As a consequence,

the waiting list for such health programs is long, but once enrolled, there are significant benefits.

Unique features Brazil is a country of contrasts. From north to south there are important differences in climate, culture, beliefs, and development, but there are some commonalities, especially in "family values." The Brazilian culture is largely built on a Portuguese and Italian heritage where families form the social basis. Thus, care of older persons depends most on families, usually women, regardless of income or social class.

Among poorer Brazilians, older people can remain responsible for the livelihood of the entire family, including young unemployed individuals. As a result, older individuals may continue to work longer since their pension could not support multiple family members. They do not have sufficient additional income to purchase health insurance, so rely solely on the SUS.

In contrast, wealthy families purchase expensive health plans (which may reach US $5000 per month) with extensive coverage. Middle income groups may purchase limited health insurance that covers only acute care.

In recent years, new regional preventive and medical services are being developed, often offered at no charge, organized by public and private universities, charitable and philanthropic groups. Many older Brazilians benefit from such services beyond those provided by the government.

A case study An older patient sustaining a stroke with moderate to severe impairments would always be admitted to an acute hospital if she lived in a region with organized health care. If she had health insurance, she would be treated in a private hospital and if not, a public hospital would provide care at no cost to her. Thrombolysis could be offered, if indicated, in both hospitals. After medical treatment she would probably stay at the public hospital for rehabilitation, because there are no public rehabilitation services in most of the country. If she had generous health insurance she could access a private home care company for as long as she required. Nurses, physiotherapists, occupational therapists, and medical visits would be provided periodically for as long as needed.

In the public sector, she could only return home if she was independent in activities of daily living (ADL) or if her family or community would care for her. If her recovery was slow, a hospital social worker would process an application for government support for care in a long-term care facility or chronic care hospital. The process is complex and can take a long time.

Asia: China

China has a population of 1386 million people, of whom 8% are aged over 65 years. Life expectancy at birth is currently 75 years.

The health care system The health care system in China is organized by systematic service provision through a three-tier network and administrative establishment by the National Health and Family Planning Commission, with offices at each level of government. In urban areas, community clinics form the first level of health care units by providing primary care for residents. District hospitals, the middle-layer, deliver secondary services. Complicated cases are referred to the city general hospitals, the top tier of the system. In rural areas, the village clinics deliver basic health services. More complex needs are provided by township health centers, the middle tier of the rural health care network. County hospitals provide tertiary care for the rural health system. In both urban and rural areas, the components are integrated and predominantly public.

The system is currently funded by a combination of state budget, social insurance, and private payments. In general, costs of primary care are covered by a mixture of various social medical insurance programs and out-of-pocket payment, depending on employment status and residency of the care receivers. Employees of the industrialized sectors are covered by a state medical insurance program, financed by contributions by both the employee and the employer, and subsidized by the state. Farmers, who account for 50% of the total population, are covered by a cooperative medical insurance scheme subsidized by the government at both the state and local levels. These insurance programs cover both medical and drug costs up to 50% to 100%, depending on the types of care received and sectors in which the care receiver is employed.

In the past three decades, the system has experienced a radical reduction of government subsidization of public hospitals. At present, less than 20% of public hospital costs are financed by the government, while 80% are covered by social insurance programs and private payment. As a result, access to quality health services has become increasingly difficult for the segment of the population with limited ability to pay.

Overall organization and services for older persons Care for older persons in China is administratively divided into two categories—medical services and residential care—which are supervised, respectively, by the National Health

and Family Planning Commission, and the Ministry of Civil Affairs. Coordinating the two types of services has always been problematic. China's health systems are not adequately prepared to meet the challenges of population aging. As part of health system reform, the government is recruiting well-trained professionals, investing in long-term care and community service, and pushing for including chronic care in health insurance coverage.

Hospital Geriatric Services The annual hospitalization rate for those aged 65 years is around 8%. Only cities offer hospital-based geriatric services. Costs for inpatient and outpatient hospital services are covered by a combination of social insurance and out-of-pocket payment. While the general hospitals in large cities may have geriatric wards, the providers usually have no formal geriatric training. Indeed, few medical schools currently provide such training. Nevertheless, these hospital-based services represent an advance in the quality of services for older patients.

Long-Term Institutional Care There are more than 40,000 institutions, including nursing homes and rehabilitation centers, which provide long-term care for aged Chinese. Long-term care institutions for older persons can be categorized by sources of funding as follows: (1) municipal institutions where funding for investment and operation is provided directly from the local bureaus of civil affairs as public expenditures on social welfare, and these institutions are owned by the city governments; (2) institutions funded by private investment and subsidized by local government; and (3) institutions funded and operated by private investors.

Three types of older persons become residents in long-term care institutions: those who have no income and no family, those who either themselves or their direct family members have made publicly recognized contributions to the state, and all others who need care. For the first two types of older residents, the institutional services are paid for by the state. For the last category, services are charged to the care receivers and their families, and occasionally subsidized by local government.

Institutional long-term care for older persons is underdeveloped, with insufficient capacity. While significant proportions of community-dwelling older persons need nursing care and daily assistance, the average occupancy rate of existing facilities is only around 70%. Lack of funding for service delivery, a shortage of professionally trained providers, and inadequate regulatory oversight of care quality remain major concerns.

Community Care Over the last decade, the government has invested in community health services that integrate care for vulnerable groups, such as older and disabled people. At present, over 20,000 community health centers or clinics in the urban areas and 650,000 village clinics in rural areas are in operation. Costs for services from the community health providers are substantially reimbursed by social insurance programs. As a result, access to primary health care, which is one of the major concerns of aged community dwellers, has been improved.

There has been growth in a variety of services targeting the older population in the community, including rehabilitation and nursing care. For example, an older patient being discharged from the hospital could receive home care, which would be delivered by health care workers from community health centers. In general, community health services provide older persons with a new alternative between hospital-based care and long-term institutional care.

Geriatric Medicine The practice of geriatric medicine is growing in China. However, geriatric medicine is still a neglected specialty and limited to hospital-based settings. Currently, geriatricians as medical professionals are not officially accredited. Only a small number of doctors have had formal training, and most were trained in a medical specialty other than geriatrics. Increasingly, local health agencies organize continuing educational programs in geriatrics for practitioners. However, accredited educational programs for geriatric medicine are still rare in medical schools.

Unique features The growing aged population has led to some reorganization of the Chinese health care system, such as the development of community health services. These services reduce demand on large hospitals since an increasing amount of the costs are covered by state insurance programs. However, community health services are still in development, so only urban communities offer a range of services.

In addition, more than 90% of the population are covered by social medical insurance programs.

A case study An old woman who suffers a stroke would be directly admitted to a large general hospital for acute care. The length of stay varies from 2 weeks to a month depending on the severity and complexity of the condition, as well as the nature of the treatment provided. After discharge from the hospital, she is likely to receive postacute nursing or rehabilitation services either from community health facilities or from private service providers. She is likely to stay at home and have a family caregiver, either an adult child living with her or a hired in-home caregiver, to help her reach the community facilities for obtaining services. The social medical insurance program would cover up to

70% of her inpatient service costs and up to 90% of costs for rehabilitation services for 2 months. She might remain in a long-term care institution to continue postacute care. Costs for nursing home services are usually paid privately.

Asia: India

India has a population of 1252 million people, of whom 6% are aged over 65 years. Life expectancy at birth is currently 66 years.

The health care system The health system in India is complex in structure and function. Health is a state (province) responsibility. Health care institutions include dispensaries, primary health centers, community health centers, district hospitals, and tertiary care hospitals, with or without medical schools. The Union (federal) government is responsible for a family welfare program, which deals with policy formulation and maternal and child health issues. The Union government also regulates medical and paramedical education, international health and drugs standards, and licensing.

In addition to the state-funded health system, there is an extensive system of unregulated private health care throughout the country. The private network includes outpatient and inpatient hospital care in hospitals of widely varying size and cost. In recent years, health care has emerged as a profit-making industry with new corporate hospitals appearing across the country. More than 75% of outpatient care and 50% of inpatient care now takes place in the private sector. Distribution of health services in India is uneven. Quality health services are available in urban areas where approximately 25% of the population lives, while health service availability is not satisfactory in rural areas where 75% of the population lives. Only about 10% of the population has health security. Most of the beneficiaries of health security belong to organized labor from state-funded organizations; that is, government employees, staff of the armed forces and employees of public sector institutions, and workers of industry or commercial establishments covered by Employees State Insurance. Health care insurance, in the private or public sector, has not been implemented widely in the country despite substantial tax benefits on premiums. Most insurance involves copays. As a result, out-of-pocket spending for health care is common. This out-of-pocket cost is the single most important barrier to access to health care in the country.

Most state-funded health care is free or involves a nominal user charge. As a result, there is an imbalance between demand and supply, which affects the quality and efficiency of services. On the other hand, the unregulated private health care is costly and unaffordable for most of the population. There is a substantial difference between the quality of services in the public and private sector in terms of efficiency, cleanliness, range of services, and technology, with better provision in the private sector. In recent years, the private sector has seen a disturbing trend toward unnecessary diagnostic testing and procedures attributed to commercial interest. Overall the health system in India is suboptimal. Several schemes to improve access to health care for the rural and urban poor have been rolled out in the previous decade with mixed results. The corporate private sector on the other hand is growing steadily, with its presence now felt in community and preventive health care.

Overall organization and services for older persons The state-funded and private systems result in uneven access and quality of care. In addition, older patients compete with younger patients for access and resources at all levels. As the country begins to recognize the special health needs of older persons, new policies and programs are being developed.

Hospital Geriatric Services Care of older persons is usually a part of mainstream departments such as Internal Medicine and Surgery. The impact of population aging was not recognized at a policy level until the late 1970s. The first outpatient service in geriatric medicine was started in Madras Medical College and Hospital, Chennai. Over the next two decades, the service expanded to inpatient care and then developed into the first academic department of geriatric medicine in India. Since then, hospital-based geriatric services are becoming available mostly in public hospitals. In 2011, the Government of India started providing financial and technical support in 100 of 676 district hospitals for delivering dedicated geriatric services. The number is expected to grow to 325 by 2017. In addition eight medical schools were supported to provide tertiary level older adult age care with all support services in 2011 and an additional 12 medical schools will be covered by 2017. Geriatric services are at the discretion of the individual hospitals in the private sector.

Geriatric medicine may not be seen as valuable, especially in private corporate hospitals, where there is an emphasis on organ-focused specialization.

Long-Term Institutional Care Long-term care in India is invariably a responsibility of the family. Institutional long-term care is an evolving concept. As there is no state policy on long-term care, there are no public facilities for long-

term care of frail and cognitively impaired older persons. In recent years, a few acute care hospitals in the private sector offer a prolonged stay for patients in need of nursing and supportive care at a very high cost. A few "for-profit" organizations and NGOs are providing long-term care to patients with dementia and other disabling conditions in a few south Indian states, where the proportion of older people in the population is higher than the national average.

Old-age homes without any health infrastructure are alternatives for accommodation for those older persons who do lack shelter or cannot stay with family. There are about 50,000 old-age home beds in India. There are three types of management of old-age homes: charity, for profit, and public sector. The old-age home industry is mostly unregulated and minimum standards are needed.

Community Care The National Programme for Health Care of the Elderly, with outpatient, rehabilitation, and inpatient services, has been developed as a community program provided by district hospitals in partnership with the primary health care system. The central government provides financial assistance for manpower, medicines, and equipment; and the state governments manage the program. The impact of the program has not yet been assessed.

Geriatric Medicine In India, postgraduate training consists of a 3-year residency. While the 1990s saw the first academic department of geriatric medicine at Madras Medical College, Chennai, no further programs began until 2010, when three new departments were established at Amrita Institute of Medical Sciences, Koch; Christian Medical College, Vellore; and All India Institute of Medical Sciences, New Delhi. As of 2015, there are a total of nine postgraduate positions in geriatrics available in India every year. A proposed component of the National Programme for Health Care of the Elderly is to add Union Government support for 36 new annual postgraduate positions in geriatrics sponsored by 18 new geriatric medicine departments in 18 states by 2017. Barriers to implementing this program include lack of enthusiasm for a career in geriatrics, slow implementation of projects, and strict guidelines by the Medical Council of India, the sole regulating and licensing authority for medical education.

Unique features Despite a heritage of strong family support, India can be a difficult place to age if one lacks health and financial security. Universal pension and health insurance is not yet in place. In this climate of hopelessness, a new initiative for the very old (75+) from the central government holds promise and would be implemented all over the country by the year 2017. The National Programme for Health Care of the Elderly would earmark 50% of new beds, develop a home care program based in tertiary and secondary health care facilities, further develop human resources for care of the very old, and promote community services including influenza and pneumococcal vaccination, annual screening for early diagnosis of common health issues, information on healthy aging, yoga and alternative medicine, and use of mobile health services to improve access to health care. India is also witnessing a positive movement led by civil society institutions, visual media, and public opinion makers in support of older people.

A case study An 87-year-old woman, initially, relatively independent in ADL and intact in cognitive status, living in the extended family with support in instrumental activities of daily living (IADL), suffers from a stroke. If she is resident of a large city, she will reach a tertiary care center in the public or private sector within 2 to 6 hours, depending on recognition of the seriousness of the health issue by her family members and the family physician and, most importantly, the distance between her home and the health facility. If she is lucky to reach the hospital during the golden hours, she would be given a CT scan and thrombolysis in case of an ischemic stroke. However, if she lives in a smaller city or a village, the time difference between onset of symptoms and hospitalization would depend on the remoteness of her place of residence and distance from hospital. It is unlikely that such patients will be provided early diagnostic or therapeutic intervention.

Neurologists treat stroke in large hospitals. However, in smaller cities and smaller hospitals, stroke is managed by physicians who are not likely to be geriatricians. Access to rehabilitation services would depend on the location and size of the hospital. There is no dearth of rehabilitation professionals in India. However, their availability follows the same pattern as other health services in that much more is available in urban than rural areas. For the large majority of older Indians, stroke leads to substantial disability.

Asia: Japan

Japan has a population of 128 million people, of whom 25% are aged over 65 years. Life expectancy at birth is currently 84 years.

The health care system The delivery system is dominated by the private sector, which sponsors 80% of the hospitals and 95% of the physicians' offices. In both private and public sectors, payment is fee-for-service, but tightly regulated by a fee schedule. The national government determines the items, including dental services and drugs, their price, and

the conditions of billing. The private sector provides almost all of primary care and most inpatient care. Public sector facilities, which are subsidized by the government, provide services in isolated areas and the bulk of high-tech services. Of physicians, one-third are office-based, mostly solo practices, and the remaining two-thirds are based in hospitals.

All permanent residents must enroll in publicly mandated health insurance plans provided either by the employer, andextended to dependents, or by the local government if not employed. There is no choice of plans. Premiums differ according to the plan, reflecting the health expenditures of the enrollees. However, plans enrolling a high proportion of those with low income are subsidized by the national government and all plans must contribute to paying for the health care costs of elders 65 and older. Private health insurance is generally restricted to cash benefits while hospitalized or when diagnosed with cancer.

Health services are highly accessible, with 13 visits per year per capita, the second highest in the world and about twice that of the OECD 32 countries' average (2011). Patients pay 30% of the total amount as copayment. For those 75 and over, this rate is reduced to 10%, except for 10% of the elders who have incomes more than the average worker. Once the monthly copayment amount exceeds an average 80,100 yen (US $700) per month, the copayment rate is reduced to 1%. This ceiling is set lower for older adults and those with low income, and higher for those of high income.

Overall organization and services for older persons Hospitals and physicians' offices may proclaim any specialty and purchase any equipment. Physicians are not divided into specialists and general practitioners (GPs). Formal recognition of postgraduate training in general practice will only begin in 2017. Office-based physicians providing primary care have been trained as specialists prior to opening their practice. Most hospitals have developed from physicians' offices. Two-thirds of the hospitals have less than 200 beds, and almost all have large outpatient departments. There is little functional differentiation between hospitals and physicians' offices or among hospitals.

Hospital beds are divided into two types: general (acute and postacute care) and convalescent (chronic care). The former composes two-thirds of the nonpsychiatric beds. The latter composes the remaining one-third, which must have amenities such as a dining room in the unit. Conditions for billing are defined in detail in the fee schedule and are strictly enforced. Many private sector hospitals have both general and convalescent units.

In 1973, hospitals began to provide long-term care, when health care became free (no copayment) for older people. Although some copayment was later gradually reintroduced, this led to an unintended expansion of hospital-based long-term care. Beyond the general aging of society in Japan, this is another reason why public long-term care insurance (LTCI) was introduced in 2000. The LTCI integrated the financing and delivery of health and social services. The LTCI covered hospital convalescent beds, all Health Facility for Elders (HFE) beds, similar to nursing homes, but focused on discharging to the community, most visiting nurse and visiting rehabilitation services, and "medical management" (supervision of care by physicians). Social services provide home helpers for personal care (ADL support) and domestic tasks (IADL support), bathing service, loan of devices like wheelchairs, home reconstruction (putting in ramps and hand-bars, etc.), and nursing homes.

However, service overlaps between health insurance and LTCI remain. About half of hospital convalescent beds remained covered by health insurance and their number has continued to increase. LTCI convalescent units have decreased following the government's announcement in 2005 that they would eventually be abolished. Adult daycare and temporary "respite" stays in institutional settings were transferred to LTCI, but they have retained different standards and fees that had been set by health insurance and social services.

Unlike health insurance, LTCI services are only available after undergoing eligibility certification. This process consists of: (1) completing a 74-item form on physical examination, and mental status performed by a local government employee or person under contract, (2) putting the results into a computer, which groups the individual into seven levels or ineligible according to an algorithm, and (3) review by a local expert committee. This committee changes the level calculated by the computer, usually to a more severe level, based on the information in the forms written by the assessor and the attending physician. Income levels and the amount of informal care available are not taken into consideration. After eligibility has been determined, the individual can go to any certified care management agency of her choice for community care and be covered for LTCI services up to the amount set for each level (from 50,030 yen [US $400] to 360,650 yen [US $3000] per month), or ask to be admitted to any LTCI facility. There is a 10% copayment, with a ceiling for those with low incomes. All benefits are in the form of services, not in cash. LTCI is managed by municipalities and financed by social insurance premiums and taxes.

The implementation of the LTCI has led to dramatic increases in the number of older persons receiving services. The percentage of persons aged 65 years and older certified as being eligible increased from 10% in 2000 to 17% in

2005. In absolute terms, the number certified nearly doubled to 5.3 million in 2013, with greater increases for the lighter eligibility levels and for community care. Waiting lists for community care services have disappeared, but not for institutional care. Expenditures have doubled from 4.3 trillion yen in 2000 to 8.8 trillion yen in 2012 (1.8% of GDP), more than the 30% increase in health expenditures.

Hospital Geriatric Services There are hardly any specialist geriatric services in hospitals. However, of the total health expenditures, nearly 60% is spent by older adults 65 and over, so that most hospitals are focused on providing geriatric services, especially small to medium sized hospitals in the private sector. These hospitals also tend to deliver LTCI services, both in institutions and in the community. This facilitates the transfer of patients as their needs change. On the other hand, big hospitals have continued to focus on treating organ-specific diseases; they transfer their patients to other hospitals after the acute episode if they need postacute care.

Long-Term Institutional Care A considerable proportion of long-term institutional care is provided by hospital convalescent units financed by both health insurance and LTCI. There are two types of institutions unique to the LTCI: Health Facility for the Elderly (HFE) and nursing homes. Nursing homes are the most popular because they tend to have better physical facilities and residents are assured of being provided with care until their death. The waiting list for nursing home care is typically over 1 year. The occupancy rates of other types of LTCI facilities also tend to be high. One reason for their popularity is that most costs are covered if resident income is below average. Starting in 2015, assets will also be taken in consideration when assessing costs and will be limited to bank accounts.

The shortage of institutional care has encouraged the development of various types of "housing." Unlike the three types of formally designated LTCI "institutions," for-profits are allowed to own and operate them. They can be broadly divided into those that have in-house services, such as "adult group homes for Alzheimer," and those that have services contracted out to outside agencies, such as "housing with services." In the latter case, some have a home care agency, visiting nurse station and a physician's office located in the ground floor of the complex. Thus, they could be regarded as de facto institutions, except that the residents must pay the full costs of services and oversight responsibility is not clearly specified. The government plans on increasing the number of units from 150,000 units in 2014 to 600,000 in 2020.

Geriatric Medicine Geriatrics is not a recognized specialty, and only about one-quarter of medical schools have an independent department. As of January 2015, a Google search found 483 hospitals and physicians' offices that listed some form of geriatrics as an available specialty. Given the biological focus of medical training and the delay in the recognition of general practice as a specialty in Japan, the likelihood of geriatrics expanding rapidly is slight.

Unique features The health care system has no clear distinctions between generalists and specialists, between physicians' offices and hospitals, and between health care and long-term care. However, the fee schedule has affected provider behavior using economic incentives such as differentiating hospital beds into general and convalescent units, and increasing the number of physician home visits, while containing costs by lowering fees in areas such as MRI imaging where there have been inappropriate increases. It has also played a key role in maintaining quality by specifying and revising the conditions of payment. For example, in order to bill for rehabilitation therapy, the facility must not only meet the prescribed staffing level and equipment standards, but the patient must also have had the onset of the injury, stroke or other designated disease within 150 days. This period could be extended only for exceptional cases. This ad hoc approach to reform has been more efficient than attempting to restructure the system.

Most remarkable is the rapid expansion of community services following the implementation of the LTCI. Funding for LTCI has more than doubled since its implementation and, because benefits were restricted to services, access has improved dramatically. However, in comparison, institutional care policy has changed little, leading to a rapid growth of specialized housing. This has in turn led to a blurring of the line between "institutional care" and "community care."

A case study Under the best case scenario, the patient would be admitted to an acute stroke unit, transferred to a rehabilitation unit, and then discharged to her home. Prior to her discharge, a LTCI care manager would come and work with the hospital staff to draw a care plan: a weekly schedule for care workers to provide her with IADL and ADL support, and for visits by nurses and physiotherapists. If needed, ramps would be placed in her home before discharge. Her office-based attending physician would visit her on a monthly basis to provide medical supervision and provide information to the care manager. However, should the patient not recover her ADL functions, she would be transferred to a hospital convalescent unit or to a LTCI facility that has a bed available. She would either stay in the facility or be discharged to "housing with services." Her monthly out-of-pocket expenditures after discharge from hospital, assuming that she has an average income, would be about US $500 if she remains in the facility, and about

US $1500 if discharged to “housing with services.”

Europe: France

France has a population of 64 million people, of whom 18% are aged over 65 years. Life expectancy at birth is currently 82 years.

The health care system The health care system in France is a complex blend of administrative and service provider arrangements. It provides universal care for all legal residents, choice of providers, free health programs for the poor and disabled, and significant cost reimbursement by Social Security. Social Security is mandatory, consisting of several national private nonprofit schemes. Resources come from payroll taxes and specific taxes, and are used mainly to refund patients for the cost of ambulatory care and private hospitals, as well as direct payment to public hospitals.

General community-based medical practice is provided largely by independent “liberal” practitioners. However, fees are heavily subsidized by the national sickness insurance component of the Social Security, which contributes 66% of most health care costs and 100% in case of costly or long-term ailments.

Each person over the age of 16 has to designate a GP to his (her) sickness insurance scheme in order to obtain standard reimbursement for care, as well as for specialist consultations referred by GPs. If not, reimbursement is much lower.

Hospital care is provided by public and private hospitals. Around 63% of admissions and 64% of bed days are provided in the public sector. Public hospitals are administered by a Director appointed by the Director of the Health Ministry. There is a Directory of physicians and other health professionals who are funded mainly by the national sickness insurance according to annual activity. Patients contribute to a daily flat rate of 18 euros (approximately US $20). Private nonprofit hospitals contract with the health administration and function on the same basis as public hospitals. Around 27% of admissions and 22.5% of bed days are provided by for-profit clinics with fee-for-service physicians, paid entirely by patients and reimbursed by sickness insurance schemes at various rates. About 25% of hospital beds are in rehabilitation wards.

Overall, the Social Security scheme funds around three-quarters (76%) of total health expenditure. The remainder comes directly from individuals at the point of service or indirectly through supplemental coverage bought from private insurers, most of them nonprofit mutual insurers. Hospital services account for 46% of all recurrent health expenditures.

Overall organization and services for older persons

Introduction In general, older persons have the same access to general health care services as their younger counterparts. Specific services for older persons are mainly in the social and medicosocial care sectors. In these, responsibilities are fragmented in terms of administration, funding, and services for long-term residential, as well as home care. Since the mid-1980s, responsibility for organizing residential and home care has been decentralized to the level of the 100 local councils, assisted by the municipalities. The national government jointly administers care financed by sickness insurance at a decentralized regional level. Complexity is increased by the role of pension schemes for home help.

Hospital Geriatric Services Specialist hospital-based geriatric services vary in availability across territories. Regardless, the majority of large hospitals operate some form of inpatient acute geriatric service for frail older persons. They are funded by the sickness scheme equally with other services. Most teaching hospitals now operate specialist ambulatory geriatric medicine clinics, often including clinics for memory disorders.

Part of the geriatric service operates a postacute service model, accepting patients from acute hospital wards. Rehabilitation is generally provided in the public hospitals but rehabilitation units are also common in the private sector. Many rehabilitation wards admit a mix of older and younger patients. Some hospital geriatric units provide a blend of acute and postacute geriatric assessment and rehabilitation services. GPs who are qualified in geriatric medicine are sometimes available in smaller rural hospitals.

Long-term care hospitals with full-time physicians are specifically intended for older persons who lack physical independence, regardless of the cause. They are progressively becoming more residential. They sometimes provide postacute care.

Long-Term Institutional Care There are various types of long-term care institutions for older persons: “Etablissement d’hébergement pour personnes âgées dépendantes—EHPAD” (nursing homes for dependent older people), retirement homes, and residences with services. The first two are public or private nonprofit; the latter are mostly commercial.

Many have a part-time physician qualified in gerontology (different from geriatrics), but his or her responsibilities are often not clear as residents usually have their own private GP. Altogether, in 2011, there were 56.1 long-term care beds per 1000 people aged 65 years and older.

Sheltered housing, providing a studio apartment with kitchen and bathroom for one or two older persons has been progressively adapted to the needs of increasingly old occupants, with the installation of new equipment and the provision of some care beside community services. Therefore such facilities may be considered as part of long-term care; they represent an additional 10.0 beds per 1000 aged 65 years and older.

Community Care Since the 1960s, the government has supported a living-at-home policy that claims to be universal. Service implementation, however, has not achieved intended levels. The family still plays a major role in supporting and caring for older people. A national survey on impairment, disability, and handicap conducted in the year 2008 revealed that family help represented more than 75% of all assistance. Several measures have been taken to help informal caregivers of disabled older adults. Respite care enables the older person living at home with family to be institutionalized periodically or to attend daycare several days a week. This provides relief for the caregiver. Financial measures, such as a tax relief, help maintain the ability of families to provide care.

Home-help services and home nursing services have been designed specifically for older people. The former have been in existence for 50 years. The latter were created in 1981 and have been developing slowly. A nurse coordinates and organizes the various interventions by either registered or auxiliary nurses. The services most frequently carried out include help with ADLs, mobility, and the prevention of pressure sores. Since 1992, in order to facilitate employment, new home-help services have been designed to support handicapped persons.

In 2002, an autonomy allowance was created, specifically for dependent older persons living at home or in an institution. Responsibility for this allowance has been given to the local councils; eligibility and the amount of allowance are related to disability assessment by a medicosocial team using a national scale. This team proposes a personalized care program for those living at home. The copayment (15% on average, but up to 90%) is related to income.

Geriatric Medicine Geriatric medicine has been a recognized specialty in France since 2004. Geriatric medicine is a rapidly expanding specialty, with geriatricians representing one of the largest groups within internal medicine specialties. Geriatric practice is predominantly hospital-based, although many hospital services operate or are linked to community assessment teams, ambulatory clinics, and day hospitals. Specialist geriatricians undergo six semesters of theoretical and practical training during and after residency under the form of a Complementary specialized studies degree. An EHPAD may have a part-time GP qualified in gerontology. The qualification is obtained by a national gerontology capacity degree or a gerontology university degree.

Unique features Responsibility for financing, organizing, and providing health and social long-term care is fragmented, and there is poor coordination with acute care. The existing care system does not align well with the complex needs of older people with numerous, simultaneous, chronic, and disabling conditions.

During the last 30 years, demonstration projects have been undertaken to overcome the fragmentation of services and to achieve more coordinated care for older persons.

New developments focus on organizational models of care that target older people with dementia or who are at risk of loss of independence. One model involves enhancing case management within a multidisciplinary team that performs initial and follow-up geriatric assessment, and links health and social care providers within the geriatric team.

A case study In the best case scenario, a patient with a stroke will be admitted to a stroke unit and then discharged to a rehabilitation unit. Most often an older patient who has a stroke with moderate to severe disability would be admitted to an acute hospital. After a period of medical treatment (from 10 to 20 days), she will be transferred to a rehabilitation service, if there is some chance that she could return to the community. If function continues to improve, rehabilitation could be offered for up to 3 months. At discharge, a home visit would be conducted and an autonomy allowance may be provided. This allowance will provide an aide to assist with personal care and domestic tasks. The amount of the allowance will be determined by the patient’s disability level and the copayment will depend on her income. Home rehabilitation could be provided for several weeks or months, as needed, by an independent physiotherapist paid on a fee-for-service basis. Severely disabled patients, particularly those without a coresident caregivers, will often be referred directly for permanent residential care in long-term care hospital or nursing home.

Europe: Iceland

Iceland has a population of 0.3 million people, of whom 13% are aged over 65 years. Life expectancy at birth is currently 82 years.

The health care system Iceland's health care system is nationalized, though there are private sector providers. On the purchaser side of the system, two structures fund services: (1) the National Institute of Social Security, which is financed through the central government's budget and through employers' and employees' contributions and (2) the central government's annual appropriation, financed through general taxation, which directly allocates financial resources to hospitals and primary care services. The better and the less well-off use the same system, contributing copayments of 25% to 30% of the cost (with a limit on maximum expenditure). However, the copayments of older adults are one-third of what actively working citizen's pay; no copayments are required for hospitalization, rehabilitation, or home nursing care for older persons. Nursing home care costs the older person up to US $2000 per month, if their pensions are generous enough, and Iceland's national health insurance pays the balance of about US $5000 per month and covers whatever portion of the cost is not covered by a resident's pension. Older adults do not have to spend down assets other than their pension fund to pay for care.

Health care is organized regionally, through primary health care centers but without a gate-keeping function. Health care is funded through the central government's budget. Social services are organized regionally (albeit differently than health care) and are paid for by local governments. Social services include assistance with home care and daycare. The primary care model serves the countryside, but in the capital area of Reykjavik, there is ready access to specialty and subspecialty services.

Hospital care has become increasingly specialized with the merging of hospitals, particularly in the Reykjavik area. Similarly, geriatric hospital care has been strengthened with consolidation of services at the University National Hospital in Reykjavik. The Department of Geriatrics is divided into acute geriatrics, consultation service, rehabilitation (three units), dementia assessment and treatment unit, day hospital, and general outpatient clinic, falls clinic and memory clinic. Geriatricians participate in nursing home care delivery along with family practitioners.

Overall organization and services for older persons In 1982, the Icelandic government established laws on the affairs of older persons, which subsequently were revised in 1989 and 1999. The law's underlying principle is that autonomy of older people shall be respected. Older persons have a legal right to required services, and the state must meet their needs in a way that is relevant and economically feasible. Older persons must be supported in their homes for as long as possible, but have access to a nursing home if such a need arises. A dedicated tax of about US $40 per Icelandic person per year supports care for old people.

The laws mandated that a Nursing Home Preadmission Assessment (NHPA) be performed for anyone applying for a nursing home placement to confirm and grade the need for long-term care. A multidisciplinary team performs the NHPA; the team consists of a physician, a nurse, and a social worker. The assessment is standard in form and content and in effect is a comprehensive geriatric assessment. To be eligible, persons must have cognitive and or physical impairments to the degree that they are reliant on others or that a serious disease, such as cancer, congestive heart failure, or chronic obstructive lung disease, has entered its final phase. A diagnostic, therapeutic, and rehabilitation effort has to have been made. Similarly, people must have had a trial of appropriate home care, daycare, and respite care. Eligibility remains valid for up to 12 months. The NPHA system generates national and regional waiting lists for the 3700 nursing home dwellings currently available. Of the people with a valid certificate of need, the sickest or least functional are prioritized first for an opening. Although "home-made," this system opened the eyes of policymakers to the value of objective assessment and data gathering, and the NHPA influenced the further development of nursing home care in Iceland.

Hospital Geriatric Services Hospital care has become increasingly specialized with the merging of hospitals, particularly in the Reykjavik area. Similarly, geriatric hospital care has been strengthened with consolidation of services at the University National Hospital in Reykjavik.

Long-Term Institutional Care The content and quality of nursing home care were almost completely unknown in the early 1990s. Costs were considerable and the financing of nursing home care was variable. This began to change with implementation of the interRAI assessment system for nursing home care. Now all nursing home care is being financed based on case mix or resource utilization groups derived from the assessment data. Other spin-off effects, which are being developed, include the monitoring of quality of care and the generation of clinical guidelines for identified problematic areas, working from a database accumulated through use of the standardized assessment instrument.

Nationwide, 13% of Iceland's older people reside in nursing homes, although the figure is lower (9.7%) in Reykjavik. The average length of stay is now under 3 years. About half of all nursing home residents in Iceland have dementia, with some 20% more with less severe cognitive impairment.

Community Care Other aspects of care remain as incompletely understood as nursing home care once was. Health care policy allows older persons to stay at home as long as possible and supports them in doing so, but the needs of those in home care are not well documented. Alternatives within the spectrum of care were evaluated in 1997, when the interRAI instrument for home care became available. Collecting data at four community health centers in Reykjavik quickly raised questions about the quality of home care services. For example, older persons living in their own homes seemed to have more untreated physical symptoms than similar residents of nursing homes. This might be attributed to less teamwork in the home care setting. The typical home care recipient may go for long periods of time without seeing a physician. That so many older persons are lonely and never leave their homes leads to question the wisdom of the policy of having people stay at home as long as possible.

Home visits by family practitioners are all but extinct, except in emergencies, when it is just the on-call family practitioner who attends to the person and the primary care provider of that person is rarely involved. For the last 2 years, the interRAI HC assessment has been mandatory for all persons receiving in-home nursing care. This assessment technology is spreading to more communities.

Progress is also being made toward the eventual implementation of the other instruments in the interRAI suite. There are active plans to implement the interRAI Acute Care mini-suite of instruments at the University National Hospital in Reykjavik at the time of this writing. The mini-suite includes emergency department screener and assessment and acute care assessment for consultation and a post-acute care instrument.

Geriatric Medicine There are now 16 geriatricians and seven junior physician positions covering a population of 180,000. The geriatricians have all been trained abroad, in the United States, the United Kingdom, and Sweden. The junior positions are a part of an internship year or residencies in internal and family medicine.

Unique features Iceland's response to the need for care of old people has been both empirical and somewhat chaotic. The philosophy of care of old people is in many ways clear, but the system lacks comprehensive administration and is therefore fragmented (as is the health care system in general). The system has major drawbacks including: health care and social services within communities are not coordinated, in part because they are funded by different sources. Home nursing care is centralized while primary health care is decentralized. This means the nurses are left alone with the person and physicians do not make home visits or maintain home contact over time. This is particularly harmful when the person is too functionally impaired to visit a physician. Team work between nurses and primary care physicians with input from geriatric consultation seems to be the next most important task at the system level of geriatric care. The quality of care received by Iceland's older homebound persons is largely unknown, but with increasing use of systematic comprehensive geriatric assessment as formulated by interRAI this might change.

A case study An 87-year-old woman with acute stroke would most likely be admitted first to an inpatient neurology service, particularly if she is without cognitive problems and with limited comorbidities. If she had preexisting cognitive problems or several comorbid conditions, she would more likely be admitted to acute geriatrics. There is not yet a systematic approach to delivery of thrombolysis and this person would be an unlikely recipient of such treatment.

If she was admitted to neurology, she would be transferred in a few days to either rehabilitation or postacute geriatric care. Occupational therapists could help reconfigure her apartment, if that would make it possible for her to return home. Physical therapists could go to her home to provide maintenance therapy; respite care could be organized. She could receive meals-on-wheels, help with cleaning of the house, and home nursing care up to two times a day. Each professional would still make only very short visits. It is conceivable that she could go to a daycare center a few times each week. The issue would be how she would feel being mostly alone. She would in any case get rehabilitation commensurate with her potential for recovery. With great determination, this person could possibly go home, but the situation would be precarious and with even minor additional insults or problems, she would likely be admitted to a nursing home. That would also be the case if she was not motivated to go home, in spite of her being cognitively intact.

Europe: Italy

Italy has a population of 61 million people, of whom 21% are aged over 65 years. Life expectancy at birth is currently 83 years.

The health care system Since 1978, Italy has had a National Health Service (NHS), the Servizio Sanitario Nazionale (SSN), based on the principle of universal entitlement, with the central government providing free and equal access to preventive and medical care and to rehabilitation services to all residents. Coverage is essentially unlimited, although minimal fees may be assessed. These fees apply mainly to drug prescriptions (with the exception of so-called life-saving medications), laboratory tests, diagnostic investigations, and emergency room visits. Economic pressures led the government to recent unprecedented reforms. Italy is adopting a semifederal organization of health care delivery. Each of the 20 regions of the country is now responsible for independently organizing health services based on population needs. A national budget for health is set by the government each year (approximately 1000 euros per citizen) and then divided among the regions. In turn, the regions must allocate financial resources to nearly 300 local health agencies based on standard health-related indicators.

To guide and coordinate the care of older adults, the Italian parliament promulgated a document about frail older people needing continuing care. The "Progetto Obiettivo Salute dell'Anziano" (POSA) was not a law, but simply a series of suggestions and recommendations to local health agencies.

The POSA identified integration between health and social services as the key to satisfying the needs of these patients, delivering individualized and comprehensive care services. The POSA recommended the community-based geriatric evaluation unit (GEU) approach, with coordination by a geriatrician and participation from registered nurses, social workers, physiotherapists, and the patient's GP. Integrated home care (Assistenza Domiciliare Integrata [ADI]) and skilled nursing facility (Residenza Sanitaria Assistenziale [RSA]) were identified as the two major services.

Difficulties soon became evident. Health and social programs have been implemented irregularly in varying forms, mostly in northern regions and in rare, patchy areas of central Italy. In addition, community services are usually limited to social needs and the shift of health resources from hospital to community is not underway. Overall, the implementation of the POSA guidelines has been slow. Presently, 4.1% of persons aged 65 years or older are receiving community care and 1.8% live in a nursing home.

Overall organization and services for older persons The care system has been redesigned over the last 20 years, with shift of resources from acute care hospitals to community services. Regional health authorities assign available resources based on central government's directives, local, and political needs. As a consequence, the availability of long-term care and home care services is highly variable among the 20 Italian regions, which further widens already existing inequalities.

Hospital Geriatric Services Specialist hospital-based geriatric services vary widely in availability across regions. Use of acute hospital beds has changed in the last 20 years. There were seven acute care beds per 1000 inhabitants in the early 1990s, with marked regional differences. In 1993, hospital reimbursement shifted from a fee-for-service to a prospective system based on DRG and length of stay declined from 12.2 days in 1985 to 7.4 days in 2007. The occupancy rate for acute care increased from 69.3% in 1990 to 75.8% in 2006.

Long-Term Institutional Care Due to family structure and prior patterns of acute care use, long-term institutional care is rarely used in Italy. Only 1.8% of population 65 years or older is in long-term institutional care facilities. Italians have a family structure that—either because of choice or lack of availability—traditionally takes responsibility for the care of older persons, even when they become disabled. In southern Italy, this tradition is central to a culture that views care of older persons a natural responsibility of the family.

Long-term care is provided in residential or semiresidential facilities (RSA) and in community home care (*case protette*). RSAs are normally used for patients whose health status requires an intensive use of health care resources Health care services provided in RSAs aim to guarantee, within a specific period of time, the regaining and maintenance of residual physical and mental abilities, as well as the possible prevention of functional damage due to complex pathologies that do not need hospital admissions. RSAs can be managed either by public or private hospitals and provide care by physicians and nurses, therapists, medications, and functional aids. Costs are shared between the SSN and the patient, based on income. Patient copayments vary dramatically from region to region.

Community Care Community care is poorly implemented in Italy, with large variations across regions, but represents an effort at integrated service delivery through a home care model (ADI). The ADI care model is based on the formulation of a Personal Care Plan (Piano Assistenziale Individualizzato—PAI), according to an individual's care needs. Once discharged from hospital or upon a GP's request, a multidisciplinary unit (Unità di Valutazione Multidimensionale—UVM) of GPs, medical, nursing, and rehabilitative staff is activated to assess the patient's needs. A plan of care defines timetables, services, service providers, and responsibilities within the team and is led by a case manager. Nationally, 597,151 people received home care services in 2010; 990 cases per 100,000 were patients

receiving services under ADI, representing an increase of 11.7% compared to 2009. There is considerable regional variability in the implementation of ADI.

Geriatric Medicine Geriatric medicine is a rapidly expanding specialty, and geriatric services have progressively increased their importance within the context of evolving public health care. However, geriatric services vary across regions. In addition, public investments do not always follow demographic trends. As an example, every year the Italian Ministry of Education, University and Research (MIUR) sponsors fellowships in medical specialties, based on health care needs. For the academic year 2013–2014, 5000 fellowships were sponsored; among these 325 were fellowships in pediatrics (6.5%) and only 134 (2.7%) in geriatrics. The gap between geriatrics and pediatrics fellowships did not change in the prior 5 years and clearly does not follow demographic trends.

Unique features Italy has traditionally emphasized family care giving, particularly by female members. Older persons in need of long-term care often prefer to live at home, rather than in an institution. This choice is rooted in cultural and religious values, as well as the very limited availability of long-term care beds and high rates of home ownership among older Italians.

As Italian women have increasingly entered the labor market, and are no longer as available to serve as caregivers, the need for in-home caregivers has increased. This void has been filled by foreign-born caregivers (the *badanti*), paid either by older persons or by their families.

The high number of foreign-born caregivers is considered to be a panacea for the nationwide shortage of aides and services in general. Currently, there is an estimated one million *badanti*, costing Italian families more than €10 billion each year. These caregivers are not licensed, work without regulatory oversight, and nurture the "gray economy."

A case study Difficulties for a typical frail older person, having suffered a stroke but wishing to stay at home, are related to the limited availability of home care services. Only 2% of older adults in Italy receive home care services. Home care services are completely free, but given the paucity of resources, only young adults with cancer and/or disability or very frail and/or severely disabled older adults can access them. Therefore, older adults who are not admitted to home care and wish to stay at home—the great majority—rely almost entirely (both socially and economically) on their families or on their own resources. Either members of the family, or more commonly foreign caregivers (paid by the patient or by their family), care for the older adult at home.

Rehabilitation services provided by the NHS (and therefore free of charge) are also very limited, and preferentially reserved for young adults or healthy older adults without severe comorbidities. Private rehabilitation services are also available and easy to access if private funds are available.

If the individual or family cannot afford the costs of home care, long-term care may be the most reasonable solution. Long-term care is also paid for by the NHS, with a minimal copayment. However, due to the limited availability of beds, admission to long-term care may require a long wait (up to 6 months).

Europe: The United Kingdom

The United Kingdom has a population of 63 million people, of whom 17% are aged over 65 years. Life expectancy at birth is currently 81 years.

The health care system The predominant system is a comprehensive NHS, funded from general taxation and (mainly) free at the point of delivery. There is a strong emphasis on primary care, based around GPs (or family doctors). They are both providers of first-line medical management, and gatekeepers to secondary care. The devolved governments of Scotland, Wales, and Northern Ireland have responsibility for health affairs, resulting in divergence in policy, such as a greater emphasis on markets and performance targets in England, and free social care in Scotland.

The United Kingdom spends 9.4% of GDP on health, about the median for European countries. Only 5% of health spending is funded from insurance or private means. In general, the system performs well; a 2010 US Commonwealth Fund report on 11 developed nations, ranked the United Kingdom first overall and first for quality, efficiency, and access. There remains, however, a persistent suggestion that funding, staffing, patient experience, and access to the most modern treatments are not as good as elsewhere, and all parts of the service operate under severe pressure.

Overall organization and services for older persons There have been frequent structural reorganizations of the NHS since its foundation in 1948. Starting in 2012, the English NHS has been strategically directed by a quasi-autonomous body, NHS England. Local health care is commissioned by primary care-based Clinical Commissioning Groups from funds allocated by central government, using a nationally set tariff to reimburse a mix of NHS and private providers.

Policy promotes services delivered outside hospitals, minimizes emergency hospital utilization, including at the end of life. Despite this, emergency hospital admissions continue to increase at the rate of about 5% a year.

Best-practice hospital care, such as screening for delirium and dementia, assessing risk of venous thromboembolism, or geriatricians assessing hip fracture patients, and targets for access and safety performance are incentivized through a system of tariff "fines" for noncompliance.

Hospitals are relatively large, and provide secondary and tertiary care for populations of 200,000 to 600,000 persons. Emergency admissions are via GPs or open-access emergency departments.

Hospital Geriatric Services In some hospitals the majority of medical beds are on specialist acute geriatric medical wards, but this varies. Acute medical emergencies are usually admitted to a single admissions area under the care of an acute or general physician, pending triage to specialty-based wards. Recognizing that the predominant users of this facility are frail older people, increasingly geriatricians are responsible for their care, sometimes on dedicated "acute frailty units." These aim to ensure early senior planning, and that community alternatives to hospitals are used wherever possible. Patients who are admitted are usually very ill or very functionally impaired; half have cognitive impairment.

Old-age psychiatry is well established, but provided by separate NHS organizations from acute care. Hospital-based old-age mental health liaison services are common, making assessments, giving management advice, and education throughout the hospital, and linking with community mental health services.

Elective surgical patients will usually be "preassessed" and admitted on the day of operation. Geriatricians may undertake this assessment for more complex patients. In recent years, the NHS has made a major effort to reduce waiting times for elective surgery, which are rarely more than 3 months, mostly benefiting older people. Orthogeriatric liaison for fracture patients is widespread, and this is also available to other surgical disciplines, sometimes in the form of multidisciplinary outreach teams.

Private care is mainly confined to elective surgery. For some procedures, such as joint replacement or cataract surgery, private sector providers perform up to 30% of operations, some NHS-funded.

Long-Term Institutional Care UK policy is that older people should be maintained in their own homes for as long as possible, although, in practice, patients or relatives may not agree.

There is virtually no hospital-based long-term care. Since the 1980s, private providers have supplied almost all care home places, divided between residential homes ("board, lodging, and personal care") and nursing homes. This is classified as "social care" rather than "'health care," and involves user charges, abated or subsidized depending on income. About half of residents fund their care entirely themselves (usually by selling property). There are more people housed in the long-term care sector than all acute beds put together.

The quality of care is often criticized. Staff turnover is high, work-status is low, and the fees from public sources are incompatible with high quality. The casemix of care home residents is increasingly complex: up to 80% have dementia, most are immobile and incontinent, and median survival for nursing home residents is considerably less than a year. Medical care is provided by GPs, with variable support from community geriatricians, psychiatrists, pharmacists, and specialist nurses (including mental health, tissue viability, and continence). Medical care access is inadequate, but no clear alternative model has emerged. Some care homes have developed person-centered dementia care, end-of-life care and rehabilitation, and some are superior to hospital care.

Community Care General Medical Practices are either partnerships (with 1 to 12 medical partners) or directly employed by the NHS, operating from locality-based premises. GPs complete a 3-year training program, 2 years of which are spent in hospital specialties, but only some GPs will have training in geriatric medicine. Practices employ their own nursing and other staff. They undertake routine medical care for acute and chronic illnesses, including immunization, cardiovascular prevention, and long-term prescribing and medication review. Prescription drugs are free for older people. GPs are contractually responsible for individually "case-managing" patients over 75.

Older people with complex needs may also access community case management by senior nurses, working in partnership with GPs, providing a surveillance and coordination function, with the aim of preventing escalation of medical crises. The model of care is evolving, in particular the means of selecting those to target, and the extent to which links have been made with geriatricians. Caseloads are about 50 per nurse. The service is popular, but evaluations of effectiveness have been equivocal.

Separately, NHS community health providers employ community nurses, and provide "intermediate care" rehabilitation services. Several intermediate care models exist, the most successful being home rehabilitation, sometimes supporting early hospital discharge. The other main model is rehabilitation provided in care homes.

Intermediate care now forms the predominant rehabilitation provision, but tends to concentrate on simpler cases and those who are cognitively unimpaired.

Some geriatricians have duties outside the hospital (community geriatricians) including care home and intermediate care support. Old-age psychiatrists concentrate primarily on community-based services, have few inpatient beds, and take primary responsibility for the assessment and management of dementia.

Local government is the commissioner of "social care," which includes domestic and personal home care (provided either directly or through private agencies), such as meals at home, and daycare, and funding for care home placements, including respite care. Some home-based social care schemes are very intensive and sophisticated, such as specialist intensive home support for people with dementia. Local authorities employ social workers, some of whom are hospital-based. Resources are limited, and response times are often slow, causing some prolonged hospital stays. For patients assessed as responsible for funding their own care, delays in finding care home places (usually the responsibility of their relatives) are common, but there is wide regional variation.

Most dentistry and optometry are privately provided.

Geriatric Medicine Geriatric medicine is a well-established specialty, second in size only to anesthesia. With increasing demand, however, there is a relative shortage of geriatricians and posts remain unfilled. Training requires 5 years of higher specialist training following 3 years of junior hospital posts. Most geriatricians also practice general internal medicine, in particular for unselected medical emergency admissions. Many older people will not be admitted to hospital under a geriatrician, and a lively debate continues about how to define the most appropriate specialist for a given patient. A variety of models exist (needs based, age-related, integrated with internal medicine), with increasing attempts to define and operationalize "frailty" as a criterion.

Some subspecialization occurs, including falls, bone-health, movement disorders, continence, community, orthopedic, and mental health liaison. All-age stroke medicine is a separate subspecialty, with most stroke physicians being geriatricians (not neurologists).

Geriatricians operate in multidisciplinary teams, including nurses and various allied health professional therapists.

Unique features The large number of geriatricians, long tradition of rehabilitation, relatively low reliance on care homes, and emphasis on primary and out-of-hospital care are all distinguishing features of UK geriatric practice. There is considerable innovation and attempts to take geriatric medicine into places it did not traditionally function, such as surgical liaison.

Mental capacity legislation sets out a framework for assessing mental capacity to make decisions, and for decision-making processes for those who lack capacity. The law places strong emphasis on respecting autonomy and family engagement.

An important (but arbitrary) distinction exists between "health care," which is free, and "social care," which is means-tested (in England and Wales but not in Scotland). Residential care, the "hotel" component of nursing home care, and personal and domestic care delivered in the home are deemed "social."

Considerable effort is being made to promote service integration ("vertical" over time, and "horizontal" between different health providers and social care; which has long been the pattern in Northern Ireland), the antithesis to previous policies of fragmenting and marketizing the system.

The health and social care system is heavily regulated and inspected, with strong emphasis on performance targets (waiting times for outpatient assessment, surgery, or time spent in an emergency department before admission or discharge), and adverse events (such as hospital acquired infections or pressure sores).

A case study An 87-year-old with acute stroke, residual disabilities, social isolation, and the will to return home would almost certainly be able to do so. She would usually be admitted under a specialist stroke service, staffed by geriatricians, to receive comprehensive acute and rehabilitation care. Initial care would be multidisciplinary, with early medical, nursing, physiotherapy, occupational therapy, and speech and language therapy for communication and swallowing problems, and dietetics. Best practice would include early contact and information gathering from relatives, prior caregivers, and GP.

After medical stabilization, and when it had become clear that more prolonged rehabilitation would be required (probably after a few days), she would be moved to a subacute or rehabilitation ward, either at the same hospital or elsewhere. Depending on the local facilities available, she may move on to an intermediate care rehabilitation situation, eating either in a care home or at home. For someone living alone, typically this would be toward the end of rehabilitation, when specialized physiotherapy was no longer required, and when independent toileting was achieved.

Specialist longer-term ongoing at-home stroke rehabilitation and speech and language support may be available.

This would be supported by a domiciliary social care package providing up to four visits a day, for personal care, domestic tasks, shopping, and meals. Common difficulties will include timely access to the most appropriate admissions ward, delay in transfer to a rehabilitation ward, and delays in instituting social care, or finding a care home (if that is what she chose).

Oceania: Australia

Australia has a population of 23 million people, of whom 14% are aged over 65 years. Life expectancy at birth is currently 83 years.

The health care system The organization of the health care system in Australia is a complex blend of administrative and service provider arrangements. General community-based medical practice is provided largely by independent "private" practitioners. However, the fees are heavily subsidized by the national government through the "Medicare" scheme. Personal contributions by older and less well-off citizens are minimized. The scheme also subsidizes medical costs in private hospitals and the provision of pharmaceuticals, through the Pharmaceutical Benefits Scheme in the community and private hospital settings.

Hospital care is provided by public and private hospitals. Around 60% of admissions and 70% of bed days are provided in the public sector. Public hospitals are administered by state governments (there are nine states and territories), and are jointly funded by the national and state governments. Public hospital care is provided free of charge, regardless of financial status.

Citizens with private health insurance can use private hospitals. About 40% of the population purchases insurance from independent health insurance agencies. Persons holding private health insurance, however, can elect to use public hospitals and, when doing so, may elect to be admitted either as a "public" or "private" patient. In the latter instance, they may have some choice of their treating physician and access to slightly better physical facilities.

Primary care practitioners (or GPs) act as "gatekeepers" to specialists, including geriatricians. Medicare subsidizes only specialist consultations that are referred by GPs.

Overall, the Australian government funds around two-thirds (68%) of total health expenditure. The remainder comes either directly from individuals at the point of service or indirectly through private health insurance. Hospital services account for 35% of all recurrent health expenditure.

In spite of the level of complexity, the overall impression of the Australian health care system is one of good accessibility and equity.

Overall organization and services for older persons Specific services for older persons exhibit a similar level of complexity of administrative and service arrangements to those of the general health system. Long-term residential care is fully administered by the national government, whereas home care is a complex array of programs, some jointly administered by state and national governments and others administered by one or the other.

Hospital Geriatric Services Specialist hospital-based geriatric services vary widely in availability across jurisdictions. They are state funded, but in some states, the establishment of such services is unplanned and often left to the discretion of individual hospitals. In other states, real attempts to plan services are made. Regardless, the majority of large hospitals operate some form of inpatient geriatric service. Predominantly they offer a "postacute" service model, accepting patients from acute hospital wards. Postacute care is rarely provided in long-term care institutions.

Inpatient rehabilitation services are widely available, although the lack of any planning framework results in some areas of poor availability. Rehabilitation is generally provided in the public hospitals, but rehabilitation units also are common in the private sector. Many rehabilitation wards admit a mix of older and younger patients. Some hospital geriatric units provide a blend of acute and postacute geriatric assessment and rehabilitation services. Respite care is provided mainly in long-term care institutions.

Most major tertiary hospitals now operate specialist ambulatory geriatric medicine clinics. In many instances these include clinics for memory disorders, falls, and incontinence.

Specialist geriatrician involvement in smaller rural hospitals, often hundreds of kilometers from metropolitan centers is usually available through an infrequent (monthly or ad hoc) visiting service. Although recent expansion of telemedicine capability and payment systems is enabling many hospitals to access specialists through video-consultation.

Long-Term Institutional Care Long-term care is delivered by a mixture of government, for-profit, and not-for-profit organizations. National government funding is provided on the basis of a locally developed, dependency-based system.

User contributions are based on assets and means testing, and are subtracted from the government funding. This results in the levels of funding available for care being approximately the same regardless of the resident's ability to pay.

The level of provision of services is governed in a variety of ways. Long-term residential care is tightly controlled by the national government according to a planning formula, which stipulates the ratio of beds to aged population (70+ years) at a state and regional level. Since this strategy was introduced in 1986, there has been increasing equity of provision across the nation. Certain aspects of community care are similarly regulated. So-called "packaged care" is made available on a places-per-aged population basis. These programs (entitled community-aged care packages) attract a subsidy-linked loosely to the equivalent cost to government of low-level residential care. The other major community care program (the Home and Community Care program) provides a wide array of services but generally at a lower level of intensity than the packages referred to above. In both programs, the user contribution is modest, making home care highly affordable. Access can be limited, however, because service demand often exceeds supply.

Community Care Over the past 30 years, the national government policy has promoted a shift away from institutional to community care, although the level of provision of the former remains comparable to other developed nations. Government investment in community care is expanding considerably in real terms.

Eligibility for residential care is controlled through a national Aged Care Assessment Program, which comprises regionally based multidisciplinary teams of nurses, allied health personnel, and usually geriatricians. These services typically present themselves as services to individuals and families, offering advice and short-term case management in addition to their gate-keeping role for residential care and packaged community care.

Postacute community service provision is more complex with varying levels and types of services being provided across jurisdictions. In 2006, a national "transition care" program was established to provide short-term therapy and personal care services following hospital admission. Overall, community services are widely accessible to the majority of citizens with need. Small copayments are usually required to access services. Alternatively, more wealthy individuals will secure assistance on a privately funded basis.

Geriatric Medicine Geriatric medicine is a rapidly expanding specialty, with geriatricians representing the one of the largest specialties within internal medicine. Geriatric practice is predominantly hospital-based, although many hospital services operate or are linked to community assessment teams, ambulatory clinics, and day hospitals. Specialist geriatricians undergo training under the auspices of the Royal Australasian College of Physicians. The program comprises 3 years of general or "basic" training followed by 3 years of "advanced" training within the specialty. Medical services for residents of long-term care facilities are provided by GPs.

Unique features In the ambulatory setting, the Medicare Benefits Schedule provides two special payment arrangements that support older people. The first—the "75 plus" assessment—facilitates an annual comprehensive review by a GP of medical and functional status of all persons aged 75 years and over. Another item is designed to support "comprehensive geriatric assessment," performed by an accredited geriatrician. This enables a geriatrician to allocate up to 2 hours, with appropriate remuneration, to conduct a comprehensive case review and develop a care plan in collaboration with the GP.

In 2011, in response to the limited access to specialists for people living in rural and remote Australia, and for those living in residential aged care facilities, the government introduced generous "telehealth" item numbers to enable consultations to be conducted by video-conference. This is gradually improving access to geriatricians and other specialists for older individuals living in these settings.

A case study An older patient sustaining a stroke with moderate to severe impairments would almost always be admitted to an acute hospital. Thrombolysis could be offered, if indicated, in large metropolitan hospitals. After a period of medical treatment, around 10 to 20 days, transfer to a rehabilitation service would be typical, provided there was some prospect of returning to the community. Severely disabled patients, particularly those without a coresident carer, will often be referred directly for permanent residential care. Rehabilitation is offered for up to several months, provided functional gains continue and the prospect of returning home remains. A home visit would be conducted, with aids and appliances provided as needed. At discharge, a blend of in-home and center-based rehabilitation would be offered, for at least 3 months if required. Subsequently, daycare, personal care assistance, and general home-maker services typically would be available.

STANDARDIZING ASSESSMENT INFORMATION ACROSS NATIONS AND CARE

SETTINGS

Health care systems in different countries worldwide have elected to confront the same demographic changes with a heterogeneous array of schemes and possible solutions. In the introduction to Home Care for Older People in Europe, Raymond Ilsley noted in 1991 that it was impossible to compare systems of different countries and to identify a model of health care organization and delivery that could be considered a reference. He wrote: "We were surprised at how little experts on these services in their own countries knew about practices, or even principles, pursued in other countries. Services had emerged nationally, not through cross-country observation and learning. Because systems have developed in response to local circumstances, it is impossible to pick and choose and put together a mosaic of the best bits."

Over 20 years later, there is still little information about the effectiveness or efficiency of health care systems. Hence, health care providers and policymakers continue to find "local" solutions, but these remain limited and nonreproducible experiences. In the field of geriatric medicine and health services organization for older people, there is limited evidence on which to base efficient models of care. Currently, few data are available on health care organization; comparisons across different approaches in terms of patient outcomes and resources utilization have rarely been performed. A major obstacle to a systematic approach to evidence-based practice has been the use of different, noncomparable, assessment instruments, protocols, and procedures.

CGA is considered a core "technology" of geriatrics, and its application is thought to result in a better quality of care by providing information on comorbidities, syndromes, socioeconomic problems, and functional and cognitive deficits. CGA facilitates development of specific and sensible care plans for individual patients. CGA typically is performed with variable measures and scales according to individual geriatrician's knowledge and access, limiting the ability to measure cross-population health and functional status. Health services are even less well studied. Thus, what constitutes best practices in terms of geriatric services remains largely unknown.

Standardization of assessment information associated with CGA can provide a mechanism to draw comparisons among like services in different nations, and if configured appropriately, even across care settings within and among nations. The interRAI suite of assessment systems was designed to meet this requirement. It is described here as an exemplar of how clinical information in geriatric medicine and aged care can efficiently deliver vital information for clinicians, administrators, planners, and policymakers.

Multisetting Assessment Systems: The interRAI Suite

Typically, clinical services make use of a patchwork of syndrome-specific tools to "compile" a structure for decision support within the CGA process. On the other hand, organizations such as the interRAI research collaborative construct instruments "from the ground up." Such instruments comprise clinical observations, and derivative applications to create scales, diagnostic and risk screeners, triggers for care planning, quality indicators, and casemix systems—these are "second-generation" assessment systems. In 2006, interRAI released a "suite" of second-generation tools that shared a large core of identical clinical observations and scales, thus enabling comparisons across care settings (such as hospital, home care, and long-term care)—a "third-generation assessment system."

These instruments have been used extensively to draw comparisons across nations and jurisdictions within them. Two important multination research projects in Europe in home care and long-term care have been influential in identifying different patterns of service use, clinical outcomes, medication use, and quality issues which, in turn, have influenced policy in several nations. Data extracted from large databases (with in some cases millions of assessments) have enabled similar examinations among nations and jurisdictions and organizations within them.

These systems have been adopted at an organizational level (e.g., a nursing home) or by state or nations (e.g., the interRAI Home Care and Long Term Care systems in New Zealand). Several nations and states have adopted multiple suite instruments (e.g., Belgium and Ontario, Canada). These early suite adopters are exploring the utility of multiple compatible instruments to facilitate cross-setting continuity of care (a clinical benefit) and comparisons of caseloads across settings (a policy benefit).

The existence of large databases, often with multiple repeated assessments of individuals over time provides unique opportunities to examine utilization trends, service outcomes and quality of care. Researchers are able to use these databases to refine predictive tools, such as risk of hospitalization and transition to long-term care, which assist clinicians and planners to target preventive and supportive interventions.

CONCLUSION

In 1950, there were 205 million persons aged 65 years or older throughout the world. Fifty years later, the number had increased threefold to 606 million. By the year 2050, the number of older persons in the world will exceed the number of persons aged 5 years or less for the first time in history; it will reach nearly two billion. The older population is growing faster than the total population in practically all regions of the world, and the difference in growth rates is increasing.

However, the more developed countries are in general in a more advanced stage of the demographic transition. The proportions of older persons in those countries, therefore, will remain significantly higher than the proportions in the less developed regions well into the twenty-first century (**Figure 6-5**).

In contrast with the slow process of population aging experienced in the past by most countries in the more developed regions, the aging process in most of the less developed countries is taking place over a much shorter period of time, and it is occurring on relatively larger population bases. As a result, the number of older people is increasingly larger in the less developed countries. Over the last century, the number of older adults increased globally by an average of eight million persons every year. Of this increase, 66% occurred in the less developed countries. Over the next half century, this trend will intensify. In the more developed countries, the number of older adults will increase by about 70%, from 231 million in 2000 to 395 million in 2050. In contrast, in the less developed countries, population aging will more than quadruple, from 374 million to 1.6 billion. By 2050, nearly four-fifths of the world's older population will be living in less developed countries (**Figure 6-6**).

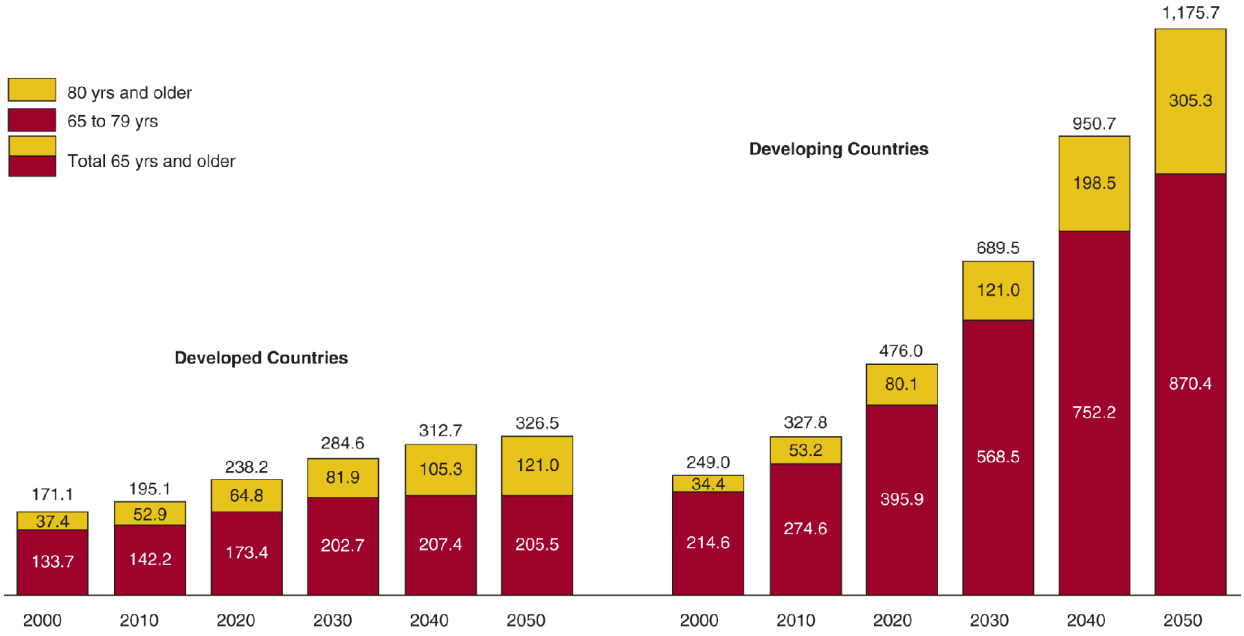


FIGURE 6-6. Population (in millions) aged 65 y and older in developed and developing countries by age: 2000–2050. (Reprinted with permission from US Census Bureau, Current Population Reports: 65+ in the United States.)

This chapter has highlighted that even the wealthiest countries in the world are finding themselves unprepared to confront the demographic changes. There is an extreme heterogeneity of the organization that each country has constructed within their respective health care services, and a substantial fragmentation into an array of services of unproven efficacy and efficiency. If this experience does not inform the policy decisions of the countries where most of the older adults will live in the future, it is highly foreseeable that there will be tremendous challenges for government and private spending in health care and, more generally, for economic growth and welfare.

One possible solution is to develop more integrated and interdisciplinary care models of services. The transition to this model will require a major reorganization of health care from education through delivery systems. Standardized assessment instruments that allow a cross-talk among different health care services might facilitate this transition to interdisciplinary care models, determine appropriate services based on need, and evaluate effectiveness and efficiency of specific services. Experiences in every country should inform practice and policy in other countries. Aging is a global issue.

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OECD, www.oecd.org.

interRAI, www.interRAI.org.

Chapter 7

Psychosocial Aspects of Aging

Steven M. Albert, Daphna Gans

Learning Objectives

- Apply the life course perspective to the aging process to show how the experience of aging depends on cultural factors, such as the conceptualization of the lifespan, as well as lifespan changes in affective experience.
- Identify core psychosocial factors and the mechanisms by which they affect health and well-being in older adults.
- Examine the significance of resilience, the process by which older individuals adapt to challenges associated with disability and declining health.
- Recognize current trends in common old-age transitions such as retirement, widowhood, and caregiving.

Key Clinical Points

1. **Lack of support (social isolation and loneliness) has a negative effect, and social engagement (volunteering, lifelong learning, and involvement in intergenerational programs) has a positive effect, on health and well-being in old age.**
2. **Social environments that promote aging in place support psychosocial health.**
3. **The aging services network is important in promoting engagement across diverse domains.**
4. **Hospice supports the psychosocial health of caregivers who provide end-of-life care.**

OVERVIEW

As people age they experience changes in physical and cognitive capacities, such as gait speed and reaction time, and also changes in emotional experience and social interests. Cultures impose an order on this continuum of change in widely shared understandings of the life course, which partition the lifespan into different stages. One of the most famous is Shakespeare's seven ages of man (*As You Like It*, II, 7). The Elizabethan stages of life include infancy, "whining school boy … creeping unwillingly to school," lover, soldier ("seeking the bubble reputation even in the cannon's mouth"), judge, and then two stages of decline: initial loss of capacities ("big manly voice, turning again toward childish treble") and finally "second childishness and mere oblivion … *sans* teeth, *sans* eyes, *sans* taste, *sans* everything." Other cultures are more charitable in their ideas about advanced age. The Samia people of Kenya describe old age as a pleasant time to sit before the fire and be fed. Such differences in thinking about the life course remind us that psychosocial aging is governed both by biological and sociocultural elements. A major focus of developmental approaches to psychosocial aging is to distinguish between invariant biological change and cultural constructions that selectively emphasize particular transitions in this continuum of change.

Life Course Developmental Perspective

There is no single age at which we can say that people cross the threshold into "old age." People age at different rates; hence, for any given age, there will be great variation in all proposed biomarkers of aging or phenotypes of healthy aging. For example, in the United States, establishment of the Social Security system linked old age to age 65. This definition of old age is more a product of social perceptions and economic necessity than anything else.

But people do have an idea of when they become old. A number of surveys have asked at what age someone is old. The start of "old age" can be assigned to a wide range of chronological ages. Choices of an age for "old age" tell us the decade when people are expected to slow down, retire, and focus on self-maintenance rather than new careers or goals. **Figure 7-1** shows the age at which respondents consider women to be old. These data are drawn from the National Council on Aging *Myths and Realities of Aging* survey, conducted in 2000 in a national probability sample of the US population. The data are weighted to reflect the sampling scheme and overrepresentation of older people and minorities. The figure plots the mean age "the average woman" is said to be "old" by respondent's age and sex.

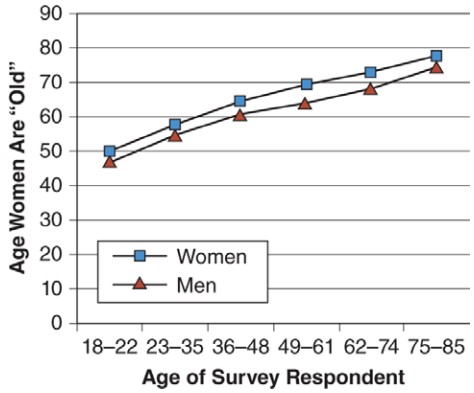


FIGURE 7-1. Reported age women are "old," United States, 2000. (Source: Albert SM, Freedman VA. *Public Health and Aging: MaximizFunction and Well-Being.* New York, NY: Springer Publishing Com 2010.)

Note the strong relationship between the survey respondent's age and his or her report of when women are old. Clearly, young people consider the start of old age to be much earlier than older people. For people around age 20, women become old at age 45 or 50. By the time respondents reach their sixth or seventh decades, old age is pushed back to the late 60s and early 70s. Note the strong gender difference in reports of when a woman is old. Female respondents date the start of old age to a later age than men, whatever the respondent's age. Women consider old age to begin 2 to 4 years later than men. These differences suggest a need to consider social elements when examining perceived age-related changes.

Cultural Variation in Definitions of the Life Course

The relevance of social or cultural factors in conceptions of the life course is evident in the "infantilization" of older adults, such as use of baby talk or saccharine language applied to the frail or very old. Cognitive anthropological studies show that cultural dimensions, such as productivity, vulnerability, and reproductive potential, underlie judgments of "young," "middle-aged," and "old." In one pile sort study, respondents were asked to group hypothetic age-linked social statuses according to similarity. Multidimensional scaling analyses revealed that respondents grouped old people and children together as opposed to people of middle age. This cultural logic may explain why baby talk is often applied to older people with cognitive impairment or other disabilities and terms typically reserved for children are often applied to older people. The reverse is also true: younger adults who are not active, not interested in new experiences or travel, not willing to switch careers, or who are slow, deliberate, or narrow-minded, are often called "old" or "old before their time."

Even this brief discussion of the use of age criteria to label behaviors suggests that attitudes toward aging and old age are mostly negative. Old age is mostly seen as a time of decline, withdrawal, vulnerability, and reversion to childhood. In this view, aging is not welcome and little should be expected of older people, except perhaps to ease decline, provide care, and protect people from exploitation or danger related to their increased vulnerability. These are the elements of "ageism": assumptions of disability or vulnerability (and hence need for protection) based on age, rather than actual competencies. A goal of developmental approaches to psychosocial aging is to avoid such oversimplifications and cultural biases to determine the range of changes in social, affective, and cognitive experience associated with aging.

DEVELOPMENTAL CONSTRAINTS ON RESILIENCE AND THE STRESS PROCESS

Understanding the role of psychosocial factors in late life requires that we first take a high altitude view of human

development to identify the basic biological and social forces that fundamentally shape the development of people as they age and the ways they respond to challenges associated with aging. These forces are typically viewed as constraints and can be briefly summarized in four propositions.

The first is that biological development follows a sequential pattern. Although there is considerable interindividual variability in biological development, overall biological resources across the lifespan resemble an inverted U-function. During childhood and adolescence, cognitive and physical abilities increase and provide the basis for the development of complex motor and cognitive skills. Physical development plateaus during early adulthood and then later declines. In old age, declines in both physical and cognitive functioning are evident.

Second, societies impose age-graded structural constraints on development. Lifespan psychologists and sociologists emphasize that all societies can be characterized as having age-graded systems that constrain and provide a scaffold for life course patterns. These patterns provide predictability and structure at both individual and societal levels. A prototypical case is childbearing in women, which is shaped by both social institutions and biological constraints.

Third, life is finite. Whatever is to be achieved or experienced in life has to be done in a limited period of time, typically fewer than 80 to 90 years. At any given point in an individual's life, the anticipated amount of time left to live may shape behavior and affect in important ways.

Fourth, genetic endowment is a limiting factor on the biological and behavioral functioning of the individual. Although the potential behavioral repertoire of humans is vast, the capacity to achieve extraordinary levels of functioning in a given domain is often constrained by genetic makeup.

In this view of development, the accumulated resilience or adaptive capacity of individuals will vary as function of the individual's location in the life course. For example, the biological and physical reserves of an individual will generally be greater for persons in young adulthood than for persons in old age. Conversely, behavioral resources and psychological reserves may be greater at older ages because of accumulated life experiences, acquisition of skills, and increased knowledge. In addition, a given stressor will likely activate different psychological and behavioral processes in varying intensities as a function of the individual's position in the life course. Finally, because of fundamental changes in age-related biological functioning, the type and intensity of biological pathways activated by stressful encounters as well as the manifestation of overt disease will also vary as a function of the individual's position in the life course.

PSYCHOSOCIAL FACTORS, HEALTH, AND QUALITY OF LIFE

Psychosocial aspects of aging are involved in changes in many domains, including work, retirement, residence, sexuality, stress, widowhood, emotionality, mental health, social support, and friendship, to name just a few of the domains that might be discussed within a psychosocial framework. Even limiting psychosocial factors to those relevant for health and quality of life nets a wide variety of topics. A broad conceptual framework identifying key psychosocial factors is presented in **Figure 7-2**. At the far left, the model identifies a broad array of *sociodemographic characteristics* that directly and indirectly shape individual development, quality of life, and health throughout the life course. For example, many of the health disparities in our society, such as differences in life expectancy or risk of low birth weight, have been linked to socioeconomic status (SES), race, and gender.

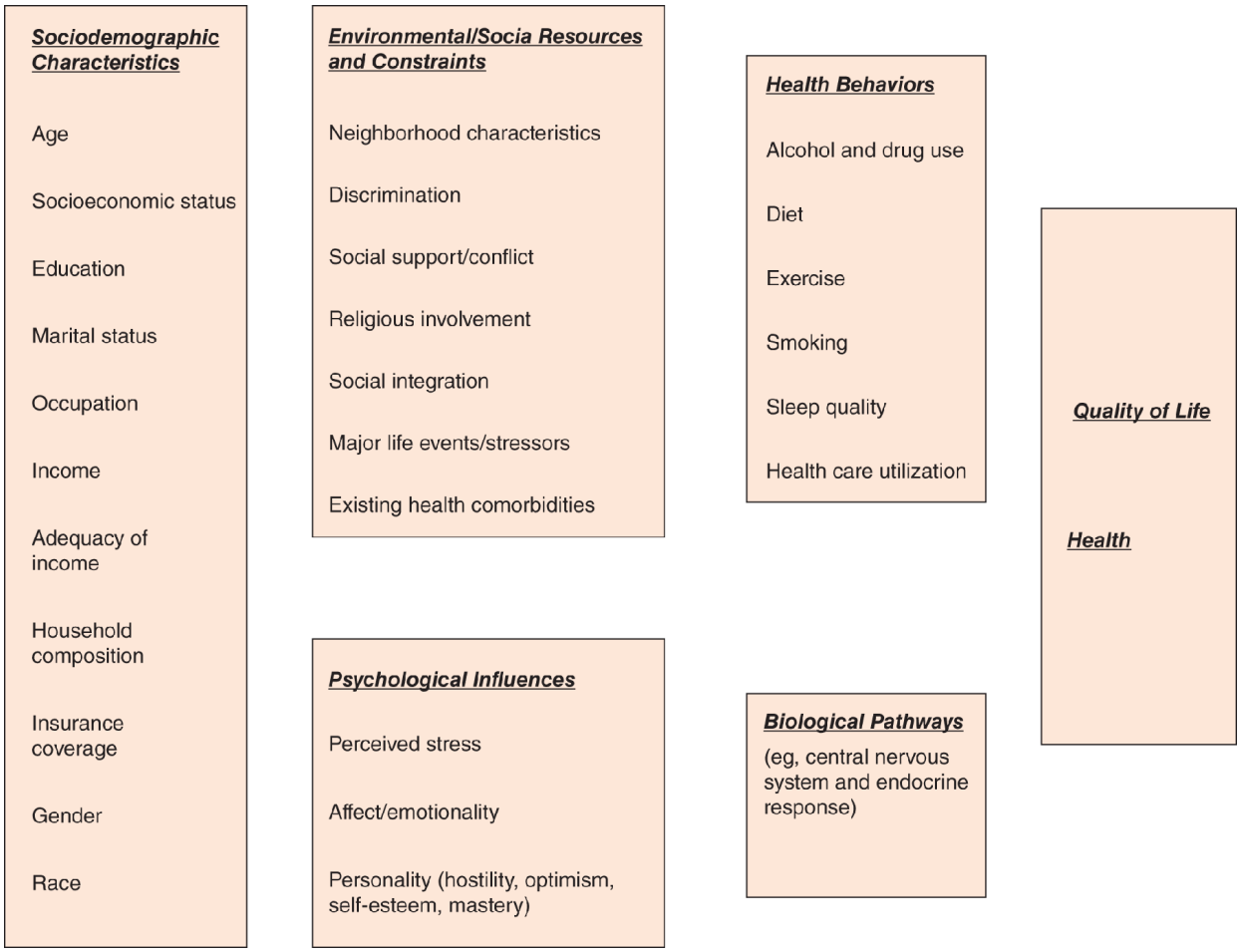


FIGURE 7-2. Psychosocial factors and health and quality of life.

Environmental and social resources and constraints include multiple indicators known to affect health outcomes, including physical and social characteristics of environments. Discrimination, negative life events, and existing comorbidities can be major sources of constraint, while religious involvement and social support are often important protective resources.

Psychological influences include both positive and negative factors, including optimism, self-esteem, mastery, and control. Negative effects, such as depressive symptoms and perceived stress, affect health through their impact on behaviors and through biological pathways. The effects of psychological and social/environmental factors on health are often mediated by *health behaviors* and through *biological pathways*, such as the central nervous system and endocrine response. Although the causal links between these groups of variables are still debated (hence no arrows are shown in the figure), all are clearly important contributors to health and quality of life. In highlighting core psychosocial factors and mechanisms linked to health and well-being, we discuss four psychosocial domains—social relationships, stress, personality, and affect—that are critical to understanding health and quality of life in old age.

SOCIAL RELATIONSHIPS

Social Integration, Friendships, and Social Networks

Social integration is the degree to which an individual is involved with others in a larger social structure and community. Maintaining social relationships is critical to the health and well-being of older adults. Involvement in satisfying relationships is associated with physical health, including, for example, decreased risk of cardiovascular disease, functional decline, and mortality. Positive social interactions further support the psychological well-being of older adults through helping them maintain meaning in life, and such interactions are also associated with increased sense of life satisfaction and happiness.

When attempting to understand the mechanisms by which social support affects health and well-being, there are two potential explanations. One, the buffering hypothesis, suggests that social ties and social support promote health by

acting as buffers to the effects of life stressors and negative events. Another is the direct effect hypothesis, which suggests that social ties and social support have a positive impact on health irrespective of the presence of stress. By the same token, negative social interactions may have detrimental effects on health and well-being.

It is important to consider the composition of social networks, which includes the number of family members, friends, neighbors, and acquaintances, and the density of social ties within networks. However, beyond network structural features, such as composition and size, it is important to examine the characteristics of networks, including diversity of ties and frequency of interactions. Research indicates age differences in the size and composition of social networks that suggest that networks grow smaller with age. Yet at older ages smaller networks include larger proportions of well-known social partners. According to socioemotional selectivity theory, discussed below, these changes serve an emotional regulatory function for older adults. Smaller networks with well-known social partners allow older adults to increase predictability in their social interactions, that is, maximize positive and minimize negative interactions. Based on this theory, the smaller size of networks in old age, therefore, does not necessarily indicate lack of support, but may instead be a protective factor for health and well-being depending on the quality of relationships with network members.

Social Isolation and Loneliness

Research suggests that a low level of social activity and social contacts is associated with poor functional outcomes. Loneliness, or perceived social isolation, rather than objective social isolation, may be most important for health effects. Population-based studies show that loneliness is associated with increased morbidity, including cardiovascular illness, coronary heart disease, and depressive symptoms, as well as mortality. Loneliness has also been associated with personality disorders and psychoses, suicide, impaired cognitive performance and cognitive decline over time, and increased risk of Alzheimer disease.

These detrimental effects of perceived social isolation indicate that lack of social support is strongly associated with health and well-being. While other risk factors, such as smoking and sedentary lifestyle, receive much attention, loneliness needs to be better recognized as a risk factor. Interventions that address social isolation, such as programs that involve enhancing social skills, providing social support, or increasing opportunities for social interaction, may help to reduce isolation; but it is also important to target loneliness directly in order to see benefits in health and well-being. Successful interventions may involve addressing maladaptive social cognition through cognitive behavioral therapy or reframing perceptions of loneliness and personal control.

Family and Intergenerational Relationships

The intergenerational solidarity paradigm is a common model for assessing intergenerational relations in the context of aging families. It allows for a comprehensive integration of behaviors, attitudes, values, views, and structural arrangements that bind generations. The intergenerational solidarity paradigm includes seven dimensions:

- Affective solidarity (sentiments of emotional closeness)
- Conflict (negative expressions of emotions and arguments)
- Associational solidarity (social interaction and frequency of communicating)
- Structural solidarity (opportunity for interaction based mostly on geographic proximity)
- Normative solidarity (filial obligation or filial norms, which includes attitudes toward help and support from adult children to aging parents)
- Consensual solidarity (perceived and actual agreement on values and opinions)
- Functional solidarity (provision or exchange of financial, instrumental, and social support)

A plethora of studies have demonstrated connections across solidarity dimensions, showing that intergenerational relations are more complex than just a sense of closeness or conflict. Studies demonstrate that the emotional content of intergenerational relationships, both positive (closeness) and negative (conflict), is associated with the likelihood of providing support in aging families.

Social Support and Family Caregiving

The widely held belief that contemporary families do not provide care for their aging members has been disproved by years of research. In fact, families continue to be the mainstay of long-term care and social support to their aging members. While a majority of older adults in the United States live in independent households, older adults rely on

children for needed support. Furthermore, families are viewed by policymakers as social units that are ready, willing, and able to meet the growing needs of older adults; in fact, they are expected to provide help to aging family members at times of need. While spouses, mainly wives, provide most family caregiving support, adult children provide the bulk of care when a spouse is absent or unable to care.

While it is difficult to classify types of support, the literature typically discusses four forms of support exchanged across generations: (1) *emotional support*: the expression of empathy, caring, concern, and love; (2) *instrumental support*: provision or direct assistance in instrumental activities (eg, transportation, shopping, cooking, cleaning, yard work, and house repair) or personal self-maintenance care, such as bathing, dressing, and feeding; (3) *informational and organizational support*: support in decision making, care coordination and management, and financial management; and (4) *financial support*: the provision of monetary exchanges across generations.

Overall, the exchange of support has a positive effect on a care recipient. However, receiving instrumental support may have a mixed effect on functional status. Greater frequency of instrumental support may increase the risk of subsequent disability. Furthermore, receipt of instrumental support may lead to feelings of helplessness, perceptions of low mastery and autonomy, and reduced self-efficacy and sense of control.

The extent to which support is given, received, or exchanged between adult children and aging parents depends on several factors, some related to the adult children, others to the aging parents, others to the relationship between adult children and aging parents, and still others to the larger contexts within which their relationship take place. **Figure 7-3** displays the many factors involved in predicting parental support, described here.

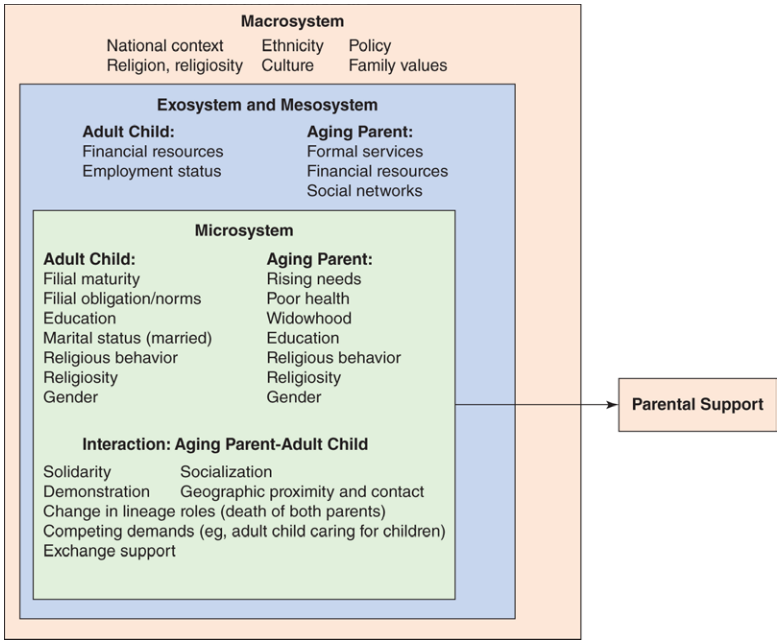


FIGURE 7-3. Conceptual framework for understanding factors affecting parental support.

Characteristics of the adult child. Findings regarding gender differences in filial norms toward older parents are mixed. In general, while both sons and daughters seem equally committed to provide care to aging parents, gender differences are apparent for specific types of support. Adult sons are more likely to provide financial and instrumental support around the house, while adult daughters are more likely to provide personal care, household chores, and social support in the form of advice.

Another predictor is income or more generally, social class, as it affects both the need and the availability of support. Financially and educationally advantaged families can more easily purchase care on the private market, thereby diminishing their sense of obligation to provide care themselves. Lower-income families are less likely to purchase services and express stronger filial obligations.

Marital disruption and remarriage have a major impact on parental support and filial obligation. Divorce disrupts the exchange of support between parents and children. Some research suggests that divorced children feel less filial obligation than those who have not experienced a marital disruption. Additionally, divorce affects the amount of resources available to help other family members and breaks ties that may be important for the needs of their parents.

Characteristics of the aging parent. Mothers typically receive more support than fathers. Parental divorce may weaken the filial norms of children, especially toward divorced fathers who are less likely to reside with their children

after the divorce and more likely to remarry. Fathers who divorce when children are younger and who do not have custody of their children, may receive less support than mothers in old age. In addition, divorces and remarriages in the parental generation may increase the number of potential care recipients per adult child by adding stepparents and other step relatives. Having more kin as potential care receivers may diminish the amount of care given to each one. Widowed and divorced parents receive more help than married parents.

Financial factors also play a role. Aging parents with higher financial resources can purchase services and may access services of higher quality, thereby diminishing the need for some types of informal care from children.

Microsystem: interrelationship between the adult child and the aging parents. Affectual solidarity between parents and their children is a major factor in the exchange of intergenerational support. Adult children who witnessed their parents care for their own parents are more likely to provide support, emphasizing the role of social learning and the demonstration of eldercare on likelihood of parental caregiving. The presence of siblings in the family is also a predictor of intergenerational assistance. Only children are relied upon for all necessary support, while individuals with siblings can share responsibilities. Most research in the United States shows that older parents who have more children receive higher levels of support.

The presence of young children in the adult child's house is a competing demand that diminishes the capacity of adult children, and especially women, to provide support to their aging parents.

Other microsystem determinants include geographic proximity and the frequency of contact. Evidence from various studies in the United States and elsewhere demonstrates that greater geographic distance and limited face-to-face contact reduce the incidence of all types of intergenerational exchanges and represents a significant barrier to intergenerational support.

Exosystem and mesosystem. The employment status of adult children should affect the likelihood of parental care under the assumption that having a job is a competing demand. However, most research shows that women's paid work does not change the likelihood of caregiving. When faced with the need to provide parental caregiving, employed women are found to use various strategies that allow them to provide that care. These include withdrawal from the labor market, sacrifice of leisure activities and sleep, passing up opportunities for promotion, use of vacation and sick days for parental care, cutting back on some housework activities, and reducing work hours.

Macrosystem. An important factor at this most general level is the national and regional policy context for supportive care. The availability of formal services, supported through government entitlements, will affect the need for informal support. The relationship between the welfare state and families has long been at the center of debate. Advocates of small government fear that services offered by the state may "crowd out" families and thus lead to less efficient service provision. This is the substitution hypothesis, which suggests that the provision of services replaces family care, and "woodwork effect," where families that would otherwise provide such support come "out of the woodwork" to accept government services.

An alternative view suggests that families and formal services may complement each other by jointly providing services. For example, formal organizations are optimal in managing technical tasks in caregiving, while primary groups, such as families, are optimal for managing nontechnical tasks. As a result, a partnership between formal organizations and primary groups may be the best approach to negotiate informal and formal care, with each partner providing a different type of support.

Finally, it is also possible that the availability of formal services may encourage support from families. This hypothesis is the exact opposite of the "crowding out" hypothesis and is sometimes referred to as "crowding in." "Crowding in" is supported by research from European states. Older adults who reside in welfare regimes that provide generous formal services are more likely to receive support from their children.

Race and ethnicity may also influence filial norms and parental support. Traditionally, African-American and Hispanic cultures were viewed as giving greater emphasis to family ties ("familism"). This cultural difference would result in differences between race and ethnic groups in responding to the needs of parents. Thus, African-American and Hispanic families would be expected to make less use of formal services and institutional placement, which is confirmed in national survey data. However, it is not necessarily the level of support that differentiates ethnic minorities from whites but rather the type of support. Specifically, black families are more involved in instrumental types of support, such as transportation and household chores, while whites were more involved in financial and emotional types of support. Interestingly, these differences are mostly seen in women; white and minority men are less likely to differ in caregiver roles. Finally, research suggests that religiosity may play a role in norms for caregiving behavior.

STRESS AND DISTRESS

Stress is the nonspecific result of a demand on the body. It is a common pathway for a variety of physical, cognitive, and emotional challenges. The stressed person will experience adverse physiologic effects (primarily in the pituitary-adrenal axis and immune system) but also clinically appreciable effects on decision making, problem solving, vigilance, social inference, and perceptual and motor skills. In this case, stress, a normal feature of our interaction with an environment, becomes *distress*, prolonged stress that overwhelms physiologic and psychological regulatory mechanisms. Recent experimental research suggests that prolonged stress may even affect the rate of aging, as measured by telomeric shortening over successive cell replication cycles.

In older people, stress from health limitation and consequent social losses becomes more common. The rising prevalence of chronic disease and disability, increased awareness of cognitive or physical limitation, loss of valued social roles, and reduction in social networks through widowhood and loss of friendships all act as stressors that increase the risk of negative mental and physical states. The adverse effects of stress are lower for those who have strong social support systems and greater personal resources, but repeated losses in multiple domains may ultimately lead to the sense that one has lost control generally.

Yet a robust finding from a variety of research settings has shown that older adults are able to maintain a sense of control even in quite challenging health circumstances. The older person unable to leave the home or nursing home floor will station herself in a strategic position to retain a view of activity and encourage social interaction. The older person unable to ambulate in his home will place himself in a chair by the window that affords the clearest view of what is happening outside the home. In these ways older people with poor health and threats to autonomy or control may yet retain some command over features of their living space.

Stressful Life Events

Stressful life events have been linked to poor mental and physical health in individuals of all ages. Researchers interested in the relationship between stress and health have generally pursued two strategies to assess life event stressors. Major life events such as illness and death of a loved one are often assessed using checklists or interviews to gauge the frequency and intensity of these types of experiences. Daily hassles, on the other hand, are the ordinary hassles of day-to-day living (eg, cooking, housework, work load, meeting deadlines, home repair, etc) measured with structured self-report or interviewer administered instruments.

Compared to younger persons, older individuals experience fewer life events overall, although they experience more events involving loss, particularly those associated with declining health and deaths of friends and loved ones. Younger individuals report more hassles in the domains of finances, work, home maintenance, personal life, and family and friends, whereas older men and women report more hassles in domains reflecting social issues, home maintenance, and health. Overall, for both younger and older individuals daily hassles are more potent determinants of physical and psychological well-being than major life stressors.

Older individuals demonstrate remarkable ability to adapt successfully to major life stressors. One important exception to this general observation occurs when older individuals are exposed to unrelenting chronic stressors, such as having to care for a spouse with Alzheimer disease. Under these circumstances the chronicity, intensity, and variety of stressors impinging on the caregiver exact a high price in physical and psychiatric morbidity, including increased risk of substance abuse.

It has long been recognized that there is considerable variability in individual response to major life stressors. The concept of *resilience*, defined as the ability to recover from or benefit from adversity, has been introduced to account for this variability. Individuals able to overcome adversity are thought to have high levels of resilience, a combination of internal personality traits such as hardiness, high self-efficacy, mastery, and optimism, along with a strong external support system. Although intuitively engaging, the empirical and clinical utility of the concept of resilience remains to be determined.

Biological Consequences of Stress

An important advance in recent decades is our increased understanding of the biological pathways through which psychosocial factors modulate changes in health. The field of psychoneuroimmunology focuses on linkages between psychosocial factors and nervous, neuroendocrine, and immune processes, which in turn have been linked to health. Much of this research has focused on stress, particularly chronic stress, and associated negative affective states, such as depression, anxiety, and anger, as disruptors of these biological regulatory systems. Stress may influence immunity

either through direct innervations of the central nervous system and immune system or through neuroendocrine immune pathways. Behavioral responses to stress may also affect immunity. For example, individuals experiencing stress may smoke more, drink more alcohol, eat poorly, and sleep less, all of which may influence immune response.

Because increasing age is associated with significant alterations in the functioning of many physiologic systems, including endocrine and immune systems, old age has become a fertile ground for examining the relation between stress, biological mediators, and disease. For example, a significant body of research views family caregiving as a chronic stressor with the ability to disrupt immune and neuroendocrine function. Compared to noncaregiver older adults, older caregivers have been found to have higher antibody titers for latent viruses, poor immune control over latent viral infections, reduced responsiveness of natural killer (NK) cells to cytokine signals, slower healing of wounds, poorer antibody responses to vaccination, and higher levels of basal cortisol. Physical health effects of caregiving include greater risk of infectious disease, hypertensive changes in blood pressure, increased prevalence of cardiovascular disease, and mortality. Taken together these findings suggest a strong link between stress, biological mediators, and illness; however, few studies have examined the progression of stress as a biological mediator of disease in the same individuals.

Personality and Health

Personality is defined as psychological characteristics and attributes and associated behavioral patterns that differentiate one person from another. Sometimes referred to as traits, dispositional tendencies, or fundamental human qualities, personality has long been of interest to researchers, especially with respect to how it develops and may change across the lifespan. The five-factor model (FFM) of personality has been influential among gerontologists and claims that personality can be defined by five broad traits—openness to experience, conscientiousness, extraversion, agreeableness, and neuroticism—that remain relatively fixed well into old age. Other important traits include mastery or control, the belief that important outcomes in life are under one's own control, as well as optimism and hostility. Despite the relative stability of these key traits, evidence of personality change in mid-life and beyond is also becoming clear as older people respond to age-related goals, opportunities, and constraints. For example, functional declines in late life may erode one's sense of mastery, extraversion, or optimism about the future.

An important emerging area of research is focused on the link between two distinct dispositional attributes and health. Enduring negative effects, such as anger, depression, and anxiety, increase the risk of morbidity and mortality, while positive effects have been linked to lower morbidity, decreased symptoms and pain, and increased longevity. For example, in one study, autobiographical writing samples collected from a group of nuns when they were in their early twenties were coded for positive emotion words and sentences. The greater the positive effect expressed in their writing, the greater the probability of being alive 60 years later.

Multiple mechanisms might account for the relation between dispositional effect and morbidity and mortality, including health practices such as diet, exercise, and sleep quality, biological processes such as cardiovascular reactivity, and the effects of the stress hormones epinephrine, norepinephrine, and cortisol. Positive effect has been associated with health-relevant hormones, including increases in oxytocin, growth hormone, and secretion of endogenous opioids. Inasmuch as individuals with positive effect are typically more pleasant to be around, they may also accrue health benefits through more positive social interactions and more attentive and higher-quality health care from health care providers.

An important unresolved question is whether positive and negative effects are opposite sides of the same coin or two independent factors. If positive and negative effects are opposite sides of the same coin, then being high on one necessarily means being low on the other, making it difficult to know whether salutary health effects are due to the presence of positive or the absence of negative effect. Evidence now suggests that individuals can simultaneously experience high levels of positive and negative effect. The two may uniquely contribute to health outcomes.

AFFECTIVE PROCESSES OVER THE LIFESPAN

Emotional life changes across the lifespan. If one talks to older people and asks about the emotions, one is likely to hear statements about the decline of emotion: "the highs are not so high anymore, but the lows are not so low either." Older people speak wistfully of their more intense emotional life at younger ages but also report a good deal of relief at getting off that treadmill.

Population surveys, such as the General Social Survey (GSS) and Eurobarometer, track the prevalence of reported effects by age and across birth cohorts and confirm this broad pattern. "Hot emotions," such as feeling excited about

something or feeling overjoyed decline in age cross-sections. For example, in the GSS the proportion reporting they were overjoyed about something at least one day in the last month was 71% in people aged 18 to 29, 56% in people aged 40 to 49, and 47% in people aged 70+. By contrast, the proportion reporting they were fearful about something was 47%, 45%, and 30% in the same age groups. The contrast confounds developmental and birth cohort effects, but such changes have been reported as well for longitudinal cohorts.

Results from the GSS and Eurobarometer surveys (which cover 72 countries and over a half million respondents) show that "life satisfaction" and depressed mood follow a U-shape distribution over the lifespan. Life satisfaction is assessed with subjective global appraisals, such as "Taken all together, how would you say things are these days—Would you say that you are very happy, pretty happy, or not too happy?" **Table 7-1** shows the age at which life satisfaction is lowest in cross-sectional surveys, adjusted for a number of important covariates, such as income, health indicators, marital status, and education. Life satisfaction is lowest at age 40 to 50 in both men and women and remarkably stable across continents.

TABLE 7-1 AGE AT WHICH LIFE SATISFACTION IS LOWEST

	MALES	FEMALES
Western Europe	45.2	47.0
Eastern Europe	46.5	48.2
Developing countries	42.6	44.3
Latin America	50.0	42.9
Asia	46.9	39.1

After Blanchford DG, Oswald AJ. Is well-being U-shaped over the life cycle? Soc Sci Med. 2008;66(8):1733–1749.

Self-reported depressed mood follows the same pattern. Using the same surveys, depressed mood is also most common at ages 40 to 50, as shown in **Figure 7-4**.

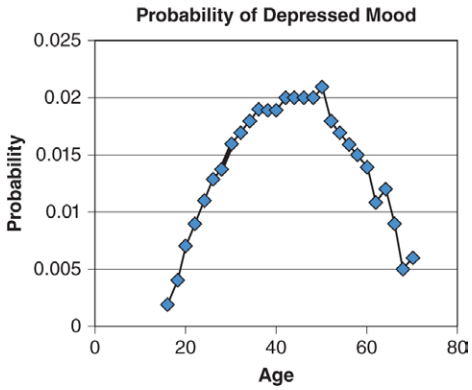


FIGURE 7-4. Depressed mood over the lifespan. (After Blanchford DG, Oswald AJ. Is well-being U-shaped over the life cycle? *Soc Sci Med.* 2008;66(8):1733–1749. Based on six questions: Lost sleep over worry? Feel constantly under strain? Could not overcome difficulties? Felt unhappy and depressed? Losing confidence in yourself? Think you are worthless?)

If we turn to changes at older ages, we find that variation in emotional experience is related less to age than to disability status, as shown by results drawn from the Women's Health and Aging Study, WHAS-I. The sample included women with moderate to severe disability, representing the most disabled third of older women living in the community, who were drawn from Medicare enrollee lists. Mental health and morale were assessed with a variety of indicators, including the Geriatric Depression Scale (GDS), the Hopkins Symptom Checklist, the Perceived Quality of Life scale, and sense of control and mastery scale. The sample of over 1000 women was divided into three age groups (65–74, 75–84, 85+) and three disability groups: women with "moderate disability" (limitations in upper extremity, lower extremity, or instrumental activities of daily living [IADLs] but no difficulty with the basic activities of daily living [ADLs], such as bathing or dressing), those with ADL difficulty who were able to manage without personal assistance, and those with ADL difficulty who received personal assistance.

Tables 7-2 and 7-3 report the affective experience of these older women. **Table 7-2** shows little variation by age group; mental health and emotional experience were quite similar across the age groups. **Table 7-3**, by contrast, shows

the very strong association between disability in the sample and virtually all the indicators. For example, the proportion with depressed mood was 13.1% in women with moderate limitations, 16.4% in women with ADL difficulty not receiving help, and 29.3% in women with ADL difficulty who received personal assistance. The corresponding proportions by age group for depressed mood were 18.6% (age 65–74), 17.3% (age 75–84), and 14.3% (age 85+).

TABLE 7-2 AFFECTIVE EXPERIENCE, WOMEN'S HEALTH AND AGING STUDY I, BY AGE GROUP

	AGE GROUP		
	65–74	75–84	85+
High level of depressive symptoms, % GDS > 13	18.6	17.3	14.3
High level of anxiety, %	2.8	4.0	5.1
Satisfied with help received from family and friends, %	79.1	81.1	78.2
Satisfied with help you give to family and friends, %	77.6	70.1	68.0
Satisfied with amount of variety in your life, %	65.9	62.1	62.3
Satisfied with the meaning and purpose of your life, %	76.4	75.8	75.7
I can do just about anything I really set my mind to do, % strongly agree	48.6	45.1	44.4
I feel helpless in dealing with the problems of life, % strongly agree	8.8	10.3	12.3

Tables 8-1 through 8-5 from Guralnik JM, Fried LP, Simonsick EM, Kasper JD, Lafferty ME, eds. The Women's Health and Aging Study: Health and Social Characteristics of Older Women with Disability. Bethesda, MD: National Institute on Aging; 1995; NIH Pub. No. 95-4009.

TABLE 7-3 AFFECTIVE EXPERIENCE, WOMEN'S HEALTH AND AGING STUDY I, BY DISABILITY STATUS

	DISABILITY STATUS		
	MODERATE	ADL DISABILITY: NO HELP	ADL: HELP
High level of depressive symptoms, % GDS > 13	13.1	16.4	29.3
High level of anxiety, %	2.1	4.4	4.7
Satisfied with help received from family and friends, %	83.6	79.3	74.8
Satisfied with help you give to family and friends, %	84.0	71.1	56.2
Satisfied with amount of variety in your life, %	70.0	63.6	51.4
Satisfied with the meaning and purpose of your life, %	79.7	74.8	72.1
I can do just about anything I really set my mind to do, % strongly agree	51.4	45.2	40.2
I feel helpless in dealing with the problems of life, % strongly agree	9.3	6.8	20.0

WHAS I (Guralnik JM, Fried LP, Simonsick EM, Kasper JD, Lafferty ME, eds. The Women's Health and Aging Study: Health and Social Characteristics of Older Women with Disability. Bethesda, MD: National Institute on Aging; 1995; NIH Pub. No. 95-4009): "Moderate disability": self-reported difficulty in two of three domains: upper extremity, lower extremity, or IADL. Summarized from Tables 8-1 through 8-5.

Results from WHAS-I show the strong effects of disability and poor health on mood yet also the great resiliency of older people in the face of health limitation. Satisfaction with help received from family and friends was reported by about 80% of women, regardless of age or disability status (though note the gradient in satisfaction by severity of disability: 83.6%, 79.3%, and 74.8%). Still, about three-quarters of women with the most severe disability reported satisfaction with help. While "satisfaction with help provided to others" decreased from 84% in those with moderate limitations to 56.2% among women receiving assistance with ADL tasks, still over half the sample with the lost severe disability reported they were able to provide to a satisfying degree.

Likewise, "satisfaction with variety in life" declined from 70% to 51.4% across categories of disability, but again more than half of the women with quite severe disability still report satisfaction in this domain. "Satisfaction with the meaning and purpose of your life" was stable across age and disability categories; about three-quarters of these women, whatever their age or level of disability, reported satisfaction.

Finally, this sample of women on the whole reported relatively low self-efficacy. Less than half reported confidence they could accomplish "anything I really set my mind to do." On the other hand, a minority of respondents reported "helplessness," less than 10% in the less severe disability groups and 20% in women receiving assistance with ADL tasks.

This inquiry suggests that disability has only a mild impact on mental health and general well-being. This is an important result. Most of the women in this sample were able to maintain mental equipoise despite quite severe disability.

One theory advanced to explain these changes in emotional experience with age and disability involves "socioemotional selectivity." The theory begins with recognition of the effect of limited time. Aging, health limitation, losses, and disability give time a different significance. Present-oriented goals are given greater value than future-oriented goals. Thus, older people will be more content with ongoing satisfying social experiences rather than novel experiences that may be emotionally "risky" (because they may be unsatisfying). They will be less interested in experiences that require new information or expanding horizons. This awareness of limited time thus leads to motivational changes that promote well-being and social adjustment, but that also limit health-related information seeking and skew older adults' attention to positive information. These theoretic predictions have been confirmed in a variety of experimental settings and may have a neural substrate.

A related theory of psychosocial aging suggests that emotional change is part of a more general "selection, optimization, compensation" process. This theory begins with recognition of age-related declines in the availability and efficiency of resources. Successful aging thus requires selection of domains to focus limited resources, optimizing investments of time, energy, and emotion to maximize gains, and compensation for losses—thus ensuring the maintenance of functioning and a minimization of losses. Minimizing losses in the emotional domain is consistent with socioemotional selectivity.

ENVIRONMENTS TO SUPPORT PSYCHOSOCIAL HEALTH

Aging in Place

Aging in place refers to the ability to remain in one's home and community even when facing health and challenges in function. Surveys show that the majority of older adults prefer staying in their home rather than moving to an institutional setting even with deteriorating health, and research findings suggest a positive relationship between aging in place and the well-being of older adults. The familiarity of the surroundings and the embedded social network and social support of neighbors may support the older adults' well-being. It is well documented that a move to a nursing home may be associated with morbidity and mortality, and thus staying at home may contribute to maintaining stable health. Additionally, beyond the benefits to older adults and their families, aging in place may contribute to the community as a whole as older adults remaining in the community may support others through volunteering or caregiving activities. Furthermore, aging in place may be superior to institutional care because of lower costs to families and government-funded long-term care. However, residence in skilled nursing facilities may be cost-effective relative to home care in the case of older adults who require 24-hour care or advanced medical technologies.

Successful aging in place relies on the availability of supportive physical, social, and economic elements within the infrastructure of cities, towns, and communities. Since such elements may contribute to other age groups in the community and the community as a whole, it is common to refer to communities that make a focused effort to increase safety and accessibility as *age-friendly cities* or *livable communities*. A recent publication by the Stanford University

Center on Longevity and MetLife Mature Market Institute provides a summary of the most important elements of a livable community required for successful aging in place. These elements, depicted in **Figure 7-5**, provide the economic, social, and environmental support needed to sustain current and future generations of older adults in their communities, and include the following:

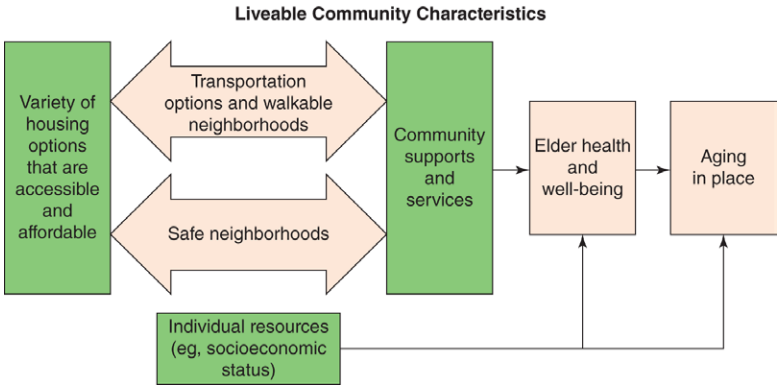


FIGURE 7-5. Aging in place, characteristics of livable communities. (Illustration from MetLife Mature Market Institute and Stanford Center on Longevity, March 2013. Livable community indicators for sustainable aging in place. MetLife Mature Market Insti New York, NY.)

- Accessible and affordable housing options and availability of home modification services to adopt the home environment to the needs of an aging individual.
- Availability of appropriate transportation options to ensure accessibility to and from the community and mobility within the community, along with safe walking conditions (ie, well-maintained sidewalks, rest areas, and recreation parks). The communities should further ensure safe driving by providing protected left-turns, reasonable signage, and adequate lighting. Safe walking and driving conditions promote independence of older adults, an important contributor to health and well-being.
- Availability of wide range of supports and services and opportunities to participate in community life, including health care services, supportive services, groceries with healthy food options, and opportunities for flexible employment, volunteering, recreation, and socialization.

The World Health Organization (WHO) has developed a guide for global age-friendly cities and included similar elements in its discussion of environmental features that support aging in place, as depicted in **Figure 7-6**. Both the MetLife and WHO models recognize that the physical, social, and economic environment is critical, but that successful aging in place also requires adequate individual resources, such as availability of supportive care in cases of disability in the ADLs, either through paid in-home services or from family or other informal caregivers. These in turn depend on socioeconomic determinants and personal resources.

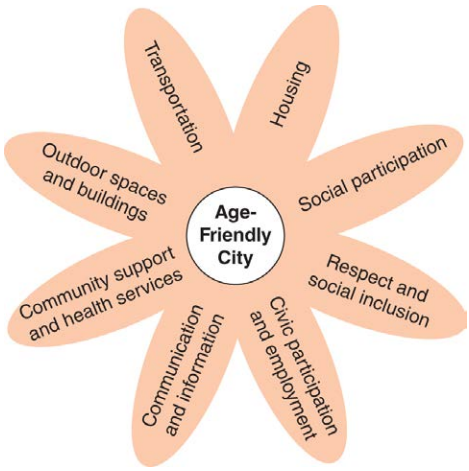


FIGURE 7-6. Aging in place: age-friendly domains. (From World Health Organization, 2007. *Global Age-Friendly Cities: A Guide.* Geneva, Switzerland: WHO Press; 2007. http://www.who.int/ageing/publications/Global_age_friendly_cities_Guide_English.pdf.)

Long Term Care: In-Home and Community-Based Services and Supportive Housing

Long-term care encompasses a wide spectrum of personal care services provided to individuals who need continual support. One end of the spectrum of services is informal care provided at home by a family member, typically a spouse or adult child. On the other end is around-the-clock care provided by trained clinical teams in a skilled nursing facility. Between the two we find a variety of services that vary in the intensity, location, and cost of care.

The different options available to an older adult at home, in the community, and if needed, in residential settings are shown in **Figure 7-7**. Options for supportive care in the home include paid in-home health care, provided by nurses and allied health professionals, and homemaker services, provided by paraprofessionals who assist with instrumental (such as shopping, filling prescriptions, preparing meals, cleaning) and self-maintenance activities (such as bathing, dressing, toileting, feeding). Other in-home services include home-delivered meals, social visiting from neighborhood organizations or programs such as the Senior Corps Companions, and support for medical equipment, such as oxygen, lymphedema support, adjustable beds and chairs, lifts, and respiratory devices. Home modification to address mobility limitation may also be considered an in-home service. Community supports for aging in place include adult day care, congregate meals, senior center programming, and transportation services. These services in the home and the community are designed to help older adults to age in place by addressing their needs as well as the needs of informal family caregivers.

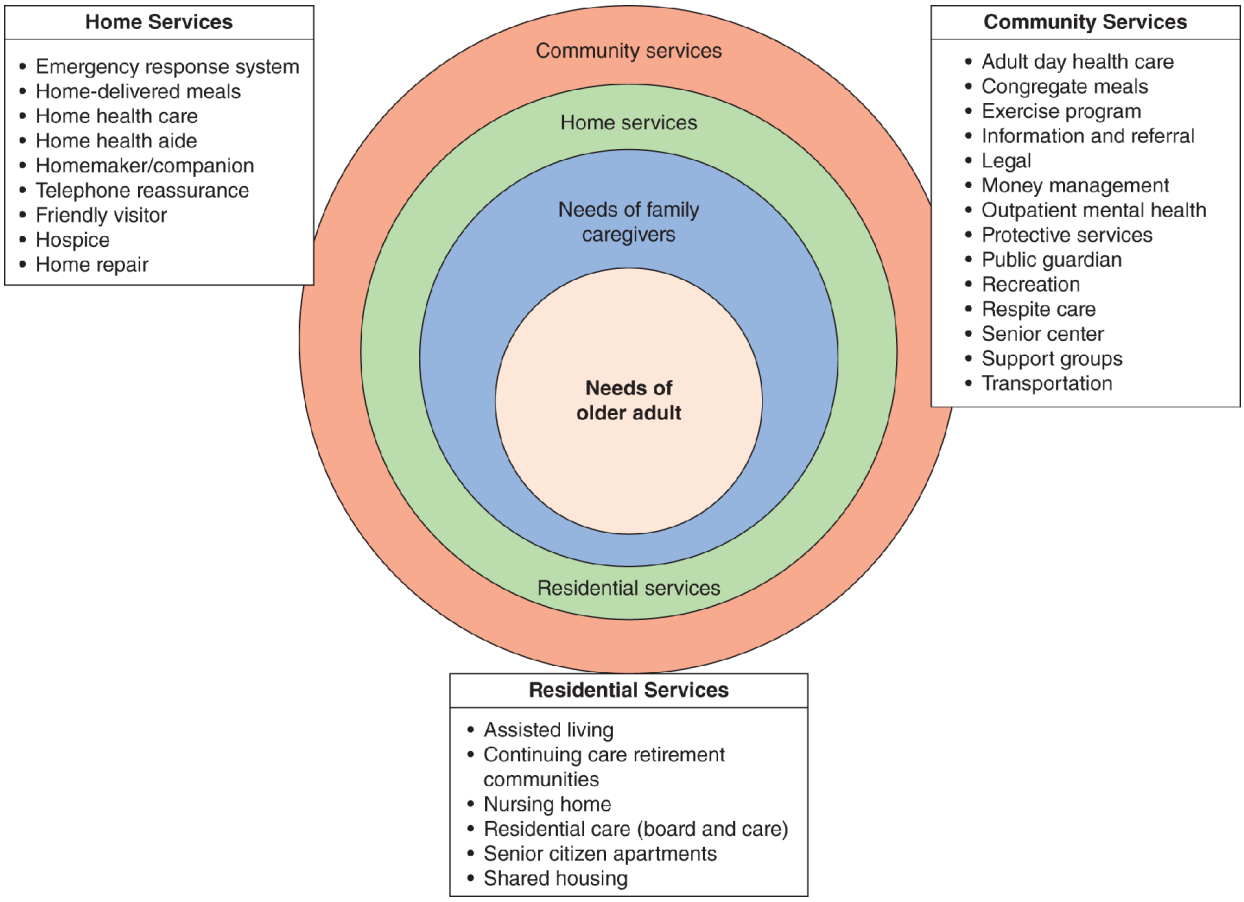


FIGURE 7-7. Long-term care: home, community, and residential settings.

The services range in intensity and frequency. Some provide a very specific solution to a specific problem and thus support older adults who are otherwise independent. For example, home-delivered meals, or "Meals on Wheels," cover one-third of the daily nutrition needs of older adults. Subsidized transportation services may allow otherwise independent adults to get to and from activities. Other services may provide a more intense level of services for individuals who need a more comprehensive set of supports, such as home health aides for personal care or adult day programs for people with mild to moderate dementia. Given adequate assessment and care management, individuals with substantial needs can be maintained in their homes. Indeed, care management services provided through Medicaid and Administration on Aging Title III funds often require that these older adults be "clinically eligible for nursing home care."

Similarly, residential services offer varying degrees of support based on the continuum of care. These range from independent living residences with occasional nursing or social service support (as in naturally occurring retirement communities, or NORCs), to assistive living communities and personal care homes (residences integrated with health services and communal meals and housing services), to skilled nursing facilities. Some of these residential services offer the continuum of care whereby residents can move from more independent living settings to more supportive settings as their needs change.

It is important to note variability in the functional trajectory of older adults. This variability is important for targeting services to support aging in place. A linear progression from high to low functioning, with a corresponding predictable transition from least to most supportive setting, does characterize this population well. In fact, it is often the case that older adults will face a health crisis, such as a hip fracture, which will require that they be temporarily placed in a more restrictive environment, such a skilled nursing home or rehabilitative setting. Once they regain functioning, they may go back to a less supportive environment, either in a residential setting or in the community. Well-planned transitions after such health events, so called "warm handoffs," are critical for maintaining older people in the community. Adjustment of medication, reassessment of in-home supports, updating of care management plans, adequate communication between providers, and appropriate clinical follow-up are all required to ensure aging in place. As part of the ongoing rebalancing of Medicaid long-term care funding in the United States, we can expect funding for in-home and community-based services (HCBS) to grow and greater opportunities for aging in place. Currently, these initiatives are mostly limited to the Medicaid-eligible population. Older adults who do not qualify for Medicaid must rely on long-term care insurance or purchase such services through the private market, which is in many cases unaffordable and not always available and appropriate. Several models have developed over the past few years to address the needs of older adults who are not eligible for government programs.

Villages and Naturally Occurring Retirement Communities

A new and growing approach to aging in place is the "Village" model. Developed as grassroots organizations, these villages provide older adults living in the community with a combination of supportive services, such as transportation, housekeeping, and companionship, and a referral service for vetted community services, potentially at a reduced rate using their bargaining power. Villages are similar to the NORC with Supportive Services Program (NORC-SSP), as they provide supportive services to allow for successful aging in place, yet are initiated, governed, and funded (through membership fees) by the consumers they serve rather than by an agency. The first village, Beacon Hill village, was developed in 2001, and since then, at least 120 villages are operating across the United States and in Canada, Australia, and the Netherlands, with over 100 additional villages in development. While each village operates with autonomy as a response to the local needs, the village to village (VtV) network provides help in establishing and managing villages.

SUPPORTING PSYCHOSOCIAL HEALTH THROUGH THE AGING SERVICES NETWORK

About a quarter of community-resident older adults aged 65 or older report disability in personal self-maintenance tasks (or ADLs). About two-thirds of these older adults receive personal assistance or use medical equipment to allow them to maintain community residence. In older adults receiving in-home and community-based services, depressive symptoms are common in these older adults. In seniors receiving home-delivered meals or home health nursing, for example, 10% to 15% meet criteria for major depression. As shown in the Women's Health and Aging cohort, discussed earlier, the association between ADL disability and depressed mood is strong in community samples as well.

Given the association between these vulnerabilities and risk of psychiatric illness, the need for scalable prevention models for this population has become increasingly clear. Shortfalls in the geriatric health workforce make the need even more pressing, suggesting that effective prevention models that can be implemented in community aging-services settings would be valuable additions to current medical and mental health care.

A productive way to support psychosocial health among older adults is to harness community-based agencies that provide aging services. These agencies have regular contact with vulnerable olders and are sometimes the only source of such contact. For example, virtually all aging services providers provide social visiting or other "check-in" services, in which agency staff or volunteers call seniors who receive services to stay in contact and unobtrusively determine new needs. These kinds of contact may uncover mental health needs and could be explicitly harnessed for assessment of depressive or anxiety symptoms and, when needed, referral. But the challenges of developing such programs are not

trivial. How should staff or volunteers, who often lack mental health training, be trained? What kind of supporting staff needs to be attached to agencies in case of need for mental health services? What kind of referral pipeline would best link aging services providers to mental health services?

A number of such programs have recently been developed and assessed in randomized trials. Many have achieved status as evidence-based programs and have undergone stringent review by the federal Administration for Community Living (ACL). The ACL Center for Disability and Aging Policy review process (ADEPP, "Aging and Disability Evidence-Based Programs and Practices") involves assessment of both quality of research and readiness for dissemination for interventions that have already shown effectiveness in randomized controlled trials or quasi-experimental studies, with results published in peer-reviewed journals. Here we highlight three that harness aging services providers to support psychosocial health.

PEARLS, the Program to Encourage Active, Rewarding Lives for Seniors is designed for older adults with subthreshold depression. It involves problem-solving treatment, social and physical activation, and potential recommendations to patients' physicians regarding antidepressant medications. Patients receiving the PEARLS intervention were more likely to have reduction in depressive symptoms and achieve complete remission from depression than patients in a control education condition. They were also more likely to report improvements in health-related quality of life. Trained counselors deliver the program in a participant's home. The cost to implement PEARLS is about $630 per patient.

IMPACT (*I*mproving *M*ood-*P*romoting *A*ccess to *C*ollaborative *T*reatment for Late Life Depression) uses a team approach designed to integrate depression treatment within primary care. In the IMPACT model, a nurse, social worker, or psychologist works with the patient's regular primary care provider to develop a course of treatment. The cost of implementing IMPACT is about $500 per patient per year.

Can service providers in the community screen older adults for depressive symptoms and deliver appropriate psychosocial interventions? In one effort, social workers making home visits screened older adults receiving home care services (homemaker, nurse, home-delivered meals, social visiting, or medical equipment) with the two-item Patient Health Questionnaire (PHQ-2). Older adults reporting PHQ-2 items (anhedonia or dysphoria) were referred to a psychiatric social worker at one of the agencies, who followed up by telephone with the PHQ-9. Participants with subthreshold disease were referred for problem-solving therapy. People who met criteria for depression were referred to physicians for evaluation and treatment.

Results were mixed. Over 12 months, agencies were able to screen only three-quarters of their caseloads. About a third of older adults reported symptoms of anhedonia or dysphoria (n = 480). The agency psychiatric social worker was able to screen only a third of these people with the PHQ-9, and 92 met criteria for subthreshold depression. Of these 92, only 28 accepted a session of problem-solving therapy.

This effort suggests that integration of screening and delivery of psychosocial interventions in agencies is challenging. Even highly motivated agencies were unable to screen their caseloads fully. Handoffs between agencies for more intensive screening, and from agencies to the research team for delivery of the intervention, were challenging. Problem-solving therapy was not readily accepted even with endorsement by agency social workers. For these reasons, current trials to promote psychosocial health are set within aging services providers but include centralized screening, randomization, in-home assessments, and follow-up.

PROMOTING ENGAGEMENT

Volunteering

Civic engagement is the process by which individuals actively participate in the life of their communities through individual and collective activities. The engagement can range from participating in collective activities such as voting, to participation in religious, spiritual, or community groups, to volunteering time in unpaid productive activities. Older adults commit more hours to their volunteering activities than any other age group, although more recent birth cohorts are less likely to volunteer than earlier cohorts. Volunteering contributes to the community and the society at large and is associated with a variety of personal benefits to older adults. Estimates of the overall economic impact of volunteering activities to the global economy are as high as $400 billion yearly, but estimates of the value of volunteering by older adults are currently unavailable.

Most research focuses on the personal benefits of volunteering and seeks to assess psychosocial, physical, and cognitive benefits. A recent systematic review and meta-analysis provided strong evidence that volunteering is

associated with positive outcomes across a number of domains. In the psychosocial domain, volunteering is associated with a reduction in depressive symptoms and improvements in life satisfaction and social support. In the physical aspect, volunteering is associated with better overall health, reduced functional limitations, and lower mortality risk. While less research is available on the effects of volunteering on cognitive functioning, a randomized control trial of the effect of group volunteering in elementary schools, Experience Corps showed improvements in memory and executive functions. While postretirement volunteer activities show positive effects on health and well-being, these activities are also important for generative reasons: while helping those in need, this kind of engagement taps into broader prosocial or altruistic interests of individuals, which in itself is satisfying and may offer psychological reward (the so-called "positive glow" associated with helping others). The systematic review indeed showed that the benefits to older volunteers are increased if volunteer opportunities have such a prosocial component and if people feel they are appreciated for their contribution.

Experience Corps, mentioned earlier, was a major randomized controlled trial to assess the health effects of volunteering. This program places groups of older adults in public elementary schools to work with children in kindergarten through third grade as tutors and teacher aids. Each volunteer serves about 15 hours per week, usually over 3 to 4 days, throughout the school year. Volunteers work with students to promote reading and arithmetic skills, as well as problem solving and conflict resolution. The program aims to improve children's academic performance, for example, by boosting school attendance, graduation rates, and performance on standardized tests; but it also aims to improve older adult outcomes by simultaneously enhancing the psychosocial, physical, and cognitive well-being of adult volunteers.

Experience Corps was hypothesized to promote these outcomes through specific pathways, as shown in **Figure 7-8**. To increase volunteers' social engagement and social support as well as improve retention, volunteers were trained and sent to schools in teams. To improve physical health, volunteers were expected to volunteer over 3 to 4 days to ensure that volunteers were physically active, with increases associated with walking to and from the school and within schools. To enhance cognitive activity, volunteers received extensive 30-hour formal training as teacher aids over a 2-week period.

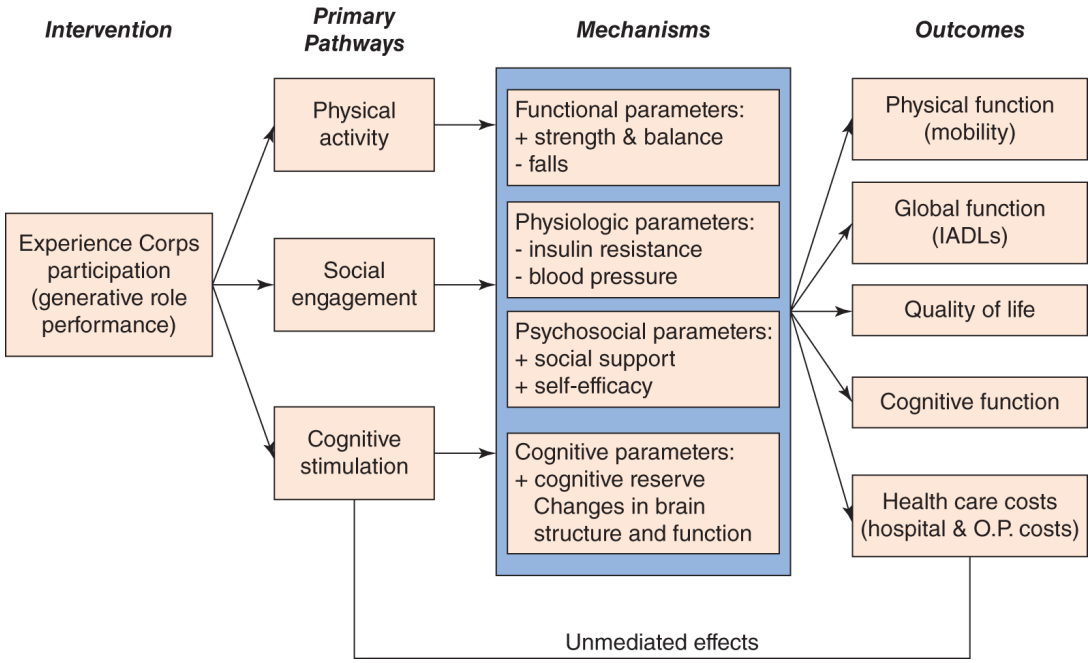


FIGURE 7-8. Causal pathways through which volunteering may support psychosocial, physical, and cognitive functioning. (From Fried LP, Carlson MC, Freedman M, et al. A social model for health promotion for an aging population: initial evidence on the Experience Corps model. *J Urban Health.* 2004;81(1):66–78. Reprinted with permission.)

Additionally, interaction with children in the classroom was expected to improve cognitive functioning by providing opportunities to enhance mental flexibility and coordination skills. For example, by providing literacy and library support to children, older adult volunteers exercised their own verbal learning, memory, and problem-solving skills. The training itself was intended to increase self-efficacy and confidence through teaching skills that will enable success in this new role. The findings from the randomized control trial demonstrated significant differences in change

from baseline to follow up on a variety of factors between program volunteers and a control group of waitlisted volunteers in many of the measured domains of psychosocial, physical, and cognitive well-being.

Another important effort to promote volunteerism among older adults is the *Senior Corps* program. Senior Corps, funded by the US Corporation for National and Community Service, provides aid to senior citizens while promoting a sense of community. There are about 360,000 volunteers in the program nationwide each year. Senior Corps focuses on helping individual aged 55+ to become mentors, coaches, or companions to people in need, and in this way contribute their job skills and expertise to the community. The Senior Corps has three flagship programs, including (1) *Senior Companions*, in which volunteers provide assistance and friendship to adults who have difficulty with daily living tasks, as well as support to family caregivers by providing much needed respite; (2) *RSVP*, which connects interested seniors to service opportunities, such as organizing neighborhood watch programs, tutoring or mentoring disadvantaged children, and teaching English to immigrants; and (3) *Foster Grandparents*, in which older volunteers tutor children, serve as mentors to at-risk teenagers and young mothers, help with care for premature infants and children with disabilities, and work with abused or neglected children.

Lifelong Learning

Much like volunteer activity, continued learning in old age has been associated with positive effects in psychosocial, physical, and cognitive health. One of the leading organizations in this area is Road Scholar educational adventures, formerly known as Elderhostel, a not-for-profit world organization facilitating lifelong learning in various locations in the United States and internationally. Some of these learning opportunities allow for a grandparent-grandchild combined learning experience, thus including an intergenerational component.

Another important model in this area includes the Osher Lifelong Learning Institutes (OLLI). The Osher Foundation supports 119 lifelong learning programs on US university and college campuses, with one or more programs in each of the 50 states and the District of Columbia. The Foundation also supports a National Resource Center to enhance programming and outreach. These efforts involve a membership-based community of adults, “age 50 and better,” who take classes on campus, both traditional classes with undergraduates but also classes taught by members, who, in many cases, are retired academics and teachers. Osher classes are combined with off-campus learning, field trips, book clubs, and volunteer efforts. The program requires a campus setting and caters largely to college communities. Still it is a scalable model that may be appropriate for a wider array of environments. For example, senior centers might adopt such a lifelong learning approach, and web-based programs may allow more distributed learning networks for older adults. Given the importance of cognitive and social engagement for health outcomes in older adults, lifelong learning programs may be a particularly valuable investment for promoting engagement.

Intergenerational Programs

Intergenerational programs also promote engagement. These programs seek to cross generations and bring together different age groups for a focused purpose. The programs may include educational endeavors, such as the Road Scholars Grandparent and Senior Corps Foster Grandparent programs discussed earlier, but can take other forms as well. Intergenerational day care, for example, promotes contact between children and older adults who receive services in the same physical facility, allowing opportunities for intergenerational interaction, benefiting both young and old. In addition to providing opportunities for service to both the young and the old, intergenerational programs also decrease ageism and improve attitudes toward aging, thus strengthening bonds across generations.

LIFE EVENTS AND TRANSITIONS

Older adults face many life transitions or changes in roles related to age and declining health. A key age-related transition is retirement. Major health-related transitions include bereavement due to loss of a spouse or partner and the onset of caregiving when a spouse or partner experiences declines in health.

Retirement

The loss of employment represents a meaningful life event for older adults, and in the early literature was described as a transition to a “roleless role” that clashes with the emphasis on productivity and a busy work ethic and thus must lead to negative effects on the retiree’s well-being. Yet empirical studies did not find uniformly negative effects of

retirement and, in fact, demonstrated important heterogeneity for the effects of retirement on health and well being. While some research showed that retirees were more likely to report negative effects (such as depressive symptoms, loneliness, lower life satisfaction, and reduced activity) relative to older adults who remain employed, other research showed that older adults are satisfied following retirement. Using longitudinal data from two nationally representative samples from the Health and Retirement Study, researchers demonstrated that there were multiple paths following retirement over time, with about two-thirds of people experiencing minimum changes in psychological well-being, about a quarter of individuals showing initial negative well-being effects followed by improvement, and a small group of people that showed immediate positive changes.

Current retirement trends suggest that older people are now maintaining full employment to later ages (in 2010, about a quarter of people aged 65+ were working full time). More importantly, retirement is no longer an abrupt overnight transition from a full-time career to no employment. Instead, current retirement behavior suggests that many older adults remain in work in later years, choose partial retirement through reducing work hours, take bridge jobs if their long-term career ends, or even start their own businesses. It is also clear that volition and choice are important in adjustment to retirement, with those choosing to retire reporting greater satisfaction than those who felt obligated to retire. Good health and adequate income are also important determinants of postretirement adjustment.

Widowhood, Bereavement, and Grieving

The transition to widowhood is considered among the most stressful transitions in later life. Characteristics of the end-of-life period were found to influence the well-being of the surviving spouse. If the end of life was not accompanied by physical discomfort and took place in a supportive setting with involvement of family, strains associated with the bereavement period were ameliorated. Research suggests that men and women who report greater independence are better able to adjust to loss of a spouse or partner than men who are instrumentally dependent on their wives and women who are emotionally dependent on their husbands. This may suggest that successful coping in widowhood may require altering traditional gender roles.

Widowhood is a transition that leads to the reconfiguration of family roles and functions. While less likely than their married counterparts to have a confidant, widowed individuals are more likely to receive support from children, friends, and relatives. Widows are also more likely than their married counterparts to pursue volunteer roles, which in turn can lead to improved health and well-being.

Caregiving

When caregiving for an older adult is needed, the spouse is the first line of defense. Spousal caregivers seem to exhibit levels of depressive symptoms similar to adult children caregivers yet derive less emotional rewards from caregiving. Wife caregivers tend to suffer greater adverse effects than husband caregivers (especially when caregiving duties restrict outside activities); they also experience greater caregiver burden and depression than husbands. Caregiver adjustment is also affected by marital quality prior to assuming caregiving duties. In marriages with higher levels of marital disagreement pre-caregiving, spousal caregivers report a greater decline in happiness and a greater increase in depression during the caregiving period than spouses in more cordial marriages. A caregiver's well-being is further sensitive to the condition of the spousal care recipient, with those caring for spouses with dementia experiencing higher levels of negative effects on well-being.

Grandparents Raising Grandchildren

Older adults are the first of line of defense when the parental generation is unavailable due to incarceration, disease, substance abuse, or other conditions. Caregiving grandparents typically face challenges beyond their role as caregivers. They tend to live in poverty and rely on public assistance, are less educated, and in many cases do not have access to adequate health care.

The demands of caring for grandchildren have negative effects on the physical health and mental well-being of custodial grandparents. Adopting the role of childcare provider at a time when such care is unexpected leads to increased stress. Additionally, in many cases, the grandchildren exhibit emotional and behavioral problems due to their childhood circumstances that further exacerbate the level of grandparent's stress. Support networks, such as extended family members, have been found to play a buffering role in the negative effects of grandparental caregiver stress. Additionally, research has shown that some grandchildren report a sense of satisfaction that mitigates these negative effects. It is also important to note that cultural expectations for care arrangements have mental health implications.

For example, a cross-cultural comparison found that African-American grandmothers who were sole providers for their grandchildren were less distressed than comparable white grandmothers. In cultures that rely on extended families, caregiving stresses associated with grandparent care for grandchildren may have less negative effects.

While caregiving is less common in the Western world than it is in other parts of the world, grandparents are increasingly acting as supplementary caregivers who provide part-time care to grandchildren. Evidence is mixed on the effects of such part-time care on the well-being of grandparents.

PSYCHOSOCIAL ASPECTS OF PARTICIPATING IN HEALTH CARE DECISIONS

Cognitive, physical, and sensory limitations in older adults often limit informed decision making in medical encounters. Yet older adults continue to show interest in making informed health care choices, and patient-centered care will require innovations that promote engagement of older adults in care decisions. It is valuable to ask if older adults feel they are adequately informed about their health care choices and to identify the psychosocial correlates of "informed care."

In one large cohort of very old adults (mean age 86), participants were considered "informed" about their health care choices if they reported that (1) their doctor or other health care professional checked to see that they understood their condition and care, and (2) the doctor or other health care professional gave them enough or more than enough information about their medical condition. Participants reported on their most recent medical encounter.

By this standard, three-quarters of participants met criteria for informed care. Informed care status did not differ by gender, race, level of education, or self-reported health or disability. Informed care was also not associated with features of the medical encounter, such as being accompanied to the appointment, use of the Internet to look up medical information, or prescribing of new medicines, tests, or treatments. Cognitive performance also did not distinguish informed respondents from others (though participants with dementia or who were unable to complete the interview were excluded). Differences related to informed care were apparent in only two domains. Participants who met criteria for informed care were more likely to prefer sharing treatment decisions with their doctor compared to those who were not informed and they were also less likely to report depressed mood (4.4% vs 9.4%).

Thus, a majority of very old adults feel that clinicians should seek to inform them about their medical status. Informed care is associated with greater partnerships with health care providers and better mental health. Efforts to increase involvement of older adults in their care may thus offer important psychosocial benefit.

PSYCHOSOCIAL ASPECTS OF QUALITY OF LIFE AND VALUATION OF LIFE

Quality of life (QOL) includes two overlapping domains. *Health-related quality of life* specifies elements of daily function and well-being that change as a result of disease or therapeutic intervention. A satisfactory QOL measure in this sense allows researchers to rank different health conditions (and treatments) according to their impact on domains of health, such as mobility, independence in bathing and dressing, sensory acuity, mood, and absence of pain. The more negative the impact in these areas, the greater the quality of life impact of the health condition. *Environment-based quality of life*, by contrast, is not a health impact measure but rather registers the effect of personal resources or environmental factors on daily experience. Environment-related QOL domains include features of the natural and built environment (such as economic resources, housing, air and water quality, community stability, access to the arts and entertainment), as well as personal resources (such as the capacity to form friendships, appreciate nature, or find satisfaction in spiritual or religious life).

Maintaining the distinction between the two types of QOL is important. Health-related quality of life domains—patient reports of functional status, discomfort, pain, energy levels, and social engagement, for example—will track more closely with clinical measures of disease than environmental indicators. Recognizing this distinction eliminates much of the confusion about the "idiosyncrasy" of QOL ratings. However, the two types of QOL are also related in important ways. An impoverished environment (eg, poor air quality, noise, lack of social stimulation) may affect health-related QOL. By the same token, health limitations may require environmental changes, such as reliance on assistive devices or personal assistance care, which affect environmental sources of QOL. The older adult with cognitive impairment faces threats to both dimensions of QOL: dementia directly affects function and well-being and also forces environmental changes that may further reduce opportunities for quality in daily life.

A good test of whether a domain falls within the category of health-related QOL is whether this domain changes

with successful medical treatment or change in care environment.

Sample domains of this type, recorded in the Sickness Impact Profile (SIP), include ambulation, mobility, body care and movement, communication, alertness behavior, emotional behavior, social interaction, sleep and rest, eating, work, home management, and recreation. The Medical Outcomes Study (MOS SF36) identified a related set of eight domains: health perception, pain, physical function, social function, mental health, role limitation from physical causes, role limitation from mental health causes, and vitality. Others, such as the Health Utilities Index (HUI), stress still different domains, in this case a "within the skin" approach that restricts QOL to domains that are closely connected to clinical conditions.

QOL can be assessed as the difference between a population norm and mean value for patient samples, or more directly as a "utility" rating, that is, a numeric rating of how preferred (and thus how much better) one health state is relative to another. One common way to derive utilities for health states is to ask how many years of life people would be willing to give up to live without a health condition or disability.

The psychological analogue to quality of life is valuation of life. M. Powell Lawton raised this issue directly by examining psychological factors involved in people's reports of willingness to live in impaired states of health or with poor quality of life. Valuation of life (VOL) is "the extent to which the person is attached to his or her present life, for reasons related to a sense not only of enjoyment and absence of distress, but also hope, futurity, purpose, meaningfulness, persistence, and self-efficacy." VOL can be measured by reports of hope, the sense that life has meaning, and continued commitment to personal projects, that is, goal-driven activity. Valuation of life is an independent correlate of the wish to live even when we adjust for many factors associated with the wish to live, such as health state, cognitive capacity, mental health, perceived quality of life, and personal mastery. Valuation of life was a significant independent correlate of the wish to live under a great range of severe health limitations, including states of mobility impairment and severe pain, but not in the case of dementia or nursing home residence. It may be that perceived meaningfulness and purpose in life do not lead to the wish to live at any cost.

However it is measured, health-related QOL declines with age. This is a central, inescapable consequence of the increased prevalence of chronic disease with greater age and the effects of senescent changes in many physiologic domains. As we have seen, older people adjust their daily lives to accommodate these decrements, and adjustment strategies may reduce the effects of such decrements on health-related QOL. Still, cross-sectional studies show strong declines in health-related QOL with increasing age. Valuation of life may not show so clear a pattern. At this point few data are available for assessment of VOL over the life course. Investigations in this area will be important to help clarify decision making at the end of life. Here we need to ask when the wish for a shorter life is an expression of discouragement based on depression, and when it is an expression of discouragement based on a judgment that life no longer has intrinsic value because impaired health does not allow meaning, purpose, or desired personal projects.

In contrast to health-related QOL, environment-related QOL may remain high throughout life and may even improve with greater age. With retirement, for example, older people have greater leisure time; and with children gone, houses paid for, and successful investments, they may have greater disposable income as well. As a result, older people have increased opportunities to develop interests and create satisfying environments. These freedoms and opportunities counterbalance declines in health-related QOL and may be responsible for the great resiliency older people show in the face of declining health.

PSYCHOSOCIAL ASPECTS OF END OF LIFE

Dying in America has changed markedly in the past quarter century and continues to evolve as the population ages, treatment of chronic disease becomes more effective, and clinicians, policymakers, and the public debate practices related to end-of-life care. Older adults with life-limiting illness and their caregivers face an increasing array of treatment choices at the end of life as well as expansion in settings for receiving care, including hospice (which mostly involves in-home services). Over 40% of deaths in the United States involve hospice care, though such care is often implemented only 1 to 2 days before death, preventing patients and families from receiving the full benefit of hospice care. As hospice becomes the predominant model for end-of-life care, it is important to monitor psychosocial costs and benefits of hospice.

In population-based surveys of family caregivers who have provided end-of-life care, use of hospice services was associated with overwhelmingly greater satisfaction with quality of dying, quality of care at the end of life, and decisions regarding care and treatment. On the other hand, use of hospice involves greater investment of time and effort on the part of family members, as evidenced by the higher proportion of caregivers who administer medications

and report taking time off from work during end-of-life care compared to caregivers who do not make use of hospice. Notably, despite this greater involvement in end-of-life care, caregivers who make use of hospice do not report a greater prevalence of depressed mood, anxiety, or postdeath persistent grief, suggesting that involvement in hospice buffers the negative impact of greater involvement in end-of-life care.

Aggressive treatment at the end of life remains common among older adults. An analysis of nearly 30,000 Surveillance, Epidemiology, and End Results (SEER) patients aged 65+ showed an increase in aggressive cancer care near the end of life, as indicated by the proportion starting a new chemotherapy regimen within 30 or 14 days of death; the proportion with more than one emergency department visit, more than 14 days in hospital, or an intensive care unit (ICU) admission in the last month of life; or the proportion of hospice patients with length of stay fewer than 3 days. Nearly 20% continued to receive chemotherapy in the last 2 weeks of life. Dying during a hospital admission remains common among chronically disabled older people. Finally, aggressive interventions before death are common in people with advanced dementia, as shown by high rates of hospitalization, emergency room admission, parenteral therapy, and feeding tube placed in the last 3 months of life among people with dementia residing in skilled nursing facilities. The difficulty of preparing for end-of-life treatment is visible in recent discussions on the best way to withdraw older patients who are approaching the end of life from statins and other medications that are no longer appropriate.

Families face the challenge of limiting inappropriate care for older adults who are dying or who are unlikely to benefit from aggressive hospital interventions because of frailty or multimorbidity. The combination of multiple chronic conditions in advanced old age makes risk of death high even when individual conditions are reasonably managed; also, healthy but frail older persons are particularly vulnerable to acute events, such as a hip fracture or infection, that raise the risk of death. Life table analyses suggest annual mortality of 8% to 10% in people age 85+ and over 30% for people aged 90+. This high risk of death suggests that clarifying preferences for end-of-life treatment is important for the very old. Yet “the talk,” discussion of end-of-life treatment preferences among older people and their families, is often difficult. Older people are more likely to initiate such discussions than their adult children. Adult children may resist such discussions and are often more in favor of aggressive treatment at the end of life than parents.

Making use of hospice, and the clear articulation of preferences for end-of-life treatment associated with it, lowers medical care utilization in the last year of life. In a matched cohort of Medicare beneficiaries with poor-prognosis cancer, 42% of older adults using hospice had a hospital admission, in contrast to 65.1% of nonhospice users. Fourteen percent of the hospice group died in the hospital, compared to 74.1% among nonhospice enrollees. Likewise, older adults completing Physician Orders for Life Sustaining Treatment (POLST) are less likely to receive aggressive treatment at the end of life.

Do decisions to complete a POLST or enroll in hospice reduce the risk of anticipatory grief or severe persistent grief related to loss of a loved one? The effect of choices to limit care at the end of life on the mental health of survivors is unclear.

Current estimates suggest that 9% to 25% of older people are unable to recover from the emotional challenges of the death of a loved one and develop persistent or complicated grief. *DSM-V* has defined this complex bereavement disorder as a trauma or stress-related condition lasting 6 or 12 months after the death. In older adults, complicated grief is associated with disability, cognitive impairment, and suicidal thinking. New measures are available now to assess persistent grief, such as the Inventory of Complicated Grief, and a number of trials have shown that psychotherapy targeted to complicated grief is more effective than standard grief-focused interpersonal psychotherapy. Efforts are underway to examine whether grief responds to pharmacotherapy (antidepressant treatment) and whether current interventions can reduce the elevated suicide risk associated with persistent grief. Preparation for the end of life through completion of advanced directives, following the POLST paradigm, or articulating end-of-life treatment preferences in a family setting may also reduce the risk of persistent grief. The same may be true for anticipatory grief.

A final consideration is distress and regret at the end of life, which may be impairing even if not accompanied by frank depression or anxiety. Such distress often reflects active questioning of the meaning of life, such as whether a person has made good use of a life and left an appropriate legacy. Since patients with a higher sense of meaning experience less distress at the end of life, interventions that bolster meaning may reduce this existential distress and accordingly lower the risk of poor mental health at the end of life. One promising approach to supporting meaning at the end of life is dignity therapy, a short-term psychotherapy that has been shown to improve well-being in people with life-limiting illnesses. In dignity therapy, patients complete a guided elicitation of the major accomplishments of their life, which, after editing and revision, is shown to family and placed in the medical chart as a statement of the value of the life lived. Articulating roles and accomplishments over life helps the patient build a legacy and may support hopefulness even with the approach of death. Research to examine the effects of enhancing dignity at the end of life may also show benefit for family caregivers.

CONCLUSION

Psychosocial factors are critical contributors to the health and quality of life of older individuals. We have focused on those factors that appear to be most promising in terms of explaining variability in health outcomes using a broad conceptual model that shows how psychosocial factors contribute to behaviors and biological processes linked to illness and quality of life. These effects do not occur in a vacuum but rather are set within the larger social and cultural contexts in which people live. The life course perspective shows how the experience of aging depends on cultural factors, such as the conceptualization of the lifespan, as well as biologically driven lifespan changes in social and affective experience. Although there is still much work to be done, a significant advance of the last decades is research showing how psychosocial factors get "under the skin" to affect the physiology and functioning of the organism, and hence health and quality of life. Continued advances in mind-body science along these lines will enhance our understanding of the relationships between biology, psychology, and social experience and will provide new opportunities for intervention.

A second theme of this chapter is the remarkable resilience of older individuals. Despite significant declines in multiple functional domains in late life, most older individuals adapt well to the challenges they face and maintain high quality of life. Depression and dissatisfaction with life do not come at the end of life, but earlier, in mid-life. While psychosocial health is clearly affected by disability, it is remarkable that majorities of older people report high levels of positive effect and involvement in daily life. This resilience reflects finely tuned adaptive mechanisms that maximize the ability to cope with major life challenges. Common old-age transitions such as retirement, widowhood, health decline, and caregiving, are challenging, but older people are able to navigate these changes in status through selection, optimization, and compensation to maximize function and well-being. Consistent with the greater socioemotional selectivity of old age, the landscape of affective and social experience changes and may look narrow to younger people; but the greater reports of satisfaction and happiness typical of old age suggest that these processes help buffer more challenging features of aging.

Finally, a third theme is the strong association between social engagement and well-being. Lack of support (social isolation and loneliness) has a negative effect, and social engagement (volunteering, lifelong learning, and involvement in intergenerational programs) a positive effect, on health and well-being in old age. Beyond these social factors, many kinds of intervention support psychological health. For example, the aging services network is important in promoting engagement across diverse domains, with clear benefit. Social environments that promote aging in place, involvement of older adults in their care and in health decision making, and supporting family caregivers who provide end-of-life care all offer benefit and show it is possible to promote engagement across multiple levels and domains. New models of engagement, such as school-based volunteering and intergenerational programs, suggest that engaging older adults may be good for older adults but also offer great benefit to other age groups. This kind of programming will likely become more important as increasingly larger cohorts of older people reach old age in better health.

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Chapter 8

Sex Differences in Health and Longevity

Steven N. Austad

Learning Objectives

- Understand the demographic metrics that define the female longevity advantage.
- Identify disease patterns that differentially affect men and women.
- Describe the health impacts of hormone transitions and replacement therapies for men and women.

Key Clinical Points

1. **Women live longer than men in every country and in every historical epoch for which reliable information exists.**
2. **Women appear more resistant than men to multiple fatal diseases, acquiring them at lower rates and/or later in life.**
3. **Despite their broad survival advantage, women are more likely to suffer from physical ailments than men later in life.**

THE ROBUSTNESS OF SEX DIFFERENCES IN LONGEVITY

Women live longer than men in every country and in every historical epoch for which reliable information exists. This fact is documented in the Human Mortality Database (www.mortality.org), which compiles historical demographic information from 37 countries over periods for which data are particularly dependable. Accordingly, the length of these records varies. Japan, currently the longest-lived country in the world, has good records beginning only in 1947 as most earlier records were destroyed during World War II. By contrast, Sweden has the longest period of reliable birth and death records of any country. Beginning in 1751 these records are moderately reliable, and they are very reliable from 1860 to the present day. Sweden's life expectancy over these 250+-year period dipped as low as 18 years during periods of famine or pestilence and risen as high as today's 82 years. However, in each and every year, regardless of overall life expectancy, women have outlived men (**Figure 8-1**). The same is true for each of the 37 countries in the Human Mortality Database for every year on record!

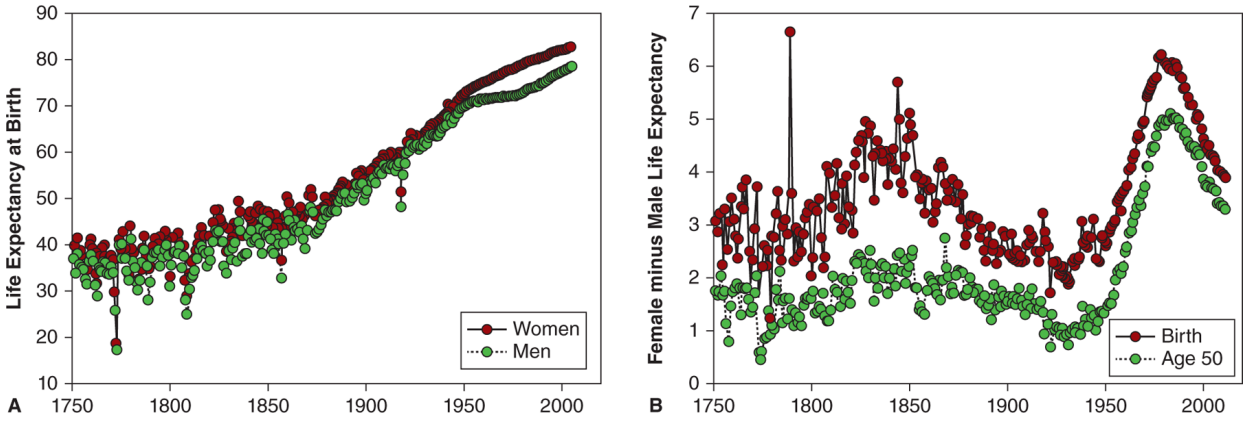


FIGURE 8-1. Demographic data from Sweden from 1751 to the present. **A.** Male and female life expectancies at birth show a steady increase after 1800 with occasional brief decreases due to war, famine, or infectious disease. **B.** Sex difference (Female minus Male) in life expectancy at birth and at age 50 is always positive, indicating greater female survival in all years for both ages. (Source: Human Demographic Database.)

Understanding Life Expectancy

To interpret sex differences in longevity—call it the "life expectancy gender gap"—it is useful to understand the meaning of two demographic parameters. The first of these is life expectancy itself. Life expectancy, unlike its name suggests, does not measure the expectation of future life, which is by its nature not really knowable. Life expectancy, as typically used in describing human longevity, measures past life. That is, as most commonly reported, life expectancy is equivalent to the average age of death of all individuals who died during a specific period—usually 1 year. So life expectancy in the United States in 2010—76.4 years for men, 81.2 years for women—is the average age of all people who died during 2010. More technically, such a measure is called the *period* life expectancy *at birth* because it is the average of deaths at any age from birth during a defined *period*. Unless otherwise specified, life expectancies reported in this chapter (as they are in the literature generally) will be period life expectancies at birth. Life expectancy can be calculated for any other age as well. Life expectancy at age 50, for instance, is the average age of death of those who survived for at least 50 years. Such a measure is useful for eliminating the impact of infant mortality or other early-life events such as military combat, therefore providing better comparisons on the health of older populations. Life expectancy from age 50, as at birth, uniformly favors women not only in Sweden (**Figure 8-1B**) but in all other countries and at all times recorded in the Human Mortality Database.

Prior to the middle of the twentieth century, most deaths worldwide occurred in infancy. Consequently life expectancy at birth was not particularly informative about the health of the older population. For example in 1773, the year in which Swedish life expectancy at birth fell dramatically to 18 years (**Figure 8-1A**), about half of all deaths occurred before age 5. Most adults died in their 40s and 50s, however. Thus the 18-year life expectancy at birth would be highly misleading if used as an indicator of typical ages of adult deaths. Life expectancy at age 50 is considerably more informative about survival of older adults and shows that in 1773, there was a relative small life expectancy difference (1 year) between men and women. However, as infant and early-life mortality in developed countries has plummeted in recent decades (only 5% or fewer of deaths now occur before age 50 in most industrialized countries), life expectancy—even life expectancy at birth—has become an increasingly useful measure of health in old age because virtually all deaths occur in older adult age groups.

Note that these "period" life expectancies combine deaths from people who were born at different times. That is, a 50-year-old who died in 2010 would have lived through a considerably different health environment than a 90-year-old who died in the same year. For instance, antibiotics and vaccinations against a number of common infectious diseases did not become widely available until the latter half of the twentieth century, so people born earlier in the century survived threats to health not faced by later generations. Sometimes it is useful to compare survival of people who were *born* during the same period—thus lived in similar health environments from birth—rather than who *died* during the same period. Life expectancy of people born during the same period is called *cohort* life expectancy. Cohort life expectancy can be dramatically different from period life expectancy because it records deaths that occur after—often many decades after—rather than during the eponymous year. Compared to the 18-year period life expectancy in Sweden in 1773, cohort life expectancy was 39 years for women, 36 years for men, and at age 50 it was 20.6 years for women, 18.5 years for men. A disadvantage of cohort life expectancy is that it can only be calculated precisely when

all the people born at a certain time have died. Therefore, it can only tell us about the relatively distant past. Cohort life expectancies can also fluctuate wildly with events like wars or epidemics where people of a certain age are particularly prone to die. French men from the 1895 birth cohort, for instance, had a 16-year life expectancy disadvantage compared to women, due to the massive war casualties among 19- to 24-year-old men during World War I. Regardless of how it is calculated, life expectancy of women always exceeds that of men wherever records are reliable. The gender gap in life expectancy may be one of the most robust features of human biology known.

Other useful demographic parameters for understanding health are mortality rates and survival rates. These simply report the relative chances of dying or surviving over a defined age, or time, interval, respectively. Sometimes rates are expressed as number of deaths or survivors per 100,000 people and sometimes as percentages or probabilities. These rate metrics can be somewhat more refined than life expectancy, which is a sum of survival rates over a large time interval, because rates can focus on specific ages, such as between survival from age 30 to 40, for instance. Annual mortality rates for each gender shown at 5-year intervals for the United States in the years 1900 and 2000 are illustrated in **Figure 8-2A** and will be discussed later.

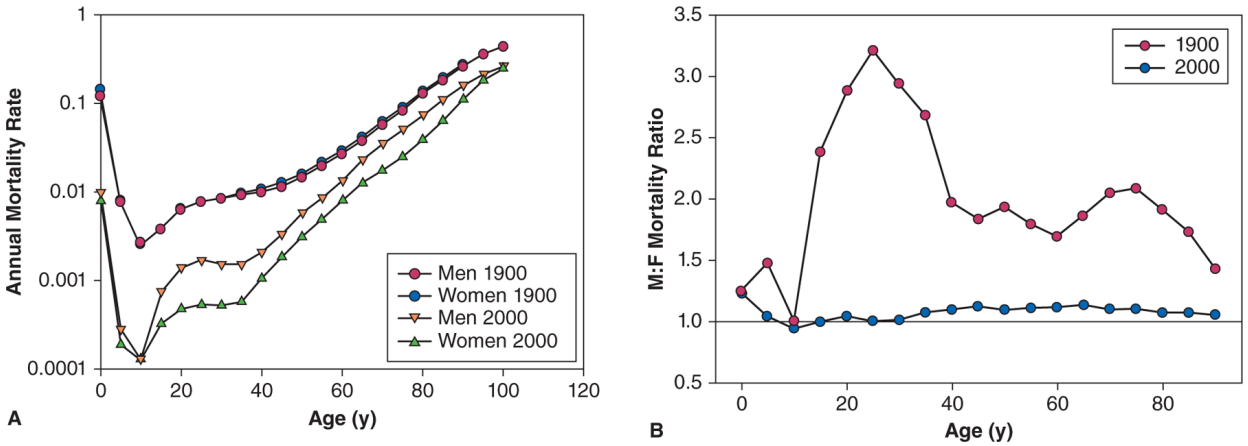


FIGURE 8-2. A. Age-specific mortality in men and women in the United States in the years 1900 and 2000. Note the logarithmic scale for mortality. In 1900, life expectancy at birth in the United States was 46.4 years for men and 49.0 years for women; in 2000, the analogous numbers were 74.0 years for men and 79.4 years for women. **B.** Ratio of male-to-female age-specific mortality. The reference line at 1 marks where male and female mortality is equivalent. (Source: US Social Security Administration, 2005.)

Reliability of Birth and Death Records

An occasional report surfaces at a place and time where men lived longer than women. Invariably the report is from a time and place marked by high levels of illiteracy and/or unreliable age records and whenever it is possible to investigate further, the report has been found to be flawed. For instance, since 1950 the United Nations has assembled detailed population statistics for as many countries as would provide them with data in their annual *Demographic Yearbook*. It would be an impossible task for United Nations' demographers to evaluate the reliability of this data on a country-by-country basis. Therefore, they uncritically report the information they are given. In countries without extensive administrative infrastructures, the data are often suspect. For example, the 2007 edition of the *Demographic Yearbook* reported life expectancy for men from Qatar was more than 3 years longer than that of women, surely an interesting finding if credible. However, to credit this data one would have to believe that in 2007 Qatari men lived about 2 years longer on average than Japanese men, the consensus longest-lived men in the world at that time. Also, since more than 80% of men residing in Qatar are immigrant workers, one would need to believe that the ages of all those men were known accurately. Since 2007 Qatari men's reported life expectancy has declined by more than 3 years, and that of Qatari women's has increased by about the same length, such that now like in the rest of the world women in Qatar are reported to live longer than men. Other examples in which the *Demographic Yearbook* at one time or another has reported a slightly greater male than female survival include India in the first half of the twentieth century and Afghanistan in 2004—the latest available data from a country where maintaining accurate birth and death records is not a high governmental priority. In 1962 Pakistan reported that men live about 5 years longer than women. This unexpected sex bias had disappeared by the next reporting, and now Pakistani women are reported by the United Nations to live 4 years longer than men.

Misinformation about age is particularly rife for exceptionally old people, especially among men, wherever record-

keeping is less than exquisite. In countries with good birth records, the accumulated effects of women's lifelong survival advantage means that with advancing age there is a progressive excess of women compared to men. Again, using Sweden with its precise, comprehensive birth and death records as an example, there are currently 105 women born per 100 men. By age 80, there are roughly 150 women per 100 surviving men, by age 90 there are 200 women per 100 men, and by age 100 there are nearly 350 women per 100 men. The Gerontology Research Group (www.grg.org) is a global e-group of researchers in gerontology that tracks and seeks to validate reports of supercentenarians (age 110 or older). According to their records about 95% of supercentenarians are women.

But in countries or during times with less reliable birth records, men have apparently had a remarkably improved ability to survive to extreme ages. For instance, the same 2007 *United Nations Demographic Yearbook* that listed Qatari men living longer than Qatari women reported that Costa Rican men who managed to reach age 100 still had a life expectancy of 11.7 years! Costa Rican female centenarians could expect to live 5.7 years more. However, many studies of centenarians in countries with much higher life expectancies than Costa Rica plus excellent birth records agree that even with exquisite health care 100-year-olds can expect to live no more than 2 to 2.5 additional years. Thus, the quality of the Costa Rican data for the oldest individuals of either sex gives cause for concern. As governmental birth registration was a haphazard to nonexistent affair in many countries including the United States until relatively recently, anomalies in official survival records for very old people are not surprising nor are they confined to Costa Rica. According to "official" government records, for instance, you were more likely to live long enough to celebrate your 100th birthday if you resided in Argentina, Bulgaria, Russia, or Ireland in 1900 than in present-day Sweden or Japan. Even early official Swedish government records are clearly flawed. They report, for instance, a higher rate of survival to 100 years in 1760 than in 1860. In fact, it was not until 1921 that the survival rate to 100 years in Swedish men reached the same level as its records reported in 1760.

Impact of Age-Specific Mortality on the Gender Gap in Longevity

Life expectancy differences are the product of survival differences over the life course. A reasonable question is whether women survive better than men at all ages, or is their survival advantage confined to certain periods of life? Using the United States as an example, during a period in which the gender gap in life expectancy was particularly small (the year 1900 when the gap was 2.6 years), and a period during which it was larger (the year 2000 when it was 5.4 years), several patterns appear (**Figure 8-2**). First, age-specific mortality, the probability of dying in a specific year, drops sharply from birth to age 10 for both sexes during both historical periods, then climbs at varying rates thereafter. Second, from age 35 on, that climb is log-linear, the so-called Gompertz mortality pattern—a hallmark of aging in which mortality accelerates at a constant rate. From age 50, mortality rate doubling, which is determined by the slope of the line, is virtually the same—about 8 years—in the year 2000 as it was in 1900. It is just that mortality declined by a nearly equivalent amount at all ages. Finally, although survival was markedly improved at all ages, the largest gains over this 100-year time span were those prior to age 50. Women clearly gained significantly more than men.

The logarithmic scale of **Figure 8-2A** makes it difficult to distinguish sex differences in mortality pattern particularly in 1900 where the differences were small, so the ratio of male-to-female mortality is shown in **Figure 8-2B**. This analysis shows that in 1900 when overall mortality was high, women survived better during the first years of life, there was little sex difference during childhood, adolescence, and the early reproductive years, then women gained a small but consistent survival advantage throughout the rest of life. Similar patterns are seen in 1900 Sweden and 1947 Japan which also had life expectancies of around 50 years, although in both these cases female mortality slightly exceeded male mortality through the teenage years. It is apparent that as mortality fell and life expectancy increased throughout the twentieth century, women benefited more than men. In particular, men died at much higher rates than women at all ages from age 20 onward. The huge peak in mortality difference shown in **Figure 8-2B** through the 20s and 30s is as a result of excess male deaths from accidents, homicides, and suicides. This pattern is seen in many, but not all countries. In current Japan, for instance, although male mortality is roughly double that of females through their 20s and 30s, the largest mortality differences are at ages 60 to 80.

Special attention should be paid to lower female than male mortality in the first years of life. A gender gap favoring females in survival from birth to 1 year appears to be as universal as greater female life expectancy, being found in every year of every country in the Human Mortality Database. Given that female babies less than 1 year are unlikely to receive better care than male babies, particularly in the distant past, this survival difference likely reflects an important biological difference between the sexes. The gender gap in survival even extends to prematurely born infants. Neonatologists consistently report that response to therapy and survival among prematurely born infants also

favors female over male babies. Thus females appear better designed for survival than males perinatally and even prenatally.

A similar pattern of increasing mortality differences between the sexes over the course of the twentieth century has also been observed in analyses of cohort mortality. A recent examination of birth *cohorts* from 1800 to 1935 across 13 developed countries found that the gender gap in adult (ages 40–90) mortality rates widened dramatically among those born in the late nineteenth and early twentieth centuries (thus typically dying in the latter half of the twentieth century). This widening gap—termed excess male mortality by the authors—was particularly noticeable at ages 50 to 70 years. The causes for these changes are examined below.

Temporal Trends in the Gender Gap

Even with the most reliable demographic records, there is considerable variability in the magnitude of the sex difference in life expectancy across time and countries. It may be difficult to avoid biological explanations for the seemingly universal advantage that women have over men in terms of life expectancy. However, the magnitude of the gender difference above a certain irreducible biological minimum is likely to be affected by cultural, environmental, and behavioral factors. Investigation into this variation might provide insight into how some of these factors affect health. For instance, in Sweden between 1750 and about 1950, variability in the gender gap is considerably more pronounced in life expectancy at birth than at age 50 (**Figure 8-1B**), indicating that the magnitude of the gap was largely driven by sex differences in survival in early and midlife. However, since the middle of the twentieth century when early-life deaths became a much smaller contributor to life expectancy calculations, the gap has changed in parallel fashion whether measured from birth or from age 50. During this time a striking pattern has emerged. Between 1950 and about 1980, the gender gap rose from near its lowest magnitude to its highest sustained level, then plummeted at its most rapid historical level to its current 4-year difference. Such a clear pattern demands explanation.

First, though, it should be pointed out that **Figure 8-1B** is misleading in one sense. It depicts the gender gap as absolute difference in number of years. Between 1750 and 1950, the period during which the differences appear consistently lower than they became later on, Swedish life expectancy climbed from about 40 years to more than 70 years. An absolute difference of 3 years in life expectancy is arguably more meaningful if overall life expectancy is 40 years rather than 70 years. If the difference is expressed as a percentage of male life expectancy (**Figure 8-3A**), a somewhat different picture emerges. The gender gap was actually larger for the most part prior to 1850, then declined until the 1930s after which it rose abruptly, although never reaching earlier levels, and then it declined rapidly.

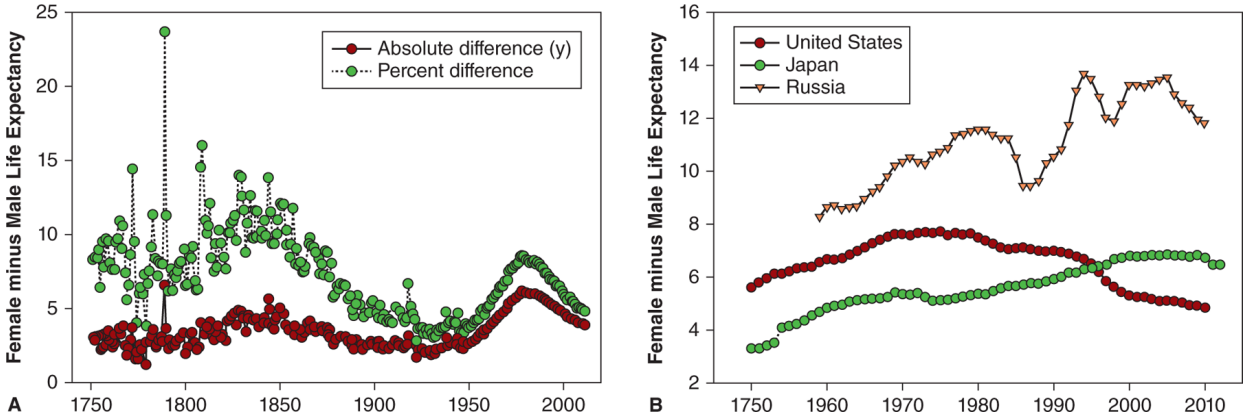


FIGURE 8-3. Gender gap in life expectancy. **A.** Sweden since 1751 expressed in absolute difference versus as a percentage of male life expectancy. **B.** Absolute differences in three countries. Note that when Japan's difference was little more than 3 years (early 1950s), overall life expectancy in Japan was still low by modern standards (60–63 years).

Before discussing possible reasons for this pattern, it might be revealing to look at patterns in several other representative countries (**Figure 8-3B**). For some time countries of the former Soviet Union have had the world's largest gender gap in life expectancy. In Russia that difference now approaches 12 years. This large difference is not due to exceptionally long-lived women, but to exceptionally short-lived men. Russian women are in fact among the shortest-lived women in the industrialized world—their current life expectancy of 75 years is only marginally higher than it was in the 1960s. But health and longevity of Russian men is abysmal. Their life expectancy of 63 years is a consequence of poor diet, poor sanitation, a virtual absence of preventative medical care, and dreadful health habits. As a result, 25% of Russian men die by age 55 compared with only 10% of women. To place this statistic in an

international perspective, only 5% of Swedish or Japanese men die by age 55. The main factors driving the Russian gender gap in life expectancy are smoking and alcoholism. Russian men have traditionally had among the highest smoking prevalence in the world and until recently Russian women had particularly low prevalence. This has been a rather constant contributor to the overall poor health of Russian men compared to women, but fluctuations in the life expectancy gap has also marched in lock step with the availability of vodka. Specifically, in 1985 when then Soviet leader Mikhail Gorbachev drastically cut vodka production and did not allow it to be sold before lunch-time, the gender gap abruptly shrunk as men began living longer. When President Yeltsin later liberalized alcohol availability, the gap expanded again just as abruptly. Since 2006 when new restrictions were implemented, the gap has again begun to shrink. Recently, there has been a substantial rise in smoking prevalence among Russian women—it rose from 7% in 1992 to more than 20% today. Combining that unfortunate trend with continuing governmental control of vodka production, the Russian gender gap in life expectancy may continue to contract, ultimately looking more like that in the rest of the world.

Russia is something of a special case because of its high rate of male alcoholism. More generally, has there been a consistent pattern of change in the gender gap as overall life expectancy has rocketed upward in most industrialized countries in recent decades? Again using Sweden as an example, the life expectancy gap both at birth and at age 50 rose dramatically after World War II, but has fallen steadily since the 1980s (**Figure 8-1B**). This is the most common pattern among high-income countries. Similar patterns of rapid increase in the gender gap after World War II, followed by a rapid decrease beginning in the 1980s or 1990s and continuing to the present have been seen in the United States, Canada, Australia, Iceland, France, and most European countries. The life expectancy gender gap is not declining everywhere, however. In Japan, where life expectancy at birth has grown explosively—nearly 5 years per decade—since the end of World War II, the sex difference also steadily increased until the 2000s where it appears to have stabilized at about 7.5 years (**Figure 8-3B**).

The major reason for these various patterns—at least after World War II when causes of death were more reliably recorded—appears to be largely the delayed impact of historical smoking habits. This is indicated by the fact that although death rates from most common causes have been declining in both sexes in recent years, in the United States and most of Europe women's deaths from lung cancer and respiratory diseases have declined slowly if at all, compared to a relatively rapid decline among men. Smoking of course adversely affects multiple aspects of health in addition to its effects on the lungs, but lung cancer and respiratory diseases serve as convenient indicators of smoking's impact on general health. As noted previously, women in most western countries took up smoking in large numbers more recently than men and have been slower to stop. In Sweden, smoking is now more prevalent among women than men. An example of the delayed effect of smoking can be seen in data from the United States (**Figure 8-4**). As with smoking itself, deaths due to respiratory diseases and lung cancer (now the number one cause of cancer deaths in women) peaked among women somewhat later and have so far declined more slowly than among men. In Japan where the gender gap in life expectancy has not closed appreciably, smoking prevalence among women has always been—and continues to be—very low compared with men. Importantly, both history and biology suggest that despite the recent contraction of the gender gap in life expectancy across most high-income countries, there is likely to be an irreducible floor to the gap of probably about 3 to 4 years.

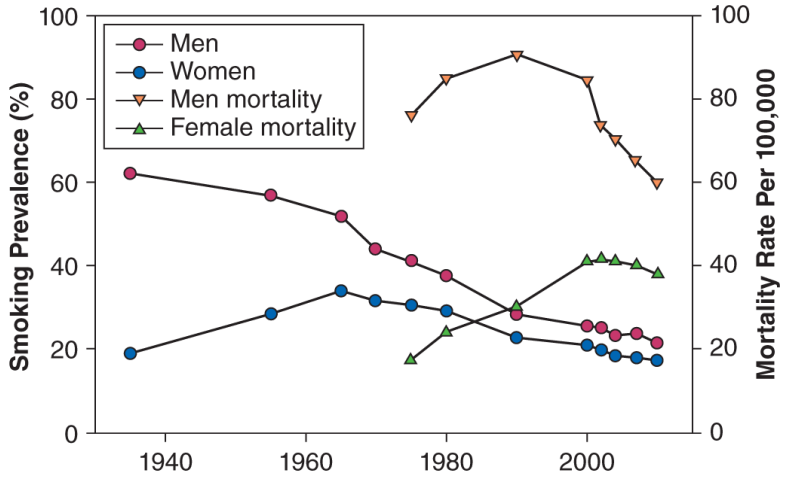


FIGURE 8-4. Historical changes in smoking prevalence and mortality rate from lung and bronchial cancer in the United States. Note that

smoking among women reached its peak later and declined more slowly than among men and lung cancer death rates followed suit with a delay of several decades. (Sources: United States Centers for Disease Control *and Prevention* and National Cancer Institute SEER Database.)

Somewhat surprisingly, the gender gap is now playing a role in the US declining rank in life expectancy among countries internationally. In 1950, the United States ranked 12th in the world in life expectancy, sexes combined. By 1985, US women ranked 19th out of 187 countries, men ranked 29th. As of 2010, despite life expectancy increasing by more than a decade over the last 60 years, the United States ranked 39th for women, 40th for men—near the bottom of all industrialized countries. US women, in particular, have gained in life expectancy at only about half the rate of other high-income countries over the past 30 years. A recent study by the US National Research Council, launched to investigate the reasons for this pattern, concluded that a major contributor was that Americans, particularly women, began smoking in large numbers earlier and more intensively than women in Europe and Japan. They are now experiencing the delayed consequences of that behavior. Damage from smoking was calculated to account for nearly four-fifths of the sluggish improvement in US women's life expectancy relative to Europe and Japan, compared to only two-fifths of men's improvement. As US women also began reducing smoking earlier than in many other high-income countries, it is expected that their life expectancy rank may begin to rise over the next several decades.

DO WOMEN AGE MORE SLOWLY THAN MEN?

Does the universal difference in life expectancy between men and women suggest that men age more rapidly than women? This is not an easy question to answer as it requires defining aging—a task that defies simplicity.

Demographic Evidence

One definition often favored by demographers is that aging in a population can be measured by the rate of increase in age-specific mortality. By this definition, men and women age at surprisingly similar rates (**Figure 8-2A**). Note in the figure that in the United States whether one considers data from 1900 when life expectancy was 46.4 years and 49 years for men and women, respectively, or data from 2000 when life expectancy reached 74 years for men and 79.4 years for women, age-specific mortality increases from age 40 in almost perfectly parallel fashion in the two sexes. Women simply die at lower rates throughout later life. The same general pattern is seen in almost all countries with reliable death statistics. An exception is Russia in which higher death rates among men younger than 55 make the slope of mortality rate increase somewhat lower for men that women. So at least by this metric, women do not age more slowly than men. They are simply better designed for survival regardless of age.

Causes of Death

Another way to define relative aging rates might be to compare the ages at which they get major diseases of later life. Do women tend to die of the same diseases as men, they just get them later? If so, then plausibly women age more slowly than men. Alternatively, maybe women are more resistant than men to only one or a few major causes of death such as cardiovascular diseases and stroke and except for that difference, perhaps they would age at the same rate as men. This latter hypothesis seems unlikely given that the major causes of death have changed historically, while women have always lived longer. It is also not supported by available evidence. Men die at higher rates than women from a broad swathe of diseases with one particularly interesting exception.

Comparing causes of death between the sexes and even within a sex over time requires some careful thinking. One common metric of comparison is the simple percentage of deaths caused by a disease. Using this metric, some causes of death have decreased over the past 50 years (eg, heart disease, stroke) while others have increased (eg, cancer, diabetes; **Table 8-1**). This metric can be seriously misleading though. For instance, in 2010 roughly 25% of all men's deaths in the United States were due to heart diseases, whereas for women the analogous figure was about 24%. Thus, at first glance heart disease seems to be roughly an equivalent health problem for men and women. Similarly, cancer causes a higher percentage of deaths today (23%) than it did 50 years ago (16%). Does this mean that we are getting progressively worse at preventing and treating cancer?

TABLE 8-1 SEX DIFFERENCES IN TOP CAUSES OF DEATHS IN THE UNITED STATES OVER THE 50-YEAR PERIOD BETWEEN 1960 AND 2010

DISEASES	1960		2010	

Gender (life expectancy)	Men (66.6)	Women (73.3)	Men (76.4)	Women (81.2)
Heart disease (1)				
Percent of all deaths	40	37	25	24
Age-adjusted rate	376	206	225	143
Age-adjusted ratio (male to female)	**1.8**		**1.6**	
All cancers (2)				
Percent of all deaths	15	17	24	22
Age-adjusted rate	143	111	210	147
Age-adjusted ratio	**1.3**		**1.4**	
Chronic lower respiratory disease (3)				
Percent of all deaths	0.7	0.4	5.3	5.9
Age-adjusted rate	6.8	4.8	49	38
Age-adjusted ratio	**1.4**		**1.3**	
Stroke (4)				
Percent of all deaths	9.5	14	4.2	6.2
Age-adjusted rate	85	75	39	38
Age-adjusted ratio	**1.1**		**1.0**	
Alzheimer disease (6)				
Percent of all deaths	0.01	0.04	2.1	4.7
Age-adjusted rate	0.2[a]	0.3[a]	21	27
Age-adjusted ratio	**0.7**[a]		**0.8**	
Diabetes mellitus (7)				
Percent of all deaths	1.2	2.4	2.9	2.7
Age-adjusted rate	12	15	25	18
Age-adjusted ratio	**0.8**		**1.4**	
Chronic kidney diseases (8)				
Percent of all deaths	1.2	1.3	2.0	2.1
Age-adjusted rate	6.8	4.8	19	13
Age-adjusted ratio	**1.4**		**1.4**	
Influenza and pneumonia (9)				
Percent of all deaths	3.9	3.9	1.9	2.1
Age-adjusted rate	35	22	18	13
Age-adjusted ratio	**1.6**		**1.4**	

ND, no data.

[a]Standardized to 100,000 population, not age-adjusted rates.

Numbers in parentheses represent rank in percent of total deaths in 2010. Causes among top 10 not listed are unintentional accidents (#5) and suicides (#10), both heavily male-biased. The 1960 age-adjustment used the 1940 US standard population, whereas the 2010 adjustment used a different—year 2000—standard population. Therefore, comparisons of age-adjusted values cannot meaningfully be made across years.

US National Vital Statistics Reports.

Obviously not. The occurrence of heart disease or cancer, like 9 of the 10 top causes of death (excluding only cause #10—suicide) in the United States today, accelerates with age. Today, we live roughly 9 years longer than we did in 1960. Thus, we are more frequently succumbing to cancer today compared with 50 years ago simply because we are not dying of other things first. We are also *less* frequently succumbing to heart diseases *despite* not dying of other

things first *and despite* living longer. This is truly one of the signature accomplishments of modern medicine.

A critical limitation of using percent of deaths caused by specific diseases is that it masks information on the ages at which death occurs. Presumably, heart disease or cancer should be considered a more serious health problem if it kills earlier in life rather than later. In addition, delaying the onset or progression of these diseases should be considered a sign of medical progress. There is a meaningful health difference in other words between dying of a heart attack at age 50 versus age 80.

The confounding impact of age in the interpretation of health trends can be removed by using age-adjusted mortality rate. This metric gives the relative probability of dying from a disease while controlling for age. If the percent of deaths caused by a particular disease is similar, but the age-adjusted rate is lower for women than men, it indicates that women are contracting the disease later in life or are surviving longer with the disease. For instance, there is currently minimal difference between sexes in percent of deaths due to heart disease (24.9% for men, 23.5% for women), but a major difference in the age-adjusted rate (225.1 vs 143.3 per 100,000 for men vs women, respectively), indicating that women typically have heart attacks later in life or are better at surviving them. The former is true. US women have their first heart attack 8 years later than men on average, but are in fact *less* likely to survive (probably because they are 8 years older when it occurs).

Sex-specific profiles of deaths can be compared as they were reported over a 50-year interval using the 1960 and 2010 US Vital Statistics Reports (**Table 8-1**). Because the age-adjustment for 1960 was calculated based on a different standard population than in 2010, comparison of age-adjusted rates between years is not meaningful. Age-adjustment in this case is useful for making comparisons within years. However, the ratio of male-to-female age-adjusted rates does allow comparison of gender bias in death rates across years.

Note that across this 50-year time interval, life expectancy increased by 9.8 years for men, but only 7.9 years for women, emphasizing how the current rate of life expectancy gain in the United States is somewhat higher for men than women. Also note the dramatic reduction in percent deaths due to heart diseases, stroke, and respiratory infections. As might be expected with the much older population in 2010, percentage of total deaths from a range of diseases of aging such as cancers, chronic lower respiratory disease, diabetes, chronic kidney disease, and especially Alzheimer disease (AD) increased fairly dramatically as well.

In 1960, males died at higher age-adjusted rates for 8 of the top 10 causes of death (**Table 8-1**). Males died at 80% higher rates from heart diseases and 60% higher rates from influenza and pneumonia. Not shown in the table for 1960 are accidents, cirrhosis of the liver, and tuberculosis, all of which were male-biased as well (male/female age-adjusted ratios: 1.3, 2.1, and 2.8, respectively). The comparative female resistance to dying of infectious diseases such as pneumonia, influenza, and tuberculosis is not specific to the United States. In Japan in 1960, men died of tuberculosis at twice the age-adjusted rate of women. Such resistance in fact may help explain the historical female survival advantage. In 1900 and presumably earlier, pneumonia/influenza was the leading cause of death, followed closely by tuberculosis. Not shown for 2010 are deaths from accidents, cause #5 (age-adjusted sex ratio: 2.0), and cause #10, suicides (age-adjusted sex ratio: 1.4). By 2010, 9 of the 10 top causes of death were male-biased, although only slightly so for stroke. Thus across a span of 50 years despite better overall improvement in health and survival among men than women, men still died at higher age-adjusted rates from virtually all of the top causes of death.

The trend for men to die at greater age-adjusted rates from a diversity of causes is by no means unique to the United States. Among the 28 countries of the European Union, in which life expectancy ranges from 74 years (Latvia, Lithuania) to 83 years (Iceland), men die at higher age-adjusted rates than women of nearly every top cause of death as well. The same is true in Japan, the country with the highest life expectancy in the world.

In sum, as women do seem to contract multiple diseases of aging (fatal diseases anyway) later in life than men, it is at least arguable that despite the demographic evidence, women age more slowly than men.

It is important to note the source and limitations of the US national statistics as presented in **Table 8-1**. These data are compiled from causes of death listed on US Standard Death Certificates filled out by a physician, medical examiner, or coroner at the time of death. Determining cause of death is an inexact process and frequently opens to interpretation even with a complete autopsy; complete autopsies are infrequently done today. Even in cases where the cause of death would be clear upon autopsy, for example myocardial infarction (MI), studies have found that death certificates frequently misattribute the cause. This is particularly an issue for chronic diseases.

Diabetes mellitus is one chronic disease for which death reporting may be problematic. In the United States, diabetes deaths were female-biased by 25% in 1960 but male-biased by 41% in 2010. In fact, over the 50-year period between these two reports, there has been a steady gradual shift from female-to-male bias. (Other studies both from the United States and Europe reported female bias in deaths from diabetes in the first half of the twentieth century as well.) Now, however, similar male biases to those found in the United States are reported across the European Union

as well as in Japan. Changing diagnostic criteria for diabetes and variable death certificate reporting are likely contributors to these differences.

Women and dementia An outlier in the pattern of virtually complete female dominance in resistance to lethal disease appears to be AD, which according to 2010 US national statistics is our sixth leading cause of death and which kills women at substantially higher rates than men whether raw percentages or age-adjusted rates are used (**Table 8-1**). That is, US women currently die more than twice as often as men from AD *both* because they live longer *and* because they are generally more susceptible. In comparing the 2010 to the 1960 data in **Table 8-1**, the percentage of total deaths reported due to AD (called senile psychosis in 1960) increased more than 200-fold for men and more than 100-fold for women over this 50-year period. As diagnostic criteria for AD were not well established in 1960, AD was dramatically underdiagnosed then and so very few deaths were attributed to AD. Thus, the 1960 data are not interpretable. A more accurate portrayal of what AD means at present on American death certificates is probably "AD and other dementias," which is how causes of death are categorized in the United Kingdom. For UK women, AD and other dementias have now surpassed heart disease as the number one cause of death, whereas for men it is now #5.

The current female bias in deaths from AD is consistent with a large body of data from the rest of developed world. In Japan and across Europe, the age-adjusted sex ratio of Alzheimer deaths is similar to ours. **Figure 8-5**, which summarizes 31 independent studies from across Europe, shows the relative prevalence of AD as it accelerates with age in each gender. Inspection of that figure suggests that as populations become older, AD will become more and more female-biased.

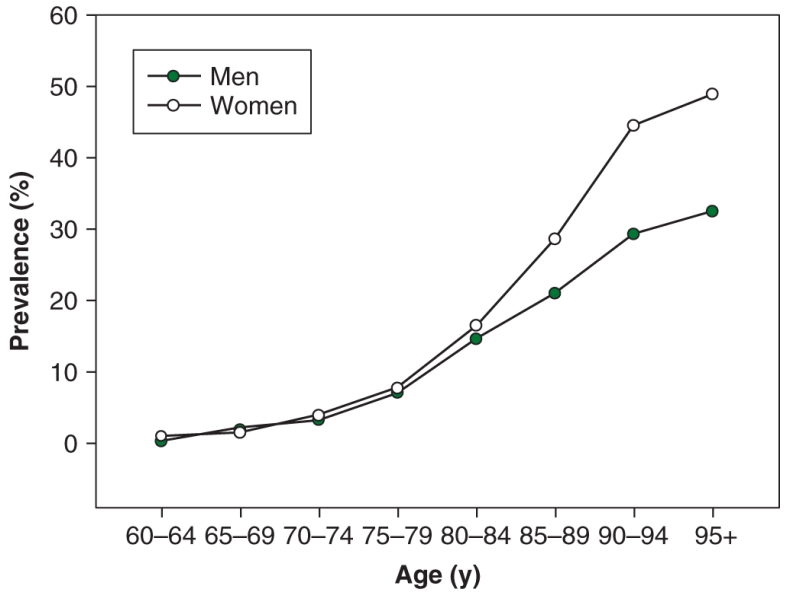


FIGURE 8-5. Relation of age and gender to prevalence of Alzheimer disease. Summarized from 31 studies from across Europe. (*Data from* Alzheimer's Europe.)

Sex hormones, health, and disease The pattern of women's increased susceptibility to dementias in addition to their consistently increased resistance to most other fatal diseases relative to men, provokes speculation about the role of sex hormones in health and disease. This has been a fraught topic in aging research at least since the late nineteenth century when French-American physiologist Charles-Édouard Brown-Séquard began injecting himself with a cocktail of macerated dog and guinea pig testicles and subsequently proclaimed that he was rejuvenated in both mind and body.

Sex hormones such as testosterone, estrogens, and progestins decline with age in both sexes, although male testosterone decline is considerably more gradual than the relatively abrupt change across the menopausal transition in women. That restoring these hormones to youthful levels will have a generalized rejuvenating effect is a plausible hypothesis. The reverse is also plausible. That is, one could equally reasonably speculate that declining hormone levels with age are an adaptive response to reduce hormonally induced adverse health effects with increasing age. Returning hormones to youthful levels, according to this hypothesis, may actually cause harm.

What does the empirical evidence indicate? Millions of men have undergone testosterone replacement therapy to treat declining libido and erectile dysfunction, as well as to improve strength and physical performance. The female advantage in longevity and disease susceptibility might suggest that long-term testosterone replacement, however good

it might be for strength and libido, might enhance susceptibility to a host of aging-related diseases. Also, given increased female susceptibility to AD and other dementias, testosterone replacement could plausibly be protective against AD. Unfortunately, high-quality information on potential long-term positive or negative health outcomes of testosterone replacement, although under study in men, is not yet available. Therefore, presumptive adverse health outcomes of testosterone replacement such as increased risk of cardiovascular diseases, infections, or prostate cancer are still largely conjectural.

However, some historical information from the complete removal of gonadal hormones is provocative. For instance, a review of longevity records for 81 eunuchs employed as guards or servants of the royal court of Korea during the seventeenth and eighteenth centuries found that eunuchs lived on average 20 years longer than intact men of similar rank and status—a result notable mainly for the magnitude of the difference. These findings echo a previous study comparing nearly 300 castrated men with more than 700 intact controls who lived in the same institution for the intellectually disabled in the United States in the early twentieth century. This study found not only a large (> 13 year) difference in life expectancy favoring the castrated men but also a bigger survival advantage the earlier-in-life surgery was performed. Whether these studies have any relevance to men living with modern hygiene, diets, and medical monitoring is of course not clear.

Women have been receiving various forms of hormone replacement (HR) to treat menopausal symptoms for decades. Data from observational epidemiology and laboratory rodent studies indicated that replacing female hormones postmenopause would likely lead to multiple health benefits, including reduced cardiovascular disease and reproductive cancers. However, observational studies can be misleading if, say, women receiving HR are systematically different in terms of health practices from those who do not, and the relation between studies with laboratory rodents and free-living humans is always uncertain.

To clarify the overall health impact of HR, the US Women's Health Initiative (WHI) enrolled more than 16,000 participants of 50 to 79 years in a randomized clinical trial of HR in the 1990s. Results of these studies are complex, but clear health benefits were certainly not found. In fact the combined estrogen–progestin arm of the study for nonhysterectomized women was stopped early because of an excess of adverse events. HR is clearly successful at reducing menopausal symptoms such as hot flushes, night sweats, and loss of libido, and in the WHI reduced the risk of hip fracture and diabetes. However, there were significant increases in the risk of stroke, pulmonary embolism, deep vein thrombosis, and for those women with a uterus who were on combined HR (estrogen plus progestin), an increase in breast cancer risk. There are layers of complexity buried within the results, but however interpreted, the hopes for a generalized rejuvenating effect of HR were clearly dashed.

Given that women have an elevated risk of dementia, including AD, compared with men and that common forms of dementia develop after the age of menopause, does HR at least protect against dementia? For women who already have AD, there is no clear positive evidence that HR improves cognition despite at least nine clinical trials addressing that issue. Evidence for HR as preventative is also sparse and not particularly promising. For instance, the memory study arm of the WHI found that women with a uterus, who were on combined HR, developed dementia at *double* the rate of women on placebo! For women on estrogen replacement alone, there was no benefit, but no additional risk either.

Women in the WHI differed from many women in that they did not start HR until roughly 10 years after menopause on average, whereas historically women often began HR much earlier to relieve menopausal symptoms. Some evidence from small and observational studies hints that the timing of HR might ultimately prove to be protective against later life dementia in women. However, so far this "timing hypothesis" remains largely speculative. In sum, the relationship between sex hormones—whether male or female—and AD-and-dementia risk remains unresolved, but attention to the conspicuous gender difference could yield insight into this growing health problem.

HEALTH DISPARITIES AND GENDER

On average, global health and longevity continue to improve for both men and women in all countries not torn by war or epidemic diseases. However, averages sometimes conceal important underlying patterns, particularly patterns having to do with variation within countries. One of those patterns has to do with how gender interacts with other determinants of health and longevity such as income, education, race, health habits, or access to medical care. The United States has been particularly well studied in this regard, motivated by a desire to understand why despite spending far more on health care than any other country, US life expectancy—especially among women—increasingly lags behind most other high-income countries.

As noted earlier, the gender gap in life expectancy in the United States grew rapidly from about 1950 to around 1980 and has been steadily shrinking since the early 1980s (**Figure 8-3**). This pattern is due to a more rapid gain in women's life expectancy relative to men's prior to the early 1980s followed by a slower gain thereafter. Specifically, over the quarter century between 1985 and 2010, life expectancy of US women increased by only 2.9 years (78.0–80.9) compared with 5.3 years (71.0–76.3) for men. Although life expectancy of neither gender grew as rapidly as in many other high-income countries, the growth for women was particularly slow—only 50%, 55%, and 73% the rate of Japanese, French, and Swedish women, respectively. Compare that with the equivalent figures for men. US men's life expectancy grew 13% *faster* than Japanese men's, 78% and 88% as fast as French and Swedish men.

A useful tool for assessing whether this national pattern could be due to inequalities in health within the United States is a county-by-county analysis. Not only are life expectancies and mortality rates available for each of the 3143 counties in the United States, so are data on income, racial composition, education level, and a host of other variables potentially informative for understanding the reasons underlying observed health disparities. There is tremendous variability among counties across the United States in all these variables. For instance, per capita income varies by more than sixfold from the poorest to the richest county, and the life expectancy gap between the longest- and shortest-lived counties is nearly 18 years for men and 13 years for women. This gap is greater than the life expectancy gap between Sweden and Nicaragua. Reiterating the larger historical and international perspective presented earlier, despite this striking variation among US counties, female life expectancy exceeded male life expectancy in every county for every year between 1960 and the present.

Several interesting patterns appear in such an analysis. First, variability among county life expectancies has been consistently greater for men than women since at least 1960. Second, life expectancy inequalities *within* each gender were smallest in the early 1980s when the gap *between* genders was at its maximum. Since then, within-gender inequalities have steadily risen for both sexes.

The period between 1985 and 2010 has been particularly well studied. An astonishing finding has been that while the most advantaged counties have continued a steady increase in life expectancy for both sexes, there has been little change in life expectancy over the past 25 years for the least advantaged counties. This is particularly true for women for whom more than 42% of counties in the United States showed no increase in women's life expectancy whatsoever across the entire 25-year period. Furthermore, nearly 10% of counties showed a significant *decrease*. Analogous figures for men reveal that fewer than 5% of counties showed no increase and fewer than 1% showed a decrease. A separate county-by-county study traced mortality rates (rather than life expectancy) from the early 1990s through 2006 and found similar results. Average mortality rates fell by 9.8% over that period for men and only 1.5% for women. Male mortality rate actually increased in only 3.4% of counties, whereas women's mortality rate increased in almost 43% of counties! In sum then, although national averages continue to show steady gains in life expectancy during the past 25 years, for a significant fraction of women there have been no gains—or even losses—in life expectancy over that time period.

Two additional patterns emerge from an inspection of the causes of death. First, mortality due to cardiovascular disease has been falling steadily for both sexes for the past 60 years. As mentioned previously, this should be considered a major medical and public health triumph. During the period—roughly 1960 to 1980—when the gender gap in life expectancy was increasing, men were more frequently dying from lung cancer and chronic respiratory diseases than women. Since then as the gender gap has been shrinking, reduction in cardiovascular disease has continued although at a slower rate for women relative to men, and the relative rate of increase in deaths from lung cancer and chronic respiratory diseases has risen. Second, that pattern was particularly marked in counties in which women lost life expectancy in recent years. Clearly these patterns, as with the international patterns, reflect differences in current and past smoking behavior. Beyond that, there is a puzzling geographic component above and beyond obvious socioeconomic factors. Most counties with increased women's mortality were in the South, or in counties in the West with a significant proportion of Native American residents. Local diets would be one obvious place to look for clues to the reasons for this geographic component. Possibly more interesting than what variables were associated with decreasing life expectancy, are variables that were not. No simple correlations were found, for instance, between change in life expectancy and per capita income, educational attainment, percent of adults who were obese, availability of primary care providers, or proportion of the population lacking health insurance.

If instead of focusing on the counties that did worse over time, we focus on the ones that did better, which after all was the overwhelming number of counties for men and the majority for women, we find more of the expected explanatory factors. The two most significant associations with improved men's survival were percent of adults with a college degree and percent of Hispanic residents. The Hispanic effect is due to the so-called Hispanic paradox, the observation that Hispanics of both sexes live longer than Caucasians of equivalent socioeconomic status. Still

significant, but somewhat less strongly associated, were population density (the higher, the better), and median household income. Similarly, in counties in which women's health improved over these study years, significant associations were seen with higher proportion of Hispanics, higher proportion with college degrees, higher population density, and higher median household income. For neither sex was obesity or obvious medical care factors, such as percent of the population with health insurance or number of primary care physicians, statistically involved.

It is important to understand that the lack of statistical association between a socioeconomic or behavior factor and increasing versus declining survival in a county-by-county study does not indicate that a particular factor is unimportant for health or survival. For example, many studies have identified obesity as a significant contributor to poor health. The lack of association with obesity described above just means that a county-by-county analysis is too crude a tool to pick up a likely obesity effect.

The trend in the United States for women to gain less than men in life expectancy over time is particularly apparent if one examines differing education levels and ethnicities. Education generally can be considered almost a miracle drug for improved health and life expectancy regardless of ethnicity. For instance, among Caucasian Americans, the impact of having 16 years or more of education compared with having not completed high school was a difference in life expectancy of 10.4 years for women and 12.9 years for men. To emphasize the magnitude of this education effect, it is comparably greater than the magnitude of life expectancy difference between Sweden and Paraguay. Education is hypothesized to exert its impact via better health habits, better ability to deal with stress, and more effective management of chronic conditions. More disturbing is the impact of low education. Caucasian women and men with less than a high school diploma actually lived about 5 and 3 years less, respectively, in 2008 than they did in 1990! Puzzlingly, this temporal decline in life expectancy for poorly educated Americans was not seen in African-Americans or Hispanics. In fact, in those ethnic groups life expectancy rose over that time period for all education levels, including those not completing high school.

In sum, health disparities within the United States are generally larger for men than women, but a substantially larger fraction of women than men are showing worse health now compared with 25 years ago.

THE HEALTH-SURVIVAL PARADOX

As robust and widespread as is women's survival advantage over men, equally robust, widespread, and puzzling, is men's health advantage over women. Although women live longer than men everywhere, women also display greater overall rates of physical illness and functional limitations than men from adolescence throughout life. In the United States, for instance, women make more doctor visits, spend more days in hospital, miss more work due to illness, and take more medications than do men. Women also self-report more functional limitations and are overrepresented relative to their proportion of the population in residential care facilities.

This health-survival paradox is a worldwide phenomenon. In most of the world's 187 countries, unlike in the United States, women's life expectancy is increasing slightly faster than men's. Also, increasing faster in women than men is the number of unhealthy years they live. One measure of ill health is "years living with disability (YLD)," which is the severity-adjusted prevalence of disability. Across countries of the world per capita YLD is generally higher for women than for men, particularly at young and middle ages. Thus the additional unhealthy years lived by women compared to men are not just those at the end of life. Additionally, self-reported health surveys of people over 50 years from 13 countries (United States, United Kingdom, 11 continental European countries) revealed that despite more men than women being overweight and currently smoking, women in all countries were more likely to have functional difficulties or disabling conditions. Similarly consistent differences were found in a comparative study of the United States, Jamaica, Malaysia, and Bangladesh, in which participants were asked about their ability to perform a variety of tasks, such as walk a certain distance, bend over, or climb stairs (**Figure 8-6**).

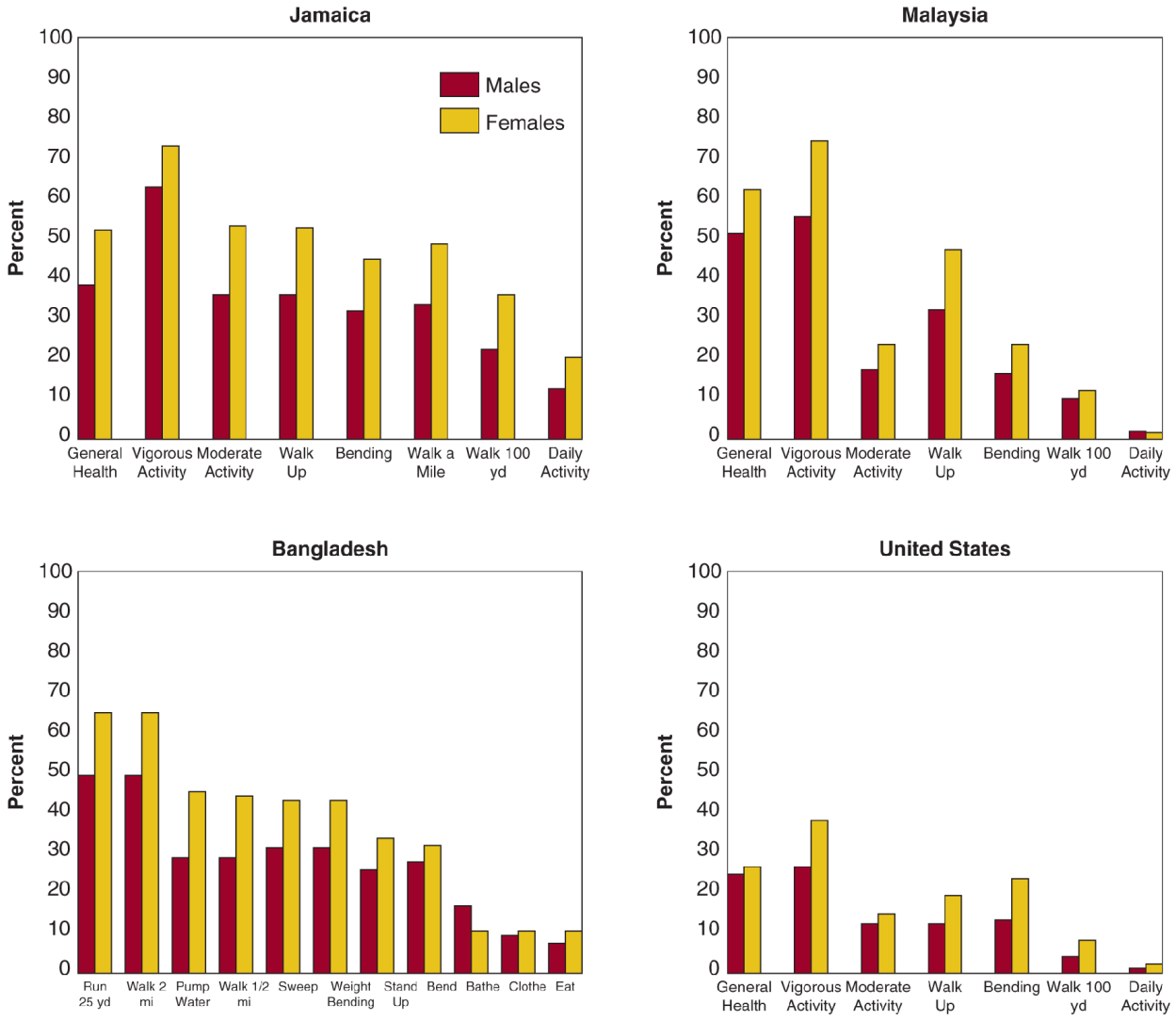


FIGURE 8-6. Self-reported health across several countries. Proportion of respondents reporting fair-to-poor ability to perform these tasks. (Reproduced with permission from Rahman O, Strauss J, Gertler P, Ashley D, Fox K. Gender differences in adult health: an international comparison. *Gerontologist.* 1994;34(4):463.)

One hypothesis to explain the health-survival paradox is that women are more attentive to physical discomfort and more willing to seek medical attention when they perceive it. However, empirical evidence to support such an explanation is uneven and sometimes contradictory. Also, if this hypothesis is valid, it would have to be a worldwide phenomenon rather than a cultural feature of wealthy, Western countries. **Figure 8-6** shows that the same patterns obtain in poor, culturally diverse countries such as Jamaica, Malaysia, and Bangladesh. A second plausible hypothesis is that because men die at higher rates than women throughout life, ill men are more likely to die than ill women. Thus the surviving men will be more highly selected for health and vigor than surviving women. If this sex-selection hypothesis is valid, one would predict that the sex differences in various health metrics would increase with age as more and more ill men die while more and more ill women survived. As intriguing as is this hypothesis, several large cross-national studies have failed to find such predicted divergence in health status with age. They find instead a relatively constant male health superiority throughout life.

The ubiquity of these health differences between the sexes beg for a biological explanation. One of the most consistent findings among dozens of studies investigating sex-based morbidity differences is that women are subject to more bone and joint diseases, including idiopathic back pain and osteoarthritis. Chronic pain can limit activities and cause sufferers to seek medical attention. In addition it can have more far-reaching, secondary health consequences from sequelae such as sleep deprivation and chronic stress. So, a plausible, if partial, biological hypothesis for the health-survival paradox may be sex differences in joint components such as cartilage and ligaments. Uterine connective tissue undergoes extensive remodeling and increasing elasticity during pregnancy under the influence of various reproductive hormones. Could it be that a side effect of the responsiveness of women's cartilage, tendons, ligaments, and muscle to female reproductive hormones is an increased susceptibility of women to joint instability and

resultant inflammation and pain? Provocatively, female athletes in sports such as soccer and basketball are 5 to 10 times more likely to suffer anterior cruciate ligament knee injuries than male athletes, and most are from noncontact events. Also, the prevalence of idiopathic knee osteoarthritis is similar in men and women prior to menopause, but much greater in women after menopause, again suggesting a hormonal influence on joint health. Women also tend to have more robust inflammatory and immune responses than men, perhaps helping to account for their greater resistance to infectious diseases, and also greater susceptibility to autoimmune and inflammatory joint diseases such as osteo- and rheumatoid arthritis. Taken together, these sex differences may contribute to the health-survival paradox.

SEX DIFFERENCES IN LONGEVITY IN A MAMMALIAN CONTEXT

If the virtually ubiquitous female survival advantage in humans has a biological basis, as it seemingly must, is it a typical mammalian trait or something idiosyncratic to humans and/or our closest relatives, the great apes?

This turns out to be a surprisingly difficult question to answer. First we must consider whether to credit evidence from nature or only from protected captive populations, such as those on farms or in zoos or research institutions. In mammals generally, males are the dispersing sex. That is, males typically leave the area in which they were born, disperse far and wide, and then compete with other males for breeding opportunities. Females tend to stick closer to home in the vicinity of female relatives and typically do not compete for mates. The dangers associated with dispersal and mating competition might bias survival in the wild toward females. In fact, it does for a variety of species such as African lions, red deer, and pilot whales. But is that behavior-driven sex difference in survival the type of survival difference that is relevant to the human gender gap? It might be relevant—at least at some times and places if **Figure 8-2B** is anything to go by. Note that in 2000, men in the "mate-competition" years from the teens to the early 30s have the highest mortality relative to women during any period of life. The analogous data from many countries look remarkably similar. That difference is primarily due to what has been called "testosterone dementia"—homicides, suicides, and accidents—possibly driven at least in part by male-to-male competition.

More generally, is there an intrinsic mammalian survival difference between the sexes that persists in the absence of deaths from violence, as it does in humans? To answer this question, the most informative data will be from captive populations. Turning to such populations, there is little clear pattern in the species we know best. For instance, female laboratory rats typically live longer than males, but laboratory mice show no consistent sex difference across more than a hundred studies. A comparison of male and female dog and cat longevity has not been done, despite all that is known about these popular companion species. Interpretation of longevity among these pet groups is difficult because of the enormous influence of the owners on decisions about neutering and medical interventions. In some cases, such as guinea pigs, hamsters, and horses, males are the longer-lived sex. It appears as if there is no generalized superiority in female survival among mammals. It may be a human specialty.

It would be interesting to know whether the sex difference in survival has been a feature of our species over our entire evolutionary history or whether it emerged, for instance, with the appearance of farming, civilization, or medical record-keeping. Unfortunately, reliable birth and death data for modern hunter-gatherers are scant, and interpretation of findings from these relict tribes now confined to marginal habitats *vis à vis* our evolutionary history is not clear. However, study of our closest relatives among living primate species might provide clues as to human's earliest existence as a species.

Among primates as a whole, sex differences in survival are complex. In captive populations of species in which males are significantly involved in parental care, such as owl or titi monkeys, males live slightly longer than females. For other species with little male involvement in parental care, such as baboons, which have abundant longevity records both in captivity and in the wild, there appears to be no substantial difference in life expectancy between the sexes. However, among the great apes, our very closest relatives, the pattern is quite clear. Female chimpanzees, gorillas, and orangutans outlive males of the same species wherever data are available from either wild or from captive populations. Thus, it appears that we have inherited greater female survival from our closest primate ancestors. The physiological mechanism(s) underlying this difference are even less obvious for these species than for our own. Male chimpanzees are more prone than females to heart disease, the number one killer of captive chimpanzees. But that is about the sum of our knowledge of sex differences in health and longevity among the great apes.

CONCLUSION

Several robust features of human biology emerge from considering sex differences in health and longevity. Most particularly, women appear more resistant than men to multiple fatal diseases, acquiring them at lower rates and/or later in life. Women also appear to be more resistant to a range of infectious diseases from early in life. A notable exception to this pattern is AD and other dementias, to which women are more susceptible than men worldwide. Despite the broad survival advantage, women are more likely to suffer from physical ailments than men later in life even controlling for age effects. It is tempting to hypothesize that differential lifetime exposure to sex hormones contributes to both the positive and negative sex differences. Yet to date, no simple answers on how lifetime sex hormone exposure relates to diseases and disabilities of later life have materialized. In the United States, there is a puzzling trend over the past several decades for women to gain life expectancy at a slower rate than men, and some groups of disadvantaged women are even shorter-lived today than they were decades ago. Learning more about sex difference in health and longevity will be critical to determining how to reduce health disparities in both sexes.

Since the US National Institutes of Health (NIH) Revitalization Act of 1993, women have been required to be adequately represented in NIH-funded clinical studies. Today, roughly half of clinical research participants are women. However, similar attention has not been paid to sex balance in studies with laboratory animals or cells, which are heavily male-biased. Mechanistic understanding of health and disease relies to a large extent on studies of laboratory animals or cells. In May 2014, the NIH issued a policy statement promising to redress this imbalance through program oversight and review, as well as through collaboration with publishers. One desired outcome of this new direction would be a better understanding of biological sex differences in health. Ultimately, would it not be desirable that men live as long as women and women achieve the lifetime health of men?

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Part II

Principles of Geriatrics

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Chapter 12.	Assessment of Decisional Capacity and Competencies
Chapter 13.	Prevention and Screening
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Chapter 18.	Critical Care
Chapter 19.	Subacute Care
Chapter 20.	Nursing Home Care
Chapter 21.	Community-Based Long-Term Services and Support and Home Care
Chapter 22.	Rural Aging
Chapter 23.	Quality of Care
Chapter 24.	General Principles of Pharmacology and Appropriate Prescribing
Chapter 25.	Complementary and Alternative Medicine
Chapter 26.	Team Care
Chapter 27.	Social Work
Chapter 28.	Self-Management of Health Behavior
Chapter 29.	Rehabilitation
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Chapter 32.	Anesthesia
Chapter 33.	Surgical Outcomes
Chapter 34.	Nutrition and Obesity
Chapter 35.	Malnutrition and Enteral/Parenteral Alimentation
Chapter 36.	Disorders of Swallowing
Chapter 37.	Oral Health
Chapter 38.	Low Vision: Assessment and Rehabilitation
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Chapter 40.	Menopause and Midlife Health Changes

Chapter 41. Sexuality, Sexual Function and the Aging Woman
Chapter 42. Gynecologic Disorders
Chapter 43. Sexuality, Sexual Function, and Androgen Replacement Therapy in the Aging Male
Chapter 44. Benign Prostate Disorders

Chapter 9

Evaluation, Management, and Decision Making

Daniel D. Matlock, Carmen L. Lewis

Learning Objectives

- To understand the modern legal and ethical framework of clinical decision making
- To describe how and why decision making is different and more challenging for older adults
- To recognize the importance of incorporating patients' and families' outcome goals as the drivers of medical decision making

Key Clinical Points

1. **The patients' and families' perspectives, goals, and values should be the major drivers of medical decision making.**
2. **Age-related changes, multifactorial symptoms, changing accuracy of diagnostic tests, changing patient goals, and family perspectives all sum in making decision making more challenging for older adults.**
3. **The history and physical should include a detailed assessment of the person's social/living situation, functional status, mood, and cognition.**
4. **Ascertainment of patients' preferences, which are known to vary among older patients and patients with multiple health conditions, should occur early and often.**

OVERVIEW: A COMMENT ON PERSPECTIVE

Any discussion of decision making must begin with a discussion of the importance of perspective. All decisions are viewed through the lens of the decision maker. In medicine, decisions can be viewed from many perspectives including the patients, the clinicians, the health care system, and even society. This array of lenses with differing motivations and incentives can lead to widely disparate decisions. For example, a doctor may recommend an expensive medication such as a new chemotherapy in the interest of helping a patient live longer. The patient on the other hand may not be singularly focused on survival and/or may find the side effects intolerable. The health care system in which the physician works may be eager to reap the reimbursements of an infusion associated with the medicine. Meanwhile, society may be concerned that the high costs and marginal benefits of medications such as this provide relatively little value to the society as a whole.

This chapter is not meant to be an exhaustive discussion of the science of decision making. As such, a detailed discussion of the contemporary politics and economics of cost-effectiveness, insurance design, cost-sharing, and other issues essential to understanding decision making at the health care system or societal level are beyond the scope of this chapter. Rather, this chapter will take a clinical perspective focusing on the challenges and opportunities for

clinicians, patients, and others involved in the complicated evaluation and management of decision making with older adults.

THEORETICAL FOUNDATION OF MODERN MEDICAL DECISION MAKING

Modern medical decision making sits largely on an ethical foundation. Grounded firmly on the ethical principle of autonomy, emphasis on a patient-centered approach has been rising since the early twentieth century when courts began charging physicians with battery for performing operations to which patients did not consent. While judges have softened this to negligence over time, court cases such as those involving Karen Ann Quinlan, Nancy Cruzan, and Terri Schiavo and acts of Congress such as the Patient Self-Determination Act continue to affirm a patient's and/or surrogate's right to determine their medical therapy.

The movement, often called "patient-centered care" is based on an underlying assumption that people make decisions in a normative way. Normative decision theories, such as expected utility theory, are based on an ideal that people can approach decisions rationally and are able to cognitively weigh the risks and benefits of various interventions to make a good decision. However, there is a disconnection between the rhetoric of "good" decision making and the reality of decision making. Descriptive theories of decision making demonstrate that humans are subject to cognitive biases that cause decision making to deviate from the normative/rational approach. One of the most famous descriptive theories is prospect theory developed by Dan Kahneman and Amos Tversky. One aspect of this theory demonstrates that the way options are framed influences the decisions that are made. In a classic example, respondents were asked to imagine that an unusual Asian disease is expected to kill 600 people. They were given the choice of two alternative programs which were mathematically identical according to the normative expected utility theory. In option A 200 people will be saved, and in option B there is one-third probability that 600 people will be saved and two-thirds probability that no one will be saved. When the options are presented as gains ("people will be saved"), 72% of the respondents chose to save the 200 people rather than take riskier option B. However, if options were presented as a loss ("400 people dying") 78% of the respondents chose the riskier option B. This experiment elegantly demonstrates how decisions can change drastically simply based on framing; that when options are presented as gains, people tend to be risk averse, and when options are presented as losses, people tend to be risk seeking. Of note, the respondents to that survey were medical professionals highlighting the point that clinicians and patients alike are equally susceptible to these biases. Prospect theory is just one example from the growing field of behavioral economics (also referred to as cognitive psychology). The influences and applications of these theories to modern medical decision making is an active area of research.

The challenge for all clinicians and patients making decisions at the bedside is in finding ways to build a bridge between the legal and ethical mandate to promote patient-centered care and informed consent and the behavioral aspects where decision making is not always rational. Ultimately, good decision making involves elicitation of the patients' priorities among general, often competing health outcome domains such as including longevity versus comfort/symptom relief to assure that these preferences drive all evaluation and management decisions.

DECISION MAKING AND OLDER ADULTS: UNIQUE CHALLENGES

Clinical decision making for older adults, including diagnosis, treatment, and desired outcomes, is different and more challenging than it is for younger patients. Generally, the primary goal of medical care in younger adult patients is diagnosis of the disease causing the presenting symptoms, signs, and/or laboratory abnormalities. Treatment is targeted toward the pathophysiologic mechanisms deemed responsible for the disease. Survival is generally paramount. Relevant clinical outcomes are determined by the specific diseases and usually include cure if the disease is acute, and control or symptom modification if the disease is chronic.

In older adults, the conventional disease-specific approach is not optimal in older patients for several reasons. First, age-related physiologic changes in most organ systems affect diagnostic test interpretation and responses to treatments. Additionally, the average 75-year-old suffers from 3.5 chronic diseases. With multiple coexisting chronic diseases, there is a less consistent relationship between the pathology, the disease, and the clinical manifestations. One disease may obscure the presentation of another and treatment of one may increase the severity of another. With multiple coexisting diseases, it becomes difficult, and often impossible, to assess the severity or manifestations of individual diseases and to ascribe health and/or functional status to specific disease processes.

Second, many distressing symptoms or impairments among older persons, such as pain, dizziness, fatigue, sleep problems, sensory impairments, and gait disorders cannot be ascribed to a single disease; instead, they result from the accumulated effect of physical, psychological, social, environmental, and other factors. A clinical focus solely on diagnosing and treating discrete diseases may lead to expensive diagnostic testing with inconclusive results. Worse, it may even lead to harm if unnecessary and invasive interventions are inappropriately pursued. While clinicians may be reluctant to treat symptoms in younger and middle-aged patients without a specific diagnosis, treatment focused on improving symptoms in older patients with multimorbidity is often appropriate, because comfort and function are often the primary goals among this population.

Third, diagnostic test characteristics may be altered by age and comorbidity, making selection and interpretation of tests more complicated than for younger patients. Furthermore, both the benefits and harms of treatment regimens may differ in the face of age-related physiologic changes and coexisting health conditions.

Fourth, older patients vary in the importance they place on potential health outcomes. When asked, older persons are able to prioritize among the often competing goals of increased survival, comfort, cognitive function, and physical function. Optimal clinical decision making in the care of older patients includes the articulation of patient preferences or goals of care; the identification of the diseases, impairments, and nondisease-specific factors affecting the attainment of these preferences and goals; and the selection of treatment options based on the modifiable impediments to individual patient goals. The multiplicity of impairments and diseases; the contribution of psychological, social, and environmental factors to health conditions; the enhanced likelihood of harm as well as benefit from many interventions; and the variability in goals and preferences all combine to make clinical decision making in the care of older persons very complex.

Fifth, clinical decision making is further complicated in older patients because other persons, including the spouse, adult children, other relatives, and significant others, are often actively involved, particularly when cognitive impairment is present. Involvement of family and friends is helpful and often crucial, since they may provide additional sources of information, facilitate adherence to treatment recommendations, and offer both emotional and instrumental support. Up to 70% of older adults lose the capacity to make decisions prior to death and require surrogates. Conflicts may arise, however, when goals of the patient and family differ. Striking a balance between patient confidentiality and family involvement, between independence and support, and between patient and family goals is a constant challenge. When based on an understanding of these factors, however, the clinical care of older persons is both effective and immensely gratifying.

DECISION MAKING: THE CLINICIAN'S PERSPECTIVE

Clinicians are tasked with evaluating a patient including performing a history and physical examination, initiating a diagnostic workup when appropriate, and determining what medically reasonable options are appropriate given the patient's unique situation. Clinicians must then explore the patient's goals and share in the decision making to assure that the chosen treatments align with the patient's goals.

Evaluation: The History

The clinical interview is an important element of the decision-making process. It can be used to establish a diagnosis and monitor treatment and prognosis. The altered, often attenuated, presentation of diseases, the coexistence of multiple processes, and the underreporting of symptoms and conditions in older patients mandate a reordering of the importance of various components of the history. The chief complaint, the cornerstone of history-taking in younger patients, has decreased relevance in older persons. Indeed, overreliance on the chief complaint leads to the oft cited, though inaccurate comment that older persons are "vague" or "poor historians." Rather, they may be accurately reporting the often vague, nonspecific manner in which they experience their illnesses.

Social history Social history is of paramount importance in the care of older adults. Knowing a person's living arrangements and financial situation as well as the organization of their support system is essential in decision making with older adults. Problems in these domains are prevalent among older adults. Indeed, these factors are central when discussing major decisions around increased support at home versus institutionalization.

Review of symptoms and syndromes The review of systems takes on greater importance in older persons and is often the vehicle by which treatable health conditions are revealed. Complementary to the conventional review of systems, physicians should perform a review of syndromes, targeting modifiable multifactorial geriatric syndromes

common in older persons including sleep problems, incontinence, pain, dizziness, falls, depressive symptoms, fatigue, anorexia, and weight loss. Difficulty, degree of dependence, and change in ability in both self-care or basic activities of daily living (ADL—eating, dressing, grooming, bathing, walking, and transferring) and instrumental activities of daily living (IADL—taking medication, handling finances, using transportation, preparing meals, housekeeping, communicating outside the home, and shopping) are also integral components of the history in older persons. These functional activities often are the primary outcomes targeted in the treatment of older patients.

Assessment of mood, affect, and cognition The clinical history of older persons should also include assessments of cognitive function, affect, and mood (depressive symptoms). These topics are discussed in detail in Chapters 62 and 63. Briefly, mood and affect can be screened for easily with tools such as the two-question depressive screen (In the past month, have you been sad, blue, or down in the dumps? Have you lost interest in most things or been unable to enjoy them?). More formal, systematic assessments should be undertaken if there is any question of depression. Cognitive status can be screened for with short tests such as the Mini-Cog. The Mini-Cog combines the three-item recall and the clock-drawing test (CDT). In a community-based study, the best performing scoring algorithm for the Mini-Cog was when the participant was judged to have dementia if either the three-item recall score was 0 or 1 to 2 and a CDT score was rated between 1 (mild) and 3 (severe). This scoring had a sensitivity of 99%, a specificity of 93%, a positive test likelihood ratio of 14.1, and a negative test likelihood ratio of 0.01. This scoring algorithm had a better sensitivity than other more commonly used cognitive tests. The Mini-Cog has several advantages, which makes it a useful screening tool. It takes less than 5 minutes to complete, is unaffected by language or education, and can be scored by untrained raters with minimal loss of accuracy. Knowing the cognitive status of an older adult also has important implications in decision making.

Evaluation: The Physical

Physical examination The physical examination in older persons differs from younger persons as well. The purpose of the physical examination in younger persons is primarily to diagnose specific diseases. The physical examination in older persons, however, also serves to identify treatable impairments such as muscle weakness, gait instability, or sensory impairments, and to directly observe the performance of key functional tasks.

Functional examination While the technique of physical examination in an older person is often the same as in younger persons, direct observation and functional testing play particularly important roles in older persons. Observing the older patient as they walk down the hall, get on and off the examination table or sit up to the edge of the bed are valuable and time-efficient ways to ascertain relevant information concerning muscle strength, joint range of motion, and gait stability as well as difficulty with daily functional tasks. Similarly, buttoning and unbuttoning a shirt or blouse, taking shoes on and off, and writing a sentence are simple tests of fine-motor coordination, manual dexterity, and motor planning. Reading a prescription bottle or a magazine provides information on visual acuity. Observing a patient's ability to follow multiple-step commands such as during finger-to-nose testing provides valuable information on cognitive and neurologic functioning. Recent weight loss can be judged from clothing that is too large, especially at the collar and waist.

Selecting components of the physical examination to perform While the content of the physical examination will be much the same for older, as for younger patients, given time constraints, high-yield, relevant, but less traditional, examination items should take precedence. The functional tests described earlier are examples of high-yield items that should be part of the standard examination. For example, during day 5 of a hospitalization, it is likely more important to see if your patient can sit up or stand than to listen to the heart sounds. Other high-yield examination elements might include postural blood pressure, inspection of ear canal for cerumen, visual acuity, and foot examination.

Evaluation: Diagnostic Testing

Diagnostic testing poses additional challenges among older adults. The value of a diagnostic test is best determined by considering whether the test is accurate, the target disorder is dangerous if left undiagnosed, the test has acceptable risks, and effective treatment exists. All of these criteria are relevant as older patients often have multiple health conditions and limited life expectancy changing both the accuracy and value of diagnostic testing. Also, because older adults vary in the emphasis they place on outcomes other than mortality, even a good diagnostic test may not be appropriate for an individual patient.

Deciding whether a diagnostic test is important requires consideration of its ability to change the probability of disease prior to test completion (called the pretest probability of the target disorder) to a probability of the disease after test completion (called the posttest probability). As for the physical examination, the coexistence of diseases and age-related changes may affect the sensitivity, specificity, predictive value, and interpretability of laboratory, imaging, and other ancillary tests. Consequently, most tests have lower value among older adults. In addition, age-referenced normal values and ranges have been developed for some, albeit, not most laboratory tests.

In older persons, there are additional issues to consider including the ability of the patient to complete the test and whether the test does more good than harm. A patient with significant gait impairment, for example, is not going to be able to complete an exercise stress test. And, it may not be appropriate to consider a particular diagnostic test in someone with multiple comorbidities and poor quality of life if the purpose of that testing does not align with the patient's goals. For example, a diagnosis of dyslipidemia is not clinically relevant in someone with advanced cancer.

Establishing whether a test does more good than harm would theoretically require randomizing patients to a diagnostic strategy that includes the test under investigation or to one in which the test is not available and following patients in both groups forward in time to determine the frequency of patient-important outcomes. While such trials are rare, there are a few of them. Consider for example a recent Cochrane review of studies that evaluated the impact of screening for prostate cancer. Five randomized trials including more than 341,342 patients found no statistically significant difference in prostate cancer mortality between men randomized to prostate cancer screening and controls (risk ratio [RR]: 1.00, 95% confidence interval [CI]: 0.86–1.17). However, neither study assessed the effect of prostate cancer screening on all-cause mortality, nor did they explore other important outcomes such as quality of life or anxiety.

In deciding whether to perform a laboratory, imaging, or other ancillary test, the clinician should consider the issues outlined in **Table 9-1** and the principles described in this chapter. This decision process is illustrated for the example of noninvasive imaging for carotid stenosis. Consider for example, an 80-year-old patient who presents with a transient ischemic attack. A carotid Doppler ultrasound is ordered and reveals greater than 70% stenosis of the carotid artery on the affected side. Magnetic resonance angiography (MRA) is ordered and the patient's family wants to discuss whether to proceed with the test. Before the MRA is done, several issues should be considered in addition to ensuring that surgery is available and effective in your setting. Would the patient consider carotid endarterectomy? If the answer is no, further diagnostic testing is not warranted. Are there significant comorbidities or contraindications to the surgery? For example, if a patient has advanced dementia and poor functional status, the benefits of surgery would be questionable both because of their competing morbidities limiting the time through which they might benefit and the greater difficulty they might have in participating in the perioperative care and rehabilitation. If surgery might be contemplated, then it is appropriate to determine whether there are accurate and reliable tests for diagnosing carotid stenosis available in your setting.

TABLE 9-1 ISSUES TO CONSIDER IN DECIDING WHETHER TO PERFORM A DIAGNOSTIC TEST AND HOW TO INTERPRET RESULTS

- How will the results be used?
  - Establish a diagnosis
    - Is there a safe and effective treatment?
    - Do comorbid conditions preclude treatment or make it ineffective?
    - Will the patient accept the treatment?
  - Establish prognosis
    - Does patient want the information?
  - Monitor disease progression or response to therapy
- Definition and interpretation of normal (see Table 10-2)
- Is the test accurate in the patient for whom it is being considered?
- Can the test distinguish persons with and without the targeted condition?
- Do the potential consequences of the test justify its cost and inconvenience?
- Can the test be performed and interpreted in a competent fashion?

A recent systematic review of the accuracy of noninvasive imaging tests compared with intra-arterial angiography

for significant carotid stenosis in symptomatic patients can help with the last question noted above. Forty-one studies including 2541 patients were included in this review. The accuracy of the four imaging techniques for diagnosing significant carotid stenosis is provided in **Table 9-2**. For diagnosing 70% to 99% stenosis, the specificity was lowest for MRA and Doppler ultrasonography. Thus, MRA may result in inappropriate surgery in up to one in seven patients. This systematic review suggests that noninvasive testing cannot appropriately be used to recommend carotid endarterectomy. Patients should be made aware that they will likely require intra-arterial angiography, which does carry a small but real risk of complications. Unless the clinician considers patient outcome goals and risk preferences as well as the accuracy of the diagnostic tests, some patients will have surgery who do not need or desire it and some medically treated patients will have preventable strokes.

TABLE 9-2 ■ ACCURACY OF NONINVASIVE IMAGING TECHNIQUES FOR DIAGNOSING 70% TO 99% CAROTID STENOSIS COMPARED WITH INTRA-ARTERIAL ANGIOGRAPHY

IMAGING TECHNIQUE	SENSITIVITY (95% CI)	SPECIFICITY (95% CI)	+LR	–LR
CEMRA	95% (88–97)	93% (89–96)	13	0.06
DUS	89% (85–92)	84% (77–89)	5.6	0.13
MRA	88% (82–92)	84% (76–97)	5.5	0.14
CTA	77% (68–84)	95% (91–97)	15	0.24

CEMRA, contrast-enhanced magnetic resonance angiography; CTA, computed tomographic angiography; DUS, Doppler ultrasonography; LR, likelihood ratio; MRA, magnetic resonance angiography.

Adapted with permission from Kelly A, Holloway RG. Noninvasive imaging techniques may be useful for diagnosing 70% to 99% carotid stenosis in symptomatic patients. ACP J Club. 2006;145(3):77.

DECISION MAKING—INCORPORATING THE PATIENT'S PERSPECTIVE

Patient-centered care dictates that clinical decision making should occur within the context of individual preferences and goals. Ascertainment of these preferences, which are known to vary among older patients and among patients with multiple health conditions, should occur early and often. Older persons rarely volunteer their preferences. Active solicitation of priorities and preferences, therefore, needs to be an integral part of the patient and family interview. Good patient-centered care does not mean that the doctor tells the patient what to do. This is the paternalism that modern ethics and Western legal systems have largely overturned. At the same time, good patient-centered care does not entail putting a smorgasbord of options in front of a person and telling them to choose—an approach that has even been called patient abandonment. Rather, decisions should be shared between the clinicians and their patients. Clinicians bring expertise in the medical information and patients bring expertise in themselves and what is important to them. Then, a shared decision is less about information provision and more about a conversation between two experts.

Matching Treatments to Patients' Goals

A body of research suggests that patients are not adequately informed when receiving medical interventions. Recently, a large survey demonstrated that patients scored low on their knowledge when asked about nine common conditions, even if they had received those procedures. Perhaps even more concerning is the literature that patients often receive care that they would not want. Many patients, especially older patients, have difficulty in choosing among a set of treatment options. Rather than having patients to make specific treatment choices, which is difficult and often not feasible for the large number of medical decisions that older adults face, encouraging patients to prioritize among different outcome domains allows them to express directly what is most important to them regarding their health care. The elicitation of priorities among general, often competing health outcome domains, including longevity, comfort/symptom relief, cognitive functioning and physical functioning should ideally drive all evaluation and management decisions.

The process of goal elicitation can be complicated and requires a clinician adept in handling the communication challenges that will arise. First, the setting for the discussion may need to be adapted to the specific impairments of some older persons. Impairments in hearing, visual acuity, and cognition, each prevalent among older persons, mandate a quiet, well-lit, and unhurried setting—not easily obtained in today's health care environment—in order to have a

meaningful discussion. Multiple encounters may be required to complete the history and to gather the necessary information. While the patient remains the key informant, the discussion often needs to be supplemented by information obtained from the family, friends, and other care providers, particularly if the older person has cognitive impairment.

Second, the process of goal elicitation can be emotional. Sometimes, a patient or family may articulate a goal that is just not feasible given their situation (eg, remaining by themselves in their home). Here, the task of the clinician is in helping the patient redefine goals that are feasible. This can be a difficult and emotional conversation for all involved. Often, to help patients define their goals, they must enter into the complicated discussion of prognosis. An area of active research is in improving clinicians' communication skills with patients to facilitate these patient-centered discussions.

CONCLUSION—THE ART

As noted above, decision making with older adults is challenging in many ways. For most, life comes with multimorbidity and functional decline and the traditional disease-focused models do not work. While a lucky few have truly compressed morbidity, the majority of older adults experience gradual decline, mounting morbidity, and frailty. However, underneath the challenge is a deep richness. Helping patients and families clarify their outcome goals and assuring that treatments align with those goals will never be automated by a machine. Perhaps more than anywhere else, the art and humanity of the sacred practice of medicine thrive when caring clinicians engage in decision making with older adults.

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Chapter 10

Principles of Geriatric Assessment

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Learning Objectives

- To distinguish between geriatric assessment and comprehensive geriatric assessment
- To identify the core components of geriatric assessment by individual clinicians
- To learn practical approaches to geriatric assessment that can be administered within the constraints of a busy office practice
- To understand the core components of comprehensive geriatric assessment
- To know the evidence-based strengths and limitations of comprehensive geriatric assessment
- To recognize how some important components of comprehensive geriatric assessment have been integrated into new health care innovations

Key Clinical Points

1. **Geriatric assessment extends beyond the traditional disease-oriented medical evaluation of older persons' health to include assessment of cognitive, affective, functional, social, economic, environmental, and spiritual status, as well as a discussion of patient preferences regarding advance directives.**
2. **Observing patients walking and performing balance maneuvers best assesses balance and gait disorders. Qualitative gait assessment can be performed while the patient is entering or leaving the examining room and can be augmented by measuring gait speed. Patients who take more than 13 seconds to walk 10 m are more likely to have recurrent falls.**
3. **Although in 2014, the US Preventive Services Task Force (USPSTF) concluded that there is insufficient evidence on the balance of benefits and harms of screening for cognitive impairment, clinicians should assess cognition when there is suspicion of impairment.**
4. **Much of the germane information of the medical history can be obtained from old records, other professional or nonprofessional staff, or by self-report from patients or family members completing forms.**
5. **By delegating the administration of screening instruments for many of the important geriatric problems to trained office staff, the clinician may spend a short period of time reviewing the results of these screens and then decide which dimensions, if any, need greater evaluation.**
6. **In virtually all studies of comprehensive geriatric assessment, the process itself has resulted in improved detection and documentation of geriatric problems. However, such identification of problems has not always led to improved outcomes.**
7. **The best evidence for effectiveness of comprehensive geriatric assessment is for inpatient geriatric units and home assessments of younger-geriatric patients.**
8. **Concepts of comprehensive geriatric assessment have been incorporated into new successful models of care (eg, Geriatric Resources for Assessment and Care of Elders [GRACE] and Guided Care), specialty care, and disease management programs.**

Geriatric assessment is a broad term used to describe the health evaluation of older patients, which emphasizes components and outcomes different from that of the standard medical evaluation. This approach recognizes that the health status of older persons is dependent on influences beyond the manifestations of their medical conditions. Among these are social, psychological and mental health, and environmental factors. Geriatric assessment also places high value on functional status, both as a dimension to be evaluated and as an outcome to be improved or maintained.

Although in the strictest sense geriatric assessment is a diagnostic process, many use the term to include both evaluation and management. Moreover, geriatric assessment is sometimes used to refer to evaluation by the individual clinician and at other times refers to a more interdisciplinary process, comprehensive geriatric assessment (CGA). The terminology is further clouded because the latter process has evolved since its inception with respect to sites where the assessment is provided, the participating health professionals, the nature of the assessment, and the amount of follow-up and management that is included. Accordingly, any discussion of geriatric assessment must be precise in its description of the process of interest.

This chapter is divided into four components: (1) geriatric assessment by the individual clinician, with an emphasis on the outpatient setting; (2) a strategic approach to geriatric assessment for the practicing clinician; (3) CGA and evidence for its effectiveness; and (4) lessons learned from geriatric assessment that have been applied to health care delivery of older persons.

GERIATRIC ASSESSMENT BY THE INDIVIDUAL CLINICIAN

Geriatric assessment (**Figure 10-1**) by the individual clinician extends beyond the traditional disease-oriented medical evaluation of older persons' health to include assessment of cognitive, affective, functional, social, economic, environmental, and spiritual status, as well as a discussion of patient preferences regarding advance directives. Assessment instruments can be used to guide these evaluations but do not substitute for clinical skills and judgment, including the skill of eliciting important items from the patient's history and physical examination. Information obtained from assessment instruments can direct the clinician's attention to issues that are particularly relevant to an individual patient. Systematic assessment of the multiple domains noted above ensures that the evaluation is comprehensive. Some clinicians may prefer to rely on less formal questions to probe into potential problems. Examples of potential open-ended questions are provided later in this chapter.

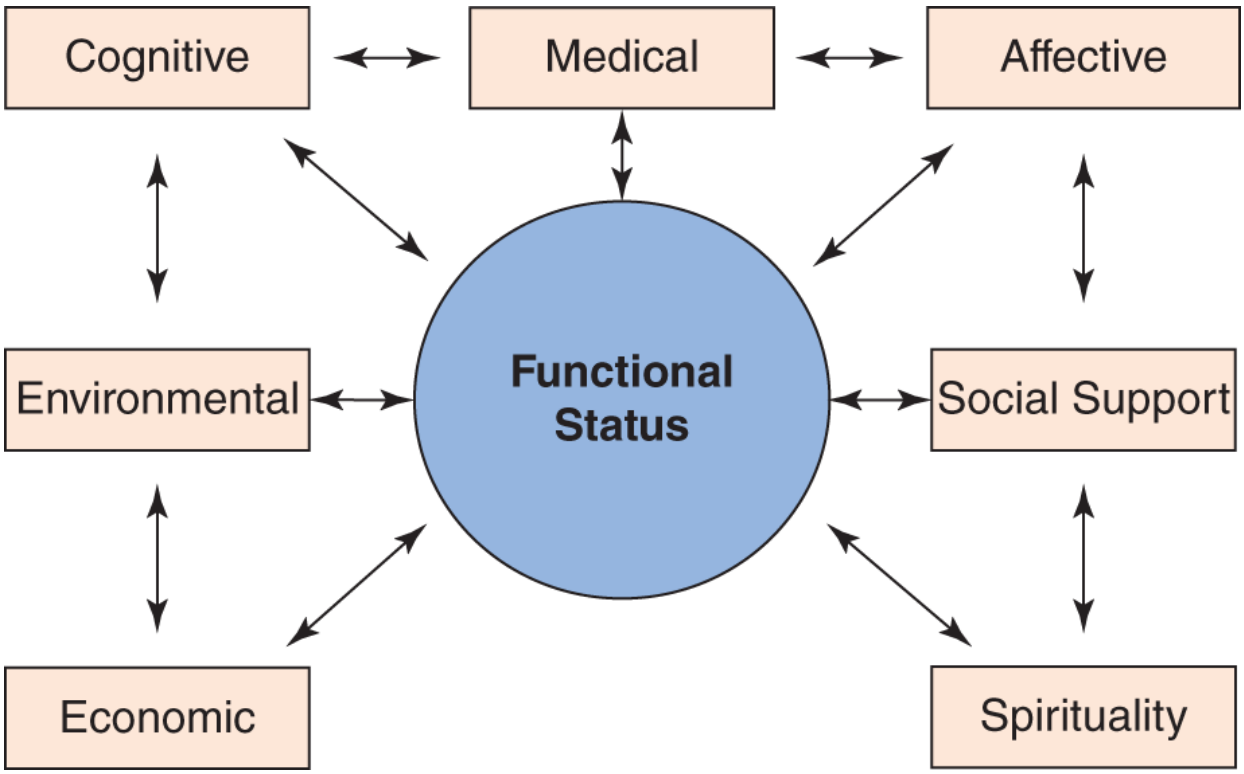


FIGURE 10-1. Interacting dimensions of geriatric assessment.

Geriatric assessment differs according to the setting where the patient is being evaluated. In the hospital setting, the initial assessment is usually directed at the acute medical problem that precipitated the hospitalization. As the patient begins to recover and plans are initiated for discharge, other components (eg, social support, environment) assume increasing importance in the assessment. The inpatient setting can be problematic for geriatric assessment because of the rapidly changing status of several key dimensions. For example, a patient may temporarily become "dependent" on all measures of functional status when acutely ill and gradually improve prior to discharge. Because patients may overestimate their functional status based on their previous level of functioning, direct observational methods (eg, by nurses or physical therapists) may provide a more accurate assessment. The patient's full potential to participate in rehabilitation may not be known until near the time of discharge.

Nursing home geriatric assessment requires that attention be directed to selected aspects of assessment such as nutritional status and self-care activities. Other components such as functional status at the instrumental or intermediate activities of daily living (IADLs) level (eg, shopping, meal preparation) are less relevant in this setting. Geriatric assessment conducted in the patient's home provides an opportunity for an entirely different type of assessment; environmental factors (eg, home safety) and insights into functional status (eg, cleanliness of the home) can be directly assessed while other aspects of the traditional examination (eg, the gynecologic examination) are much more difficult.

Because the primary site of most clinicians' practices is the office setting, assessment techniques are described primarily for this setting. When appropriate, differing, or particularly important information about assessment in other settings is added.

Components of the Geriatric Assessment

In addition to the standard medical history and physical examination, the clinician should systematically search for specific conditions that are common among older persons and that might have considerable impact on function. In the course of the traditional medical evaluation, these problems may go unnoticed because older patients fail to report them spontaneously. For example, they may not recognize that falling is a treatable medical problem. They may also be embarrassed to mention problems with maintaining urinary continence or with sexual function. Finally, they may believe that these symptoms, such as hearing loss, are normal aspects of aging that cannot be helped.

Visual Impairment

Visual impairment is a common and often underreported problem in the older population. Each of the four major eye diseases (cataract, age-related macular degeneration, diabetic retinopathy, and glaucoma) increases in prevalence with age. Moreover, presbyopia is virtually universal and the vast majority of older persons require eyeglasses. Visual impairment has been associated with increased risk of falls, functional and cognitive decline, immobility, and depression. The high rates of vision disorders and their associated sequalea, the brevity of the screening process, and the treatments available for visual impairment justify screening for visual impairment. However, the revised 2009 USPSTF guidelines conclude that evidence is insufficient to determine whether screening older adults for vision impairment improves functional outcomes.

The standard method of screening for problems with visual acuity is the Snellen eye chart, which requires the patient to stand 20 ft from the chart and read letters, using corrective lenses. Patients fail the screen if they are unable to read all the letters on the 20/40 line with their eyeglasses (best corrected vision).

Several interviewer and self-administered instruments to detect functional problems caused by visual impairment have been developed, including the Activities of Daily Vision Scale, VF-14, VFQ-25, and the Cataract Symptom Scale. These are primarily used in research settings, but may hold promise as screening instruments in the future.

Hearing Impairment

Hearing impairment is among the most common medical conditions reported by older persons, affecting approximately one-third of those 65 years or older. Hearing impairment is associated with reduced cognitive, emotional, social, and physical function, as well as increased hospitalizations, and the use of amplification devices has led to improved functional status and quality of life of older persons.

Screening for hearing loss can be accomplished by several methods (**Table 10-1**). The most accurate of these is the Welch Allyn AudioScope 3 (Welch Allyn, Inc., Skaneateles Falls, NY), a handheld otoscope with a built-in

audiometer. The AudioScope 3 can be set at several different levels of intensity, but should be set at 40 dB to evaluate hearing in older persons. A pretone at 60 dB is delivered and then four tones (500, 1000, 2000, and 4000 Hz) at 40 dB are delivered. Patients fail the screen if they are unable to hear either the 1000- or 2000-Hz frequency in both ears or both the 1000- and 2000-Hz frequencies in one ear, indicating the need for formal audiometric testing.

TABLE 10-1 SIMPLE TESTS OF HEARING LOSS

QUESTION/TEST	TIME TO ADMINISTER	LIKELIHOOD RATIO			
		POSITIVE		NEGATIVE	
		For 25 or > 30 dB loss	For > 40 dB loss	For 25 or > 30 dB loss	For > 40 dB loss
Audioscope	1–2 min	3.1–5.8	3.4	0.20–0.40	0.05
Single question: "Do you think you have a hearing loss?"	< 1 min	2.5	3.0	0.40	0.26
Whisper test	1 min	5.1	N/A	0.03	N/A
Hearing Handicap Inventory for the Elderly	2 min	3.5	3.1	0.52	0.43

A simple alternative is to rely on patient's own subjective report of hearing loss. A self-reported hearing loss question involves asking patients whether they feel they have hearing impairment. An affirmative answer is then considered to be a positive test for hearing loss, and patients should be referred to an audiologist.

Another alternative is the whispered voice test, which is administered by whispering three to six random words (numbers, words, or letters) at a set distance (6, 8, 12, or 24 in) from the person's ear and then asking the patient to repeat the words. The examiner should be behind the person to prevent speech reading and the opposite ear should be covered or occluded during the examination. Patients fail the screen if they are unable to repeat half of the whispered words correctly.

A self-administered test of emotional and social problems associated with impaired hearing, the Hearing Handicap Inventory for the Elderly—Screening Version (HHIE-S) was developed. Although this questionnaire is brief and easy to administer, its accuracy when compared to audiometry is inferior. Another screening instrument that uses socio-demographic information coupled with three simple questions (see **Table 10-1**) about hearing loss has high accuracy in identifying older persons with hearing loss.

A 2011 review of the evidence on screening of hearing loss in older adults found that inquiring about self-perceived hearing loss or the whisper test at 2 ft had similar rates of detecting hearing loss as the tone-emitting otoscope or formal hearing questionnaire. In 2012, the USPSTF concluded that there was insufficient evidence to formally recommend hearing screening for this population.

Malnutrition/Weight Loss (See Also Chapter 35)

Malnutrition is a global term that encompasses many different nutritional problems that are associated with diverse health consequences. Both extremes of body weight place older people at risk for subsequent functional impairment, morbidity, and mortality. Among community-dwelling older persons, the most common nutritional disorder is obesity. In addition, a small percentage of community-dwelling older persons have energy or protein energy undernutrition, which places them at higher risk for death and functional decline. Protein energy undernutrition is defined by the presence of clinical (physical signs such as wasting, low body mass index [BMI]) and biochemical (albumin or other protein) evidence of insufficient intake. Although the importance of low serum albumin and low cholesterol as prognostic factors for mortality in community-dwelling, hospitalized, and institutionalized older persons has been demonstrated, these tests may reflect inflammation rather than malnutrition.

Several methods of nutritional screening can be applied in office settings. On their initial visit, patients should be asked about weight loss within the previous 6 months. All patients should be weighed at every office visit. Height should also be measured on the initial visit to allow calculation of BMI (weight in kg/[height in meters]^2). Several self-administered nutritional questionnaires are available, most notably the Nutrition Screening Initiative's 10-item

checklist and the Mini-Nutritional Assessment (MNA). The use of the MNA can help detect risk of malnutrition while albumin and BMI are still in the normal range. Although the validity of these instruments has been questioned, they are being increasingly used in community-based screening programs.

In hospitalized older persons, malnutrition has been associated with higher mortality rates, delayed functional recovery, and higher rates of nursing home use. The simplest and most practical method is for the nursing staff to report daily to the physicians on the percentage of the diet that the patient is eating. This can be accomplished in the context of interdisciplinary team rounds. More formal instruments such as the Malnutrition Screening Tool, which asks two questions, "Have you been eating poorly because of a decreased appetite?" and "Have you lost your weight recently without trying?" can be used. However, the timing of the assessments, frequency, and how they would be used are uncertain. Intake can also be measured through formal calorie counts. Laboratory monitoring is less likely to be useful. Although serum albumin levels can drop acutely during inflammatory states, physiologic stress, and in response to trauma or surgical conditions, this protein has a long half-life (approximately 18 days) and may provide an idea of the patient's baseline nutritional status. Prealbumin, which has a much shorter half-life (approximately 2 days) may be a better means of monitoring response to nutritional treatment.

Urinary Incontinence

Urinary incontinence (UI) is common, estimated to affect 11% to 34% of older men and 17% to 55% of older women, and is underrecognized. Patients may be embarrassed to raise the issue; they may also regard it as a normal aspect of aging. Urinary incontinence has been associated with depressive symptoms in older adults and is a major factor in nursing home placement. Moreover, effective treatments are available for incontinence. As a result, screening for urinary incontinence has increasingly been recognized as an indicator of quality of care. For example, asking about and documenting the presence or absence of UI biannually, and determining whether the UI, if present, is bothersome to the patient or caregiver are Assessing Care of Vulnerable Elders (ACOVE) quality indicators.

Asking two questions can screen for incontinence: (1) "In the last year, have you ever lost your urine and gotten wet?" and if so, (2) "Have you lost urine on at least six separate days?" In a research setting, those who answered positive to both questions had high rates (79% for women and 76% for men) of urinary incontinence as determined by a clinician's evaluation (see Chapter 53).

The 3IQ questionnaire is another brief interviewer-administered instrument with high sensitivity and specificity that has been developed to distinguish between urinary stress and urge incontinence in women in primary care settings (**Table 10-2**).

TABLE 10-2 ■ THE THREE INCONTINENCE QUESTIONS (3IQ)

1. During the last 3 mo, have you leaked urine (even a small amount?)

   Yes No → Questionnaire completed

2. During the last 3 mo, did you leak urine: *(Check all that apply.)*
   a. When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?
   b. When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?
   c. Without physical activity and without a sense of urgency?
3. During the last 3 mo, did you leak urine *most often*: *(Check only one.)*
   a. When you were performing some physical activity, such as coughing, sneezing, lifting, or exercise?
   b. When you had the urge or the feeling that you needed to empty your bladder, but you could not get to the toilet fast enough?
   c. Without physical activity and without a sense of urgency?
   d. About equally as often with physical activity as with a sense of urgency?

Definitions of type of urinary incontinence are based on response to question 3:

Response to Question 3	*Type of Incontinence*

a. Most often with physical activity	Stress only or stress predominant
b. Most often with the urge to empty the bladder predominant	Urge only or urge predominant
c. Without physical activity or sense of urgency cause	Other cause only or other predominant
d. About equally with physical activity and sense of urgency	Mixed

Balance and Gait Impairments and Falling

Over one-third of community-dwelling persons over age 65 fall every year. Falls are independently associated with functional and mobility decline. Patients who have fallen or have a gait or balance problem are at higher risk of another fall. The risk of falling can be assessed by asking all older patients if they have fallen in the last year, and then performing a multifactorial falls assessment by testing balance, gait, and lower extremity strength (see Chapter 48). Performing a multifactorial assessment on patients who screen positive for falls, and then treating their risk factors for falling can reduce falls by 30% to 40%. Moreover, the assessment of these components may also help identify methods to improve the patient's function beyond reducing the risk of falling. Screening for falls and falls assessment, if the screen is positive, is recognized as indicators of quality of care. The Medicare Star Rating System includes screening for falls as one of the quality components that determines health plan ratings and subsequent payment.

Clinicians should ask their older persons specifically about falls and fear of falling, which should be included in the review of systems at the initial visit and at least annually. The use of a previsit questionnaire can also help elicit this information. The report of any fall should prompt subsequent questions by the clinician to determine the circumstances of the fall. Patients with recurrent falls or falls with any injury should receive a more detailed evaluation, including assessment of gait and balance, orthostatic blood pressure readings, vision testing, a foot examination, and a review of their medications that may contribute to the risk of falling (see Chapter 48). Patients can also be given the Centers for Disease Control and Prevention (CDC) home safety checklist. Their risk of osteoporotic fracture should also be assessed using the FRAX, the World Health Organization (WHO) Fracture Risk Assessment Tool (http://www.shef.ac.uk/FRAX/).

Observing patients walking and performing balance maneuvers best assesses balance and gait disorders. Once the clinician is trained to assess gait, this evaluation can be performed while the patient is entering or leaving the examining room. Several simple tests of balance and mobility (**Table 10-3**) can also be performed quickly in the office setting, including the ability to maintain a side-by-side, semi-tandem, and full-tandem stance for 10 seconds; resistance to a nudge; and stability during a 360-degree turn. Quadriceps strength can be briefly assessed by observing an older person arising from a hard armless chair without the use of his or her hands. The timed "up and go" test is a timed measure of the patients' ability to rise arm chair, walk 3 m (10 ft), turn, walk back, and sit down again; those who take longer than 20 seconds to complete the test should receive further evaluation. Gait speed is also a helpful marker for recurrent falls. Patients who take more than 13 seconds to walk 10 m are more likely to have recurrent falls. The short physical performance battery incorporates; chair stands; side-by-side, semi-tandem, and full-tandem stance; and gait speed to calculate a summary score that assesses quadriceps strength, balance, and gait speed.

TABLE 10-3 ■ SIMPLE TESTS OF LOWER EXTREMITIES: STRENGTH, BALANCE, GAIT, AND FALL RISK

QUESTION/TEST	TIME TO ADMINISTER	COMMENTS
Timed up and go	< 1 min	Sensitivity 88%, specificity 94% compared to geriatrician's evaluation using cutpoint > 15 s
Gait speed over 10 m	< 30 s	• 13 s predicts recurrent falls (likelihood ratio: 2.0; 95% CI, 1.5–2.7)
Office-based maneuvers Observed gait Resistance to nudge Tandem/semitandem stand Rising from chair 360° turn	2–3 min	Some are part of performance-oriented assessment of mobility
Functional reach	2 min	Adjusted odds ratios for > 2 falls within 6 mo

		8.1 if unable to reach 4.0 if reach ≤ 6″ 2.0 if reach ≥ 6″ but <10″
Short physical performance battery	5–7 min	Combines quadriceps strength, standing balance, and gait speed to generate a score 0 (worst) and –12 (best)

The performance-oriented assessment of mobility is a standardized battery that measures gait and balance; it has been widely used in research and in clinical settings, but may take too long to administer to be practical in most office settings as a screening test. The ability to stretch as measured by functional reach, a test of balance, can predict subsequent recurrent falls.

Polypharmacy (See Also Chapter 24)

Polypharmacy in older patients is associated with adverse drug reactions, reduced adherence, and inappropriate medication usage. Older persons often receive care from multiple providers and they may fill prescriptions at several pharmacies. Patients should be instructed, therefore, to bring in all current medications—both prescription and nonprescription medications—to each visit, for a through medication reconciliation and to check for potential drug-drug interactions.

Given the burden of complex comorbid disease in many older adults, it is important to balance guidelines for chronic disease management with the individual patient's goals of care, as well as risk factors for adverse drug events such as cognitive impairment, frailty, and renal impairment. Clinicans should also beware of the "prescribing cascade," when an adverse drug event is misattributed to a new medical condition, generating additional medication therapy instead of prompting a medication review and discontinuation of the offending drug. The Beers criteria have been developed by the American Geriatrics Society to assist clinicians with identifying and avoiding potentially inappropriate medications for older adults.

Cognitive Assessment

Because the prevalence of Alzheimer disease, other dementias, and cognitive impairment rises considerably with advancing age, the yield of screening for cognitive impairment increases with age. Although in 2014, the USPSTF concluded that there is insufficient evidence on the balance of benefits and harms of screening for cognitive impairment, clinicians should assess cognition when there is suspicion of impairment. Several screens are available for clinical use (**Table 10-4**) and some can be performed in 5 minutes or less (eg, the Mini-Cog, which combines three-item recall and clock drawing; the Memory Impairment Screen [MIS]; and the General Practitioner Assessment of Cognition [GPCOG]). Longer screens that are commonly used include the Mini-Mental State Examination (MMSE), which takes 7 to 10 minutes to administer and must be purchased for use, and the Montreal Cognitive Assessment (MoCA), which takes 10 to 15 minutes to administer. None of these instruments establish a diagnosis of dementia, which requires a clinical evaluation that includes assessment of the functional impact of the patient's cognitive status.

TABLE 10-4 ■ COMMONLY USED COGNITIVE SCREENS

INSTRUMENT	TIME TO ADMINISTER (MIN)	STRENGTHS	LIMITATIONS
GPCOG • **Patient** • **Informant**	 2–5 1–3	• Developed for and validated in primary care • Informant component useful • Little education bias • Multiple languages accessible at www.gpcog.com.au	• Patient component scoring has an indeterminate range that requires an informant score to determine pass or fail • Informant component alone has low specificity
Mini-Cog	2–4	• Developed for and validated in primary care and multiple languages/cultures	• Use of different word lists may affect failure rates

		• Little education/language bias • Short administration time	
MIS	4	• Verbal memory test (no writing/drawing) • Little education bias	• Does not test executive function or visuospatial skills
MMSE	7–10	• Most widely used and studied worldwide • Often used as reference for comparative evaluations of other assessments • Required for some drug insurance reimbursements	• Education/age/language/culture bias • Ceiling effect (highly educated impaired subjects pass) • Proprietary—unless administered from memory, test needs to be purchased at www.parinc.com
MoCA	10–15	• Designed to test for mild cognitive impairment • Multiple languages accessible at www.mocatest.org • Tests many separate domains	• Lacks studies in general practice settings • Education bias when ≤ 12 y of education • Limited use and evidence base because more recently developed

Although normal results on these tests vastly reduce the probability of dementia and abnormal results increase the likelihood that the patient has dementia, these tests are neither diagnostic for dementia nor do normal results exclude the possibility of this disorder. Patients who have abnormal findings on a cognitive screening test should receive more in-depth evaluation of memory, language, visual-spatial, and executive function.

Among hospitalized patients, mental status should be assessed at the time of hospital admission and then periodically because older persons are especially prone to develop delirium during the hospital stay. Abnormal findings on the mental status examination in hospitalized patients must be interpreted in the context of change from baseline and the clinical situation. The Confusion Assessment Method, which has a revised scoring system to indicate severity, provides a guide to interpreting such changes and assesses acute change or fluctuating course, inattention, disorganized thinking, and altered level of consciousness (see Chapter 47).

Affective Assessment (See Also Chapter 71)

Major depression and other affective disorders are common among older adults and are likely underdiagnosed, as symptoms may be underreported, present atypically, or be masked by cognitive impairment or other neurologic diseases such as Parkinson disease. Given their association with increased disability, health care utilization, morbidity, and mortality, and decreased quality of life, clinical detection and treatment of affective disorders is paramount. A brief two-item screening inquiry asks about the frequency of depressed mood and anhedonia over the past 2 weeks, and, if positive, can prompt further screening by completing the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is increasingly used to detect and monitor depression symptoms in older adults, and provides a reliable and valid measure of depression severity. A score of greater than 10 has a sensitivity of 88% and a specificity of 88% for major depression. A variety of other screens for depression, including the Geriatric Depression Scale, which has 5-, 15-, and 30-item versions, are available and each has its advantages and disadvantages.

Assessment of Function

Measurement of functional status is an essential component of the assessment of older persons. The patient's ability to function can be viewed as a summary measure of the overall impact of health conditions in the context of his or her environment and social support system. Moreover, in older persons, the ability to function consistent with their personal lifestyle desires should be an important consideration in all-care planning. Therefore, changes in functional status should prompt further diagnostic evaluation and intervention. An early indicator of impending functional disability is self-perceived difficulty with performing functional tasks. Measurement of functional status is also valuable in monitoring response to treatment and may provide prognostic information that will help plan for long-term care.

Functional status can be assessed at three levels: basic activities of daily living (BADLs), IADLs, and advanced activities of daily living (AADLs). BADLs refer to self-care tasks such as bathing, dressing, toileting, continence, grooming, feeding, and transferring. IADLs refer to the ability to maintain an independent household such as shopping

for groceries, driving or using public transportation, using the telephone, meal preparation, housework, home repair, laundry, taking medications, and handling finances, whereas AADLs refer to the ability to fulfill societal, community, and family roles as well as participate in recreational or occupational tasks. These advanced activities vary considerably from individual to individual but may be valuable in monitoring functional status prior to the development of disability.

Scales that measure functional status at each of these levels have been developed and validated. Questions that ask about specific BADL and IADL functions have also been incorporated into a variety of more generic health-related quality-of-life instruments (eg, the Medical Outcomes Study Short-Form 36 [SF-36] and its shorter version, the SF-12). Some AADLs (eg, exercise and leisure time physical activity) can also be ascertained by using standardized instruments, but open-ended questions about how older persons spend their days might provide a better assessment of function in healthier older persons.

There has been increasing interest in assessment of physical functioning by directly observing the performance of functional tasks. Instruments have been developed for use in ambulatory, nursing home, and hospital settings, and predictive validity has been demonstrated for many. The National Institutes of Health (NIH) has developed a set of physical performance measures (the NIH toolbox) for use in research settings. To date, these instruments are rarely incorporated into clinical practice, but some demonstration projects are in place that are attempting to use performance-based instruments in practice, much like vital signs, to monitor patients. Some studies have demonstrated that combining self-reported functional with performance-based measures can provide more refined prognostic information than either method alone.

Assessment of Social Support

The composition of the older patient's social support structure can be assessed by asking a few questions about relationships such as family, friends, neighbors, and caregivers when obtaining the social history. The quality of these relationships should also be determined. For very frail older persons, the availability of assistance from family and friends is frequently the determining factor of whether a functionally dependent older person remains at home or is institutionalized. If dependency is noted during functional assessment, then the clinician should inquire as to who provides help for specific BADL and IADL functions and whether these persons are paid or voluntary help. Even in healthier older persons, it is often valuable to raise the question of who would be available to help if the patient becomes ill. Early identification of problems with social support may prompt planning to develop resources should the necessity arise. For vulnerable older adults, clinicians should be mindful of signs of elder abuse, neglect, or exploitation, and if suspected, are mandated to report cases to Adult Protective Services.

Economic Assessment

Many older adults live on fixed incomes, and the rising costs of medical expenses coupled with that of paid caregivers and residential facilities can cause financial hardship that may manifest as medication nonadherence, weight loss, or the appearance of self-neglect. Although some clinicians feel uncomfortable assessing the economic status of their patients, inquiring about financial stress may prompt referral to social work or other agencies and help prevent the associated poor health outcomes. Furthermore, insurance status is routinely collected by office staff and a patient's income can be assessed and eligibility determined for state or local benefits (eg, In-Home Supportive Services through Medicaid). For the frail and functionally impaired older adult, clinicians should partner with patients and families to provide anticipatory guidance regarding the resources that may be required to pay for care at home or in a residential facility.

Environmental Assessment

Environmental assessment encompasses two dimensions, the safety of the home environment and the adequacy of the patient's access to needed personal and medical services. Particularly among frail individuals and those with mobility and balance problems, the home environment should be assessed for safety. Although most physicians do not personally conduct environmental assessments, the CDC has developed a home safety checklist (http://www.cdc.gov/HomeandRecreationalSafety/Falls/CheckListForSafety.html) that patients and their families can complete. For those receiving home health services, in-home safety inspections can be performed, including recommendations for installation of adaptive devices such as shower bars and raised toilet seats.

Older persons who begin to develop IADL dependencies should be evaluated for the geographic proximity of

necessary services such as grocery shopping and banking, their need for use of such services, and their ability to use these services in their current living situations. Increasingly, some of these services are available online though many older persons, particularly those who are frail, do not feel comfortable using the Internet to purchase services. Older drivers are at increased risk for motor vehicle accidents secondary to functional impairments, medications, and medical conditions. The National Highway Traffic Safety Administration (NHTSA) has produced materials to help physicians talk with older drivers about safe driving (http://www.nhtsa.gov/Driving+Safety/Older+Drivers/Talking+with+Older+Drivers+about+Safe+Driving).

Spirituality

Spirituality, whether affiliated with a formal religious denomination or nonreligious intangible elements, has increasingly been recognized as an important influence on health and quality of life. Frequent attendance of religious services has been associated with lower health care utilization and mortality rates. Formal instruments for assessing spirituality have been developed, such as the FICA tool for spiritual assessment, but these are not widely used in clinical practice. Simply asking older persons whether religion or spirituality is important to them may provide insights that may facilitate their care. Especially in hospital settings, involvement of pastoral care may be valuable in supporting the patient and in framing medical decisions in the context of the patient's personal belief system.

Advance Directives

An Advance Health Care Directive enables patients to make sure that their health care wishes are known in advance and considered if for any reason they are unable to speak for themselves. It also allows a patient to appoint a Durable Power of Attorney, or health care proxy, who will have legal authority to make health care decisions in the event that patient is incapacitated or whereupon the patient grants such authority. Discussions of advance directives are especially important for older patients and should be initiated early on, to discuss the patients' goals and preferences for care should they experience progressive cognitive impairment or acute illness. Physicians can assist patients by focusing on patients' overall goals of care, rather than specific detailed interventions, and incorporating these goals into the patients' current clinical situation. A particularly important time to discuss such preferences is prior to surgery because of the possibility of surgical complications or postoperative delirium, which may preclude discussions following the procedure. Such discussions should be revisited any time there are significant changes in a patient's medical condition and a better understanding about prognosis becomes available, as patients often revise their thoughts about the burdens and benefits of treatment. Cultural differences regarding preferences for advance directives and end-of-life care should be recognized and respected. Overall, patients are receptive and grateful for discussion of their goals and preferences for care, and increasingly advanced directive counseling discussions have been incentivized and recognized in quality-of-care measures, with various tools being developed to support advanced care planning in practice.

A Strategic Approach to Geriatric Assessment

The practice of medicine in office settings is in a state of transition from a previous era of medicine when physicians practiced more like individual artisans to an approach in which physicians function as members of a health care team. Much of the germane information of the medical history can be obtained from old records, other professional or nonprofessional staff, or by self-report from patients or family members completing forms, rather than from direct physician interview. Although many physicians are reluctant to delegate data gathering, this efficiency allows the physician to spend more time following up on issues raised by the available information, conducting the physical examination, discussing treatment, and providing health education.

One effort adopted by many clinical practices has been the use of previsit questionnaires that can be completed by the patient or proxy before the clinical encounter. These questionnaires typically gather information on past medical history, medications, preventive measures, and functional status, including information on who helps when the patient is functionally dependent. As a result, they can markedly reduce the time needed to conduct an initial assessment and can ensure a consistent level of comprehensiveness for every patient. By including validated screening instruments, they can also be used to case-find individuals with common geriatric syndromes. With the advance of technology and electronic health records, there is the potential for patients, families, or caregivers to complete such questionnaires electronically and the information obtained can be seamlessly integrated into the electronic health record. To date, however, this potential has rarely been fulfilled.

A second method of streamlining the office visit is to delegate the administration of screening instruments for

many of the important geriatric problems to trained office staff. Thus, the clinician may spend a short period of time reviewing the results of these screens and then decide which dimensions, if any, need greater evaluation. Several groups have demonstrated the feasibility and yield of using office staff to administer case-finding and screening instruments that assess many of the dimensions described above. This approach can dramatically improve the practitioner's efficiency and increase the number of new and treatable problems detected in their older patients. However, using office-based staff to screen or case-find has cost implications. Office staff must be properly trained to administer these instruments, which can be quite time consuming (10–20 minutes). This time must be taken from other office tasks and the cost of screening may be considerable. Clinicians must also be able to effectively act on this information to improve clinical outcomes. Nevertheless, as physicians become increasingly pressured to increase their productivity, such methods may be the only way to feasibly ensure that older patients' diverse health needs are addressed comprehensively.

A third approach has been to integrate screening for geriatric conditions into the office workflow and then use structured clinical visit notes or electronic health record templates to guide more detailed assessment and the clinician toward appropriate management steps. This approach has been demonstrated to improve the quality of care for falls, dementia, and UI. Portions of the structured visit note can be delegated to office staff, further increasing efficiency. In this manner, the workflow of patient care can be redesigned, quality can be continuously monitored, and steps to improve quality can be implemented.

This approach to increasing efficiency can be applied to many geriatric conditions. **Table 10-5** shows a strategy that optimizes the clinician's time by employing the most efficient methods to obtain assessment information. The initial step provides the clinician with basic information that can quickly be processed and followed with more extensive data gathering, when appropriate. Such a strategy begins with the previsit questionnaire and then is supplemented by information obtained by office staff. These two data sources are reviewed by the clinician and additional information is obtained from the patient and family at the time of the visit.

TABLE 10-5 STRATEGY FOR EFFICIENT OFFICE-BASED ASSESSMENT

	METHOD AND DEPTH OF ASSESSMENT[a]				
ASPECT BEING ASSESSED	PREVISIT QUESTIONNAIRE	OFFICE STAFF ADMINISTERED	CLINICIAN ROUTINE	CLINICIAN AS NEEDED	REFERRAL[b] AS NEEDED
Past medical history	D		R		
Geriatric syndromes/health conditions					
Visual impairment	B	B	R		Ophthalmologist or optometrist
Hearing impairment	B	B (if needed)	R		Audiologist
Urinary incontinence	B	B	R	D	Geriatrician, urologist, or gynecologist
Malnutrition	D		R		Dietitian or social worker
Sexual dysfunction	B		R		Urologist or geriatrician
Polypharmacy	B		R		Pharmacist or geriatrician
Dental problems	B		R		Dentist
Gait, balance, falls	B	B	B	D	Physical therapist
Affective problems	D		R	D	Psychiatrist

Cognitive problems		B	R	D	Geriatrician, psychiatrist, or neurologist
Functional disability	D		R	D	Physical or occupational therapist social worker
Environmental problems	D		R		Home health
Preventive services	D		R		

[a]B, brief screen (eg, < 2 min); D, detailed evaluation (usually 5 min or more); R, review of collected information.
[b]Examples of referrals to specific health professional or comprehensive geriatric assessment might be used.

COMPREHENSIVE GERIATRIC ASSESSMENT

CGA is based on the premise that a systematic evaluation of frail older persons by a team of health professionals may uncover treatable health problems and lead to better health outcomes. This evaluation typically includes four dimensions: physical health; functional status; psychological health, including cognitive and affective status; and socioenvironmental factors. Early randomized clinical trials provided convincing evidence that such programs conducted in hospital-based and rehabilitation units, which typically required several weeks of treatment, could lead to better survival rates, improved functional status, and more desirable placement (eg, home rather than nursing home) following discharge from the hospital. Conceptually, CGA is a three-step process: (1) screening or targeting of appropriate patients, (2) assessment and development of recommendations, and (3) implementation of recommendations, including physician and patient adherence with recommendations. Each of these steps is essential if the process is to be successful at achieving health and functional benefits.

Within this broad conceptualization, CGA has been implemented using many different models in various health care settings (**Table 10-6**). Because of changes in length of hospital stays, an increasing number of CGA programs are relying on postdischarge and community-based assessment. Furthermore, most of the early programs focused on restorative or rehabilitative goals (tertiary prevention), whereas many newer programs are aimed at primary and secondary prevention.

TABLE 10-6 SPECTRUM OF COMPREHENSIVE GERIATRIC ASSESSMENT–LIKE INTERVENTIONS

	MOST INTENSIVE		LEAST INTENSIVE
Setting	CGA, GEM, and rehabilitation units	CGA consultation inpatient or outpatient	Community-based and in-home outreach programs
Targeting	Most restrictive		Least restrictive
Process	Large team, extensive evaluations		Screening and referral
Cost	Very expensive		Relatively inexpensive

CGA, comprehensive geriatric assessment; GEM, geriatric evaluation and management.

The purpose of the first step, targeting, is to distinguish older patients who are appropriate and will benefit from CGA, from those who are either too sick or are too well to benefit. To date, no easily administered targeting criteria have been demonstrated and validated to readily identify patients who are likely to benefit from CGA in different settings. Specific strategies used by CGA programs to identify older persons who are most appropriate for CGA have included chronological age, functional disability, physical illness, geriatric conditions, psychosocial conditions, and previous or predicted high health care utilization. All of these criteria have randomized clinical trial support for their effectiveness in identifying older persons likely to benefit from CGA. However, the definitions of these criteria and the interventions that have followed have varied from study to study.

Most CGA programs exclude patients who are unlikely to benefit because of terminal illness, severe dementia, complete functional dependence, and inevitable nursing home placement. Exclusionary criteria have also included

identifying older persons who are “too healthy” to benefit.

The second step of CGA, the assessment process itself, continues to be highly variable across programs. The types of health care professionals included in the assessment team, the content of information collected, and the types and intensity of services provided have differed in studies of the effectiveness of CGA. In many settings, the CGA process relies on a core team consisting of a physician, nurse, and social worker and, when appropriate, draws upon an extended team of various combinations of physical and occupational therapists, nutritionists, pharmacists, psychiatrists, psychologists, dentists, audiologists, podiatrists, and opticians. Although these professionals are usually on staff in hospital settings and are available in the community, access to and reimbursement for these services have limited the effectiveness of the CGA process. Frequently, the composition of the team is determined by local expertise and availability of resources rather than programmatic needs. Increasingly, CGA programs are moving toward a “virtual team” concept in which members are included as needed, assessments are conducted at different locations on different days, and conferencing is completed via telephone or electronically.

Traditionally, the various components of the evaluation are completed by different members of the team. There is considerable variability in which professional conducts the assessments. For example, the medical assessment of older persons may be conducted by a physician, nurse practitioner, or physician’s assistant. The core team may conduct only brief initial assessments or screens for some dimensions. These may be subsequently augmented with more in-depth evaluations by additional professionals. For example, a dietitian may be needed to assess dietary intake and provide recommendations; an audiologist may need to conduct a more extensive assessment of hearing loss and evaluate an older person for a hearing aid.

Components of Comprehensive Geriatric Assessment

The key elements of the process of care rendered by CGA teams can be divided into six steps: (1) data gathering; (2) discussion among the team; (3) development of a treatment plan; (4) implementation of the treatment plan; (5) monitoring response to the treatment plan; and (6) revising the treatment plan.

Data Gathering

In early studies of CGA, the data-gathering process simply identified the members of the team and mentioned that each conducted an evaluation. Such descriptions are problematic because of the variability of evaluations among health professionals. A formal training process can reduce this variability, but a popular approach is to standardize the assessment. Standardized assessments can either use instruments developed specifically for clinical purposes or assemble standard instruments that have previously been studied for validity and reliability. The advantage of the former is that teams can customize the information being gathered to best suit the clinical needs of the program. The advantage of the latter is that patients in the program can be compared to patients in other programs. Frequently, however, these instruments were developed for purposes other than to guide clinical decision making and may provide information that is not very helpful in the care of patients.

Discussion Among Team

Following initial data gathering, the team meets to discuss the patient’s geriatric needs. Although any member of the team could theoretically lead the conference, the leadership is usually determined by local culture. Each conference typically begins with short discipline-specific presentations followed by interactive discussions among professionals. Sometimes additional information will need to be obtained before final recommendations can be made. The team then identifies problems that need action and might be responsive to treatment.

Development of the Treatment Plan

Based on this discussion, the team develops an initial treatment plan and goals for the patient. Whenever possible, the patient and, as appropriate, family members should be included in the development of the treatment plan. Through techniques such as motivational interviewing, patients can be asked to identify their priorities and readiness to make changes. Based on these, care plans can be created with patients as active partners.

Some CGA programs use protocols that are triggered by specific geriatric conditions, whereas others rely on the experience and clinical judgment of the team. If the number of recommendations resulting from CGA is large, it is necessary to prioritize recommendations. CGA teams should advise primary care physicians and patients to focus on the major recommendations, those that are most likely to produce the desired outcomes. The urgency of

recommendations must also be determined. Although some recommendations may need to be implemented immediately to confer short-term benefit such as stopping a medication that may be the cause of delirium, many more may be better implemented once the patient is stable.

At the time of the assessment, a plan for implementation of each recommendation must be developed. It needs to be determined who will assume responsibility for initiation and completion of the recommendation. Similarly, the team must establish a plan for monitoring the patient's progress as treatment is being delivered.

Implementation of the Treatment Plan

Because of the problem of poor adherence to CGA recommendations, the issue of implementation is particularly critical to the success of CGA consultation programs. Among inpatient CGA models, poor implementation rates may explain some negative trials of hospital consultation models of CGA. Failure to implement recommendations is usually attributable to three problems: (1) poor receptivity among primary care physicians whose patients have been assessed using consultative models; (2) inadequate resources to implement recommendations; and (3) poor continuity or follow-through on recommendations after hospital discharge. In ambulatory settings, patient adherence to recommendations emanating from CGA looms as an even larger obstacle to implementation. Patients may simply choose not to return to see the CGA team (in continuity of care models) or ignore recommendations in a consultative model. Including patients in developing treatment plans can help engage them in implementing the plan.

A variety of options for implementation are available ranging from direct implementation of recommendations by the team to merely advising physicians and patients by a note in the chart or verbally. In consultative models of CGA in some ambulatory settings, patients have been provided with direct advice and instructions on how to approach their physicians to discuss CGA recommendations (patient empowerment). This method, coupled with direct communication to primary care physicians, has resulted in high implementation rates of CGA recommendations. Other approaches to improve adherence by primary care physicians have been by direct telephone contact, letters, faxes, and e-mail.

Monitoring

To ensure that recommendations are implemented and to follow a patient's progress through the treatment plan, patients must be monitored directly by the CGA team or by the primary care physician. If the team is to monitor the patient, key issues are how frequently and for how long this monitoring should occur. The more intensively and the longer patients are followed, the more resource-intensive the consultation becomes. In some models (described below), the CGA team may temporarily assume primary care for several months before returning the patient to the primary care physician for ongoing care.

Revising the Treatment Plan

By monitoring the patient, CGA teams can continually assess the patient's progress toward meeting the goals established by the team. If progress is not proceeding according to expectations, the team may need to reevaluate the patient and resume the team discussion. Treatment recommendations and implementation plans may need to be revised. Again, engaging the patient is important as readiness to change or goals may have changed. Any modification will require additional monitoring. The frequency and extensiveness of reevaluations and additional discussions are important influences on the cost of CGA consultation.

Effectiveness of Comprehensive Geriatric Assessment

In virtually all studies of CGA, the process itself has resulted in improved detection and documentation of geriatric problems. However, such identification of problems has not always led to improved outcomes. Meta-analysis, a technique to pool the findings of individual trials to provide more precise estimates of effectiveness, has been used to evaluate models of CGA in several settings.

Inpatient Units and Services

Geriatric evaluation and management units (GEMUs), also referred to as acute care of the elderly (ACE) units, which are often designed to be environmentally friendly to older persons, confer two advantages over consultation models. First, physicians staffing the unit generally assume primary care of the patient, thus facilitating the implementation of recommendations. Second, the availability and experience of a dedicated team of providers (eg, nurses and therapists) increases the consistency and geriatric orientation of hospital and postacute care. Because of logistical barriers of

having dedicated geriatric inpatient units, some programs have attempted to recreate the core elements of ACE units for hospitalized older persons who are not located on a single unit (mobile ACE services). Similar in concept to cardiac care units (CCUs) and stroke units, these units assemble resources for a specific patient population. A meta-analysis of 22 trials found that recipients of inpatient units were more likely to be active in their own homes at up to 6 and 12 months when compared to general medical care. They were also less likely to be institutionalized, die, or deteriorate functionally, and were more likely to have better cognition. These outcomes were most apparent in geriatric units compared to mobile units.

Posthospital Discharge Assessment and Management

Studies of CGA have found inconsistent benefit for posthospital discharge programs with no benefits on most health outcomes but some finding reductions in readmission rates and overall costs. A systematic review found that many of the components of CGA were parts of care transition interventions that were effective in reducing rehospitalizations and emergency department visits. CGA programs for patients discharged to home from the emergency department were found to be effective at reducing emergency room visits and hospital admissions.

Outpatient CGA

The evidence for outpatient CGA has been inconsistent. Some individual studies have shown benefit on quality of care and functional decline; there have not been benefits on hospitalization or nursing home placement. Moreover, a meta-analysis of controlled trials found no benefit of outpatient CGA on survival.

In-Home Assessment

Home assessment programs are a variation of CGA that focuses primarily on preventive rather than rehabilitative services and are aimed at patients at low rather than high risk of nursing home admission. Multiple meta-analyses have found home assessments to be consistently effective in reducing functional decline (if a clinical examination is performed) as well as overall mortality among younger patients (73–78 years).

Lessons Learned From Geriatric Assessment

Despite unresolved issues regarding the effectiveness of CGA, the principles of CGA have been incorporated into a number of programs that have been demonstrated to be effective. Several new models of outpatient care for older persons modify the basic structure of care delivery. These models adopt various components of CGA including targeting, assessment, and interventions.

Geriatric evaluation and continuity management is a direct outgrowth of CGA. These programs differ from CGA in that they become the source of ongoing primary care usually by interdisciplinary teams in geriatrics clinics. Others (eg, GRACE and Guided Care) are comanagement models in which health care professionals (eg, nurses, social workers) collaborate with primary care physicians either individually or as a team. These bring CGA into primary care physicians' offices rather than creating a separate parallel delivery system or relying on primary care physicians' acceptance of CGA recommendations. Both of these models have evidence supporting benefit on health-related quality of life and reduced utilization in some populations.

In addition, CGA has been adapted to specialty treatment of older persons including oncology, emergency department postdischarge management, inpatient orthopedic care, and the preoperative evaluation of older patients. Elements of CGA have also been incorporated into disease management programs, including stroke and heart failure.

In summary, geriatric assessment continues to evolve as an integral component of the care of older persons. As assessment techniques become better standardized and validated, more efficient yet comprehensive approaches are possible. To date, implementation of such strategies has not occurred on a widespread basis. Cost, logistical, and training issues are still important barriers. However, as national initiatives to improve quality move forward, screening for geriatric conditions and appropriate assessment of patients who screen positive will gain more acceptance. Advances in technology and newer approaches to data collection have unleashed possibilities for incorporating geriatric assessment and management that could not have been imagined a decade ago. The research agenda still must include testing whether these more efficient strategies can lead to better health outcomes.

CGA has also changed considerably as medicine has become increasingly cost conscious. Though effective, the long-stay units can no longer be sustained and the emphasis must shift to extending the effective components and principles into less expensive settings and programs. Although several examples of such successful progeny have

already been developed and tested, undoubtedly, additional generations of CGA-like interventions will be forthcoming.

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Chapter 11

Mental Status and Neurologic Examination

James E. Galvin

Learning Objectives

- Learn about normal neurologic aging and aging-associated changes in neurologic examination.
- Recognize the significance of focused history taking and accurate bedside techniques to examine older adults with neurologic diseases.
- Understand the rationale and learn new skills to assess mental status, memory, attention, orientation, visuospatial, language, and executive function in the older population.
- Learn correct ways to examine cranial nerves, motor and sensory system, coordination, gait, and higher cortical functions in older adults.

Key Clinical Points

1. **An extensor plantar response is not a normal aging-associated change and is always associated with some pathology in the upper motor neuron.**
2. **Comprehensive mental status examination includes observational, cognitive, functional, and neuropsychiatric evaluations.**
3. **Altered level of alertness is always associated with cognitive deficits and an underlying medical illness that is almost always treatable.**
4. **Language assessment involves evaluation of all aspects of communication, including spontaneous speech, comprehension, repetition, naming, reading, and writing.**
5. **Reduced hearing for high-pitched sounds and lack of perception of background noise are common findings in older adults and do not suggest a pathologic finding.**
6. **Mild muscular wasting without weakness or focal neurologic signs can be encountered in normal aging and commonly affect hand and foot muscles, calf, and shoulder girdle muscles.**
7. **Ocular motility is commonly limited in older adults and can exhibit restricted convergence and limitation of conjugate upward gaze.**

THE NEUROLOGY OF AGING

What Is Normal Neurologic Aging

The diagnosis of neurologic disease in the older adult requires recognition not only of abnormal signs and symptoms but also an understanding of what changes are expected as part of the normal aging process. To distinguish neurologic dysfunction related to disease from the neurologic changes associated with normal aging, the clinician must conduct a comprehensive mental status and neurologic examination. When establishing a neurologic diagnosis, the clinical history (ie, history of the present illness, past medical history, social habits, occupational experience, family illness and disorders) assists the clinician in generating a differential diagnosis that can be further explored and refined by pertinent observations documented on the mental status and neurologic examinations. The mental status assessment

should evaluate cognition, emotion, and behavior. Because cognitive and affective disorders occur commonly in older adults, historical information should be obtained not only from the patient but a reliable informant such as the spouse, adult child, or caregiver. The neurologic examination should be performed on all older adults regardless of the chief complaint as up to 60% of older patients have either a primary or secondary neurologic sign or symptom. A complete mental status and neurologic examination provides the necessary data to develop reasonable diagnostic hypotheses and drive the necessary laboratory, imaging, or specialized assessments to care for the patient.

Age-Related Changes in the Neurologic Examination

Before discussion of the individual components of the examination, it would be useful to discuss changes that are expected as part of the aging process (**Table 11-1**). Normal age-related changes are due to progressive and irreversible changes associated with tissue senescence and the inability of nervous system to repair and regenerate secondary to the ravages of time. The frequency and qualitative characteristics of these changes vary from individual to individual but are present in many older adults.

TABLE 11-1 NEUROLOGIC CHANGES ASSOCIATED WITH NORMAL AGING

Psychomotor slowing
Decreased visual acuity
Smaller pupil size
Decreased ability to look upward
Decreased auditory acuity, especially for spoken language
Decreased muscle bulk
Mild motor slowing
Decreased vibratory sensation
Mild swaying on Romberg test
Mild lordosis and restriction of movement in neck and back
Depression of Achilles tendon reflex

Cognitive changes There continues to be a debate regarding the extent of cognitive changes associated with aging due largely to differences between cross-sectional and longitudinal study designs. When comparing older adults to young adults on similar cognitive tasks such as the Wechsler Adult Intelligence Scale, older adults generally score lower on both performance and verbal subtests. However, when differences in performance are considered in light of motor slowing and educational attainment, these changes are less apparent. Longitudinal evaluation of older adults has generally demonstrated little change in verbal intelligence with aging while performance is influenced significantly by motor and processing speed. Forgetfulness therefore is *not* a part of normal aging. While it may take longer to process new information and retrieve well-learned information, new learning and memory formation occurs in older adults. This is one reason why delayed recall of word lists is effective in discriminating older adults with cognitive impairment from those without.

Changes in cranial nerve function Visual and hearing changes are common in older adults. Visual acuity declines due to a number of ophthalmologic (cataracts, glaucoma) and neurologic (macular degeneration) causes. Pupillary size is typically smaller with age and pupils are less reactive to light and accommodation, forcing many older adults to use glasses for reading. There is also a restriction in eye movement in upward gaze. Also associated with aging is a decline in speech discrimination due to presbycusis, a progressive elevation in the frequency threshold for hearing. There are also age-related degenerative changes in inner ear including loss of hair cells, atrophy of stria vascularis, and thickening of the basilar membrane.

Changes in motor function There is a progressive decline in muscle bulk and strength associated with aging. Most of the muscle loss is found in the intrinsic muscles of the hands and feet, and around the shoulder. There is a weakening of the abdominal muscles which may accentuate spinal lordosis and contribute to low back pain. Muscle loss is associated with denervation on electrophysiologic studies and with type II atrophy on muscle biopsy. In addition to loss of strength and muscle bulk, changes in the speed and coordination of movement increases with advancing age. The changes may interfere with activities of daily living (dressing, putting away the dishes, getting out of a chair) and

recreation activities (golfing, shuffleboard). On examination, these changes may manifest as mild bradykinesia and dysmetria on finger-nose-finger and heel-shin tests.

Changes in sensory function By far the most common change will be the loss of vibration perception in the lower extremities and to a lesser extent position sense may be affected as well. As vibration sensation becomes impaired in lower extremities, there is an ascending pattern, from toe to ankle and knee. Pain and temperature sensation is also diminished in the older adult, but in the absence of a pathologic cause, usually does not elicit much symptomatology. The mild impairment in position sense often manifests as a mild swaying during the Romberg test.

Changes in gait and station Changes in gait and station in old age may be attributed in part to decreased muscle strength, weakening of abdominal muscles, arthritis and degenerative joint disease, diminished vibration and position sense, impairment in motor speed, and coordination. These changes make it more difficult for older adults to tandem, heel or toe walk for extended periods of time. Despite this, many older adults have adequate postural righting reflexes and are not likely to spontaneously fall (distinct from what is seen in Parkinson disease). Instead, polypharmacy, drug-drug interactions, and adverse effects from medications are significant risk factors for falls.

Changes in deep tendon reflexes The most common age-associated change is the depression or loss of the Achilles tendon reflex. Other reflexes usually remain present but are diminished in response. An extensor plantar response (Babinski sign) is *not* a normal age-related change but instead is always associated with some underlying pathology in the upper motor neuron.

THE NEUROLOGIC HISTORY

There is no substitution for a carefully elicited history detailing the onset, duration, quality, and location of symptoms. The history helps the clinician develop a differential diagnosis and focus on the neurologic examination. The history will also guide the formulation of diagnostic evaluations and develop a treatment plan. In addition, a compassionate clinician will be able to build a trusting relationship with the patient that will enhance patient adherence to medical recommendations. As a general comment, to avoid bias, it is often useful to gather historical facts de novo and not read other records or review laboratory studies such as imaging before taking the history and performing the physical examination. Here we discuss two aspects of neurologic history taking—from the patient, and when available from an informant.

The Neurologic History From the Patient

An accurate history requires that absolute attention is paid to detail, both verbal (what the patient is saying) and nonverbal (what the patient is doing). This is critical to match the chief complaint with the patient's body language. For example, someone complaining about severe low back pain that appears to be sitting comfortably in the chair may raise suspicion. Likewise, the older adult who offers no complaints but is noted to have a rest tremor should prompt more detailed questioning. One of the most important attributes of a skilled clinician is the ability to be a good listener and to focus in on critical historical points. The most effective historians gather information by a combination of open-ended and structured questions. After asking the patient why they are in office and offer a chance to express concerns or worries in their own words, specific topics can be addressed by focused questioning.

Another important aspect of the history is to elicit qualitative and quantitative aspects of the chief complaint. It is not enough to elicit a history of a "headache" or "pain." What are the characteristics of the complaint, when did it start, what makes it better, what makes it worse? Has this happened before, and if so, did it present in the same fashion? Use simple scales to quantify the extent of the complaint by asking, "On a scale of 1 to 10, with 10 being the worst (symptom)…." These qualities can help focus a differential diagnosis and help to build trust with the patient.

The Neurologic History From an Informant

In many instances, gathering information from a third party will be invaluable in determining the onset, duration, and extent of the neurologic problem. In cases where there are problems with cognition or alertness, this may be the only reliable way to gather information. Again using both open-ended and structured questions will often provide the clinician with important information about the chief complaint and assist in the development of a differential diagnosis. If possible, interviewing the information in an area separate from the patient may provide a true picture of what is transpiring.

MENTAL STATUS EXAMINATION

The elements of a comprehensive mental status examination include observational, cognitive, functional, and neuropsychiatric assessments. Although each of these elements is presented separately, they are interrelated and collectively characterize the neurobehavioral function of the patient. The initial contact with the patient affords the opportunity to assess whether a cognitive, attention, or language disorder is present. Questioning of an informant may bring to light changes in cognition, function, and behavior that the patient either is not aware of or denies.

Observational Assessment

Observation of a patient's level of arousal or alertness, appearance, emotion, behavior, movements, and speech provides insight into their mental status.

Level of consciousness An accurate assessment of a patient's mental status and neurologic function must first document the patient's alertness or level of arousal. Altered levels of consciousness can directly impact the patient's cognitive performance on mental status testing and influence the examiner's interpretation of the test results and may be indicative of a medical or neurologic condition requiring immediate medical intervention (eg, cardiopulmonary intervention, neurosurgical evaluation).

Abnormal patterns of arousal include hypoaroused or hyperaroused states. Decreasing levels of arousal include lethargy, obtundation, stupor, and coma. The lethargic patient is drowsy or fatigued and falls asleep if not stimulated, however while being interviewed, the patient will usually be able to attend to questioning. Obtundation refers to a state of moderately reduced alertness with diminished ability to consistently engage the environment. Even in the presence of the examiner, if not stimulated, the obtunded patient will drift off. The stuporous patient requires vigorous stimulation to be aroused. Responses are usually limited to simple "yes/no" responses or may consist of groans and grimaces. Coma, which represents the end of the continuum of hypoarousal states, is a state of unresponsiveness to the external environment. In older adults, hypoarousal states can be associated with systemic infection, cardiac or pulmonary insufficiencies, meningoencephalitis, increased intracranial pressure, toxic-metabolic insults, traumatic brain injury, seizures, or cerebrovascular disease. Coma requires either bilateral hemispheric dysfunction or brainstem dysfunction. Another important consideration is the role of polypharmacy. Drug interactions are more common in the older adult and can significantly impair consciousness.

Hyperarousal states on the other hand, are characterized by anxiety, autonomic hyperactivity (tachycardia, tachypnea, and hyperthermia), agitation or aggression, tremor, seizures, or exaggerated startle response. In older adults, hyperarousal states are most often encountered in toxic-metabolic disorders including withdrawal from alcohol, opiates, or sedative-hypnotic agents. Other causes include tumors (both primary and metastatic), viral encephalitis (particularly herpes simplex), cerebrovascular, and hypoxemia. Some patients may experience fluctuating periods of both hypo- and hyperarousal.

Appearance Assessment of a patient's physical appearance should acknowledge body size and type, apparent age, posture, facial expressions, eye contact, hygiene, dress, and general activity level. A disheveled appearance may indicate dementia, delirium, frontal lobe dysfunction, or schizophrenia. Wearing excessive makeup or flamboyant grooming or attire in an old individual should raise the suspicion of a manic episode or frontal lobe dysfunction. Patients with unilateral neglect may fail to dress, groom, or bathe one side of their body. Patients with Parkinson disease may display a flexed posture, whereas patients with progressive supranuclear palsy have an extended, rigid posture. The overall appearance of an individual should also provide information regarding their general health status. The cachectic patient may harbor a systemic illness (eg, cancer) or have anorexia or depression.

Emotional state and affect Affect describes the mental representation of external reality and the patient's internal feelings about external reality, while emotional state describes the objective display of emotion through facial grimaces, vocal tone, and body movements, and the subjective component of how the patient reports what he or she feels internally: "I feel sad, happy, apprehensive, cynical."

Depression is the most frequent mood disturbance in older adults and occurs in a variety of neurologic disorders (**Table 11-2**). Euphoria or full-blown mania occurs less often than depression in the course of neurologic illness. Euphoria is most common with frontal lobe dysfunction (trauma, frontotemporal degenerations, and infections) and with secondary mania. Anxiety occurs in a variety of neuropsychiatric conditions including anxiety disorders,

metabolic encephalopathies (eg, hyperthyroidism, anoxia), toxic disorders (eg, lidocaine toxicity), and degenerative diseases (eg, Alzheimer disease, Parkinson disease). Objective and subjective emotional components may be incongruent in certain psychiatric disorders (eg, schizophrenia and schizotypal personality disorder) and in neurologic conditions such as pseudobulbar palsy.

TABLE 11-2 CAUSES OF DEPRESSION IN OLDER ADULTS

Idiopathic
Secondary to life situation (loss of spouse, child, friends)
Cerebrovascular accident
Hypothyroidism
Alzheimer disease
Parkinson disease
Frontotemporal dementia
Dementia with Lewy bodies
Head injury
Drug withdrawal
Drug intoxication (alcohol, barbiturates, sedative-hypnotics)
Medications (β-blockers, reserpine, clonidine)
Multiple sclerosis
Epilepsy

The range and intensity of the observable component of emotion should be noted. Constriction or flatness is observed in apathetic states; for example, in the context of negative symptoms of schizophrenia, severe melancholic depression, or in demented patients with apathy. Increased intensity, on the other hand, is seen in mood disorders such as bipolar illness, and in personality disorders such as borderline personality.

Lability is a disorder of emotional regulation. Patients with marked lability are irritable and shift rapidly among anger, depression, and euphoria. The emotional outbursts are usually short-lived. Labile mood is seen in mood disorders such as bipolar illness and in certain personality disorders such as borderline personality. It also may occur in frontotemporal dementia and pseudobulbar palsy.

Behavior Behavioral observations can reveal important information regarding the mental status and neurologic function of the patient. A variety of personality alterations can be encountered with focal brain lesions. Orbitofrontal dysfunction may be characterized by impulsiveness or undue familiarity with the examiner, lack of judgment or lack of social anxiety, and antisocial behavior. Individuals with dorsolateral frontal lobe dysfunction may be inattentive and distractible. Apathy (lack of motivation, energy, emotional reciprocity, social isolation) may be caused by medial frontal dysfunction. Dementias are associated with increased rigidity of though, egocentricity, diminished emotional responsiveness, and impaired emotional control.

Movement Observation of patient's movements may provide evidence of parkinsonism, chorea, myoclonus, or tics (**Table 11-3**). Psychomotor retardation (ie, slowed central processing and movement) may be indicative of vascular dementia, subcortical neurologic disorders, parkinsonism, medial frontal syndromes, or depression. Psychomotor agitation may be indicative of a metabolic disorder, choreoathetosis, seizure disorder, mania, or anxiety.

TABLE 11-3 COMMON MOVEMENT DISORDERS AND SIGNS

SIGN	DESCRIPTION	ETIOLOGY
Bradykinesia	Slowed initiation and sustained movements	Parkinson disease, drug-induced, may be normal variant
Dyskinesia	Abnormal involuntary movements either slow or fast	Drug-induced, Huntington disease, Parkinson disease, idiopathic
Action or postural	Fast frequency (10–15 Hz) associated with	Benign, essential tremor, drug-induced

tremor	movement (action) or sustained posture (postural), may improve with small amount of alcohol	
Rest tremor	Low frequency (3–5 Hz) with pill rolling quality, may involve extremities or chin	Parkinson disease, drug-induced
Intention tremor	High frequency (10–15 Hz), worsening as approaching target	Cerebellar disease
Myoclonus	Lightning fast movements from brief muscle contractions	Stroke, sleep, Huntington disease, epilepsy, Creutzfeldt-Jakob
Asterixis	Sudden loss of limb tone during sustained muscle contraction, sometime considered “negative” myoclonus	Hepatic, renal, or pulmonary disease, drug-induced, encephalopathy, bacterial infection
Chorea	Brief, rapid, irregular contractions	Huntington disease, Sydenham chorea, drug-induced
Ballismus	Large-amplitude, jerky movements with flinging of extremities	Subthalamic nucleus lesions
Tics	Sequenced coordinated movements or vocalizations that appear suddenly	Tourette, drug-induced
Dystonia	Sustained muscle contraction with twisting or repetitive movements, may be painful	Idiopathic, infarcts, drug-induced
Athetosis	Slow, writhing movements predominantly proximal	Huntington disease, infarcts
Akathisia	Internalized restlessness with urge to move	Drug-induced, encephalopathy, Parkinson disease, restless legs syndrome

Speech and communication Observation of spontaneous speech is the first step in formal language testing and can be assessed during history taking as well as in the course of the mental status examination. The examiner first observes spontaneity of speech as well as the timber, pitch, and modulation of voice. Mutism may be encountered in several neurologic conditions such as akinetic mutism, vegetative state, locked-in syndrome, catatonic unresponsiveness, or large left hemispheric lesions. Akinetic mutism is characterized by absent speech in the setting of alert-appearing immobility. The patient’s eyes are open, and the individual may follow environmental events. The patient exhibits regular sleep-wake cycles but may be completely inert or display brief movements or postural adjustments spontaneously or in response to vigorous stimulation. Akinetic mutism may be seen with large frontal lobe injuries, bilateral cingulate gyrus damage, or midbrain pathology. Akinetic mutism should be distinguished from a vegetative state where the patient exhibits sleep-wake cycles with open eyes. A vegetative state can occur after severe brain injury. Locked-in syndrome occurs with bilateral pontine lesions, rendering the patient mute and paralyzed. Intellectual function, however, is not impaired and the patients can communicate by eye movements or eye blinks.

Spontaneous speech is characterized by its rate, rhythm, volume, response latency, and inflection. Accelerated speech may be encountered in mania, disinhibited orbitofrontal syndromes or festinating parkinsonian conditions, whereas a reduced rate of speech output can occur as a component of psychomotor retardation. Response latencies may be prolonged or the patient may impulsively interrupt the examiner, anticipating the question. Perturbed speech prosody (loss of melody or inflection) can be encountered in brain disorders affecting the right hemisphere or the basal ganglia. Empty speech with hesitations or circumlocutions can be exhibited in patients with word-finding difficulties. Word-finding impairment may occur in aphasias, metabolic encephalopathies, physical exhaustion, sleep deprivation, anxiety, depression, or dorsolateral frontal lobe damage in the absence of an anomia.

Aphasia is characterized by impairment in oral and/or written communication. Deficits will vary depending on the location and extent of anatomic involvement. Aphasias are generally characterized as nonfluent or fluent (**Table 11-4**). Nonfluent aphasias are characterizes by a paucity of speech, often with a hesitant quality. There is impairment in word searching and writing. The patient may appear frustrated or depressed because of awareness of the language deficit and the inability to communicate with family and health care providers. Fluent aphasias are characterized by empty speech. Word production is normal or may be increased but there is a lack of comprehension about what words mean, often associated with impairment in reading ability. The patient often displays little insight to the language deficit and instead may become agitated because others are not following the conversation.

TABLE 11-4 CHARACTERISTICS OF APHASIAS

FEATURE	BROCA APHASIA	WERNICKE APHASIA	CONDUCTION APHASIA	GLOBAL APHASIA	TRANSCORTICAL MOTOR	TRANSCORTICAL SENSORY	TRANSCORTICAL MIXED	PURE ANOMIA	THALAMIC
Anatomic localization	Inferior frontal (Broca area)	Superior temporal (Wernicke area)	Arcuate fasciculus	Middle cerebral artery distribution	Supplemental motor areas	Inferior parietal	Watershed areas	Angular/supramarginal gyrus	Dorsomedial or ventral anterior nuclei
Fluency	Nonfluent	Fluent	Fluent	Nonfluent	Nonfluent	Fluent	Nonfluent	Fluent	Nonfluent
Repetition	Impaired	Impaired	Impaired	Impaired	Normal	Normal	Normal, may be only preserved language function	Normal	Normal
Rhythm of speech	Effortful with dysarthria	Quickened, long-winded, effusive	Normal	Severely impaired, mute	Slightly effortful	May appear normal	Effortful, slow	Normal	Effortful, slow
Content	Agrammatical, telegraphic	Mispronunciation and neologism (nonsense words)	Occasional use of wrong words	Abnormal	Agrammatical	Circumlocution, tangential	Variable impairment	Often normal, but uses descriptive language	Variable
Paraphasias	Common	Common	Common	Common	Variable	Variable	Variable	Common	Variable
Comprehension—spoken	Good	Abnormal	Variable	Poor	Good	Abnormal	Abnormal	Normal	Abnormal
Comprehension—written	Worse than spoken	Better than spoken	May be normal	Poor	Good	Fair	Fair	Abnormal	Good
Writing	Impaired, with grammatical and spelling errors	Preserved, but inaccurate	Variable	Severely impaired	May be impaired	Preserved	Variable	Abnormal with spelling errors	Good
Naming	Poor	Poor	Fair	Poor	Poor	Good	Variable	Poor	Poor
Other findings	Hemiparesis, apraxia	Visual field deficits, hemisensory loss, apraxia	Mild hemiparesis, neglect	Hemiplegia, visual field deficits	Hemiparesis	Neglect, sensory loss	Variable with mild motor and sensory findings	Gerstmann syndrome (acalculia, agraphia, finger agnosia, left-right confusion)	Cognitive impairment, hemiataxia, hemiparesis, hemisensory loss

Cognitive Assessment

The assessment of cognitive function should be conducted methodically and should assess comprehensively the major domains of neuropsychological function (attention, memory, language, visuospatial skills, executive ability). The patient's age, handedness, educational level, and sociocultural background may all influence cognitive function and should be determined prior to initiating or interpreting the evaluation.

Attention Two tests are useful in assessing attention: digit span forward and continuous performance tests. In the digit span forward test, the patient is asked to repeat increasingly long series of numbers (eg, 1, 3-7, 4-6-3, 5-1-9-2, etc). The examiner says the numbers at a rate of one per second. A normal forward digit span is seven digits; fewer than five is abnormal. Concentration is evaluated by a continuous performance test. An example would be to say the months of the year in reverse order, starting with the last month of the year (December). Distractible patients tend to lose track and skip 1 or 2 months. Serial subtraction can also be used to test concentration but heavily dependent on educational attainment and mathematical abilities. Confusional states such as delirium are characterized by impaired attention.

Memory Learning, recall, recognition, and memory for remote information are assessed in the course of mental status examination. Asking the patient to remember three words and then asking him or her to recall the words 3 minutes later can help assess learning, recall, and recognition. However, the shorter the list, the more easy it is to remember, particularly in high-functioning individuals. When told to remember items, patients will often remember the first two items heard (known as "primacy") and the last two items heard (known as "recency"); therefore, longer lists of 10 words may be preferable. After a delay, recall of fewer than five words is considered abnormal. Patients having difficulty with recall may be given clues (eg, the category of items to which the word belongs or a list of words containing the target) to distinguish between storage and retrieval deficits. Prompting and clues will not aide patients with storage deficits (eg, amnesia); patients with intact storage but poor recall (eg, retrieval-deficit syndrome) may be aided by clues. Amnestic deficits are thought to be caused by lesions in the hippocampal-thalamic circuit while retrieval deficits are likely due to lesions of frontal-basal ganglia circuitry.

Information is gathered on the patient's remote memory function while taking a history of the patient's illness,

inquiring about the patient's life events (marriage, births of children, etc), and asking about important historical events. An informant may also be helpful here to verify these events. The temporal profile of remote memory may be diagnostically important. Amnestic syndromes such as dementias usually feature normal, nonmemory cognitive functions, a period of retrograde amnesia following the onset of the disorder, variable periods of anterograde amnesia, and intact remote memory beyond the period of the retrograde amnesia. Psychogenic memory loss may include variable patterns of amnesia particularly in long-term events (eg, not recall birth of children, not recall being married).

Language Language assessment entails the evaluation of all aspects of communication including spontaneous speech, comprehension, repetition, naming, reading, and writing. Aphasic disturbances are characterized as fluent or nonfluent. Fluent aphasias are characterized by normal or excessive amounts of speech, preserved phrase length, intact speech melody, usually in combination with a paucity of information. Phonemic paraphasias (substitution of one phoneme for another); semantic paraphasias (the replacement of one word with another); or neologistic paraphasias (the construction of new words) may occur. Wernicke, transcortical sensory, conduction, and anomic aphasias are fluent aphasic syndromes.

Nonfluent aphasias feature reduced verbal output, short or one-word replies, agrammatism, poor speech initiation, reduced speech prosody, and dysarthria. There are few paraphasias. Broca, transcortical motor, global, and mixed transcortical aphasias are nonfluent aphasic disorders. Interestingly, nonfluent aphasic patients may have preserved abilities to curse fluently and sing well-learned songs (eg, "Happy Birthday") with few errors.

Primary progressive aphasia is a disorder seen in patients with asymmetric frontotemporal degeneration that involves dominant hemisphere. Progressive nonfluent aphasia involves primarily unilateral left frontal, left frontoparietal, or left frontotemporal degeneration and is characterized by agrammatism, paraphasias, and anomia. Bilateral temporal lobe atrophy and hypoperfusion with more pronounced involvement of the left anterior temporal lobe may cause semantic dementia that is characterized by progressive loss of knowledge about objects, people, facts, and words; it is often accompanied by visual agnosia (inability to name or recognize objects presented visually).

Language comprehension is tested by asking the patient to follow increasingly complex linguistic constructions. The easiest commands are one-step orders such as "stand up" and "turn around," "open your mouth," and "stick out your tongue." Asking the patient to point to room objects or body parts is the next level of comprehension difficulty. Finally, more complex questions, such as "If a lion is killed by a tiger, which animal is dead?" are asked. Impaired comprehension usually implies dysfunction of parietotemporal regions of the left hemisphere. Comprehension is abnormal in most fluent and global aphasic syndrome but may be preserved in nonfluent syndromes. In older adults, it is important to establish that hearing is intact before testing comprehension. Failure to comprehend commands may reflect the inability to hear as opposed to impaired comprehension.

Repetition is assessed by asking the patient to repeat increasingly long phrases or sentences. Generally begin with simple phrases such as salutations ("Hello") and progress to more complex phrases ("Around the ragged rock, the rugged rascal ran"). Omissions and paraphasic substitutions may disrupt accurate repetition. Repetition is impaired in Wernicke, Broca, conductive and global aphasia but is generally preserved in transcortical aphasias.

Naming tests involve asking the patient to name objects, parts of objects, and colors. Errors include paraphasias, circumlocutory responses, and simply making no response. Aphasic patients may use descriptive terms rather than giving the proper name. For example, a "watch" becomes "the thing you tell time with." Anomia occurs in aphasia, dementia, delirium, and can sometimes be seen as a consequence of head trauma. Adequate vision and object recognition must be ensured before errors are ascribed to naming deficits.

When assessing reading, the patient's ability to read aloud and to comprehend what is read must both be tested. Adequate vision must be ensured before failures are ascribed to an alexia. Most aphasias have concomitant alexias however the converse may not be true. In alexia with agraphia and alexia without agraphia, reading abnormalities may occur in the absence of other signs of aphasia.

Mechanical or aphasic abnormalities may cause agraphia. Micrographia is a characteristic aspect of parkinsonism in which the script becomes progressively smaller as the patient writes a sentence or extended series of numbers or letters, and mechanical agraphias occur in patients with limb paresis, limb apraxia, or movement disorders such as tremor and chorea. Aphasic agraphias accompany aphasic syndromes and errors similar to those noted in verbal output are present in written form. In Gerstmann syndrome (agraphia, acalculia, right-left disorientation, finger agnosia), alexia with agraphia, and disconnection agraphia (occurring with injury of the corpus callosum), agraphia occurs without aphasia. Agraphia also occurs in dementia and delirium.

Orientation Orientation to time is tested by asking the patient to identify the correct day of the week, date, month, and year. Although some patients may make excuses (eg, they are retired, they don't need to know, etc), count only correct

answers. This should be followed by asking the patient to guess the correct time of day without looking at a watch or clock. The patient should be within 1 hour of the correct time. Orientation to place is assessed by asking about city, county, state, and current location. If the patient is from out of town, major landmarks may be substituted for less well-known information such as county. Lastly, orientation to situation can be assessed by asking the patient why they are in the office today.

Abstraction Similarities, differences, idioms, and proverb interpretation can all be used to assess abstracting capacity. These tests are heavily influenced by culture and educational attainment. Abstraction abnormalities are a nonspecific indicator of cerebral dysfunction. Patients with frontal lobe disorders have disproportionately severe abstracting disturbances.

Judgment and problem-solving abilities Assessing judgment assists in exploring the patient's interpersonal and social insight. Judgment is impaired in many neurologic conditions. Damage to orbitofrontal subcortical circuit (eg, in frontotemporal dementia, trauma, or focal syndromes) produces marked alterations in social judgment. Problem solving can be assessed by giving a scenario "If in a strange town, how would a person locate a friend they wished to see?" Correct answers might include use of phone book, the Internet, or city directory.

Visuospatial skills There are a number of visuospatial abilities including spatial attention, perception, construction, visuospatial problem solving, and visuospatial memory. Constructional tasks are most widely used to assess visuospatial ability. In the clock-drawing test, the patient is asked to draw a clock and draw the hands of the clock to indicate a specific time. The hands should be of different lengths. Watching the patient complete the clock is sometimes as informative as the finished product.

Patients with executive dysfunction may draw a clock face that is too small to contain the required numbers (poor planning), whereas patients with unilateral neglect will ignore half of the clock face.

Tests of copying involve having the patient reproduce figures such as a circle, intersecting circle and triangle, overlapping pentagons, cube, or more complex figures. Abnormalities include failures to reproduce the shapes accurately, perseveration on individual elements, drawing over the stimulus figure, or unilateral neglect. Drawing disturbances are common with many types of neurologic conditions including focal brain damage, degenerative disorders, and toxic and metabolic encephalopathies.

Calculation In assessing calculation skills, patients are asked to add or multiply one or two digits mentally or to execute more demanding problems with pencil and paper. Calculation abilities are related to education and occupation. Acalculias may occur in association with a number of aphasic syndromes while visuospatial disorders lead to incorrect alignment of columns of numbers. Primary anarithmetias (inability to do math) are produced by damage to the posterior left hemisphere.

Executive function Executive function is assessed by asking the patient to perform tasks mediated by frontal-subcortical systems. Frontal-subcortical systems are complex neural circuits that include the dorsolateral prefrontal cortex, striatum, globus pallidus/substantia nigra, thalamic nuclei, and connecting white matter tracts. Patients with executive dysfunction manifest perseveration; motor programming abnormalities; reduced word list generation (left dorsolateral dysfunction); reduced nonverbal fluency (right dorsolateral dysfunction); poor set shifting; abnormal recall with intact recognition memory; loss of abstraction abilities; poor judgment; and impaired mental control. These abnormalities are common following head trauma, frontal lobe degenerations, frontal lobe neoplasms, multiple sclerosis, Huntington disease, and other basal ganglia disorders, subcortical infarctions, and in some brain infections such as syphilis.

Digit span backward is a test of mental control and complex attention, as well as executive dysfunction. It entails saying increasingly long series of numbers and asking the patient to say them backward (give 2-5-8, response should be 8-5-2). A normal digit span in reverse is five digits; fewer than three is abnormal.

Word list generation Word list generation is a very useful test and involves asking the patient to think of as many members of a specific category (most commonly animals) as possible within 1 minute. Normal individuals can name approximately 18 animals within 1 minute; fewer than 14 is considered abnormal. Word list generation deficits occur with anomia, frontal-subcortical systems dysfunction, and psychomotor retardation. It is a highly sensitive test but lacks specificity.

Informant assessment In many instances, asking questions of the informant will provide a wealth of information regarding the baseline abilities of the patient. There are several structured interviews that are short, easy to administer,

and do not require specific training. Functional abilities and activities of daily living can be assessed with the Functional Activities Questionnaire, the Physical Self-Maintenance Scale, Instrumental Activities of Daily Living Scale, or the Barthel index. Baseline cognitive abilities can be assessed with brief informant interviews such as the AD8 or the IQCODE. The AD8 was developed in a research sample and validated in a clinic population and asks eight questions regarding change in the patients' memory, orientation, judgment and problem-solving abilities, executive function, and interest level. Endorsement of two or more items suggests cognitive dysfunction and should trigger a more formal evaluation.

Neuropsychiatric Assessment

The neuropsychiatric interview of the patient includes the evaluation of thought form, thought content, and insight. The new onset of disturbances in any of these domains in older patients is unusual in the absence of a brain disease. Their emergence should trigger the search for a neurologic or psychiatric condition.

Thought form Formal thought disorders such as tangentiality, circumstantiality, loose associations, illogicality, derailment, and thought blocking are much less common than disturbances of thought content as a manifestation of psychosis in neurologic diseases. Thought disorders have been observed in the psychoses accompanying epilepsy, Huntington disease, and idiopathic basal ganglia calcification.

Perseveration and incoherence are disorders of the form of thought that are common in neuropsychiatric conditions. Perseveration refers to the inappropriate continuation of an act or thought after conclusion of its proper context. Intrusions are a special case of perseveration with late recurrences of words or thoughts from an earlier context. Perseverations and intrusions are seen in aphasias and dementing illnesses. Incoherence refers to the absence of logical association between words or ideas. It is observed in delirium, advanced dementias, and as part of the output of fluent aphasia.

Thought content Several types of disorders of thought content occur in neurologic diseases. Delusions are the most common manifestation of psychosis in neurologic disorders and are characterized by false beliefs based on incorrect inference about external reality. Common types of delusions encountered involve being followed or spied on, theft of personal property, spousal infidelity, or the presence of unwelcome strangers in one's home. Theme-specific delusions such as the Capgras syndrome (the belief that someone has been replaced by an identical-appearing impostor) may also be observed in neurologic illnesses. Delusions are common in a number of dementia etiologies including Alzheimer disease and dementia with Lewy bodies, and may occur in vascular dementia, frontotemporal dementia, and Huntington disease.

Hallucinations occur in many neurologic disorders. Hallucinations are sensory perceptions that occur without stimulation of the relevant sensory organ. Hallucinations and delusions occur together in psychosis; hallucinations are nondelusional when the patient recognizes the sensory experience to be unreal. Hallucinations may involve any sensory modality (visual, auditory, tactile, gustatory, olfactory) and may be formed (eg, people or things) or unformed (flashing lights or colors). Hallucinations occur with ocular and structural brain disorders as well as Charles Bonnet syndrome, epilepsy, narcolepsy, and migraine. Well-formed visual hallucinations (children, furry animals) are a prominent early sign in dementia with Lewy bodies. Less well-formed visual hallucinations occur in the moderate to severe stages of Alzheimer disease. Gustatory or olfactory hallucinations are most common in seizure disorders, bipolar and schizophrenia, and with tumors located in the medial temporal lobe. Tactile hallucinations are most commonly associated with schizophrenia, affective disorders, or drug intoxication or withdrawal.

Insight Patients with neuropsychiatric disease may display limited insight and be unaware of their medical conditions or limitations in function, thus assessment of a patient's insight into the severity of their illness can yield useful diagnostic information and assist in developing a therapeutic plan. For example, Alzheimer disease patients have impaired insight into their memory and cognitive difficulties, whereas patients with vascular dementia and dementia with Lewy bodies often exhibit more appropriate concern regarding their cognitive dysfunction. Lesions of the right parietal lobe are associated with unawareness, neglect, or denial of the abnormalities of the contralateral side.

Behavior and personality A variety of changes in personality and behavior have been described in neuropsychiatric disease in the older adult. Personality changes may include increased egocentricity and thought rigidity, impaired emotional control and diminished emotional responsiveness, loss of interest and apathy, and lack of concern for the feelings of others. No brief personality rating scales are available but in the proper setting the Neuroticism-Extroversion-Openness Five-Factor Inventory (NEO-FFI) can be used to evaluate personality. Behavioral changes

including irritability, depression, anxiety, hallucinations, delusions, and vegetative changes can be assessed with the Neuropsychiatric Inventory (NPI). Both long and short forms of the NPI are available.

NEUROLOGIC EXAMINATION

The neurologic examination includes assessment of cranial nerve function, strength, coordination, sensation, muscle stretch reflexes, pathologic/primitive reflexes, and neurovascular status. Examination of head and neck may provide additional important information.

Cranial Nerve Examination

Cranial nerve I: olfactory In normal aging, loss of olfaction may be a nonspecific or clinically insignificant finding. Olfaction may be impaired following head trauma, infection, zinc deficiency, vitamin A deficiency, frontal lobe dysfunction, vitamin B_{12} deficiency, and frontal lobe tumors (olfactory groove meningioma). Olfaction is tested by asking the patient to identify a variety of odors. When testing, it is important to use simple and familiar odors (coffee beans, vanilla, or cinnamon). Complex scents such as perfumes and noxious agents (ie, ammonia) should not be used. Ideally, the patient should close their eyes and each nostril should be tested separately.

Cranial nerve II: optic Examination of the optic nerve includes visual inspection of the nerve head, testing of visual acuity, and mapping of the visual fields. In aging, visual acuity may be impaired and can be due to a number of neurologic and ophthalmologic causes. First, casual inspection of the corneal, sclera, and mucosal tissue should be carried out to evaluate structural abnormalities. Visual acuity can be evaluated with a Snellen visual chart or Rosenberg card held 14 in from the eye. Screening should be done in a well-lit environment and to the patient's advantage allowing them to use their corrective lenses. If they do not have their glasses with them, refractive errors can be partly corrected by using a pinhole. Visual fields are tested at the bedside by confrontation. The examiner should face the patient, sitting or standing at a similar height and each eye should be tested independently. The patient is asked to look at the examiner's nose and the examiner's arms are extended laterally. The patient is asked to differentiate between one or two fingers. Each quadrant should be tested separately. After testing each eye individually, both eyes should be tested simultaneously for visual neglect. Monocular visual field deficits can be associated with glaucoma. Abrupt changes in visual fields or acuity should alert the clinician to potential vascular etiologies. Homonymous field deficits reflect disruption of the optic pathways posterior to the optic chiasm.

Pupillary examination should include evaluation of size and shape. Up to a 1-mm difference in size is generally considered normal. Pupillary responses are tested with a bright flashlight (not the ophthalmoscope). A normal pupil reacts to light by constricting; the contralateral pupil should also constrict. The pupils also constrict when shifting focus from a distant object to a near object (accommodation) and during convergence such as when patients are asked to look at their nose. Abnormalities of pupillary responses are associated with a number of neurologic disorders (**Table 11-5**). A review of medications is also important as a number of drugs can affect pupillary size. Mydriasis (pupillary dilation) can be caused by atropine-like drugs, while miosis (pupillary constriction) can be caused by parasympathomimetic drugs.

TABLE 11-5 CAUSES OF PUPILLARY CHANGES IN OLDER ADULT

MIOSIS (PUPILLARY CONSTRICTION)	MYDRIASIS (PUPILLARY DILATATION)
Pontine lesion	Dorsal midbrain syndrome (Parinaud)
Organophosphates	Amphetamines and sympathomimetics
Cholinergic agents	Anticholinergic agents
Opioids (except meperidine)	Meperidine
Pilocarpine-like agents	Atropine-like agents
Barbiturates	Cocaine
Phenothiazines	Phenothiazines
MAO inhibitors	Antihistamines
Phencyclidine (PCP)	Lysergic acid diethylamide (LSD)
Argyll-Robertson (syphilis)	Seizures/postictal state
Horner syndrome (usually unilateral)	Thyrotoxicosis
Hypothermia	Hypermagnesemia
	Third nerve compression (usually unilateral)

			CONSENSUAL RESPONSE		
SITE OF LESION	PUPIL SIZE	DIRECT RESPONSE	IPSILATERAL	CONTRALATERAL	ACCOMMODATION
Retina	Normal	Impaired	Impaired	Normal	Normal
Optic nerve	Normal	Lost	Lost	Normal	Normal
Optic chiasm	Normal	Normal	Normal	Normal	Normal
Optic tract	Normal	Normal	Normal	Normal	Normal
Optic radiation	Normal	Normal	Normal	Normal	Normal
Oculomotor nerve or nucleus	Dilated	Lost	Normal	Lost	Lost
Argyll-Robertson	Constricted	Lost	Normal	Lost	Normal
Sympathetic	Constricted	Normal	Normal	Normal	Normal

A careful examination of the optic nerve should be performed in all patients. It is not always necessary to do a dilated examination, but the room should be darkened to increase pupillary size. The sharpness of optic disc margins, the ratio of optic cup to disc, venous pulsations, the caliber of blood vessels, and the presence of exudates, hemorrhages, emboli, and retinal pallor should be noted. Papilledema is characterized by blurring or elevation of the disc margins with the loss of normal venous pulsations and reflects raised intracranial pressure. As pressure increases, hemorrhages may be found adjacent to the disc. Glaucoma increases the size of the optic cup relative to the disc.

Cranial nerves III, IV, and VI: oculomotor, trochlear, and abducens The oculomotor, trochlear, and abducens nerves mediate ocular motility, pupillary responses, and eyelid position. The trochlear nerve innervates the superior oblique muscle, the abducens nerve innervates the lateral rectus muscle, while the oculomotor nerve innervates the remainder of the extraocular muscles. The oculomotor nerve also innervates the levator muscles of the eyelid and carries parasympathetic nerves to the pupil. Testing each eye individually helps to identify ocular motility dysfunction. In aging, ocular motility may be reduced. Normal older adults can exhibit restricted convergence and limitation of conjugate upward gaze. Other nonspecific concomitants of normal aging include the evolution of small sluggishly reactive pupils, loss of Bell phenomenon (upward eye deviation on eye closure), and the inability to dissociate ocular movements from head movements. The clinician should be concerned when an older patient exhibits new-onset diplopia, pupillary asymmetry, nystagmus (**Table 11-6**), or extraocular movement disorders. Ptosis (drooping of the upper lid) can be caused by a number of disorders (**Table 11-7**). Isolated abducens palsies may be a sign of elevated intracranial pressure since the sixth nerve has the longest intracranial course.

TABLE 11-6 TYPES OF NYSTAGMUS AND OCULAR OSCILLATIONS

MOVEMENT	DESCRIPTION	LOCALIZATION

Physiologic end-stage	Fine, regular horizontal jerking at extremes of lateral gaze	No pathologic significance
Jerk	Horizontal and rotary	Vestibular disorder
Vertical	Jerk movements in vertical plane	Posterior fossa disease, sedatives, anticonvulsants
Downbeating	Rhythmic, horizontal gaze still possible	Cervicomedullary junction lesion
Upbeating	Rhythmic, horizontal gaze still possible	Lesion in pons, cerebellar vermis or medulla
Ocular bobbing	Arrhythmic, coarse movement with horizontal gaze palsy	Pontine lesion
Seesaw	Vertical dysconjugate movements with rotary component	Lesion by optic chiasm
Periodic alternating	Horizontal nystagmus with periodically alternating direction	Lower brainstem
Rebound	Horizontal jerk nystagmus transiently after sustained gaze to opposite side	Cerebellar pathways
Convergence-retraction	Eyes converge and move rhythmically back into the orbits on attempted upgaze	Periaqueductal gray (midbrain)
Ocular dysmetria	Overshoot or terminal oscillation of saccadic movements	Cerebellar pathways
Hypometric saccades	Slowed movements	Parkinson disease, basal ganglia
Opsoclonus	Chaotic multidirectional conjugate saccades	Paraneoplastic syndrome (neuroblastoma, breast, lung)
Square-wave jerks	Small saccades interfering with visual fixation	Progressive supranuclear palsy
Ocular myoclonus	Rhythmic oscillations, usually vertical	Associated with palatal myoclonus, brainstem lesion

TABLE 11-7 CAUSES OF PTOSIS IN THE OLDER ADULT

Congenital
Myopathic causes
- Myasthenia gravis
- Oculopharyngeal muscular dystrophy
- Myotonic dystrophy
- Polymyositis
- Hypothyroidism

Horner syndrome
Vasculitis
Diabetes mellitus
Third nerve lesions (ptosis is rarely isolated finding)
- Nuclear lesion in mesencephalon
- Third nerve compression

Cranial nerve V: trigeminal The trigeminal nerve is divided into three divisions: ophthalmic, maxillary, and mandibular. The first two divisions are pure sensory nerves mediating facial and corneal sensation. The third division

carries both sensory fibers and innervates the muscles of mastication. The corneal reflex is mediated by the ophthalmic division and can be tested by lightly stimulating the cornea with a wisp of cotton. When the cornea on one side is stimulated, both eyes should close. Facial sensation is tested with a safety pin or cold handle of a tuning fork. Motor function is tested by asking the patient to bite down or open the jaw against resistance. Tumors of the middle fossa and in the cerebellopontine angle may compress the fifth cranial nerve and produce a cranial nerve syndrome with decreased corneal reflex and sensory loss on the ipsilateral face. Tic douloureux (trigeminal neuralgia) is a paroxysmal pain disorder triggered by touching sensitive zones usually within the mandibular division. The cause may be idiopathic, due to compressive lesions or demyelination at the root entry zone.

Cranial nerve VII: facial The facial nerve supplies the facial musculature, lacrimal and salivary glands, and taste fibers of the anterior tongue. The motor function is tested by asking the patient to wrinkle their forehead, close their eyes, and smile. Unilateral weakness may cause a flattening of the nasolabial fold. If very weak, the patient may experience drooling. The eyelid is usually not severely affected with central lesions and the upper forehead is spared. In peripheral lesions such as Bell palsy (**Table 11-8**), patients are unable to close their eye or wrinkle their forehead. The facial nerve also innervates the stapedius muscle of the middle ear which helps to modulate tympanic membrane vibration. This motor branch can be damaged during closed head trauma leading to hyperacusis, an increased perception of sound. The sense of taste is not often tested, but can be done at the bedside using sugar, salt, or lemon juice. The patient is asked to stick their tongue out and a small amount of solution is placed on one side of the tongue. The patient is asked to describe the taste, and then allowed to drink some water before the next solution is applied.

TABLE 11-8 CAUSES OF BELL PALSY

Idiopathic
Pregnancy
Guillain-Barré syndrome
Lyme disease (may present as bifacial weakness)
Herpes zoster (Ramsay Hunt syndrome)
Neoplasms
Sarcoidosis
Head trauma
Acute intermittent porphyria
Lead poisoning
Brainstem infarction (rare)

Cranial nerve VIII: cochlear and vestibular Hearing and vestibular function are mediated by the eighth cranial nerve. Evaluation of hearing at the bedside is sometimes difficult. Use of a 512-Hz tuning fork can help discriminate conduction from sensorineural hearing loss. The Rinne test is done by placing a vibrating tuning fork on the mastoid process. As soon as the patient is unable to detect sound, the tuning fork is moved to a position near the external auditory canal. If the patient has normal hearing, air conduction should be better than bone conduction. If the patient has conduction deafness, the sound will not be heard because of pathology in the middle ear. In nerve deafness, air conduction is better than bone conduction but both will be reduced. The Weber test looks for lateralization. The tuning fork is placed in the middle of the skull and the patient is asked to decide where they best hear the sound. In normal hearing, the sound is heard equally in both ears. In conduction deafness, vibrations are best heard in the abnormal ear. In nerve deafness, the sound is best appreciated in the normal ear. Decreased hearing for high-pitched sounds and lack of perception of background noise are common findings in normal aging and by themselves should not be considered a pathologic finding. Sensorineural deafness is characterized by loss of high-pitched sounds while conduction deafness is characterized by loss of low-pitched sounds. Tinnitus or ringing in the ears is a common symptom in adults. Tonal tinnitus is subjective and heard only by the patient. Nontonal tinnitus is more objective because in certain circumstances, the tinnitus can be heard by the examiner. The differential diagnosis of tinnitus is presented in **Table 11-9**.

TABLE 11-9 DIFFERENTIAL DIAGNOSIS OF TINNITUS

TONAL TINNITUS	NONTONAL TINNITUS
Otitis media	Contraction of muscles in eustachian tube
Disorder of tympanic membrane	Contraction of stapedius muscle
Inner ear disorder (hair cells, organ of Corti)	Contraction of tensor tympani muscles
Cochlear nerve lesion	Palatal myoclonus
Acoustic schwannoma	Carotid bruit
Meningioma	Arteriovenous malformations
Neurofibroma	Glomus jugulare tumor
Ménière disease	
Head trauma	

Vestibular lesions produce nystagmus and vertigo. Vestibular nystagmus is horizontal or combined horizontal-rotatory and is typically accompanied by vertigo and nausea, whereas lesions disrupting vestibular connections in the central nervous system can produce nystagmus in any direction but are usually not associated with vertiginous or nauseous sensations. When characterizing nystagmus, only the fast component should be described. The complaint of dizziness in older adults is not uncommon; however, the examiner must determine whether the dizzy patient is experiencing light-headedness or true vertigo. If true vertigo is present, then the clinician should further discern whether it is peripheral (vestibular) or central (brainstem) in origin as well as associated features (**Table 11-10**). Causes of vertigo associated with vestibular disease include benign positional vertigo, Ménière syndrome, and trauma.

TABLE 11-10 CAUSES OF VERTIGO AND ASSOCIATED FINDINGS

ANATOMIC LOCATIONS	CAUSES	OTOSCOPIC EXAMINATION	OTHER NEUROLOGIC FINDINGS	TESTS OF EQUILIBRIUM	NYSTAGMUS	HEARING LOSS
Labyrinth	Benign positional, trauma, Ménière, drug toxicity, viral infection	Usually negative	None	Ipsilateral past pointing, lateral pulsion to side of lesion	Horizontal or rotary to side opposite lesion, paroxysmal, positional	May be normal, sensorineural or conduction deafness
Vestibular	Vestibular neuronopathy, herpes zoster	Zoster vesicles in auditory canal, tympanic membrane, and palate	7th and 8th cranial nerves	Ipsilateral past pointing, lateral pulsion to side of lesion	Positional	Sensorineural
Cerebellopontine angle tumor	Acoustic neuroma, meningioma, glioma, glomus jugulare	Normal	Ipsilateral 5th, 7th, 9th, and 10th cranial nerves, ataxia, increased intracranial pressure	Ataxia	Gaze paretic, positional, coarser to side of lesion	Sensorineural
Brainstem and cerebellar lesions	Infarct, gliomas, encephalitis	Negative	Multiple cranial nerves, sensory or motor tract signs, ataxia, dysmetria	Ataxia	Horizontal and/or vertical, gaze paretic	Normal
Cortical lesions	Infarct, glioma, trauma	Negative	Fluent aphasia, visual field cuts, hemimotor/sensory findings, seizures	Usually no change, mild ataxia	Usually absent	Normal

Cranial nerves IX and X: glossopharyngeal and vagus The ninth and tenth cranial nerves control pharyngeal and

laryngeal function, taste, and the gag reflex. Glossopharyngeal lesions cause asymmetric elevation of the palate and deviation of the uvula. Hoarseness, aphonia, and dysphagia occur with vagus nerve lesions. In normal aging, the gag reflex can be reduced and, when accompanied by a decrease in the cough reflex, can result in difficulty handling bronchial secretions. Glossopharyngeal neuralgia is a rare paroxysmal pain syndrome involving the posterior pharynx or tonsils usually triggered by excessively hot or cold foods or liquids.

Cranial nerve XI: accessory nerve The spinal accessory nerve innervates the upper half of the trapezius and the sternocleidomastoid muscle. In normal older adults, frank weakness of the trapezius or sternocleidomastoid muscle is not a typical finding and, if present, should be investigated further. A delayed shrug may be an indication of a mild ipsilateral hemiparesis.

Cranial nerve XII: hypoglossal The hypoglossal nerve innervates the tongue. Patients are asked to stick their tongue out; deviation to either side implies a lesion on the side of deviation. The tongue should also be examined for atrophy and spontaneous muscle contractions (fasciculation) suggesting upper motor neuron disease. Fasciculation is best detected on the lateral aspects of the tongue. Tongue weakness is also common in pseudobulbar palsy.

Motor System Examination

Muscle bulk, strength, tone, and coordination are assessed as part of the motor system examination.

Muscle bulk Muscle bulk is examined by visual inspection and palpation. Muscle wasting may occur with disuse; muscle, nerve, or spinal disease; and in generalized weight loss secondary to malnutrition, systemic illness, or advanced brain diseases. Mild muscular wasting without associated weakness can be encountered in normal aging most commonly involving the intrinsic hand and foot muscles, calf and shoulder girdle muscles.

Muscle tone Muscle tone may be increased or decreased in neurologic disorders. Muscle tone is decreased in muscle and peripheral nerve disease, with cerebellar disorders, early in the course of many choreiform disorders, and acutely following an upper motor neuron lesion. Increased muscle tone is encountered in spasticity with pyramidal tract lesions and rigidity with extrapyramidal disorders. Cogwheel rigidity of Parkinson disease is best palpated when manipulating the distal limbs, usually in a circular motion. “Gegenhalten” refers to the active resistance to movement encountered in advanced brain diseases.

Strength Strength is graded as 0 (no evidence of muscle contraction), 1 (muscle contraction without movement of the limb), 2 (limb movement after gravity eliminated), 3 (limb movement against gravity), 4 (limb movement against partial resistance), or 5 (normal strength). Distal weakness is most indicative of peripheral neuropathies, whereas proximal weakness is more consistent with primary muscle disease. In aging, mild generalized weakness may occur; however, focal weakness is indicative of a neuropathologic process. Focal weakness often is subtle and may be detected only with careful examination. Hemiparesis occurs with lesions of the pyramidal system. When testing strength, the examiner should attempt to isolate individual muscles (thumb abduction) rather than testing whole groups (hand grip) to detect subtle signs of weakness. A pronator drift is seen with mild forms of weakness.

Abnormal movements During the interview and examination, the clinician should be observant for any movement that is not purposeful including tremor, chorea, dyskinesias, and ballismus. Tremor is usually described as action (associated with a movement) or rest (disappears with movement of affected extremities). “Essential” tremor is a usually benign hereditary condition associated with movement or sustained posture and may involve arms, legs, head, chin, or voice. Essential tremors often improve after drinking small amounts of alcohol.

Sensory Examination

Primary modalities, including light touch and temperature are tested to assess sensory function. Sensory examination is quite subjective and it is important to consider the consistency of responses and how sensory complaints relate to other signs and symptoms. Peripheral causes of sensory loss typically present bilaterally and are largely symmetric. Unilateral sensory loss occurs with lesions of primary sensory cortex or its projections.

Light touch Evaluation of light touch is not particularly helpful in discriminating pathology but is useful in defining the presence or loss of sensation. Lightly stroking the fingers or a wisp of cotton across the skin may help elicit dermatomal patterns of sensory loss for further evaluation.

Pain and temperature Pain and temperature sensation is carried by small unmyelinated fibers. Pain can be assessed

with the use of a disposable safety pin while temperature can be assessed with the handle of the reflex hammer or tuning fork. The loss of pain sensation due to a metabolic or toxic peripheral neuropathy typically follows a stocking glove pattern, while lesions due to a radiculopathy follow a defined dermatome.

Vibration Vibration is carried by large myelinated fibers and is assessed with a 128-Hz tuning fork. The tuning fork should be struck and placed on a bony prominence. Causes of pathologic decreased vibratory sensation include peripheral neuropathies, diabetes, tabes dorsalis, vitamin B_{12} deficiency, and myelopathies.

Position Proprioception is assessed by having the patient close their eyes and the examiner gently moves toes or fingers in the vertical plane. Skin proprioception can be assessed by lightly stroking the skin in an up or down fashion. The Romberg sign is performed to assess the integrity of the dorsal columns. The patient is asked to stand with their feet together and eyes closed. The presence of a sway suggests a positive test. If the problem is due to a proprioceptive deficit, the patient is able to correct themselves with their eyes open. Position sense loss can be caused by peripheral neuropathies, diabetes, tabes dorsalis, vitamin B_{12} deficiency, and myelopathies.

Cerebellar Examination

Cerebellar function and coordination may be disrupted by many types of motor and sensory abnormalities. Tests of coordination include rapid alternating movements, fine finger movements, finger-to-nose movements, and heel-knee-shin maneuvers. During aging, there is an overall decrease in speed of coordinated movements that is of no pathologic consequence. However, gross abnormalities in cerebellar function are not anticipated and should be evaluated thoroughly (**Table 11-11**).

TABLE 11-11 ELEMENTS OF ATAXIA AND CEREBELLAR DYSFUNCTION

SIGN	DESCRIPTION
Dysmetria	Overshooting or undershooting a target
Dysdiadochokinesia	Impairment in rapid-alternating movements
Tremor	Coarse, rhythmic movement on action
Ataxic speech	Abnormal variability of volume, rate, and phonation
Dysarthria	Slow and slurred speech
Gait ataxia	Wide-based, unsteady

When unilateral cerebellar dysfunction is present, patient will overshoot target but may improve after a few trials. Dysdiadochokinesis occurs when the patient is asked to rapidly change hand or finger movements; difficulties in maintaining smooth movements are characteristic. Cerebellar lesions can also affect muscle tone causing hypotonia. Cerebellar tremors tend to be coarse and irregular, worsening in the terminal one-third of a movement.

Gait and Station

Gate and posture depend on motor, sensory, and cerebellar function. In normal aging, posture becomes more flexed, slowed, and may have a slightly unsteady quality. When assessing gait in the older adult, it is important to recognize gait abnormalities that may be secondary to joint pain and arthritic conditions. Gait is assessed by having the patient walk straight for at least 10 yd, making a turn and maneuvering in a tight corridor. It is important to note the presence of arm swing and the distance of the stride. The patient should also be asked to tandem walk, walk on their toes and heels and if possible walk up a few steps. Postural stability is assessed by asking the patient to stand with their shoulder-width apart. A forceful pull is given to their shoulders and the righting response is assessed. The clinician should be prepared to catch the patient. One or two steps of retropulsion are considered normal. **Table 11-12** lists common causes of gait disturbance in the older adult.

TABLE 11-12 GAIT ABNORMALITIES IN THE OLDER ADULT

GAIT	CAUSE	DESCRIPTION	ASSOCIATED SIGNS
Festinating	Parkinson disease	Slow, shuffling picks up speed and	Postural instability, rest tremor,

		may require wall or furniture to stop	bradykinesia, decreased arm swing, masked face, rigidity
Antalgic	Joint pain	Slow, gingerly pace	Facial grimaces
Spastic	Stroke	Stiff extremity, may require circumduction or scissor movements	Scuffing toe of affected leg across ground, weakness
Ataxic	Cerebellar disease	Wide-based	Dysmetria, dysdiadochokinesis
Sensory ataxia	Peripheral neuropathy	Wide-based, high steps with foot slapping	Sensory loss, weakness
Apraxic	Normal pressure hydrocephalus	Feet appear “nailed” to floor, lower extremity bradykinesia	Dementia, urinary incontinence
Stooped	Lumbar stenosis	Forward flexion	Pain, lordosis, kyphoscoliosis
Myopathic	Proximal myopathy, myasthenia gravis	Uses arms to help push themselves up stairs or out of a chair (Gowers sign)	Muscle cramps, weakness, myoglobinuria
Astasia-abasia	Psychosis, malingering	Wildly lurching, “herky-jerky” movements, however patient does not fall	Signs of intoxication, delusions, hallucinations, secondary gain.

Muscle Stretch Reflexes

Decreased muscle stretch reflexes are found in muscle, peripheral nerve, and nerve root disorders, while increased reflexes occur with upper motor neuron lesions. Lateralized hyperactive reflexes in conjunction with spasticity and the Babinski sign are indicative of a contralateral lesion of the pyramidal system. In aging, deep tendon reflexes tend to become hypoactive. Ankle reflexes may be absent in normal aging, but knee reflexes persist. Reflexes are initially hyperactive in cervical and lumbar spondylosis; however in advanced cases, absent or diminished reflexes may be found as nerve roots become compromised.

Pathologic and Primitive Reflexes

The Babinski sign is dorsiflexion of the great toe with plantar stimulation. It is produced by upper motor neuron lesions. The grasp reflex (involuntary gripping of objects in or near the patient’s hand) occurs in patients with advanced brain disease and with lesions restricted to the medial frontal lobes. The sucking reflex (sucking movements of the lips, tongue, and jaw elicited by stimulation of the lips) occurs in patients with frontal lobe and diffuse brain dysfunction.

The palmomental reflex (ipsilateral contraction of the mentalis muscle in response to stroking of the thenar eminence of the hand) can be seen in normal-aged individuals and may be regarded as pathologic when it is unilateral or when it does not fatigue with repeated palmar stimulation. The glabellar reflex (Myerson sign) is elicited by tapping the patient between the eyes. After a few blinks the patient should suppress further blinking. Patients with Parkinson disease and other basal ganglia disorders will continue to blink.

Higher Cortical Function

Cortical sensory modalities, including two-point discrimination, graphesthesia, and stereognosis should be assessed. Two-point discrimination is best performed with calipers. Graphesthesia is performed with the patients eyes closed and numbers are traced onto the palm with the back of the reflex hammer. Stereognosis is also performed with the patients eyes closed. Common objects are placed into the patients’ hand and they are allowed to move them about without using the other hand. Deficits imply dysfunction in the contralateral parietal lobe. Cortical sensory function should be assessed independently for each upper extremity. It is important to first assess primary sensory modalities. In the presence of prominent sensory loss, cortical sensory function cannot be assessed.

Neurovascular Assessment

Examination of vascular system, including auscultation for cranial and carotid bruits, palpation of peripheral pulses, and assessment of blood pressure (lying, sitting, and standing) complements the neurologic examination and should be performed on every patient.

CONCLUSION

A variety of neurologic disorders (eg, stroke, Parkinson disease, Alzheimer disease) preferentially present in older adults. A comprehensive mental status and neurologic examination should be performed in every patient to document changes in neurologic function (ie, memory/cognition, behavior/personality, cranial nerves, motor function, and sensory perception) associated with pathologic conditions that affect the nervous system, and distinguish them from the functional changes associated with normal aging. Limited memory and cognitive function changes occur as one age. Subtle changes in memory that do not interfere with normal functioning in society and that do not impair activities of daily living occur in normal aging. More significant declines in memory and cognitive function can be encountered in dementia (**Table 11-13**).

TABLE 11-13 DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Neurodegenerative Disease
Alzheimer disease
Dementia with Lewy bodies/Parkinson disease
Frontotemporal dementia
Huntington disease
Progressive supranuclear palsy
Corticobasal degeneration
Creutzfeldt-Jakob and other prion diseases
Wilson disease
Neuronal ceroid lipofuscinosis
Vascular Disease
Vascular dementia
Cerebral amyloid angiopathy
CADASIL
Vasculitis
Hydrocephalus
Demyelinating Disorders
Multiple sclerosis
Leukodystrophies
Traumatic Brain Injury
Metabolic Disorders
Hepatic encephalopathy
Hypothyroidism
Storage disorders
Electrolyte disorders (sodium, calcium)
Nutritional Disorders
B_{12} deficiency
Wernicke-Korsakoff syndrome (thiamine)
Mitochondrial Disorders
Toxic Disorders
Alcoholism
Drugs
Heavy metals

Neoplasia
Primary brain tumors (meningiomas, gliomas)
Metastatic disease
Paraneoplastic syndromes
Infection
HIV
Neurosyphilis
Progressive multifocal leukoencephalopathy
Subacute sclerosing panencephalitis
Whipple disease
Epilepsy

Altered cognitive function in the setting of a clear sensorium is consistent with dementia secondary to a neurodegenerative process or medical illness. Dementias (eg, Alzheimer disease, frontotemporal dementias, dementia with Lewy bodies) are characterized by a specific constellation of signs and symptoms. In Alzheimer disease the individual typically exhibits limited insight into their cognitive deficits that involve memory, language, and visuospatial skills. Patients with frontotemporal dementias present with a predominance of features consistent with frontal and/or temporal degeneration. These individuals exhibit early changes in behavior and personality, such as social inappropriateness, disinhibition, apathy, perseveration, and oral/dietary changes. Other accompanying features may include language/speech impairment, executive dysfunction, and preserved posterior functions (eg, visuospatial ability, calculations). In dementia with Lewy bodies, patients may exhibit fluctuating cognition, recurrent well-formed and detailed visual hallucinations, and extrapyramidal signs consistent with parkinsonism. Dementia can occur as a consequence of other neurologic and medical illnesses such as cerebrovascular disease, vitamin B_{12} deficiency, hypothyroidism, Parkinson disease, and meningoencephalitis.

Delirium on the other hand causes alteration in sensorium and level of consciousness and is usually due to medications (**Table 11-14**), infection, head injury, or metabolic derangements. Associated features include disruption of sleep-wake cycle, intermittent drowsiness and agitation, restlessness, emotional lability, and frank psychosis (hallucination, illusions, delusions). Symptoms of delirium are often worse at night and occur in up to 20% of hospitalized patients. The risk increases in the older adult and the longer the hospital stay. Predisposing factors include advanced age, dementia, impaired physical or mental health, sensory deprivation (poor vision or hearing), and placement in intensive care units.

TABLE 11-14 EXAMPLES OF MEDICATIONS CAUSING DELIRIUM IN THE OLDER ADULT

α-Methyldopa
Amantidine
Anticholinergics
Antihistamines
Antipsychotics
Atropine
Barbiturates
Benzodiazepines
Bromides
Chlordiazepoxide
Chloral hydrate
Cimetidine and other H_2 blockers
Clonidine
Codeine and other opioids
Cocaine

Dextromethorphan
Digoxin
Dopamine agonists
Dopamine antagonists
Ethanol
Furosemide
Lithium
Levodopa
Nifedipine
Opioids
Phencyclidine (PCP)
Phenytoin
Prednisone and other steroids
Propanolol
Reserpine
Theophylline
Tricyclic antidepressants

A functional decline in some aspects of cranial nerve function (eg, vision, hearing, vestibular function, taste, and smell) can be anticipated in normal aging and should be distinguished from pathologic conditions afflicting the nervous system. Similarly, older individuals experience decreased mobility as they age. Subtle changes in gait, posture, coordination, and strength are expected concomitants of aging. However, more profound changes that significantly alter mobility and/or present as focal weakness or impaired coordination should alert the clinician to the possibility of a neuropathologic disorder.

Alterations in sensory perception can be indicative of neuropsychiatric dysfunction. Subtle deficits in vibration and other primary sensory modalities may be encountered in normal aging. However, marked deficits in sensory function are suggestive of neurologic disease and require further diagnostic testing.

In conclusion, neurologic findings of normal aging include subtle declines in cognitive function, mildly impaired motor function, and altered sensory perceptions. However, exaggerated impairments in cognitive, behavioral, motor, and sensory function suggest the onset of neurologic diseases that commonly afflict the older adult. A comprehensive mental status and neurologic examination is the foundation for identifying neuropathologic conditions that necessitate further laboratory and imaging investigation.

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Chapter 12

Assessment of Decisional Capacity and Competencies

Margaret A. Drickamer

Learning Objectives

- To review the elements of decisional capacity
- To describe ways to determine capacity
- To understand special instances where knowledge of decisional capacity should be applied

Key Clinical Points

1. **There are four necessary elements to making a capable decision: understanding, appreciation, reasoning, and expressing a choice.**
2. **Critical cortical functions involved in decision making include immediate memory, language, and executive function.**
3. **Decisional incapacity is task-specific and may be time-limited. Therefore, decision-making capacity may fall along a spectrum and the ability of an individual to make decisions often needs to be thought of in flexible terms.**
4. **An assent-consent model of surrogate decision making is key to decision making in patients who retain the ability to participate in decisions but do not have full decision-making capacity.**

INTRODUCTION

Assessing a patient's capacity to make decisions is a role with which all clinicians should be familiar. Although certain situations may call for specialized assessment, generalists, family physicians, internists, subspecialists, geriatricians, and advanced practice nurses, among other health professionals, should be sufficiently familiar with the principles and process to manage most situations. The purpose of this chapter is to explain some of the ethical underpinnings to this responsibility, to highlight the strengths and weaknesses of approaches to assessing decisional capacity, and to describe the role of the clinician in decision making.

Autonomy is defined as self-determination (see also Chapter 61). Respect for individual autonomy is understood to be an elemental principle of our society. Nonetheless, all of us face limitations on how much we can truly determine our fates. Limitations of resources and opportunity, societal and legal prohibitions, and the limits imposed by the rights of others not to have their autonomy infringed upon all limit one's self-determination. There are also limitations on who qualifies as an autonomous "self." The full right to self-determination is generally recognized to apply only to adults who are "of sound mind."

Paternalism is defined as limiting an individual's autonomy in order either to prevent that individual from doing harm to themselves or to prevent the person from missing a substantial benefit. The circumstances under which paternalism is acceptable are not defined by the action the individual may wish to undertake, or by the probable untoward consequences of an action, but rather by the individual's ability to make decisions. In other words, our wish to protect an individual from doing themselves harm does not justify paternalism; we cannot prevent an individual

from doing things that may cause them harm (drinking, sky diving, etc). We can only justify intervention if we judge that an individual lacks the capacity to make decisions. In such a case, we are responsible for protecting the person from the possible harm of an incapable decision.

The interplay between these concepts becomes apparent when the person is no longer felt to be "of sound mind." This chapter will focus on those individuals who have cognitive impairment or a clouded sensorium (fixed lesions, dementia, or delirium) and will not discuss the competence of individuals whose decisional capacity may be impaired by psychiatric illness. When patients are cognitively impaired, clinicians have an obligation to respect their rights, to protect their persons, and to consider the safety of the public. This often requires careful balancing of conflicting imperatives.

ELEMENTS OF DECISIONAL CAPACITY

In the broadest sense of the word, for an individual to be competent, that individual must be well qualified to do whatever task they are doing. In the context in which we are talking, competence is often viewed as a legal term. It refers to a judge's ruling as to whether an individual has been deemed competent to make their own decisions. An individual adjudicated to be incompetent must have a guardian appointed to make the decisions for the area (or areas) in which the person has been found to be incompetent. Although guidelines vary somewhat from state to state, it is generally accepted that a ruling of incompetence cannot be made solely on the basis of a medical diagnosis, age, level of education, or personal eccentricity. An adjudication of competence or incompetence is based on an assessment of the individual's decisional capacity and that individual's demonstrated ability or inability to carry out a plan. Therefore, the assessment of decisional capacity should include not just the patient's cognitive ability, but other factors that may be influencing the process of making a capable decision (**Figure 12-1**).

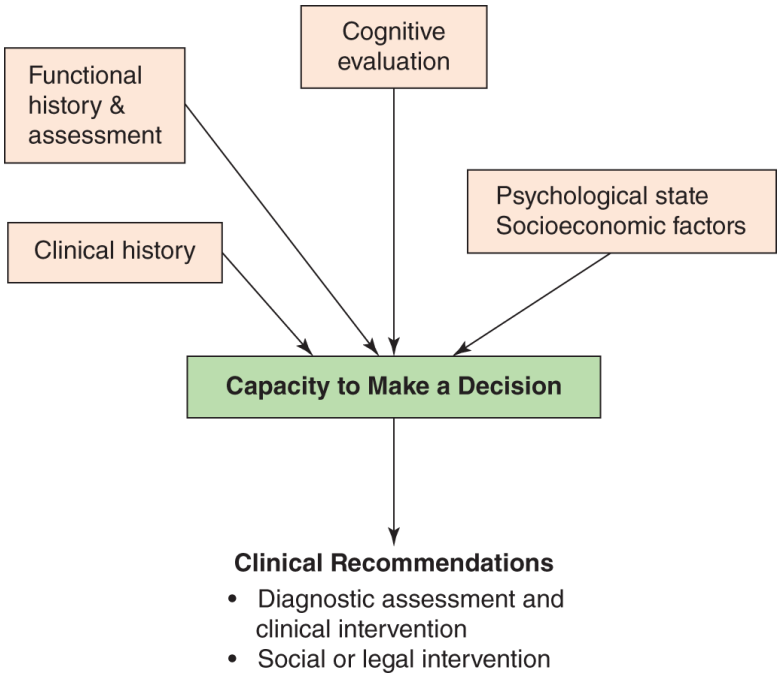


FIGURE 12-1. Components included in assessment of decisional capacity.

There are four necessary elements to making a capable decision: understanding, appreciation, reasoning, and expressing a choice (**Table 12-1**). First, the individual must be able to comprehend the information being considered sufficiently well to understand the important or relevant facts. That information must have been presented in a clear and concise manner with special attention taken to ensure that barriers such as hearing impairment, illiteracy, or language difference do not constitute the sole reasons that the person is unable to understand the information. Other issues, such as aphasia, delirium, or depression, may also interfere with the individual's ability to comprehend and retain information.

TABLE 12-1 FOUR ELEMENTS THAT CONSTITUTE DECISION-MAKING ABILITIES

ABILITY	DESCRIPTION
Understanding	1. Comprehension of appropriately communicated information 2. Retention of information long enough to be able to recall it in discussion 3. Perception of the relationship between interventions and outcomes
Appreciation	1. Recognition of how the information relates to his or her own circumstances 2. Insight into the advantages and disadvantages of a proposed solution
Reasoning	1. Manipulation of information to generate comparisons between different alternatives and their consequences 2. Justification of a rationale as a context for making these comparisons
Expressing a choice	Articulation of a clear choice with regard to a specific decision

Second, the individual must have the conceptual ability to appreciate the consequences of the decision that he or she is making. This includes both an appreciation of the risks and benefits of options and the ability to identify the consequences these risks and benefits will have on his or her life. Beginning and ending a discussion by asking the individual what their understanding of the situation is and what the consequences are of the choice that they have made is an important method of assuring that they were able to comprehend the information and that they appreciate the consequences of the decision they are making. There is some evidence that the more fully an individual understands the information provided the less likely they are to accept treatments. This is particularly true for decisions which affect quality of life. Conversely, there is evidence that the more potentially fatal the situation is, the more paternalistic they wish their physicians to be.

The individual must be able to reason, within their own frame of reference, why she or he is choosing a course of action. This is different than saying that a decision seems “reasonable” or “rational,” but rather it refers to the cognitive processing of values and beliefs in view of the information given. Judging the rationality of a decision can be tricky. Even if we feel—and even if most of society would feel—that an individual’s decision is irrational, it does not give us grounds to negate the person’s right to self-determination. Our society has a great respect for individuality and one’s right to express that individuality in a wide variety of ways. Nonetheless, an individual’s ability to give a plausible rationale for his or her decision is sometimes used as secondary evidence of decisional capacity. That is, demonstrating justification for one’s choices (eg, religious belief, personal value, etc) provides another level of assurance that the patient’s decision rests on intact reasoning, rather than a set of delusional or incoherent beliefs that may often exist in the setting of cognitive impairment or psychiatric illness. Physicians, and geriatricians in particular, have been shown to demonstrate judgement of decisional capacity that correlates well with tools that look at the rational process of decision making, but are much less capable of judging capacity when utilizing a value-based model.

Finally, the person must be able to make a choice and communicate the decision. This is the lowest bar for decision-making capacity but one which may be impaired by specific damage in language or frontal lobe function as well as in severe global cognitive impairment.

One other consideration is sometimes used in judging an individual’s decisional capacity: consistency of the person’s decision. The inconsistency of an individual’s decision with past decisions made by that person provides an important clue to possible underlying cognitive or psychiatric problems that deserve exploration. But, in itself, inconsistency does not negate the person’s right to make decisions. Inconsistency of a specific decision over time may indicate that the individual has had difficulty with remembering or understanding the information provided.

LEGAL AND PRACTICAL ASPECTS IN DETERMINING DECISIONAL CAPACITY

In protecting an individual who is incapable of making decisions, one action that may need to be taken is the application to a local probate court to ask that the individual be adjudicated to be incompetent and to have someone else appointed to make decisions. Although specifics of probate statutes vary among states, most follow a general pattern articulated in the Uniform Probate Code. Once an individual has been adjudicated incompetent, another person is appointed to represent his or her interests. This person is variably referred to as a guardian, conservator, or legal surrogate. We will use the term conservator. Although there are movements toward “limited conservatorship” that restrict the powers of the conservator to decision making in more specific areas where a person has been shown to be incapable, there are two broad categories of conservatorship that are commonly used, those of finance and of person.

Conservatorship of finance is a fairly self-evident term. Conservatorship of person grants a more global responsibility for assuring that the individual is kept safe and that decisions are made either as substituted judgment or on the basis of the individual's best interests (see Chapter 61). These decisions may involve, for example, medical care, where a person will live or what help the person will receive to maintain himself or herself. The person may retain the ability to make a will (testamentary competence), even when he or she has been adjudicated as incompetent of person and finance.

It should be emphasized that not all incapacitated individuals need to be conserved. There are no statistics available to say how many incapacitated individuals have informal care management by relatives and never require probate action. Personal experience would lead us to believe that most adults with cognitive deficits fall into this category. Probate adjudication of a conservator may not be needed if financial management has been allocated to a family member by a power of attorney prior to the individual becoming incapacitated, and if there is a general agreement among concerned and interested parties that decisions should be made either by a specific individual or group consensus. If the individual involved has granted someone a durable power of attorney for health affairs (see Chapter 61), there may not be a need for court action. A general power of attorney can cover multiple different areas of financial and personal decisions. Turning to a court will prove unnecessary even when interested parties disagree, provided they are willing to respect the individual's appointment of a surrogate decision maker.

Even when the court has been asked to take action, 75% to 85% of the time the court appoints a family member as conservator. The ability of an appointed conservator to act as an appropriate surrogate varies considerably. One advantage of having a court-appointed conservator is that the probate court has some oversight responsibilities for the management of the individual's affairs. Oversight by a judge may prove beneficial to individuals who might otherwise not be scrupulous about managing an incapacitated individual's funds. A judge who does not wish to choose a family member as conservator may appoint an individual from the community, an attorney, a social worker, or an agency to fill that role.

Although courts adjudicate the ability to make decisions as an all-or-nothing phenomenon, a person's ability to make decisions falls on a continuum ranging from complete capability to total incapacity. Furthermore, not only ability, but also circumstance, influences the need for intervention. For instance, a person's ability to capably manage financial affairs will be influenced by the size and complexity of the finances requiring management. If the need for complex medical decision making does not arise, then the ability of an individual to make those types of decisions is not questioned. If the individual is in a situation where others are managing household affairs and looking out for the person's needs, then the person's ability to care for self may not be examined. It is only when a problem arises that the individual's ability to make these types of decisions becomes an issue. Also, as mentioned above, even if the patient is incapable and others need to make decisions, this can often be handled without court participation.

Anticipatory legal measures, enacted in the course of patient care prior to episodes of incapacity, may negate the need to involve the court system. For example, a "springing" durable power of attorney may be drafted to designate a chosen person to have legal authority over financial matters at some time or event in the future when the patient is deemed unable to perform those actions. Other legal planning methods, such as designation of a conservator in advance of need or in vivo trusts, may also be useful mechanisms for securing appropriate surrogate decision makers for persons who may anticipate future incapacity.

PROCESS OF DETERMINING CAPACITY

The individual's inability to make decisions is determined in two different ways. Specific testing can measure cognitive dysfunction, and observing the person's decision-making process can demonstrate his or her inability to complete the decision-making task capably. In order to understand and apply both of these methods, one needs to understand the cognitive processes involved in decisional capacity. These processes can be understood both as discrete neuropsychiatric functions and as contributors to the holistic process of making decisions.

The brain functions that contribute to decision making are centered in the cortex and frontal lobes. Cortical (parietal and temporal lobe) functions involved in decision making include immediate memory and language. Immediate memory is defined as the ability to remember rehearsed or consolidated materials for 30 seconds to 30 minutes (eg, first repeating three objects then recalling them in 5 min). Immediate memory is clearly important in the individual's ability to participate in a discussion around a specific decision. Cortical language abilities are those that affect comprehension and the ability to produce the intended words when expressing one's thoughts in both spoken and written communication. The ability to understand language is highly correlated with an individual's ability to

comprehend the information needed to make a decision. Problems with expressive language ability from cortical lesions can lead to statements by the individual that misrepresent his or her thoughts (ie, through misuse of words, word substitutions, or paraphasic errors). The ability to understand and manipulate numbers may also be affected.

Frontal lobe functions involved in the process of making capable decisions include the abilities to concentrate, express oneself, use abstract reasoning, initiate actions, solve problems, monitor one's behavior, and use judgment. The frontal lobe is responsible for filtering out both internal and external stimuli that interfere with the individual's ability to concentrate and to understand instructions or explanations. Frontal lobe dysfunction can lead to inattention that interferes with the ability to complete necessary tasks appropriately. The intrusion of internal stimuli can lead to inappropriate and impulsive behaviors that can interfere with the individual's functioning and decision making.

Traditional Mental Status Tools

Tools commonly used for the assessment of cognition in patients serve as important triggers to further investigation of the individual's decisional capacity. Looking at performance on individual items and extrapolating to predict how performance will affect the processes necessary for decision making help the clinician to evaluate a patient. No single cut-off score on any of these tests will divide those capable of making a decision from those not capable. This is particularly true because different types of decisions require different skills. These tests also do not look at the patient's actual function. On the other hand, a score may signal a level of such diminished cognitive abilities that it is highly unlikely that persons with that score will be capable of making decisions. Looking at individual items on these tests and having knowledge of how the cognitive function tested may influence the individual's ability to make decisions is useful.

Tests of primarily cortical function, such as the Mini-Mental State Examination (MMSE) may show deficits in immediate memory, attention, rudimentary language, and simple praxis. A score of 10 or less indicates such impairment that retaining decisional capacity is unlikely.

Testing of frontal lobe or executive functioning is of great importance in assessing decisional capacity. The Executive Interview (EXIT) examination and clock drawing look primarily at executive function, although frontal lobe abilities are tested in the St Louis University Mental Status Test and the Montreal Cognitive Assessment. The EXIT 25 has been shown to have the best correlation with subjective measures of competency of any neuropsychological test. An overall score of 15 or above on the EXIT indicates very significant impairment. Again, recognizing errors on individual items and the correlative cognitive dysfunctions will be important in assessing less grossly impaired cases. Functions that may be most reflective of problems with decisional capacity include poor insight, impulsivity, poor self-monitoring, and impaired ability to plan and follow-through on the plan. Although individual items of these tests do not correlate directly with each of these functions, observing the individual as he or she does the test with these functions in mind can clarify areas of deficiency. For example, when the individual makes an obvious error, does he or she realize it and go back and correct the mistake? Is the person able to plan how to draw the face of a clock? If the person draws a clock face that is too small, does he or she notice this and correct it? Does the concrete stimulus of the numbers interfere with the abstraction of how the hands indicate time?

There are more complex neuropsychological tests that can be done to test the same areas of function in more detail. These are not practical in the clinical setting, and the clinician should refer the patient to a neuropsychologist if there is any question of the nature or severity of neuropsychological deficits.

Tests of Decisional Capacity

There are tests that are specifically designed to assess an individual's capacity for making medical decisions. These tests may utilize hypothetical vignettes to demonstrate whether the individual is capable of the four elements of decision making, namely, understanding the vignette (usually written at a sixth-grade level), appreciation of the issues and the potential options involved in solving this issue, being able to reason with the material, and then being capable of verbalizing an opinion. Two examples of such tests are the Assessment of Capacity to Consent to Treatment (ACCT) instrument in which the individual must read a series of case vignettes and then consider their responses and the MacArthur Competence Assessment Tool-Treatment (MacCAT-T), which is an example of a structured interview that allows the clinician to test the individual's ability to make a specific medical decision. The MacCAT-T focuses on an individual's ability to make a specific, real-time decision and how that patient uses their understanding and reasoning. The ACCT also measures the individual's values and emotions, including their trust of the physician, as well as reasoning. These tests are difficult to apply in everyday clinical practice.

Voluntarism, Coercion, and the Context of the Decision Making

Implicit in judging decisional capacity is that one is judging the person's ability to give informed consent. The most extreme example of coercion and lack of voluntarism were addressed by the Nuremberg code of ethics stating that individuals involved "should [have] the power of choice without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion."

The legal definition of voluntarism is when there is no evidence that the individual was "unduly" influenced by shared values, inducements, persuasion, or force. Clinicians may be required to judge whether they feel that there is coercion, for example in the Oregon Death with Dignity Act. This is obviously a difficult judgement and eliciting information which might help make this judgement is difficult. Asking an individual *why* they are making the decision that they can help to clarify inducements, but the problem of "undue" influence is still a judgement.

More psychologically based influences on decision making include emotional distress, life history, pain and suffering, genuineness, coherence with other life decisions, and experiences of power relationships. Any of these may influence a person in the moment of decision making in ways that can change their decision. Their choice might be different if these issues were to be directly addressed.

Of profound importance is the context of and quality of the interaction during the decision-making process (**Figure 12-2**). Such aspects of this interaction include trust, cultural competence, information quality, provider competence, and the quality of communication. These have a great effect on the individual's ability to understand and appreciate the personal impact of information before they can to rationalize within their own personal and cultural context and come to a decision. For medical decision making there is often a feeling of subtle or sometimes blatant coercion for a specific decision felt to be most appropriate by the medical personnel. There can be feelings of mistrust and poor-quality communication that lead to misunderstandings and thereby create an impasse in the decision-making process.

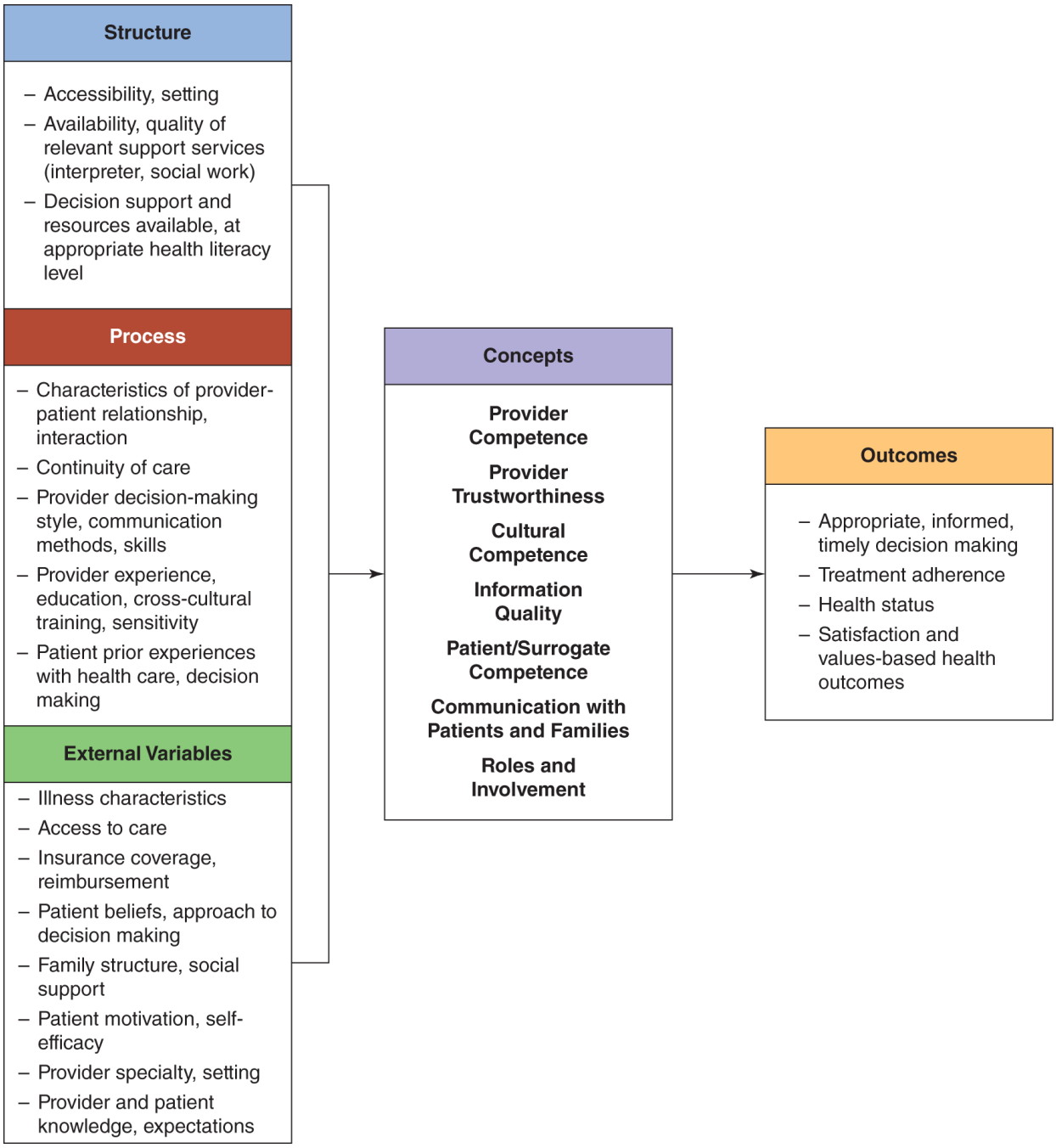


FIGURE 12-2. Quality of interaction affecting voluntarism of decisions. (From Dy SM, Tanjala SP. Key concepts relevant to quality of complex and shared decision-making in health care: a literature review. *Soc Sci Med.* 2012;74:582–587.)

CAPACITY TO MAKE SPECIFIC DECISIONS

Decisional incapacity is task-specific and may be time-limited. Although one may be adjudicated to be either incompetent or competent in the two broad legal categories of person and finance, the ability of an individual to make decisions or at least to participate in decisions needs to be thought of in more flexible terms. We will discuss incapacity in matters of person (medical decisions and ability for self-care), finance, wills, advance directives, and research.

Medical Decisions

Because patients have the right to decline medical interventions and they have the right to be informed before consenting to medical treatments, the need to make a medical decision frequently prompts the first assessment of

decisional capacity. This is often at a time when clinicians face pressure to make speedy judgments. For the patient facing these types of decisions, the neuropsychological functions of memory, language, and reasoning are the most crucial.

Documentation of a formal score for any test is not necessary in most cases when a patient faces medical decisions. A thoughtful interview with the patient and a written description of the areas in which the patient is unable to function is usually sufficient for this purpose, although learning structured observation will enhance the clinician's ability to assess capacity. It may be helpful to specifically comment on the individual's ability to understand the condition, the treatment alternatives (including no treatment), and their possible outcomes; demonstrate their appreciation of how they apply this information to their current situation; explain how their reasoning and values that have helped them form their thinking; and document their choice.

Problems of Self-Care

Formal assessments of decision-making ability may be necessary when a patient demonstrates an inability to care for self or to accept the help needed to remain safe in his or her present environment. Issues of cognitive impairment versus denial are difficult to sort through without formal testing. A person's tendency to be "eccentric" is not always easily distinguishable from dangerous behaviors stemming from increasing cognitive impairment and an inability to make decisions around self-care. Gross impairment of cortical functioning, especially short-term memory, can pose problems for day-to-day function. What is sometimes more subtle but of high impact is frontal lobe dysfunction. The inability to plan, initiate action, monitor one's behavior, and self-correct are essential to being able to care for oneself. A combination of findings on frontal lobe testing and demonstrated inability to care for oneself is often sufficient evidence for action, especially in combination with an inability to accept a level of care which would keep them safe. Alternatively, persons who demonstrate an inability to administer their own medications or safely prepare their own meals but who have accepted care, which will obviate these problems (eg, home care, Meals-on-Wheels), may be regarded as having intact decision making with respect to solving these functional deficits.

There are as yet no clinical tools specifically designed to assist clinicians in assessing a person's ability to make decisions related to self-care in the face of functional problems. A reasonable approach in this scenario, however, would involve a structured assessment where the patient must demonstrate an ability to understand and appreciate a known functional problem; understand and appreciate the practicality of potential options to solving this problem, as well as the risks and benefits of those options; describe the consequences associated with these options; choose an option; and, then explain how this choice is superior to the other options not chosen.

Problems of Finances

There are times when an individual remains able to make medical decisions and decisions related to self-care but is no longer capable of managing finances. When bills are going unpaid or gross mistakes are made in handling money, someone else will need to take over financial management. Specific tests for measuring the ability to calculate, to understand a checkbook, to monitor bank accounts, or a more formal financial management assessment, such as the Financial Capacity Inventory, can be administered by an occupational therapist or a neuropsychologist, but usually a demonstrated problem with this area is sufficient to warrant supervision. If the individual has enough insight to understand the problem and a reliable person is available to help, granting that person a power of attorney for finances should suffice. If the incapacitated person is reluctant to relinquish control, or court monitoring is deemed advisable, then the family, the clinician, or other concerned party should seek a conservator of finance.

OTHER ISSUES OF DECISIONAL CAPACTIY AND CONSENT

Legal Documents

The ability to make a last will and testament is felt to be retained even after the ability to handle finances and make decisions of person have been lost. An individual's ability to remember what he or she is doing with the estate and to express some logic behind choices is usually sufficient evidence of capability. Despite the risk of exploitation of an impaired person, the courts are usually very liberal in allowing someone to change a will, even when the person has cognitive problems.

In contrast, the ability to grant someone durable power of attorney for health affairs or to make a living will requires higher levels of cognitive function than does day-to-day decision making. Both of these areas deal with

hypothetical situations that can often be hard even for cognitively intact individuals to fully understand and conceptualize. The ACCT instrument may help to establish this ability, but is not practical for use in most clinical settings. At the very least, clinicians should question an individual's ability to fully understand the process if he or she has demonstrated problems with memory or language or has shown signs of frontal lobe dysfunction. The clinician must also recognize that even very cognitively impaired individuals may still be able to portray wishes and desires (see "Consent Versus Assent")

Temporary Loss of Decisional Capacity

Individuals may be transiently incapacitated for decision making or their ability to recover their cognition may not be known, such as when a patient is delirious or has suffered a recent stroke. In these situations, the clinician should seek an interim solution. An informal surrogate, the person granted durable power of attorney for health affairs, or a temporary conservator can make decisions while the clinician clarifies the prognosis for decisional capacity. The decisions needed during a time of uncertainty should follow the individual's prior wishes unless they are unknown and then treatment should fall on the side of aggressive protection of the individual's life or continued function until the person can make his or her wishes known or the permanence and extent of the impairment becomes clear.

Consent Versus Assent

Even when an individual is no longer able to give informed consent to a procedure or a change in living situation, he or she should still participate in the decision-making process. Substituted judgment is the process that a surrogate (legally appointed or informal) is supposed to apply as the basis on which a decision should be made. Substituted judgment enjoins one to take into account the patient's prior wishes and long-held beliefs as the basis for one's decision, "deciding as they would have decided" (see Chapter 61). Assent refers to the impaired individual's willingness to cooperate with a plan of care. It is, in essence, a way to take into consideration the individual's present desires when making a decision. Although it has been used primarily in the ethics and legal literature when looking at the role of adolescents in the process of medical decision making, the principles apply to impaired adults as well. In cognitively impaired adults, there is a continuum of incapacity, even among those who do not retain the full capacity to make decisions. An individual who is incapable of understanding the complexities of a situation or decision may retain high levels of understanding around specific aspects of the process and be able to express their opinions. Even very cognitively impaired patients can give indications of what brings them pleasure and what gives them pain. Clinicians and surrogates should consider this information in the decision-making process.

Clinicians trying to obtain consent for medical treatment or research protocols may wish to use a combination of surrogate consent and patient assent (shared decision making). This may be essential in some cases where the patient's ability to cooperate will be necessary in order to carry out the treatment or procedure. Even the courts are moving toward the recognition of the need for "limited conservatorship," which reflects that decisional capacity is not an all-or-nothing phenomenon. Decisional capacity is situation-dependent and can change with time.

Abuse or Neglect

Issues of abuse and neglect of older people are addressed elsewhere (see Chapter 54), but it is important to understand the interplay with one's ability to make decisions or consent to continuing to be in an unsafe environment. Disempowerment is inherent in the role of one who may need assistance and the belief that one has a choice in such situations may be beyond an individual's ability to understand or to appreciate the alternatives. Fear of reprisals or even placement in long-term care as well as loss of the only life that the person now comprehends, no matter how dysfunctional it is, can overwhelm the individual's capacity to weigh alternatives. Health care personnel are often the only outside element who can intervene and are often asked by protective services to help judge the person's ability to understand and consent to continue in an abusive or neglectful environment.

Informed Consent in Research

An individual's ability to consent to participate in research is also difficult to judge (**Table 12-2**). The understanding of the risks and benefits of being in a research study must be even greater than that for accepting or declining an established medical treatment. The risks and benefits are more theoretically based and therefore harder to make concrete to an individual who may be having difficulty with abstract thinking. This is an important time for dual decision making as outlined in the section above. It is also very important to establish the voluntarism of the consent.

Asking why an individual is volunteering (or a surrogate is volunteering the individual) for a research protocol may help clarify both their understanding of benefits to the individual and the voluntary nature of his or her decision.

TABLE 12-2 AGS GUIDELINES FOR RESEARCH USING COGNITIVELY IMPAIRED PERSONS AS SUBJECTS

The research must be justified on scientific, clinical, and ethical grounds but can be focused on conditions other than dementia itself.
The capacity to give consent should be assessed for each individual for each research protocol since decision-making capacity is task-specific and some cognitively impaired individuals will be able to give consent.
Advance consent to participate in research given prior to the loss of decisional capacity should, in general, be respected.
The traditional surrogates for decision making can be used to obtain consent.
Research protocols that involve more than minimal risk or do not have a likelihood of direct benefit for the subjects should be offered only to persons who are able to consent or who have an advance directive consenting to participate in research. Exceptions might be made for exceptionally promising treatments, but this should be reviewed at a national level.
Surrogates can refuse participation or withdraw the person from participation if the surrogate determines that the research protocol is not what the person intended to consent to or is not in the person's best interest, even if there is advance consent.
Only in very unusual circumstances would the refusal to participate by even an incapacitated patient be overridden.

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Chapter 13

Prevention and Screening

Sei J. Lee, Louise C. Walter

Learning Objectives

- Provide a framework for evaluating the benefit of preventive measures in older adults.
- Identify which populations benefit most from cancer screening.
- Review management strategies for asymptomatic chronic diseases.
- Identify health behaviors most beneficial for older adults.

Key Clinical Points

1. **Appropriate prevention strategies in older adults involve taking into account estimated life expectancy and time to benefit for a preventive intervention.**
2. **Person-centered approaches to prevention and screening require frank discussions of benefits and harms in the context of the patient's values and preferences.**

INTRODUCTION

Prevention and screening hold the promise of maintaining health by intervening before an illness can cause symptoms. Some preventive interventions, such as influenza vaccination, have truly minimal risks and public health benefits. However, many other interventions, such as cancer screening tests, impose risks and burdens on patients that should be considered when deciding whether to target those tests to individuals. For interventions with minimal risks, targeting is less important since many patients will benefit and few (or none) will be harmed. In contrast, for interventions with some risks or burdens, targeting is critical since some patients may be more likely to be harmed than helped by the preventive intervention.

In this chapter, we will present the evidence for several preventive interventions in older patients. First, we will focus on preventive interventions that impose some risks and burdens on patients, starting with a framework for targeting these preventive interventions and then focusing on the benefits and risks of each preventive intervention in greater detail. These interventions include cancer screening as well as treatment for asymptomatic chronic conditions such as hypertension or diabetes. Second, we will review the evidence for interventions with minimal risks. These interventions include behavioral and lifestyle modification as well as immunizations.

Screening for geriatric syndromes such as falls and incontinence are discussed in detail in their respective chapters.

FRAMEWORK FOR INDIVIDUALIZING PREVENTION

One challenge of appropriately targeting prevention in older adults is that few studies of preventive interventions have enrolled persons older than 75 years. The absence of age-specific data requires clinicians to extrapolate data about the benefits and harms of preventive interventions in younger persons and apply it to older persons. Furthermore, even if trials suggest that the effectiveness of a preventive intervention is similar in younger and older populations, challenges remain about how to apply data from trials to an individual older person. Trials show the average effectiveness of an

intervention, but they generally do not address individual patient characteristics, such as comorbid conditions or functional status, which may change the likelihood of receiving benefit or harm from a preventive intervention. Given these challenges, the need to individualize prevention and screening decisions is especially important for older people, because individuals become increasingly heterogeneous in their particular combination of health, function, remaining life expectancy, and values with advancing age.

The following framework can help individualize prevention and screening decisions so that patients who are most likely to benefit receive the intervention while patients who are more likely to be harmed avoid the intervention and avoid being harmed.

First, estimate life expectancy. By definition, prevention involves an intervention in the present to avoid illness in the future. Many preventive interventions expose patients to risks and burdens immediately for the promise of improved health later. However, older patients with a limited life expectancy may be unlikely to survive to benefit from prevention. For example, finding an asymptomatic cancer in a person who will die of something else before the cancer would become symptomatic does not benefit the person and may cause considerable harm. Thus, the first step in determining whether a preventive intervention may help an older person is to determine their overall life expectancy.

In estimating life expectancy, it is useful to have a general idea of the distribution of life expectancies at various ages. For example, when estimating the life expectancy of an 80-year-old woman, it is useful to know that approximately 25% of 80-year-old women will live more than 13 years, 50% will live at least 9 years, and 25% will live 5 years or less. **Figure 13-1** presents the upper, middle, and lower quartiles of life expectancy for the US population according to age and sex, and illustrates the substantial variability in life expectancy that exists at each age. Although it is impossible for clinicians to predict the exact life expectancy of an individual person, it is possible to use clinical judgment to make reasonable estimates of whether a person is likely to live substantially longer or shorter than an average person in his/her age cohort. Such estimates, while not perfect, would allow for better estimations of potential benefits and harms of screening than focusing on age alone.

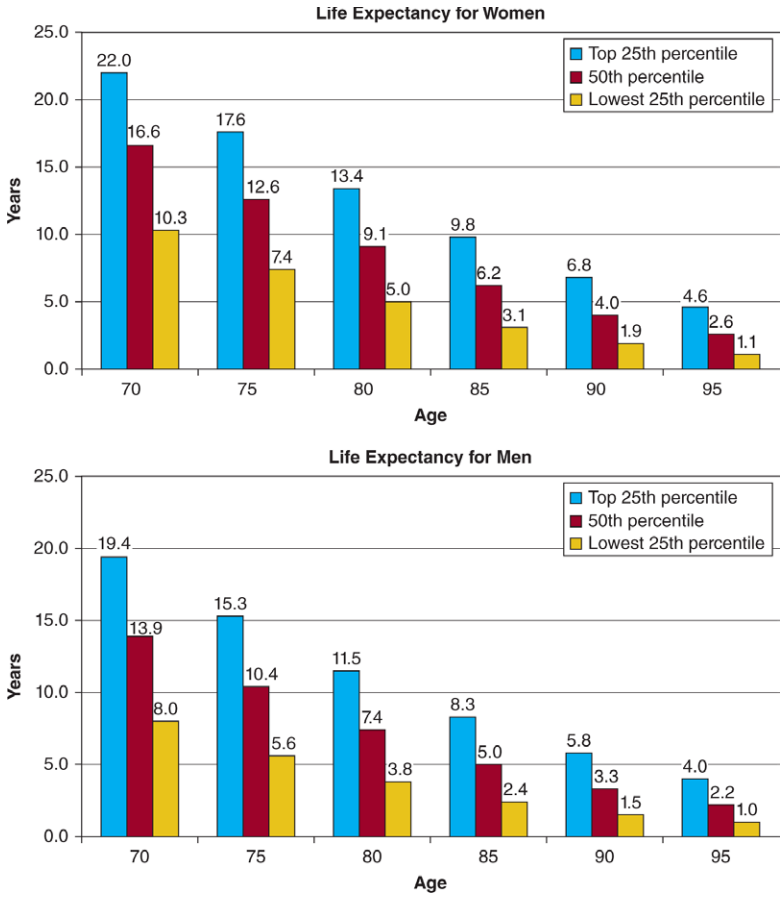


FIGURE 13-1. Upper, middle, and lower quartiles of life expectancy for women and men at selected ages. (Data from the Life Tables of the United States, 2008. Adapted from Walter LC, Schonberg MA. Screening mammography in older women: a review. *JAMA*. 2014;311(13):1336–1347.)

In addition, validated mortality risk calculators may help clinicians estimate the life expectancy of individuals

better than clinical judgment alone. A recent systematic review found 16 mortality risk calculators that have been developed and validated for older adults. These mortality risk calculators have been gathered at http://eprognosis.ucsf.edu, allowing users to input a given patient's data such as age, comorbidities, and functional limitations to obtain an evidence-based estimate of mortality risk and life expectancy.

Second, determine the time to benefit for a preventive intervention. For preventive interventions that expose patients to immediate risks or burdens with delayed benefits, the time to benefit can be defined as the time between the intervention (when harms are most likely) to the time when improved health outcomes are seen. Just as different interventions have different magnitudes of benefit, different preventive interventions have different times to benefit. Unfortunately, although there are numerous widely accepted measures of the magnitude of benefit (eg, relative risk, odds ratio, and absolute risk reduction), there are no standardized measures of the time to benefit. Studies have focused on answering the questions, "Does it help?" (ie, $p < 0.05$?) and "How much does it help?" (ie, what is the relative risk reduction ?), generally ignoring the question, "When does it help?"

Because studies have generally focused on the magnitude of benefit, the time to benefit for many preventive interventions is unclear. Survival meta-analyses of screening trials have estimated the time to benefit for a few cancer screening interventions. For preventive interventions where survival meta-analyses have not been conducted, the time to benefit can be estimated by reviewing Kaplan-Meier survival curves for the intervention and control groups. The point at which the curves last clearly separate provides a reasonable estimate of the time to benefit for a preventive intervention.

Third, review the most likely benefits of prevention. If a patient is likely to live long enough to benefit from a preventive intervention the next step is to consider the potential benefits. For example, the main benefit of cancer screening is the reduction in cancer mortality experienced by a few people whose early-stage disease is detected and treated, which otherwise would have been lethal during their remaining lifetime. While the impact of cancer screening on quality of life or functional decline has not been studied, there is good evidence that mammography, fecal occult blood testing (FOBT), and Papanicolaou (Pap) smears are effective in reducing cancer-specific mortality. However, the strength of the evidence that these tests are effective in older adults is limited by the small number of older patients included in screening trials. In addition, even screening tests likely to be effective in older populations may not provide survival benefit to individuals with life expectancies that are shorter than the time to benefit from screening.

Fourth, review the most likely harms of prevention. Since many preventive tests pose both direct and indirect harms, the potential benefits of interventions, such as cancer screening, must be weighed against the potential harms of screening (**Figure 13-2**). Harms that would be accepted to treat a symptomatic person with known disease are less acceptable when they are caused by screening tests, which benefit only a few individuals but expose all screened individuals to the harms.

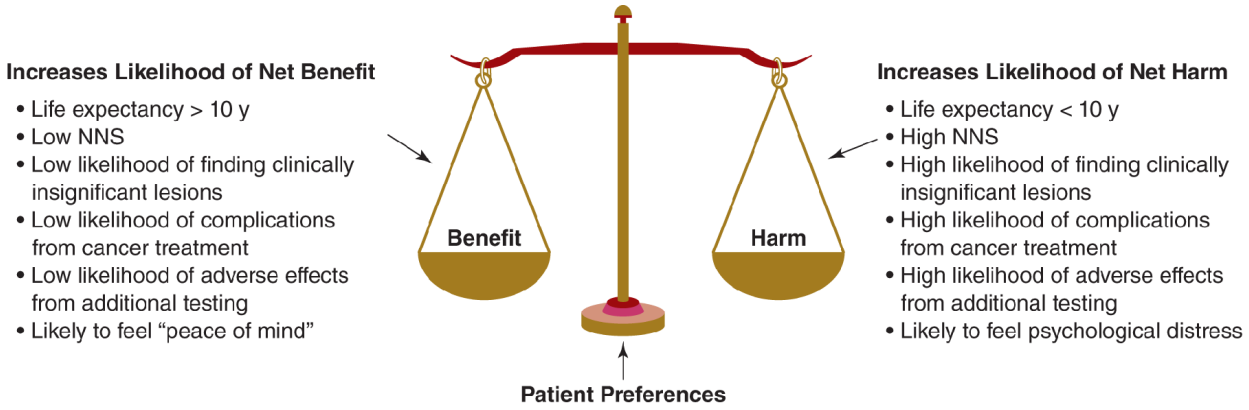


FIGURE 13-2. The benefits and harms that need to be weighed when making informed cancer screening decisions. Patient preferences act like a moveable fulcrum of a scale to shift the magnitude of the benefits or harms needed to tip the decision toward recommending the screening test (net benefit likely) or recommending against the screening test (net harm likely). NNS, number needed to screen to prevent one cancer-specific death.

Individuals who are found not to have cancer after work-up of an abnormal screening result (false-positive result) clearly have experienced harm from screening, as they were subjected to physical and psychological distress from additional testing and procedures that would not have been necessary had they not been screened. However, what is often forgotten is that in older persons some of the greatest harms from screening occur by finding and treating cancers that would never have become clinically significant. The risk of identifying an inconsequential cancer (ie,

overdiagnosis) increases with decreasing life expectancy as well as with the increasing likelihood that screening will detect certain neoplasms that are unlikely to progress to symptoms in older persons, such as ductal carcinoma in situ (DCIS). Fewer than 25% of DCIS lesions progress to invasive cancer within 5 to 10 years, yet because of the inability to distinguish which lesions will progress, many older women with DCIS will undergo surgery. Women who have surgery for DCIS that would never have become symptomatic in their lifetime have suffered serious harm from screening.

In addition to physical harms, the psychological distress caused by preventive interventions should be considered. For cancer screening, the potential psychological harms range from the emotional pain of a diagnosis of cancer in persons whose lives were not extended by screening, through the alarm of false-positive results to the stress of undergoing the screening test itself. Many older persons may have cognitive, physical, or sensory problems that make screening tests and further work-up particularly difficult, painful, or frightening. Considering factors that increase the likelihood of harm is vital to making appropriate preventive decisions.

Finally, review benefits and harms with each patient, integrating the patient's values and preferences into the decision. The final step of the framework for individualizing preventive decisions is to assess how individuals value the potential harms and benefits of a preventive intervention and to integrate their preferences into the decision. Because many cancer-screening decisions in older persons will not be answered solely by quantitative assessments of benefits and harms, talking to older persons about their values and preferences is especially important. The value placed on different health outcomes will vary among older people, as will preferences for screening. For example, some women undergoing screening mammography value "peace of mind" after a negative screening result, whereas women with dementia likely receive no such comfort. In considering the benefits versus harm of screening, clinicians must elicit how individuals value the trade-offs among longer survival, comfort, and functional status.

Clinicians should consider a person's usual approach to medical decision making to decide how to approach the discussion of preventive interventions. In some cases, clinicians will need to learn a person's values, apply them to the known benefits and harms of a preventive intervention, and make a formal recommendation. For other people, the clinician will want to discuss the benefits and harms with the person and allow the person to apply his/her values to the outcomes and come to a decision together. For people with dementia, discussion about preferences should be held with an involved caregiver. However, it should be remembered that despite being unable to articulate consent, many persons with dementia can still effectively communicate refusal. Assent from a person with dementia is essential if invasive or potentially harmful testing or treatments are being considered. If a person with dementia is likely to be frightened or agitated by a preventive test, the caregiver and clinician should forgo the test. Also, for screening tests there should be a general discussion prior to screening about the possible procedures and treatments that may be required after an abnormal screening result. Persons who would not want further work-up or treatment of an abnormal result should not be screened.

In summary, the authors recommend estimating patient's life expectancy and then comparing that life expectancy to the time to benefit for a specific preventive intervention (**Table 13-1**). The benefits and harms of prevention, such as cancer screening, should be reviewed to determine whether specific patient factors are present (such as excellent health or cognitive impairment) which suggest that a patient is more likely to benefit or be harmed by screening than the average patient. The benefits and harms should be incorporated into a discussion with the patient regarding his/her values and preferences. If the life expectancy is more than the time to benefit, the patient has a substantial chance of benefit and thus a preventive intervention should be encouraged. If the life expectancy is less than the time to benefit, the patient is more likely to be harmed than helped by a preventive intervention and thus should not be offered. If the life expectancy approximates the time to benefit, a patient's values and preferences are especially important and should play the dominant role in the decision whether to perform a preventive intervention or not.

TABLE 13-1 FRAMEWORK FOR INDIVIDUALIZING PREVENTION

1. Estimate the patient's life expectancy (LE)
2. Determine the preventive intervention's time to benefit (TTB)
3. Determine the benefits and harms with screening
4. Review benefits and harms in the context of patient values and preferences

In general:

A. If LE >> TTB, patient is more likely to be benefit. Prevention recommended.

B. If LE << TTB, patient is more likely to be harmed. Prevention *not* recommended.

C. If LE ≈ TTB, estimated benefits and harms are similar in magnitude. Patient preferences should drive decision making.

APPLICATION OF SCREENING PRINCIPLES TO SPECIFIC CANCERS

Breast Cancer

Time to benefit for screening mammography A survival meta-analysis of randomized trials of screening mammography suggested that it takes 10.7 years to prevent one breast cancer death after screening 1000 women. Since the rates of serious complications after screening mammography appears to be approximately 1 in 1000, screening mammography may be most appropriate for women with a life expectancy greater than 10 years. Further, modeling studies suggest it is cost-effective to conduct biennial screening mammography as long as an older woman has a life expectancy of at least 9.5 years.

Benefits of breast cancer screening Mammography is the only screening modality that has been shown in randomized controlled trials to decrease breast cancer mortality. A pooled meta-analysis of trials demonstrated an overall relative risk reduction in breast cancer–related mortality of 27% for women between the ages of 50 and 69. There is little information regarding the absolute benefits of screening mammography in women older than age 70, so data from trials in younger people must be extrapolated to older people.

Harms of breast cancer screening Among women aged 75 and older who undergo biennial screening mammography, the cumulative probability of a false-positive mammogram over 10 years ranges from 14% to 27% and this risk nearly doubles if women are screened annually. The risk for overdiagnosis (finding a malignancy in a patient who would never have been affected clinically by the malignancy in the absence of screening) increases with age because life expectancy decreases and there is a higher proportion of slower growing cancers in older women. However, estimating the risk of overdiagnosis has been challenging because different study designs produce different estimates of overdiagnosis, ranging from 0% to 54% for mammography. Frail older women are at increased risk for experiencing harms from screening. One study of frail community-living women found that 17% experienced burden from screening mammography as a result of work-up refusals, false-positive results, or overdiagnosis. Women with multiple comorbid conditions are also likely to experience adverse effects from surgery, radiation, and chemotherapy.

Recommendations The US Preventive Services Task Force (USPSTF) recommends mammography every 2 years for women aged 50 to 74, stating that the evidence is insufficient to assess the additional benefits and harms of screening in women of 75 years and older (**Table 13-2**). The American Cancer Society recommends starting at age 40 and "continuing for as long as a woman is in good health." The authors do not recommend screening for breast cancer if a woman has an estimated life expectancy of fewer than 10 years. For women who have a life expectancy around 10 years the decision to screen is a close call, and patient preferences should play a major role in the decision to screen. For healthy older women who have a life expectancy more than 10 years, biennial screening mammography, regardless of age, is a reasonable recommendation based on the data available. The free ePrognosis Cancer Screening iPhone app compares a patient's life expectancy with the time to benefit for screening mammography to help clinicians determine whether mammography is likely to help a patient.

TABLE 13-2 GUIDELINE RECOMMENDATIONS FOR CANCER SCREENING IN OLDER ADULTS

CANCER SITE	TEST	FREQUENCY	USPSTF GUIDELINE[a]	ACS GUIDELINE[b]	ACP GUIDELINE[c]
Colorectal	Fecal occult blood test or fecal immunochemical test (FIT) or Sigmoidoscopy or Colonoscopy	Annual Every 5 y Every 10 y	Screen all adults of 50–75 y. There may be considerations that support screening individuals of 76–85 y. Screening is not recommended for adults over age 85.	Screen all adults of > 50 y. Discontinuing screening is reasonable in persons with severe comorbidity that would preclude treatment.	Screen all adults of 50–75 y. Persons with life expectancy < 10 y should not be screened.

					ACOG GUIDELINE[d]
Breast	Mammography	Every 1–2 y	Biennial screening all women of 50–74 y. Evidence of benefits and harms is insufficient for women of 75 y and older.	Annual screening starting at 40 y, continuing for as long as a woman is in good health.	Annual screening starting at 40 y.
Cervical	Pap smear HPV test	Pap only, every 3 y HPV + Pap, every 5 y	Screening in women of 21–65 y. Discontinue at age 65 if adequate prior screening.	Screening in women of 21–65 y. Discontinue at age 65 if regular screening with normal results.	Screening in women of 21–65 y. Cotesting (Pap + HPV) every 5 y is the preferred screening method for women 30–65 y. Screening should stop at age 65 if evidence of negative adequate prior screening.
					ACCP GUIDELINE[e]
Lung	Low-dose CT scan	Annual	Screen 55–80-y-old current and former smokers with a 30+ pack-year smoking history. Discontinue screening once a person has not smoked for 15 y or develops a health problem that limits their ability or willingness to have curative surgery.	Screen 55–74-y-old current and former smokers in fairly good health with a 30+ pack-year smoking history.	In settings that can deliver the comprehensive care provided to National Lung Screening Trial participants, offer screening to 55–74-y-old current and former smokers with 30+ pack-year smoking history.
					AUA GUIDELINE[f]
Prostate	PSA	1–2 y	Do not screen men for prostate cancer with PSA test.	Screen men age 50 and over with a life expectancy > 10 y after discussion about the risks, benefits, and uncertainties of PSA screening. Follow-up screening should occur annually if PSA > 2.5 ng/mL or biennially if PSA < 2.5 ng/mL.	Biennial PSA screening in men of 55–69 y with life expectancy > 10–15 y, after shared decision-making discussions accounting for man's values and preferences.

[a]USPSTF, United States Preventive Services Task Force.
[b]ACS, American Cancer Society.
[c]ACP, American College of Physicians.
[d]ACOG, American College of Obstetricians and Gynecologists.
[e]ACCP, American College of Chest Physicians.
[f]AUA, American Urological Association.

Colorectal Cancer

Time to benefit for colorectal cancer screening A survival meta-analysis of randomized trials of screening FOBT for colorectal cancer suggested that it takes 10.3 years to prevent one colorectal cancer death after screening 1000

persons. Since the rates of serious complications after colorectal cancer screening also appear to be approximately 1 in 1000, colorectal cancer screening may be most appropriate for persons with a life expectancy more than 10 years. Randomized trials of screening flexible sigmoidoscopy show similar times to benefit. Ongoing trials of screening colonoscopy will provide additional information about whether time to mortality benefit with screening colonoscopy is similar to screening FOBT and sigmoidoscopy.

Benefits of colorectal cancer screening Methods for screening for colorectal cancer include FOBT, fecal immunochemical testing, flexible sigmoidoscopy, and colonoscopy. Nonrehydrated FOBT has the strongest evidence for screening efficacy based on two randomized controlled trials showing a relative risk reduction in colorectal cancer–related mortality of 15% to 18% for persons between the ages of 45 and 75. Studies suggest that similar mortality benefits are seen after screening flexible sigmoidoscopy.

Harms of colorectal cancer screening Approximately 1 in 10 older adults who submit a screening nonrehydrated FOBT will have a false-positive result. Colonoscopy is the standard work-up following a positive FOBT and may have serious complications, such as perforation (1/1000), serious bleeding (3/1000), and cardiorespiratory events (5/1000). Complications may be higher if polypectomy is performed or if persons are in poor health. Discomfort from flexible sigmoidoscopy or colonoscopy may occur, and many older persons may experience substantial distress from the bowel preparation.

Recommendations The USPSTF recommends colorectal cancer screening for all older adults aged 50 to 75 and that screening decisions should be individualized for persons aged 76 to 85 years based on life expectancy. Most guidelines recommend annual screening FOBT or fecal immunochemical testing and/or flexible sigmoidoscopy every 5 years or colonoscopy every 10 years for average-risk persons starting at age 50 (see **Table 13-2**). There is no evidence available to determine which screening method is preferable or when screening should stop. Most guidelines do not recommend using upper age cutoffs to decide when to stop screening. Rather, most guidelines recommend that the decision to discontinue screening should be individualized, based on whether an older person has characteristics that considerably decrease the benefit-to-risk ratio of screening (eg, limited life expectancy or conditions that increase the risk of colonoscopy, such as cardiopulmonary disease or dementia). The authors recommend against screening for colorectal cancer if a person has an estimated life expectancy of fewer than 10 years. For persons with life expectancies around 10 years, the decision to screen is a close call, and patient preferences should play a major role in the decision to screen. For healthy older people who have a life expectancy more than 10 years, colorectal cancer screening, regardless of age, is a reasonable recommendation based on available data. The free ePrognosis Cancer Screening iPhone app compares a patient's life expectancy with the time to benefit for colorectal cancer screening to help clinicians determine whether colorectal cancer screening is likely to help a patient.

Cervical Cancer

Time to benefit for cervical cancer screening A cluster randomized trial of younger women (age 30–59) suggests that cervical cancer screening with the human papilloma virus (HPV) testing leads to mortality reductions in 2 to 3 years. In contrast, screening with cervical cytology appears to lead to mortality benefits in 6 to 7 years. There are no data about the time to benefit for cervical cancer screening in women 65 years and older. The main consideration for cervical cancer screening is whether an older woman has received screening during her reproductive years because the likelihood an older woman will die of cervical cancer is remote if she has had normal screens in the past.

Benefits of cervical cancer screening The principal method for screening for cervical cancer is through the use of cervical cytology. Since screening with Pap smears was initiated, population studies in the United States show a 20% to 60% decline in mortality rates from cervical cancer. Decision models suggest that older women who have had repeated normal Pap smears during their reproductive years do not benefit from continued Pap testing beyond age 65 or 70 years. However, these models make variable recommendations about the number of normal Pap smears required prior to stopping screening.

Harms of cervical cancer screening For women older than age 70, the risk of a false-positive Pap smear result has not been studied, but for postmenopausal women with a normal Pap result in the previous 2 years, the positive predictive value of an abnormal cervical smear is less than 1%. Harms of false-positive results include needless patient concern and invasive procedures, such as colposcopy or biopsy. Discomfort and anxiety during Pap smears also occurs as does the identification and treatment of clinically unimportant cervical lesions.

Recommendations Guidelines recommend cervical cancer screening with cytology every 3 years for women aged 21 to 65. Combining cytology testing with HPV testing every 5 years may provide added benefit (see Table 13-2). Guidelines also recommend that Pap smears be discontinued in women more than age 65 who have had adequate prior screening, defined as three consecutive negative cytology results or two consecutive negative HPV results. The authors recommend cervical cancer screening in women more than age 65 who have not had adequate prior screening and are healthy enough to undergo cervical cancer treatment if found.

Lung Cancer Screening

The National Lung Screening Trial (NLST) found that among current and former heavy smokers age 55 to 74, low-dose lung computed tomography (CT) scans decreased lung cancer mortality by 20%. Specifically, for 1000 persons screened, 4 lung cancer deaths would be avoided in 6 years. However, 273 persons would have an abnormal result requiring 36 persons to get an invasive procedure with 8 persons suffering complications.

However, extrapolating this evidence to older adults is complicated by several factors. First, only 27% of the NLST participants were age 65 or more and participants were healthier than the general, age-matched US population. Second, the rate of complications from invasive procedures in the trial were one-fourth of the expected rate in the general population, suggesting that harms of screening may be substantially higher than what was observed in this trial.

On the basis of this trial, most (but not all) guidelines now recommend lung cancer screening for current and former heavy smokers, age 55 to 74 (see **Table 13-2**). The authors conclude that for current and former heavy smokers age 55 to 74, the evidence is equivocal, suggesting that the patient's values and preferences should play a dominant role in the decision to screen for lung cancer.

Prostate Cancer Screening

Although prostate-specific antigen (PSA) testing is frequently performed, there is conflicting evidence and guidelines regarding the benefits and harms of PSA testing. The USPSTF does not recommend PSA testing, suggesting that even in the ideal patient population (men age 55–69), the mortality benefit is small and takes over 10 years to be realized. In contrast the harms are common (eg, urinary incontinence and sexual dysfunction), occur immediately, and are long-lasting. The American Cancer Society and American Urological Association recommend PSA screening for men age 55 to 69 who have a life expectancy greater than 10 to 15 years (see **Table 13-2**). The authors do not recommend routine screening for prostate cancer in older men based on the available evidence.

TARGETING TREATMENT FOR ASYMPTOMATIC CHRONIC CONDITIONS

Treatment of asymptomatic chronic conditions such as hypertension and diabetes also impose immediate risks and burdens on patients for the promise of delayed benefits. More intensive glycemic control appears to decrease the risk of microvascular complications many years later. However, more intensive glycemic control clearly increases the risk for serious hypoglycemia immediately. Similarly, improved blood pressure control appears to decrease the risk of heart failure and stroke. However, initiating antihypertensive medications appears to increase the risk of hip fracture in the first 45 days. Thus, for asymptomatic chronic conditions, the risks and burdens of treatment often occur immediately while the benefits are not observed for years. This suggests that *treatment* for asymptomatic conditions can also be viewed as *prevention*, and should be targeted toward patients with an extended life expectancy who have a chance of benefiting from the delayed benefits.

Unfortunately, there is tremendous uncertainty surrounding the time to benefit for various interventions. Long-term follow-up studies of more intensive glycemic control suggests that it take 8 to 15 years for the clinical benefits to be seen (**Table 13-3**). Studies of more intensive blood pressure control suggest that it take 1 to 5 years for clinical benefits to be seen. For HMG-CoA reductase inhibitors ("statins"), the time to benefit appears to be dependent on clinical situation, with nearly immediate (< 3 months) benefit in patients with recent myocardial infarction and increasing to several years for primary prevention of cardiovascular disease (see **Table 13-3**).

TABLE 13-3 ESTIMATED TIMES TO BENEFIT FOR THE TREATMENT OF COMMON CHRONIC CONDITIONS

TIME TO BENEFIT[a]	CONDITION	INTERVENTION	IMMEDIATE RISK	DELAYED BENEFIT	DATA SOURCES

8–15 y	Diabetes mellitus	Intensive glycemic control	Hypoglycemia	Decreased vascular complications	UKPDS, long-term follow-up
1–5 y	Hypertension	Hypertension treatment	Orthostatic hypotension, falls, and fracture	Decreased stroke and cardiovascular mortality	HYVET, EWPHE, and MRCOA trials
1–3.5 y	Hypercholesterolemia	Treatment with HMG-CoA reductase inhibitors (“statins”)	Myalgias, rhabdomyolysis, and cost	Decrease cardiovascular events including death	WOSCOPS, AFCAPS/TexCAPS, MEGA trials

[a]The first number represents the time point when the event rates between the control and intervention groups diverge, representing the time at which population benefits are first seen. The second number represents the time point when event rates between the control and intervention groups reach near-maximal separation, representing the time at which maximal benefits are seen. AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; EWPHE, European Working Party on Hypertension in the Elderly; HYVET, Hypertension in the Very Elderly Trial; MEGA, Management of Elevated Cholesterol in Primary Prevention Group of Adult Japanese; MRCOA, Medical Research Council Trial of Treatment of Hypertension in Older Adults; UKPDS, United Kingdom Prospective Diabetes Study; WOSCOPS, West of Scotland Coronary Prevention Study.

In summary, treatments for many asymptomatic chronic medical conditions impose immediate risks and burdens on patients with the promise of delayed benefits. Thus, the framework of individualizing prevention applies to these conditions such that the treatment of these asymptomatic conditions should be targeted to those older adults whose life expectancy exceeds the time to benefit.

IMMUNIZATIONS

In contrast to screening interventions, the risks associated with immunizations are much lower than the benefits. Thus, targeting is less important, and nearly all older adults should receive the pneumococcal vaccination, annual influenza vaccination, and zoster vaccination.

Pneumococcal Vaccination

Pneumococcal infections represent a major cause of morbidity and mortality in older adults. The US Advisory Council on Immunization Practices (ACIP) recommends all older adults over age 65 sequentially receive both the pneumococcal conjugate vaccine (PCV13) followed in 6 to 12 months by the pneumococcal polysaccharide vaccine (PPSV23). Minor local reactions such as pain or erythema are common with both vaccines; more serious side effects are rare. The ACIP also recommends pneumococcal vaccination for adults younger than 65 who have certain risk factors such as cigarette smoking, diabetes mellitus, or chronic lung disease.

Influenza Vaccination

The influenza virus causes annual epidemics of acute respiratory illnesses every winter that disproportionately affects older adults. Vaccination has been shown to decrease the morbidity and mortality associated with influenza and is recommended for all persons older than 6 months. There is some evidence that a high-dose influenza vaccine may be more effective in eliciting immunogenic response in adults over age 65. The most common adverse events include local soreness. The risk of Guillain-Barré syndrome after influenza vaccination appears small, with estimates of 1 to 2 excess cases per 1 million persons vaccinated.

Tetanus/Diphtheria/Pertussis

Tetanus is caused by the neurotoxin expressed by *Clostridium tetani* when the ubiquitous bacteria spores are inoculated into tissues with trauma or deep puncture wounds. Tetanus toxoid vaccine is effective, but waning immunity has led to a large proportion of cases occurring in adults over 60. ACIP recommends tetanus toxoid revaccination every 10 years for all older adults.

Diphtheria is a rare, acute respiratory illness caused by a toxin expressed by *Corynebacterium diphtheriae*. National

serosurvey between 1988 and 1994 suggested that only 30% of adults aged 60 to 69 had appropriate diphtheria antitoxin concentrations. ACIP recommends diphtheria toxoid vaccination every 10 years.

Pertussis or whooping cough is a highly contagious respiratory illness that is underdiagnosed and underreported, especially in older adults. Studies suggest that acellular pertussis vaccination is equally effective among older adults as younger adults with similar low rates of adverse events and high rates of pertussis antibodies. ACIP recommends a one-time booster dose of pertussis vaccination after age 65.

In summary, the ACIP recommends that all adults receive tetanus/diphtheria (Td) booster every 10 years. In addition, adults over age 65 should receive a one-time dose of tetanus/diphtheria/acellular pertussis (Tdap) if they have not received pertussis revaccination after age 19 in lieu of Td vaccination.

Zoster Vaccination

Reactivation of herpes zoster is common (30% lifetime risk) and can result in significant morbidity from complications such as postherpetic neuralgia and ophthalmic zoster. Zoster vaccination appears to be effective, decreasing the rates of postherpetic neuralgia 67% (0.1% vaccine vs 0.4% control). The most common adverse reactions to zoster vaccinations are local and minor; serious adverse reactions are rare. Although some data exist for the use of the zoster vaccine in those 50 to 59 year, the balance of benefits and harms are less clear. The ACIP recommends zoster vaccination for adults age 60 and over.

BEHAVIORS TO MAINTAIN HEALTH

Like immunization, healthy behaviors have few, if any, adverse outcomes, meaning that they can be recommended to nearly all older adults. However, unlike immunizations, which are initiated and provided by the health care system, healthy behaviors require a personal commitment from individual patients. While the advice and encouragement from health care professionals are important, the effectiveness of any behavioral modification requires the individual patient to accept primary responsibility for initiating and maintaining healthy behaviors.

Nutrition

A healthy diet can contribute to an increase in life expectancy and better health. Healthy diets have shown the potential to lower blood pressure and blood cholesterol. Optimal diets have also been associated with lower risk of chronic diseases, notably coronary artery disease (CAD), diabetes, obesity, and some forms of cancer. National Health and Nutrition Examination Survey (NHANES) III data show potentially important decreases with age in median protein and zinc intakes as well as intakes of calcium, vitamin E, and other nutrients. Subclinical nutrient deficiencies can adversely affect health and physical functioning. Longitudinal studies have shown that caloric intake and macronutrient (fat, protein, and carbohydrate) intake decrease with age, suggesting that older adults may be at higher risk of poor nutrition than younger adults.

The traditional Mediterranean diet, dominated by consumption of olive oil, vegetables, nuts, and fruits, meets criteria for a healthy diet. Direct evidence in support of this diet has become available. For example, it has been associated with prevention of progression of cardiovascular disease and reversal of the metabolic syndrome. Such a diet appears to improve endothelial function, reduce serum markers of systemic vascular inflammation (C-reactive protein and the proinflammatory interleukins [ILs] IL-6, IL-7, and IL-18), and decrease insulin resistance. A plausible mechanism by which this diet may reduce inflammation may lie in either the antioxidants or the fiber that are common elements in the different components of the diet. Either antioxidants or fiber may effect a reduction in the transient oxidative stress associated with macronutrient intake. The latest edition of *Nutrition and Your Health: Dietary Guidelines for Americans*, available online at http://www.health.gov/dietaryguidelines/, can serve as a reference for providers in counseling adults about healthy eating patterns.

Physical Activity

Physical activity and physical fitness can help prevent or delay the onset of chronic illnesses such as CAD, type 2 diabetes, osteoporosis, and obesity; protect against the development of functional decline; improve mood; reduce stress; and, perhaps, increase life expectancy (see Chapter 115). Physical activities that improve endurance, strength, and flexibility will delay impairments in mobility and may preserve the ability to perform tasks of daily living. Regular, moderate-intensity physical activity increases muscle mass and oxidative capacity, improves immune

function, increases antioxidant defense against oxygen-free radicals, and reduces oxidative stress. The current recommendation that adults exercise at least 30 minutes on most, and preferably all days, derives from evidence that even moderate physical activity is associated with a substantial drop in all-cause mortality. The cumulative, lifetime activity pattern may be the most influential factor in terms of providing protection from most diseases, especially those with a long developmental period, as well as mediating secondary disease complications associated with CAD, diabetes, and hypertension. However, despite an enormous amount of information about the positive effects of exercise in preventing disease and increasing life expectancy, the majority of adults do not engage in regular, sufficient physical activity. Furthermore, aging appears to be associated with a rise in the prevalence of inactivity, especially among women, such that by age 75, one in three men and one in two women engage in *no* regular physical activity. Societal changes over the past 50 years, including increased dependence on cars for transportation, the advent of television and computers, and rise in number of desk jobs, have virtually engineered physical activity out of the daily routines of many older people. Thus, encouraging and prescribing physical activity for adults of all ages is imperative and can be viewed as a central tenet of preventive gerontology.

Regular participation in activities of moderate intensity (such as brisk walking, climbing stairs, scrubbing floors, yard work), which increase caloric expenditure and maintain muscle strength, is recommended, as activities of moderate intensity appear to allow health benefits to accrue. Current national guidelines suggest at least 30 minutes of moderate-intensity exercise on 5 or more days per week (Centers for Disease Control and Prevention [CDC]) or vigorous-intensity exercise (such as swimming laps, bicycling more than 10 mi per hour, jogging, or running) for 20 or more minutes on 3 or more days per week. The CDC, American College of Sports Medicine, and Surgeon General further state that daily physical activity requirements may be accumulated over the course of the day in short bouts of 10 to 15 minutes. Building activity into one's daily routine (eg, taking the stairs rather than an elevator) is a practical and efficacious way to achieve a pattern of regular physical activity. Helpful, patient-centered information about how to become more active can be found at the CDC's Physical Activity for Everyone (http://www.cdc.gov/physicalactivity/).

Several psychological and environmental factors determine physical activity behavior throughout the lifespan. Self-efficacy, or confidence in one's ability to perform a particular behavior (in this case, regular exercise), is strongly associated with both adoption of and adherence to physical activity among adolescents, young adults, and older adults. Strategies suggested by Bandura to enhance self-efficacy, such as assessing readiness for exercise using a behavior change philosophy, using motivational interviewing techniques, weekly action planning and feedback, collaborative problem solving, and addressing barriers to exercise may all enhance self-efficacy for exercise. These techniques can be learned and implemented by health care providers. Affective disorders such as depression and anxiety are inversely associated with physical activity participation at any age. Thus, evaluation for the presence of these conditions and institution of treatment may be necessary before adoption of an exercise program can occur. Social influences on physical activity appear to be strong throughout the lifespan. Peer reinforcement is particularly important in youth, while social support from spouses and friends is correlated with vigorous activity in younger and older adult populations. Finally, environmental factors, particularly safety and accessibility, influence activity participation across the age span. These latter factors are increasingly becoming a focus of community intervention efforts.

Social Connection

Ongoing involvement in a social network permits social contact (integration), the provision of social support, and the opportunity for social influence, and is associated with positive health outcomes and self-assessed well-being. Through opportunities for social engagement, such as attending social functions, getting together with friends and family, and going to church, meaningful social roles are defined and reinforced, creating a sense of belonging and identity that is made possible by the network context. Measures of social integration or "connectedness" are powerful predictors of mortality likely because ties give meaning to an individual's life by enabling and obligating them to be fully involved in their community and thereby feeling attached to it.

There are several pathways by which social networks are thought to influence health: (1) a health behavioral pathway; (2) a psychological pathway; and (3) a physiologic pathway. Regarding the health behavioral pathway, social ties have been shown to influence the likelihood that certain behaviors will be adopted and that behavior will change (see also Chapter 28). For example, marriage and friendship ties have been shown in several studies to promote a healthier diet, more regular exercise, less smoking and drinking, and more cancer screening. However, studies have also shown that family and friends carry the potential for encouraging detrimental health behaviors; for example, the presence of a smoker in one's social network has been associated with greater relapse in efforts to quit. Adherence and

nonadherence to medical treatments have each been linked to the presence of more social ties. Thus, the evidence indicates that ties can serve as role models of appropriate or undesirable behavior.

A second mechanism by which social networks influence health is via psychological pathways. Evidence suggests that ongoing participation in one's social network is essential for the maintenance of self-efficacy beliefs throughout life. For example, studies have observed the indirect influence of social support through enhanced self-efficacy in smoking cessation and exercise. In addition, it is generally accepted that social ties have a salutary effect on mental health and psychological well-being, regardless of whether an individual is under stress. Integration in a social network may also directly produce positive psychological states (a sense of self-worth, purpose, and belonging), protecting against psychological distress (depression and anxiety).

A third mechanism by which social networks influence health is via physiologic pathways. The basic premise is that human physiologic homeostasis is influenced by the social environment. Social relationships may influence health via alteration in immune response, by effects on the hypothalamic-pituitary-adrenal axis, or by cardiovascular reactivity. For example, a low number of contacts with acquaintances are associated with high resting plasma levels of epinephrine, and people with low social support have been found to have higher levels of urinary norepinephrine, regardless of their level of stress.

Depression

Depression in older adults is common, underdiagnosed, and often inadequately treated. Rates of depression vary according to the diagnostic criteria used, but 2% of adults over age 55 meet criteria for major depression while 14% report depressive symptom. Most cases of depression are recognized and treated in primary care; however, studies suggest that depression is often undiagnosed and when diagnosed, undertreated in primary care. Further, depression treatment has been shown to improve outcomes. The USPSTF recommends screening adults for depression in clinical practices that have systems in place to ensure accurate diagnosis, effective treatment, and follow-up.

BEHAVIORS WITH ADVERSE HEALTH CONSEQUENCES

Tobacco Use

Tobacco use is the largest single preventable cause of illness and premature deaths in the United States. Illnesses related to tobacco use (CAD, cancers of the lung, larynx, oral cavity, esophagus, pancreas, and urinary bladder, stroke, chronic obstructive pulmonary disease) account for one in every five deaths in the United States. Evidence from the NHANES indicates that tobacco use predicts shorter survival time for middle-aged (45–54) and older (65–74) men. Tobacco use can also multiply the risk associated with other carcinogenic agents; for example, heavy alcohol consumption, associated with esophageal cancer, carries an even greater risk when combined with cigarette smoking.

Tobacco dependence should be viewed as a chronic condition requiring ongoing assessment and repeated intervention. However, effective treatments are available that can lead to long term, and in some cases, permanent abstinence. Studies have shown that individuals at any age can benefit from quitting the tobacco habit. Benefits include reduction in the risk of CAD, malignancy, stroke, and even hearing loss, along with improved pulmonary function, arterial circulation, and pulmonary perfusion.

Studies have found that only about 35% of adults are routinely asked about their tobacco habits or counseled to quit if they use tobacco. If providers do advise patients not to use tobacco, as many as 25% will quit or reduce the amount they use. Thus, providers should ask all patients at each clinical visit about tobacco use and advise all tobacco users about the importance of quitting, emphasizing factors that have been found to contribute most to successful attempts to quit: health concerns (symptoms); a desire to set an example for children; the expense of the habit; odor of breath, home, and clothing; and loss of taste for food. Providers should then assess a patient's willingness to attempt to quit. Patients who are unwilling to attempt to quit should be provided with a brief intervention designed to increase their motivation to quit.

Patients who are willing to quit should be provided with treatments that have been identified as effective. First-line pharmacotherapies that have been shown to increase smoking cessation include nicotine replacement (gum, inhaler, nasal spray, or patch), varenicline, and bupropion. Varenicline and bupropion appear to lead to increased rates of neuropsychiatric side effects including suicidal ideation. Thus, patients started on either medication should be monitored for neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, hostility, and suicidal ideation.

Alcohol

Epidemiologic studies support a survival benefit associated with moderate (up to two 8-oz drinks per day) alcohol consumption, primarily through reduction of cardiovascular risk, including elevation of high-density lipoprotein (HDL) cholesterol. Although initial studies suggested that red wine may be especially beneficial, more recent studies suggest that the type of alcohol is not as important as the amount of alcohol intake and the pattern of use.

However, consumption of alcohol beyond a moderate level can induce adverse effects on every organ system, including increased risk of hypertension; breast, colon, esophageal, liver, and head and neck cancer; cirrhosis; gastrointestinal bleeding; pancreatitis; cardiomyopathy; seizures; cerebellar degeneration; peripheral neuropathy; cognitive dysfunction; insomnia; depression; and suicide. Counseling about problem drinking following a few screening questions is a high-impact, cost-effective service. Screening can be accomplished by taking a careful history of alcohol use or by using a standardized screening questionnaire. All adults should be counseled on the health risks associated with excess alcohol consumption as well as the risk of injury (ie, motor vehicle crashes or other equipment-related injury) after drinking alcohol. Nondependent heavy drinkers as well as those with alcoholism (a chronic illness involving a state of dependency) should be counseled about the benefits of decreasing alcohol intake. Brief counseling by primary care providers can result in a significant reduction in alcohol use. Dependent drinkers should be referred to formal alcohol treatment programs and considered for a trial of naltrexone, an opioid antagonist that reduces the pleasurable effects of alcohol and may reduce relapse to heavy drinking.

Obesity

In adults, obesity is defined as a body mass index (BMI) of 30 kg/m^2 or more; overweight is a BMI of 25 to 29.9 kg/m^2 or more. Research suggests that although obesity and underweight are associated with increased mortality, being overweight (BMI 25–29.9) is not associated with increased mortality at any age. Further, increasing evidence suggests that being obese may not be as dangerous for older adults as younger adults. NHANES data suggest that for adults of age 25 to 59, BMI greater than 35 compared to BMI 18.5 to 25 nearly doubles the risk of all-cause mortality with a relative risk of 1.8. In contrast, for adults over age 70, the all-cause mortality risk with BMI greater than 35 is not statistically different from BMI 18.5 to 25 with a relative risk of 1.2. Thus, the optimal BMI for older adults appears to be slightly higher than the optimal BMI for younger adults.

For older adults, obesity is also a risk factor for impaired mobility and other functional limitations and, disabling conditions such as osteoarthritis; sleep apnea; gallbladder disease; nonalcoholic fatty liver disease; and cancers of the breast, endometrium, and colon. Moreover, those who are obese may suffer from social stigmatization, impaired social interaction, depression, and low self-esteem. Thus, regardless of the relationship between obesity and mortality in older adults, counseling obese patients to lose weight is likely to be beneficial.

Because treatment and reversal of obesity is challenging, primary prevention is warranted. Efforts to maintain a healthy weight should start early in life and continue throughout adulthood, as this is likely to be more successful than efforts to lose substantial amounts of weight and maintain weight loss once obesity has developed. Data from NHANES I suggest that getting adequate rest may be important in obesity prevention. Sleeping fewer than 7 hours a night was shown to be a risk factor for subsequent obesity. This may be related to altered levels of leptin and ghrelin, two appetite-regulating hormones. Leptin is associated with appetite suppression and ghrelin is an appetite stimulant that is thought to play a role in long-term regulation of body weight. During sleep deprivation, leptin levels fall and ghrelin levels rise.

Adults who are trying to maintain a healthy weight after weight loss are advised to get even more physical activity than the 30 min/d (described below) that is currently recommended; the US Department of Agriculture has recommended at least 60 min/d to manage weight. Weight management leading to a slow, steady weight loss is more beneficial than a pattern of weight cycling, which actually contributes to an elevated risk of mortality. The basal metabolic rate decreases with age, in parallel with a decline in lean body mass, and body fat increases proportionally. Thus, in order to most readily achieve normalization of body weight and body composition, an energy-sufficient (but not excessive) diet should be combined with a program of regular physical activity to permit maintenance of basal metabolic rate.

Recreational Drugs

The prevalence of injection drug use among older adults is unknown. Injection drug users typically initiate injection drug use during late adolescence (under age 21); however, a sizable subgroup begins injecting during early and late

adulthood. Persons with a history of recreational drug use on only one or a few occasions are unlikely to self-identify; thus, clinicians should probe for such a pattern of usage.

Noninjection drug use (crack smokers, methamphetamine, intranasal heroin, or cocaine, etc) contributes to development of gastroduodenal ulcers, chest pain and myocardial infarction, and increased risk of death. As might be expected, higher levels of drug involvement also were associated with increased age-adjusted mortality. The normalization of recreation drug use through marijuana legalization laws and the aging of the baby boomer generation which has had greater experience with recreational drugs are widely expected to increase the rates of recreational drug use in older adults.

Prescription Drug Misuse

Prescription drug misuse is poorly described in the medical literature but is currently a more prevalent problem than illicit drug use among older adults. Misuse of prescription medications may be related to insomnia, chronic pain, depression, and anxiety. The potential misuse of benzodiazepines is well recognized and has led to prescribing recommendations that suggest only short-term use and use only for intended indications. Amphetamine-like stimulants have abuse potential, but addiction to these drugs is seldom documented. Other medications that are often misused are sedative hypnotics, opioid analgesics, and barbiturates. Chronic use of such agents may lead to physical dependency and the development of withdrawal symptoms with attempts to discontinue use. Treatment may require detoxification followed by rehabilitation.

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Chapter 14

Geriatrics Models of Care

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Learning Objectives

- Describe the common goals of geriatrics models of care.
- Understand the importance of the patient's perspective when developing and managing geriatrics practice models.
- Describe how geriatrics models fit into the context of various payment mechanisms.
- Describe the key components of geriatrics models in these settings: hospital, transitions, home care, outpatient, and long-term care.
- Outline key strategies in sustaining and disseminating geriatrics models of care.

Key Clinical Points

1. **Multiple, evidence-based practice models are available to help interdisciplinary teams to improve care for populations of vulnerable older individuals.**
2. **Choosing the geriatrics model which can best fit into your practice setting depends on the challenges which your team is trying to address, your ability to make the case for a change, and your skills to lead an interdisciplinary team toward improved care.**
3. **Measuring key outcomes at baseline and over time can assist the team in efforts to improve care.**
4. **Assessing the fidelity of the key components of the model intervention is important to implementing and sustaining geriatrics models of care.**
5. **Disseminating geriatrics models may require novel strategies to incorporate the key components of geriatrics models into the workflow and processes of routine care of older patients.**

INTRODUCTION

Over the past decade multiple geriatrics models of care have emerged. Some of these programs were originally evaluated in randomized clinical trials while others were designed as quality improvement projects. Identifying the needs of seniors as they navigate the complex health care system will allow geriatrics leaders and health care organizations to replicate evidence-based medicine models of care. Geriatrics models of care that take into account patients with multiple comorbid conditions and use interdisciplinary approaches as part of their interventions have proven to be successful.

Common goals of these geriatrics models of care include engaging patients in their plan of care, enabling patients to remain safely in the least restrictive site of care, and focusing on prevention strategies that optimize patients' functional status and quality of life.

In order to find a geriatrics model of care that fits the needs of a hospital or a health care organization, it is essential to determine the hospital or health care system's priorities. Geriatrics leaders in the organization need to build a case for the inclusion of geriatrics models of care to fit with those priorities, capitalizing on the evidence-based practices. Working with the organization, geriatrics leaders seek to identify the resources that are available to support a new model, define where the model fits within other programs, and create a strategy to implement the model.

The Patient's Perspective in Geriatrics Models

The perspective of the patient is important to geriatrics practice models. First, patients who are served by models of care are particularly vulnerable. They need health care systems to work well to assess their preferences in order to meet their unique needs. As an example, an older patient could receive optimal medical treatment for early Alzheimer dementia, but the care plan might fail to address the patient's preference to independently manage multidosed daily medications. This unmet psychosocial aspect of care may leave the patient at risk for poor adherence to a complicated schedule of medications. Addressing the perspective of the patient, on the other hand, may allow the medications to be simplified to once per day. Second, many of the models of care require the patient to receive an assessment by providers who are not the patient's primary care physician. The assessment and the patient's preferences must be coordinated with and communicated to the primary care physician. Third, the models should help patients to work toward accomplishing their health care goals. An example is when the goal of an older individual with mild cognitive impairment might be to continue driving. This perspective could be supported by providing access to a driving assessment program in the community. Fourth, models of care involve interactions with multiple professionals—each one working to complement the other and not repeating the same questions. The patient's perspective will guide the multiple professionals as they work together toward the patient's defined goals. In conclusion, the perspective of the patient can provide a single direction for the team of health care professionals, as they provide care in the setting of geriatrics models.

Geriatrics practice models are often assessed by how well they achieve optimal "patient experience" ratings. Patient experience is a combination of the quality indicators (giving the correct medical care for a specific condition) and the patient's satisfaction. These assessments are publicly reported on the Centers for Medicare and Medicaid Services' Internet homepage at Hospital Compare and Nursing Home Compare. Family caregivers often have a clear idea about whether the patient's needs were met during their interaction with the health system. They respond to surveys which ask them to rate their satisfaction and these results are compared to the surveys from patients who receive care at other local sites. Models which pause to ask the patient's goals for their visit are more likely to meet excellent ratings for patient experience. Further, family meetings with the patient and their loved ones can make sure that all of the needs/preferences are expressed and addressed. These meetings can be incorporated into most geriatrics models. In short, good communication about what matters most to the patient and family caregivers can lead providers in geriatrics practice models toward a better experience for patients.

Some published geriatrics models have not measured patient satisfaction, while others have. The reader is encouraged to pay attention to this outcome measure as they study the individual models described in this chapter. Patient perspectives can be incorporated into the development and maintenance of geriatric models in a number of different forms. Having an older person on the planning and advisory teams is one strategy. Using a "focus group" to review a model of care and get the perspective of patients and caregivers is another method. Reviewing Hospital Compare scores and narratives of older patients is still another method of defining the patient's perspective. A further method of defining the older patient's view of a model is to carefully review "near-miss" events and root cause analyses. The main idea in all of these strategies is to add a vantage point of the patient and their family caregiver when developing and guiding geriatrics models.

Geriatrics Models of Care and Quality Improvement Projects

Geriatrics models of care that have been evaluated in clinical trials have similarities and differences from those models evaluated in rigorous quality improvement projects (**Table 14-1**). Quality improvement projects and geriatrics practice models identify a need to change performance. In both strategies, outcomes are measured and a specific intervention is deployed. Likewise, there is a need to obtain institutional review board (IRB) waiver to collect outcome measures. In each there is no new science defined. Usually the results are never made available in the clinical literature. The dissemination of the work is often missing. Both strategies are intended to improve the quality, safety, and value of health care. Both are unlikely to be disseminated, unless the authors have a unique improvement to health care. In summary, both geriatrics models and quality improvement programs use systematic efforts to improve care.

TABLE 14-1 KEY FEATURES OF STRATEGIES TO IMPROVE CARE FOR OLDER PATIENTS

	PRIMARY GOAL	FUNDING REQUIRED	IRB REVIEW	OUTCOMES
Quality improvement	Change performance.	Hospital or health system quality department or patient safety department.	Protection of participants is essential; IRB exemption is required.	How the relevant outcomes change over time.
Geriatrics models	Change performance for a unique population in the context of their care.	Grants or philanthropy support initially, then incorporated in yearly budgets.	Protection of participants is essential; IRB exemption is required to record and share outcomes.	Predetermined outcomes change over time and unique lessons learned.
Research	Discovery of new knowledge.	Grant support or organizational support.	Systematic investigations require IRB review.	Predetermined clinical outcomes compared to nontreatment group.

IRB, institutional review board.

There are some differences between geriatrics models and quality improvement which should be highlighted. First of all, geriatrics models target specific interventions for older patients. They usually replicate prior work (eg, Acute Care for Elders [ACE] or Hospital Elder Life Program [HELP] models), striving to get the same dosage of the intervention as the original model. Quality improvement projects, on the other hand, define the needs that fit their unique problems. Quality improvement projects allow the team to develop their own approach to the problem. Quality improvement strategies use the "Plan-Do-Study-Act" cycle. Quality improvement projects use experiential learning strategies. Second, quality improvement programs often have a shorter time frame whereas geriatrics models of care are often deployed over long periods of time. In summary, geriatrics models deploy a specific intervention to address a problem, while quality improvement projects allow more freedom to develop and implement the intervention.

Some geriatrics models integrate quality improvement strategies to improve their outcomes. An example of this is in the HELP. The leaders who implemented the HELP program in a local community noted that the outcomes for their program were not as good as the original model. The leaders used simple quality improvement strategies to assess and manage the fidelity of the deployment of the key ingredients of the model to eventually improve the outcomes. Hence, geriatrics models of care may use a quality improvement team member to help them integrate quality improvement techniques into their project.

Geriatrics Models of Care in the Context of Different Payment Mechanisms

The financial incentive of the health system is a critical part of the environment in which models are developed and deployed (**Table 14-2**). Most geriatrics models have been developed in the last 20 years in the Medicare fee for service payment system. The fee for service payment system provides reimbursement based on the use of services and hence more care provided results in additional payment to providers and health systems. Models which would work in these systems (such as Geriatric Evaluation and Management [GEM] programs) may rely on increasing downstream revenues to the health system from the care of patients with multiple comorbid conditions. The fee for service payment system provides reimbursement to the hospital through diagnosis-related groups. In short, the Medicare fee for service payment system pays for services which are provided to the beneficiary.

TABLE 14-2 EXAMPLES OF GERIATRICS MODELS OF CARE IN THE SETTING OF DIFFERENT PAYMENT SYSTEMS

GERIATRIC MODEL	MEDICARE FEE FOR SERVICE	MEDICARE VALUE-BASED PURCHASING (EG, ACCOUNTABLE CARE ORGANIZATION—ACO)	MEDICARE HMO
Acute Care for Elders	Payment to the hospital is based on the diagnosis-related group (DRG).	Payment to the hospital will be based on the DRG, however if overall costs for a group of	Payment to hospital within a network based on DRG and reviewed by HMO.

		patients is lower than predicted, savings may be shared with the ACO based on quality measures achieved.	
GRACE model	Beneficiaries will not have access to this model and may hence use more acute-care (hospital and emergency department) services.	Beneficiaries may use more prevention/care coordination services to avoid hospitalization and decrease costs. Savings are shared between Medicare and the ACO.	Beneficiaries may use more prevention/care coordination services to avoid hospitalization and decrease costs to the HMO.
Care Transitions Intervention	Decreased risk for readmission and hospital avoids Medicare penalties.	Decreased risk for readmission and savings shared between Medicare and the ACO.	Decreased risk for readmission and savings go to the HMO.

The value-based purchase payment system provides reimbursement which spans unique episodes of care. This payment system will promote optimal health outcomes with more efficient use of resources. Examples of value-based purchase systems are in accountable care organizations (ACOs), where optimal quality of care is rewarded along with the efficient use of resources. Examples of models which could be beneficial to the patients and to the health system in the context of value-based purchasing payment models include Geriatric Resources for Assessment and Care of Elders (GRACE), ACE, and Care Transitions Intervention. Models which could work better in these ACO systems would avoid hospitalization, readmission, and emergency department visits, and improve patients' coordination of care.

Models which are deployed in a Medicare HMO payment system provide care for the beneficiary and attempt to optimally use resources. The cost savings help to keep the insurance premiums lower and likewise benefit the insurance company which owns the HMO. Models deployed in this payment system focus on helping the patients to avoid hospitalizations. The economic benefit will result in lower costs to the HMO. Models which could be deployed in this payment system include GRACE, and Hospital at Home.

Trying to deploy a model which could save money in a fee for service payment system may not be endorsed by the health system, because such a model would not make enough money to be sustainable. Geriatrics leaders need to work with their health system leaders to review models which provide excellent clinical care and fit in the payment system which rewards such care. To prepare for value-based purchasing (while in the fee for service payment model), systems may need pilot programs which assess both quality outcomes and costs of care. Piloting these models can allow the hospital to study the economic benefit, while the clinicians assess the patient outcomes.

GERIATRICS MODELS OF CARE

Over the past few decades geriatrics models of care have evolved in hospital, outpatient, long-term care, and home-care settings. Research and quality improvement programs demonstrate the potential of these models to transform the culture of senior care, improve quality of care and patient safety, improve health outcomes, reduce costs, and integrate the continuum of medical care (**Figure 14-1**).

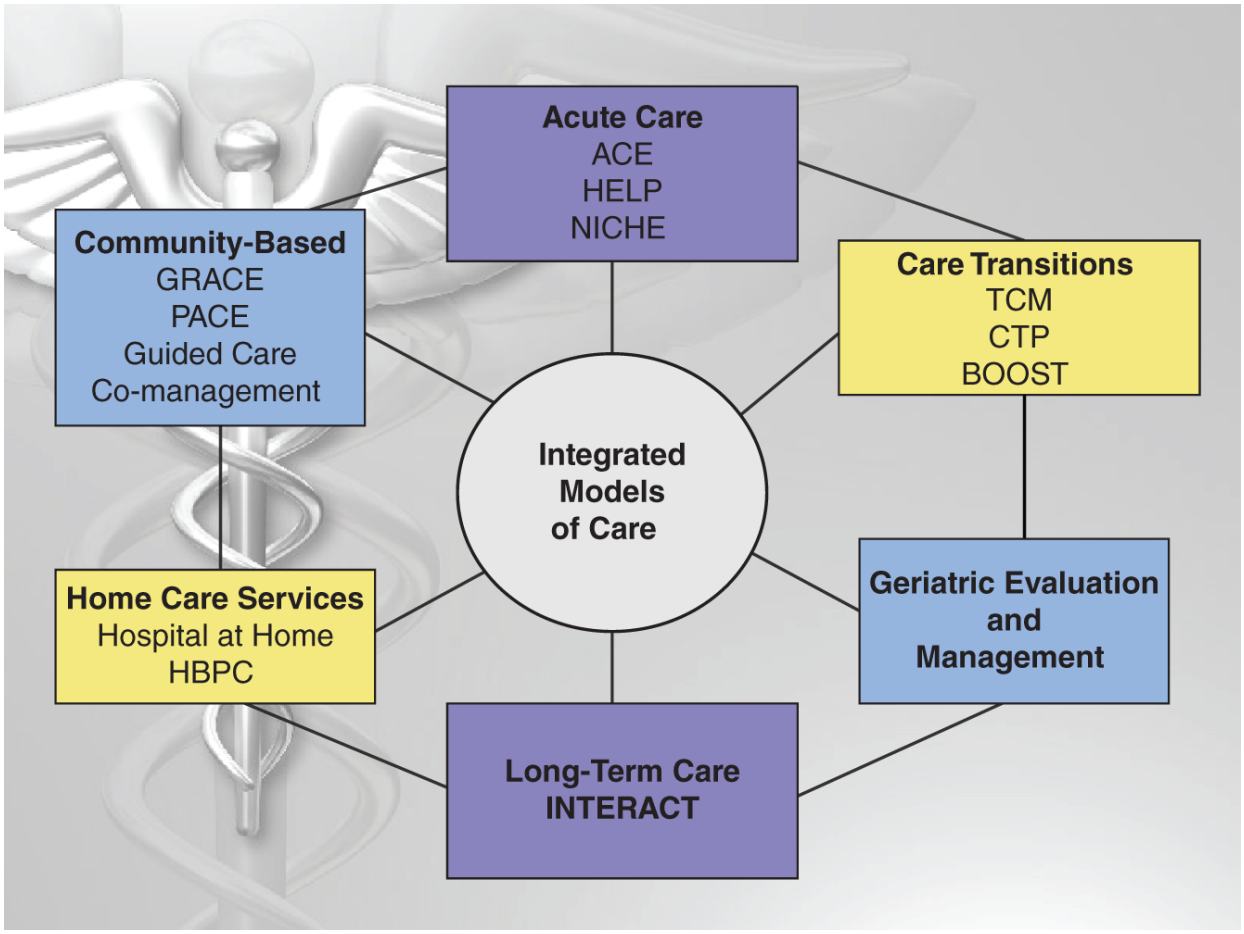


FIGURE 14-1. Integration of a portfolio of geriatrics models to provide best practice strategies at multiple sites. ACE, Acute Care for Elders; BOOST, Better Outcomes for Older Adults Through Safe Transitions; CTP, Care Transitions Program; GRACE, Geriatric Resources for Assessment and Care of Elders; HBPC, Home-Based Primary Care; HELP, Hospital Elder Life Program; INTERACT, Interventions to Reduce Acute Care Transfers; NICHE, Nurses Improving Care for Healthsystem Elders; PACE, Program of All-Inclusive Care for the Elderly; TCM, Transitional Care Model.

Hospital-Based Models

Acute care for elders The ACE model is designed to prevent functional decline and to restore independent physical functioning in hospitalized, medically ill patients. The intervention merges principles of geriatric assessment with continuous quality improvement to prevent dysfunctional syndrome (**Figure 14-2**) that results from hostile physical environments and processes of care, and negative expectations of caregivers and patients. Essential elements of the ACE program include a prepared environment to enhance patient safety and independent functioning; patient-centered guidelines for patient assessment and management by nurses; medical care review to assure appropriate and safe medical care; and interdisciplinary team (IDT)-based care, that includes planning the patient's transition to home or postacute care setting. Daily IDT rounds briefly review each admission, with attention to the patient's functional status, principal diagnoses and treatments, anticipated hospital length of stay, and postacute care needs and expectations. The original model's intervention is targeted at patients who are admitted to the ACE unit for any general medical illness. ACE units are designed to foster independent patient functioning in a safe physical environment. The ACE unit "prehab" package of interventions (see **Figure 14-2**) was informed by prior publications of acute hospital care of seniors, and models of care in outpatient and rehabilitation services.

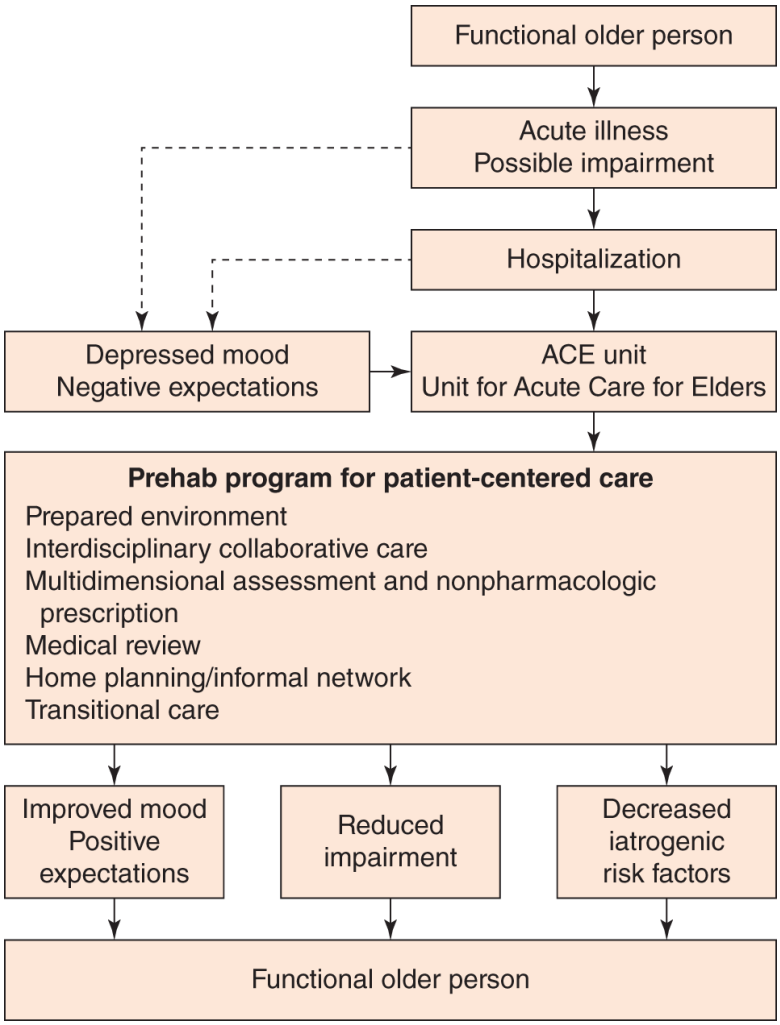


FIGURE 14-2. The conceptual model of the acute care for elders interventions to prevent hospital-acquired disability. (From Palmer RM, Counsell S, Landefeld CS. Clinical intervention trials: the ACE unit. *Clin Geriatr Med.* 1998;14(4):831–849.)

The ACE program also pays attention to patients' needs throughout their hospitalization and coordinates transitions of care based on function, cognition, and social situation. The IDT includes a geriatrician as medical director, geriatrics clinical nurse specialist (CNS), trained registered nurses, social worker, dietitian, and physical and occupational therapists. In the initial ACE unit model attending physicians and internal medicine residents are welcomed to participate in IDT rounds or, if unable, to review their plan of care with the bedside nurses. In select situations the team arranges for family/patient conferences to review diagnosis, therapies, advanced directives, and anticipated date of transition from hospital to home. Later iterations of the ACE unit include clinical pharmacists, chaplains, and hospitalists in the IDT.

The ACE model was initially studied on a medical-surgical nursing unit (the ACE unit). Three randomized clinical trials confirm the benefits of the ACE unit compared to usual care. Compared to patients receiving usual care those admitted to the ACE units are discharged with less disability, and a shorter hospital length of stay. They are less likely to transition to a skilled nursing facility. Total costs of hospitalization are slightly lower on the ACE unit. Trends toward less hospital-associated disability at discharge were shown in one study, with lower rates of disability or nursing home placement 1 year later. Caregivers, nurses, and physicians report higher satisfaction with patient care on the ACE unit compared to usual care. Other benefits of ACE demonstrated in the clinical trials and programs with elements similar to ACE included fewer patient falls and use of physical restraints, better performance-based mobility, and reduced 30-day hospital readmissions. The most consistent outcomes of trials of ACE are significant reductions in length of hospital stay and costs. These findings provide compelling evidence that ACE units present health care systems an opportunity to realign the goals of improving the patient experience, providing high-quality care, reducing costs, and avoiding hospital-acquired conditions (consistent with the "triple aim").

The strength of ACE units is their scalability in a health care system or large hospital. Targeting is limited, making admission criteria simple. Patient care is more efficient than usual care and additional costs for startup of the unit are modest compared to usual care once a unit is mature and necessary environmental alterations have been completed.

The major limitations of an ACE unit include the limited number of older patients who can be admitted to a small unit; the costs of initial model rollout, including training of nurse and team members; assembly and maintenance of the IDT; and the need to capture important metrics that demonstrate the "value proposition."

Where an ACE unit is not feasible or unable to meet the needs of many older patients the ACE program is modifiable as a "virtual ACE unit," ACE without walls, or a mobile ACE program. The concept of an ACE unit is preserved, despite loss of unique environmental adaptations, as long as these programs attempt to maintain fidelity to the four core components: safe environment, patient-centered care, and interdisciplinary team rounds to review medical care, and preparing for transitions.

The Mobile Acute Care of the Elderly (MACE) model consists of an interdisciplinary team of geriatricians, social workers, and clinical nurse specialists who consult on and provide care for older adult patients on medical-surgical units. In a clinical trial the MACE service is associated with lower rates of adverse events, shorter hospital stays, and improved satisfaction with transitions of care. Where a geriatrician is not available in a hospital, a quality improvement approach is the e-Geriatrician consultation and an automated electronic medical record spreadsheet of relevant items, called the ACE Tracker. Consultation can be offered off campus and the ACE Tracker provides a spreadsheet of quality measures, geriatric conditions, and risk factors for adverse outcomes, such as falls and pressure ulcers. The ACE Tracker informs the IDT of changes required in patient care.

ACE consult service In the ACE consult service, the consultation model applies the same core principles as ACE without the unique environment; consultation is performed by an interdisciplinary team that assesses the patient's functional status, and participates in direct patient care. Geriatric consultation can adapt to multiple clinical settings in the hospital. Geriatric consultations focus on clarifying diagnoses, goals of care, and addressing polypharmacy, delirium, dementia, failure to thrive, elder abuse and neglect, malnutrition, and depression. Through a detailed review of the medical record and by obtaining key information from caregivers and family, geriatric consultations provide recommendations to the primary team based on the description of geriatric syndromes and input from other disciplines. In some variations of the consult model the IDT provides comanagement with the primary team (eg, on gero-orthopedic units).

Hospital Elder Life Program HELP is a multicomponent intervention designed to prevent incident delirium in hospitalized older patients. The intervention consists of six standardized protocols for reducing specific risk factors for delirium: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. The intervention is targeted at patients aged 70 and older with at least one evidence-based risk factor for incident delirium (**Figure 14-3**). The HELP intervention is conducted by the interdisciplinary HELP team. The team includes an advanced practice or geriatric-trained nurse, the Elder Life specialist, a geriatrician, and a program coordinator—the Elder Life Nurse specialist. The Elder Life Nurse specialist trains volunteers and oversees the interventions. The delirium prevention strategies are carried out by highly trained and supervised volunteers. The HELP team collaborates with a unit-based interdisciplinary team that includes nursing, medicine, physical therapy, occupational therapy, pharmacy, nutrition, and chaplaincy care. The HELP team assesses and enrolls patients that meet specific criteria and designate the delirium prevention strategies based on each patient's needs. The HELP prevention strategies (see **Figure 14-3**) include a daily visitor program, therapeutic activities, an early mobilization program, nonpharmacologic sleep protocol, oral volume repletion, and a feeding assistance program.

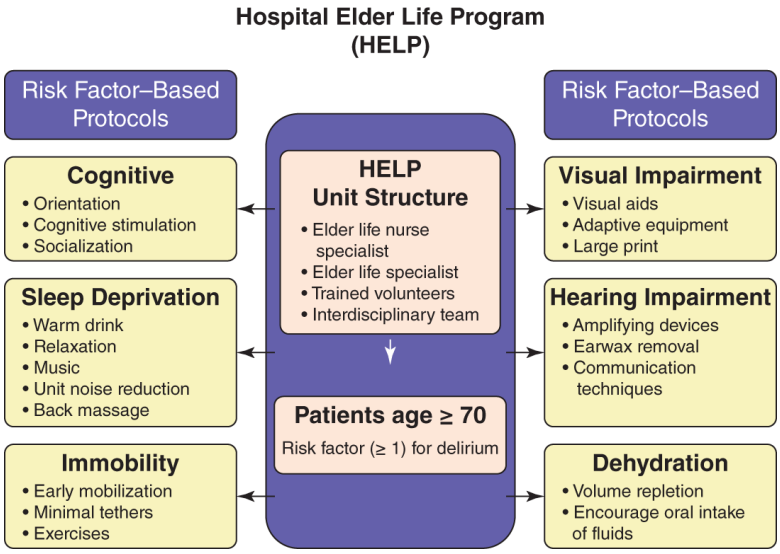


FIGURE 14-3. The Hospital Elder Life Program.

The effectiveness of HELP was demonstrated in a prospective, individual-matching strategy, the Delirium Prevention Trial. The incidence of delirium was reduced by 40% among patients receiving the HELP intervention compared to the control group receiving usual care. The days spent delirious and the total episodes of delirium were significantly lower in the intervention group, although the severity of delirium and delirium recurrence rates were not lower. The individual attention given to each patient by the volunteers and IDT improve quality of care and reduce risks of hospital-associated conditions. The HELP program has become widely disseminated, with 200 programs spanning 32 states and 11 countries. It is often integrated with other models, such as ACE units and Nurses Improving Care for Healthsystem Elders (NICHE). The HELP model allows some flexibility in fidelity to the original model design. The national HELP program assists individuals to launch HELP by gaining support of hospital administration and staff. Hospitals that register for HELP assistance gain access to HELP manuals, training videos, handouts for families and caregivers, and information about national and local conferences.

HELP can be replicated and successfully launched in medical units, surgical units, telemetry units, intensive care units, emergency departments, and nursing home settings. HELP has been demonstrated to be both effective and cost-effective for patients at moderate risk of delirium. HELP has also shown to improve quality of care of hospitalized older patients and improved patient and family satisfaction with care.

In multiple studies, HELP has been consistently associated with lower rates of delirium, functional decline, and cognitive decline, and decreased hospital length of stay and decreased rate of hospital falls. The effectiveness of HELP is directly related to adherence to the interventions and protocols. Limitations of the original HELP program include the need for trained volunteers. Recent adaptations of HELP give hospitals the option of using nonvolunteers. Some HELP programs have failed but the most successful have seen expansion of the program to many medical-surgical units and have documented substantial cost savings to their hospital. HELP offers geriatricians superb opportunities: (1) to transform quality and safety of patient care at their hospital, (2) to be an expert consultant to the HELP team, and (3) to be a leader in interdisciplinary team care.

Nurses Improving Care for Healthsystem Elders

NICHE is a nursing care model designed to help hospitals and other health care organizations to improve quality of care for older adult patients and nurse competence in geriatric practice. The program has several approaches to infuse evidence-based geriatric best practices into hospital care. At the foundation of NICHE is the model of the Geriatric Resource Nurse (GRN). The GRN prepares staff nurses to serve as the clinical resource on geriatric issues to other nurses on a medical-surgical unit. Through education and modeling by a NICHE coordinator, educational protocols and tools enable nurses to implement best practices. NICHE focuses on improving nursing skills and knowledge when caring for older adults by providing training tools to hospitals and health care organizations. NICHE promotes the use of interdisciplinary teams and helps nursing staff to apply evidence-based concepts to care for older adults. NICHE provides tools for best practices to manage pain and prevent pressure ulcers, adverse medication events, delirium, falls, and the management of urinary incontinence. At a system level NICHE provides a structure for nurses to collaborate with other disciplines and coordinate geriatrics models of care. Hospitals can achieve NICHE designation to

demonstrate the hospital's commitment to improving quality and enhancing the patient experience. Nearly 500 hospitals in the United Sates and several other countries are NICHE-designated. Many ACE units and HELP programs are based in hospitals with NICHE designation.

This model of care can be implemented in hospitals, long-term care facilities, and home health care practices. NICHE principles and resources are consistent with professional nursing practice models. The NICHE program affords geriatricians the opportunity to collaborate with GRNs to promote geriatric quality of care and patient safety across the care continuum.

CARE TRANSITIONS MODELS

Care transitions are designed to reduce the risk of hospital readmissions of vulnerable older patients. Unplanned readmissions to hospital within 30 days of discharge are considered a quality of care and safety issue as a readmission might be preventable with improved medical care and handoffs across providers. While models of acute care such as HELP and ACE might prepare patients for care transitions, they provide no direct intervention after the patient leaves the hospital. However, several models of care (during or at the end of the patient's hospitalization) have demonstrated effectiveness in reducing readmissions and costs of care.

Transitional Care Model The Transitional Care Model (TCM) is designed to improve the process of comprehensive discharge planning of a vulnerable older patient after an acute medical or surgical illness and to assure timely follow-up and nursing interventions after discharge. The intervention is conducted by a trained transitional care nurse—an advanced practice nurse or registered nurse. The nurse performs discharge planning early in the hospitalization with the patient, family, attending physician, and other health professionals; and provides home care and telephone consultation for an average of 2 months following the patient's transition to home. The TCM interventions include comprehensive assessment of the patient's goals and needs with consideration to the patient's home environment. The transitional care plan, from the hospital to the next level of care, establishes appropriate communication and sharing of information among other sites of care. Patients and families are actively involved in the patient's management. In randomized controlled trials the TCM intervention reduced 30- and 90-day hospital readmissions and total days of readmission, and reduced total costs of care for 90 days following discharge. In one study, the intervention reduced the readmission rate after 1 year by 36% and net costs by 38% in the year after discharge. Further analyses demonstrate the cost-effectiveness of the TCM. With health care reform, the TCM is attractive to ACOs and providers of integrated health delivery systems.

Care Transitions Program The Care Transitions Program (CTP) is designed to reduce hospital readmissions of vulnerable older patients. The care transitions intervention is based on four pillars and is implemented by a care transitions coach at the time of the patient's transition from the hospital (**Figure 14-4**). In the initial model a geriatric nurse practitioner meets with the patient and family at the time of discharge or within a day. The patient and family are trained by the transition coach in medication self-management, the creation of a patient-centered record (personal health record), effective communication with the primary care physician or specialists, and "red flags" that identify worsening of symptoms and how to respond. The transition coach does not provide direct patient care services, but makes at least two home visits in the month following hospital discharge. A randomized controlled trial of hospitalized older patients with at least one risk factor for unplanned readmission demonstrated reduced readmissions within 30 days by 30% and reduced readmissions within 180 days by 17%, and produced an estimated 15% net savings in total hospitalization costs 6 months after the intervention. The relatively low cost of the care transitions intervention and the current process of training of non-nurses as transitions coaches have made the model of care very attractive to health care systems. The Affordable Care Act supports transitional care services through the Center for Medicare and Medicaid Innovation Programs, enabling the CTP to emerge as a widely disseminated model of care.

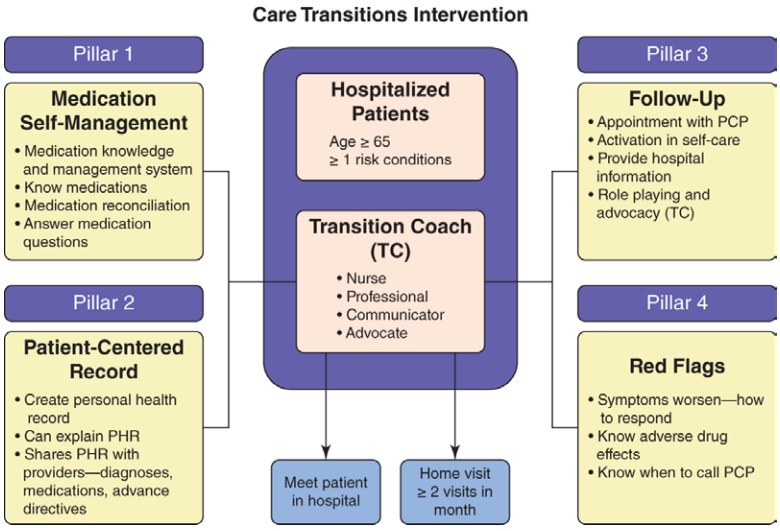


FIGURE 14-4. The Care Transitions Program.

Project Re-Engineered Discharge Although a clinical trial of middle-aged patients admitted to a single safety net hospital was the starting point for this model, Project Re-Engineered Discharge (RED) offers insights to effective care transitions of older patients. RED is founded on 12 discrete, mutually reinforcing components designed to reduce rehospitalizations and create high patient satisfaction. In Project RED, registered nurses (patient advocates) assess patients before their discharge, assist patients in the discharge planning process by setting up follow-up appointments, coordinate discharge planning with the multidisciplinary team, and send discharge summaries to primary care physicians. The clinical pharmacist contacts patients 2 to 4 days after discharge to review their medication list and consult with the primary care physicians, as needed. The RED intervention reduced the combined rate of 30-day readmissions and emergency department visits by 30%. Project RED patients were significantly more likely to be seen by their primary care physician after discharge than patients receiving usual care. Coordinated hospital care, pharmacy consultation, and early follow-up by primary care providers appear to account for the success of Project RED.

Better Outcomes for Older Adults Through Safe Transitions Project Better Outcomes for Older Adults Through Safe Transitions (BOOST) is a quality improvement program developed by the Society of Hospital Medicine designed to optimize the hospital discharge process and improve information transfer and communication among health professionals at the time of a patient transition from hospital to postacute care. The BOOST model design is influenced by other care transition models of care, notably the Transitional Care Program. Project BOOST creates a consistent, coordinated, and safe approach to care transitions that manifests in patient satisfaction, 30-day hospital readmission rates, optimized transitions, and effective communication between and among professional caregivers.

The BOOST developers created a tool for adjusting risk of readmission and preparation for transitions of care. Interventions include a list of items demonstrating general assessment of preparedness for transition from hospital and a checklist of items to review during hospitalization to prepare for care transitions. A structured approach to medication reconciliation is offered using practical tools. Medications are reviewed with the patient and/or caregiver and understanding is assessed through patient teach-back. Teach-back is also used to summarize principal diagnoses, treatments, and plans for postacute care. Communication with other providers is assured through personal communication and a discharge summary that includes principal diagnoses, reconciled medications, complications of hospitalization, appointments for outpatient tests and clinical visits, and a list of relevant contact information.

The BOOST program offers instruction and consultation to hospital teams to help them implement the program, to perform quality improvement, and to identify measures of patient safety. Project BOOST includes a comprehensive implementation guide with step by step instructions and project management tools to help interdisciplinary teams redesign hospital transitions. In-place training and expert mentoring and coaching is offered to hospitals that adopt the BOOST interventions. Teams in the hospital receive training, a curriculum for nurses and case managers, advice in how to roll out the intervention, and access to networking with other BOOST hospitals. As of 2014, BOOST has been implemented at 180 hospitals across the country.

Early experience with BOOST suggests that 30-day hospital readmissions are somewhat lower following implementation of the BOOST program as shown in the first cohort of six hospitals. The tools are welcomed by health care teams and patients with an overall positive response to the program.

COMMUNITY-BASED MODELS

Geriatric Evaluation and Management

At the heart of outpatient evaluation of at-risk (vulnerable) frail older patients is the process of comprehensive geriatric assessment (CGA). In 1987, CGA was defined in the National Institutes of Health Consensus Conference on Geriatric Assessment Methods for Clinical Decision Making as a "multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described, and explained, if possible, and in which the resources and strengths of the person are catalogued, need for services assessed, and a coordinated care plan developed to focus interventions on the person's problems." In CGA, an interdisciplinary team of health care professionals assesses the senior's medical, functional, psychosocial, nutritional, and environmental needs and submits recommendations to the patient's primary care physician. Early clinical studies of outpatient consultative CGA suggested that CGA can improve some outcomes of care, but randomized clinical trials were largely disappointing.

In meta-analysis, the evidence supporting improved health outcomes of at-risk seniors was found to be better when the process of CGA was integrated into a practice of interdisciplinary evaluation and management, recognized as GEM, in a senior health clinic or an outpatient consultative practice where an interdisciplinary team assumes comanagement of the patient with a primary care physician. The GEM model enables the interdisciplinary team to assume responsibility for the diagnostic and therapeutic management of the at-risk senior, either in the short term or in continuing comanagement with the primary care physician.

One study compared the effectiveness of outpatient GEM compared to usual care. Eligible patients were aged 70 and older and at risk for hospital readmission. After assignment to the intervention, the primary care physician's permission to participate was obtained, a home visit was made by the social worker, and a history and physical examination was performed by a nurse practitioner in the clinic and subsequently by a geriatrician and nurse. The team set priorities for the intervention including a plan of care and specific activities. The GEM team assumed primary care until individual items of the intervention were completed. On average, the GEM intervention lasted 6 months, after which the patients returned to their primary care physicians for ongoing care. Patients assigned to GEM over the 12 to 18 months of the study were less likely to lose functional ability, to report health-related limitations in daily activities, to have possible depression, or to use home care services. GEM patients and their primary care physicians expressed high satisfaction with the intervention. Caregivers of GEM patients were significantly less likely to experience increased burden. Costs of the intervention were considered reasonable and total Medicare payments were not significantly different between the two groups. Other studies of GEM have demonstrated improved outcomes on measures of quality of life but have not demonstrated significant cost savings. The outpatient GEM model is attractive to geriatricians who would enjoy providing both consultative and continuing care to at-risk seniors. The GEM model is particularly attractive to health care systems that enroll Medicare Advantage (capitated) patients, as downstream benefits could result in cost savings. However, other models of care that are more comprehensive or less expensive may prove more cost-effective than outpatient GEM consultation.

Geriatric Resources for Assessment and Care of Elders

The GRACE model of care of primary care was developed specifically to improve the quality of care for low-income seniors. The model is designed to integrate geriatric and primary care services across the continuum of care in expectation that patients will receive the recommended care. In the original model, eligible patients for the GRACE program are aged 65 or older, have an established primary care physician, are patients in the community-based health centers of a large health system, and have an income less than 200% of the federal poverty level. The intervention includes a support team of advanced practice nurse and social worker who help provide care for seniors in collaboration with the patient's primary care provider and a geriatrics interdisciplinary team led by a geriatrician. The nurse practitioner and social worker support team performs an initial and annual in-home comprehensive geriatric assessment. The assessment includes medical and psychosocial history, medication review, functional assessment, and review of social supports and advanced directives. Their findings and recommendations are reviewed with the interdisciplinary team and recommendations are summarized and discussed by the support team with the primary care physician. The interdisciplinary team also includes a pharmacist, physical therapist, mental health social worker, and community-based services liaison from the primary care practice. Based on the assessment and interdisciplinary team meeting, one or more of 12 GRACE protocols are activated. The protocols target common geriatric conditions: advance care planning, health maintenance, medication management, difficulty walking/falls, chronic pain, urinary

incontinence, depression, hearing loss, visual impairment, malnutrition or weight loss, dementia, and caregiver burden. Relevant features of the intervention also include use of an integrated electronic medical record and a web-based care management tracking tool. GRACE collaborates with an affiliated pharmacy, mental and home health services, and community-based and inpatient geriatric care services.

A randomized controlled trial of the GRACE intervention was conducted with patients who met eligibility criteria and were assigned to either usual care by their primary care physician or to the support team and geriatrics interdisciplinary team collaboration with the primary care physician. High-risk patients enrolled in GRACE had fewer visits to emergency departments, fewer hospitalizations and readmissions, and reduced hospital costs compared to the control group. The 2-year program significantly reduced costs per enrolled high-risk patient by the second year. In addition, GRACE was rated highly by primary care physicians compared to usual care. GRACE-enrolled patients also reported higher quality of life compared to those in the control group for general health, vitality, social function, and mental health. The interdisciplinary team meeting occurred within 30 days of enrollment for 85% of patients, an average of 5.3 GRACE protocols were activated for each patient, and adherence to GRACE interdisciplinary team suggestions was very high.

The GRACE model of care appears to be cost-effective for patients who are at high risk for hospital readmission and medically indigent, and who receive medical care in a health care system that provides a wide array of supportive services. A barrier to a greater implementation of the GRACE model of care is that only 10% of its costs are covered by fee for service Medicare. However, it appears to be ideal for managed-care practices and potentially for ACOs.

Several other hospitals, academic medical centers, and Department of Veterans Affairs Medical Centers have adopted the GRACE model of care. The GRACE model has been expanded to chronically ill homebound older patients as a home visitation program that includes physicians, nurse practitioners, and social workers. GRACE has been used successfully as a care transitions program for older adults who are discharged home from a hospital or skilled nursing facility. GRACE has the potential to provide coordinated care management of enrolled patients across the care continuum with shared responsibility between patients, medical care providers, and the core team. It affords geriatricians an opportunity to serve in a consultative role to the interdisciplinary team and to be the primary care physician in various settings. The geriatrician's expertise in chronic care management, interdisciplinary team care, knowledge of geriatric conditions, and training in systems-based practice brings value to the health care system and funders.

Program of All-Inclusive Care for the Elderly

Program of All-Inclusive Care for the Elderly (PACE) provides comprehensive primary care for participants who are aged 55 or older, certified by their state to be eligible for nursing home care, able to safely continue living in the community with services, and living in a PACE service area. The goal of PACE programs is to enable the participants to remain living in the community for as long as it is safe and feasible. Each PACE site receives capitated payments from Medicare and Medicaid, with funds covering health-related services required by participants. A comprehensive core of services are provided at each PACE site ranging from primary care, specialty consultation, hospital and emergency services, and long-term nursing home care. The services are primarily provided at a day health center, which in addition to medical care, provides nursing services, physical and occupational therapy, recreational therapies, meals, nutrition services, social work, and personal care. PACE also covers home health and personal care costs, necessary prescription drugs, social services, respite care, and specific medical services, primarily at the day health center. An interdisciplinary team of professional and nonprofessional staff review goals of care with participants and family members; and meet frequently to review health status of participants to identify additional services or equipment that could enable the enrollees to remain living at home, and to support caregivers' needs. As a capitated program that is financially responsible for all Medicare and Medicaid-related services, the PACE site is incented to provide services that enable the enrollees to remain living in the community and to avoid unnecessary hospitalizations or medical interventions and therapies. PACE and the interdisciplinary team have flexibility for deciding how to pay for a participant's medical and nonmedical expenses that enable them to remain living at home. This flexibility enables PACE programs to provide services or durable medical equipment under the capitation model that are not typically covered by either Medicare or Medicaid. Nationally, most participants are older, have multiple morbidities and deficits in activities of daily living, and about 50% have dementia.

As of 2014, 104 PACE programs were operational in 31 states. Although PACE programs serve primarily dual-eligible participants, the Patient Protection and Affordable Care Act created an optional long-term care insurance plan that could be used to pay for community services such as PACE, creating the potential for an increasing enrollment in

programs. Current barriers to enrollment in PACE programs include delays in enrollment of participants, limited number of sites in rural communities, lack of awareness of the program, and the requirement that enrollees transfer primary care to the PACE program.

Cross-sectional and cohort studies generally demonstrate that PACE programs enable enrollees to remain living in the community. Especially in mature programs, health care costs, hospitalization and readmission rates, and survival are better among enrollees in PACE compared to usual medical care settings that include case management and local community services. With its focus on chronic disease management, interdisciplinary care, and system-based practice, PACE is an attractive model of care for geriatricians.

Guided Care

Guided Care is a model of interdisciplinary team care for older patients with multiple morbidities. It provides primary care coordinated by a registered nurse, working with the patient's primary care physician practices, that includes comprehensive geriatric assessment, evidence-based care plans, case management, transitional care, self-management, and caregiver support. The specially trained registered nurse provides eight services to a panel of 50 to 60 of the primary care practice's older patients who are at high risk for health care use in the following year. The Guided Care nurse performs a comprehensive assessment at the patient's home and creates an evidence-based care guide with a patient-friendly action plan. The nurse monitors the patient monthly, serves as a liaison with the patient's providers, and educates and advocates for patients and family caregivers across appropriate community resources. In a cluster randomized controlled trial of older patients at three sites, the Guided Care intervention reduced the use of home health care overall. In addition, Guided Care reduced admissions to skilled nursing facilities in one staff-model health maintenance organization. Caregivers of patients enrolled in the intervention group reported significantly lower levels of depressive symptoms and caregiver strain. Quality of care of multimorbid conditions was improved and primary care physicians had high satisfaction with the model. There was a nonstatistically significant decrease in use and costs of medical care.

Nurse Practitioner Comanagement

Two clinical trials demonstrate the value of a nurse practitioner (NP) or advanced nurse to comanage patients with primary care providers. A NP comanagement model enhanced an earlier experience with the Assessing Care of Vulnerable Elders-2 (ACOVE-2) model of case finding, which is designed to improve primary care for falls, urinary incontinence, and dementia. The ACOVE-2 intervention added a NP to help comanage the geriatric conditions with primary care physicians. In a clinical trial of patients aged 75 and older with a positive screen for at least one of the three conditions, a NP provided comanagement for approximately half of patients and more than half of them received the recommended care. Quality scores for each condition were significantly better for patients receiving the NP comanagement. Results suggest that referral to a NP by primary care physicians enhances quality of care of a geriatric condition.

A clinical trial tested the effectiveness of collaborative care for older adults with Alzheimer disease in primary care practices. The intervention provided 1 year of care management by an interdisciplinary team led by an advanced practice nurse working with the patient's caregiver and primary care team. Standard protocols were used to initiate treatment and to monitor patients for behavioral symptoms of dementia, with a focus on nonpharmacologic management. Neuropsychiatric inventory symptoms were significantly reduced in the intervention group. Caregivers had significant improvement in caregiver stress.

HOME CARE MODELS OF CARE

Hospital at Home

The Hospital at Home model of care is targeted at older patients who are eligible for inpatient admission and who agree to treatment in their home as an alternative. In the initial model, patients requiring admission to the hospital for treatment of one of the target diagnoses are identified in the emergency department or outpatient setting. The sample is community-dwelling patients aged 65 and older with one of four targeted illnesses: community-acquired pneumonia, exacerbation of chronic heart failure, exacerbation of chronic obstructive pulmonary disease (COPD), or cellulitis. Eligible patients have to be medically suitable for home treatments. Hospital at Home patient care consists of direct nursing care, provision of medical equipment and medications needed for treatment of the acute illness, and evaluation

by a Hospital at Home physician either in the emergency department or shortly after the patient returns to home. Common diagnostic studies can be obtained at home. The patient is discharged when stable and transitioned to their primary care physician for medical follow-up. In a nonrandomized, controlled study, comparing eligible patients admitted to the hospital to those patients who were admitted to the Hospital at Home, length of stay was significantly shorter, patient and caregiver satisfaction was high, and delirium incidence and cost of care were lower. Acceptance of the Hospital at Home was high among patients and the intervention was found to be safe. Barriers to dissemination of the model currently exist, but with health care reform the model is more likely to become widely adopted. The model offers opportunities for geriatricians to be directors of the program and to provide the home-based acute care.

Home-Based Primary Care

Home-Based Primary Care (HBPC) focuses on the frailest subset of older adults, those with severe and disabling chronic illnesses who receive primary care in their home. The model is implemented in over 150 sites of the Veterans Affairs Medical Centers. Common conditions or illnesses of HBPC recipients include dementia, congestive heart failure, diabetes mellitus, COPD, stroke, and severe arthritis. The program delivers care coordination at home with a team of geriatricians, nurse practitioners, social workers, licensed practical nurses, and office coordinators. Periodic follow-up by members of the team is complemented by on-call telephone coverage. Studies demonstrate improved quality of life of enrolled patients.

Independence at Home

A Center for Medicare and Medicaid Innovation program, with similarities to HBPC, Independence at Home is currently being implemented at multiple sites. The model of Independence at Home has potential value for frail older patients who may be unable to make follow-up visits with a primary care physician in office due to disease complexity or frailty. The patient is seen for a first home visit within 24 to 72 hours of hospital discharge. A comprehensive evaluation of their physical, medical, and functional needs, and of their caregiver's needs, is included in this first visit. Follow-up visits involve close contact between the nurse practitioner and home health agency. Analysis of administrative data demonstrates that the model is associated with a decrease in the use of hospital resources and cost reduction. In a case-controlled study of Medicare patients enrolled in a home care intervention, total costs were 17% lower over a mean of 2 years of follow-up. With the aging of the very old population and financial incentives favoring home care versus hospital or institutional treatment of frail patients, Independence at Home offers opportunities for geriatricians to become both directors of programs and providers of home care.

LONG-TERM CARE–BASED MODELS

Interventions to Reduce Acute Care Transfers

Interventions to Reduce Acute Care Transfers (INTERACT) is a quality improvement program designed to assist skilled nursing facilities with early identification, assessment, intervention, documentation, and communication of changes in a resident's condition. The goal of INTERACT is to reduce potentially avoidable hospitalizations and to improve information transfer when admissions are appropriate. INTERACT is a publicly available program that includes a wide variety of resources to enable skilled nursing facilities to improve their clinical assessment and evaluation of residents who are at risk of hospital transfer and admission. Initially funded by the Center for Medicare and Medicaid services, INTERACT has evolved in its scope of educational tools and programs. The INTERACT website provides resources to nursing facilities to help implement the quality improvement program. The tools can be easily incorporated into health information technology. Quality improvement tools include a hospitalization tracking tool that can calculate readmission rates and a tool to perform root cause analysis of an individual transfer.

Communication tools are important clinical features of INTERACT. The focus of INTERACT is the management of acute change in condition. The "Stop and Watch" tool is an early warning instrument for use by certified nursing assistants to empower them to identify acute changes in a resident's condition that should be brought to the attention of the nurse. When the nurse believes that additional information is needed, an SBAR (situation, background, assessment, recommendation) is completed prior to calling or communicating with the primary care clinician. A hospital-to-postacute care transfer form includes information that is critical to provide to the receiving emergency department and health care providers. The INTERACT decision-support tool includes care paths for common clinical conditions and change-in-condition file cards. Advance care planning tools guide the completion of advance care plans to identify

patient's goals-of-care. Quality improvement studies of INTERACT conducted in 25 nursing homes in three states, demonstrated a reduction of 17% in self-reported hospital admissions among participating nursing homes compared to 6 months prior to INTERACT. In facilities with high engagement in the program the readmission rate was reduced by 24%. Initial analysis suggests that the savings to Medicare are substantial, creating opportunities for nursing homes to meet regulatory requirements for quality assurance initiatives. By advancing the adoption of INTERACT, geriatricians in the roles of medical directors, have an excellent opportunity to influence quality of care and patient safety and to engage in quality improvement projects.

MODELS OF CARE: LESSONS LEARNED

Lessons Learned in Implementing Models of Care

There are several important points to share with the reader as they move from studying a geriatrics model to the actual implementation of a model. The implementation of a geriatrics practice model is an exciting and fulfilling aspect of a geriatrician's career. We will provide a few tips to help the reader be effective in this role. A strong understanding of the science of the model is required, but not sufficient in deploying geriatrics models.

First of all, geriatrics models have to be deployed to address the problems in the health care delivery system at the site in which they receive care. An example would be if hospitalists are struggling with a high rate of delirium among their older patients. In this context, the geriatrics leader must lead the development of a delirium prevention model (eg, HELP) with the engagement of the hospitalists. Identifying and addressing the contextual issues will increase the chance of successfully launching the model of care. The context further includes the culture of your organization and the economics of payment for health care at your site.

Second, to start a geriatrics model, the leaders will need to study their practice and measure their current performance when compared to other sites. This assessment defines the need for the new model of care. Toward this effort one should partner with the administration of your hospital to study the problems at hand. Such a partnership with the hospital administration provides a good working relationship toward improving care.

Third, your planning team needs to develop a business plan and a communication plan with the hospital administration, in an effort to get approval to proceed with model implementation. This plan outlines the costs and the potential savings of the geriatrics model. The philanthropy (or development) office can assist in launching your model by reaching out to prospective donors and securing grant funds to cover startup costs. Often the geriatrics leaders present a description of the new model and the business plan to an administrative executive team to get input and buy-in. The geriatrics leaders should make sure that the administration has agreed to the model before moving forward with full implementation. Once your planning team has gotten the agreement from the administration, one needs to define the roles of each team member and determine what the exact intervention entails. Finally, your team will need a communication plan to make sure that all stakeholders and those who are touched by the program understand the model and their roles. In summary, there are key steps to the implementation of a geriatrics model which can assure that the project is successfully launched.

Lessons Learned in Efforts to Sustain and Manage Models of Care

While it is exciting to launch a geriatrics model, it is more difficult to keep that model going over a long period of time. Six key points deserve some attention in this regard. First, your geriatrics model "planning team" can be converted to an "advisory committee" charged with reviewing outcomes and guiding the project over time. This group can identify challenges and find resources to address the identified needs. The advisory committee is not charged with personnel decisions or day-to-day management of the model. Strongly consider having a patient on this committee to help keep the team patient-centered. An annual report should be provided from the advisory committee to the hospital or funding organization to describe key outcomes and number of lives touched by the geriatrics model.

Second, geriatric models may not initially improve outcomes. The hospital leadership should be able to define the key outcomes and explain if they are able to make a difference. If it appears that the outcomes are not being achieved, the leadership team will need to assess the fidelity of the model and the reliability of the measurement. Leaders may be able to use baseline outcome measures prior to the implementation of the interventions. The postintervention measures can help explain if the model is improving outcomes. The leadership and the advisory team can guide the program, even if initial improvement is not achieved. In advising how to move forward, we have learned to pay careful attention to (1) the communication of the model to key stakeholders, (2) the training of the professionals who

are key personnel in the model, and (3) the assessment/maintenance of the validity of the models.

Third, use yearly personnel goals as a time to align individual employee goals with the goals for your geriatrics model. As an example, the Elder Life Specialist of the HELP model could have as his/her annual goal with the consistent use of all six of the delirium prevention protocols. This effort of using yearly personnel goals helps keep the leaders and the employees focused on achieving full implementation of the geriatrics model. This effort further rewards the employees for their contributions.

The fourth point in sustaining a geriatrics model is to make sure that model leaders continue to communicate with key stakeholders. Physicians and nurses who are providing clinical care will need to understand the importance of excellent care of older individuals in their community. Likewise, other health care professionals will need to understand the program and their role in the geriatrics model. Further, community leaders from the department on aging and the local Alzheimer's Association will need to understand the geriatrics model and how they can partner with your programs.

Fifth, careful attention to the economics of your geriatrics model is important. The financial costs and savings of the geriatrics model will be important to sustaining the hospital support for the model. By following these outcomes, your team can responsibly manage resources. You can determine the direct variable costs per patient in your model and compare these costs with those of a matched cohort of patients receiving standard care. This effort can help make the case for further expansion of your program. Partner with an administrative colleague who can help to prepare these reports and can assist with program budgets.

Sixth and finally, consider comparing your outcomes with other sites to try to find "best practices." This assessment may help your team to define what exactly is being done at each site and adjust processes to further improve outcomes.

Lessons Learned in Disseminating Models of Care

A few key points should be described in regard to "scaling up" geriatrics practice models. We have learned that the geriatrics leaders must set and articulate a clear message about how the geriatrics model will be implemented broadly into practice. Your team must get agreement that the goal of spreading the geriatrics model broadly in the hospital is important to the organization's mission. Next, the geriatrics team must mobilize across a wide area to communicate the new model to "early adopters," so that the effort is implemented at new sites. Your message will need to address: Exactly what will be done? Who is eligible for the model and who is not? What will be measured to know we have made a difference? The practice model must be communicated to the opinion leaders in the field, so that their input is taken into account as the model is rolled out. Finally, the model needs to be assessed regularly to make sure that the fidelity is maintained. This means that you are doing what you said you would do. In summary, one of the most difficult aspects of implementing geriatrics models is the broad dissemination of that model into standard practice. The role of the geriatrician in this work is to lead a broad coalition of health providers toward a common goal of better care for older patients.

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Chapter 15

Transitions in Care

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Learning Objectives

- Describe what a care transition is and identify different types of transitions in care commonly experienced by older adults.
- Understand how health system fragmentation and communication failures lead to poor-quality care transitions.
- Identify outcomes of poor-quality care transitions and how these outcomes affect patients, caregivers, and the health delivery system.
- Describe features of effective transitional care and transitional care interventions.

Key Clinical Points

1. **Older adults are at increased risk for experiencing adverse outcomes following poor-quality transitions in care.**
2. **Effective communication lies at the core of safe transitions, especially for vulnerable older adults including those with cognitive impairment.**
3. **Providers managing care transitions should actively engage both the patient and their identified caregiver in decision making about and in preparing for care transitions.**
4. **High-quality transitional care programs can improve posthospital outcomes.**

INTRODUCTION

Older adults regularly experience changes in health status that contribute to frequent transitions between different levels and settings of care. These movements within and across care settings are commonly referred to as "transitions in care," and typically involve the management of a patient's care passing from one team of providers to another. Transitions in care are widely recognized as a point of heightened vulnerability for lapses in patient safety, as patients are at risk of "falling through the cracks" due to inadequate care coordination, preparation, and support prior to and during the transition period. Inadequate care coordination and management of care transitions contribute to $25 to $45 billion in unnecessary care costs resulting from hospital readmissions and other avoidable complications. Poor-quality transitions in care also contribute to substantial patient and caregiver stress and dissatisfaction. For these reasons, there is a sense of urgency in the United States to improve care management and coordination during transitions in care.

Older adults are at particularly high risk for experiencing adverse events during transitions in care. This is likely due to a number of factors including their disproportionately high rates of utilization of a range of different acute and postacute health services, increasing rates of multiple chronic conditions, and higher rates of cognitive impairment which may limit their ability to communicate or recognize care needs.

This chapter provides an overview of transitions in care commonly experienced by older adults in the United States and discusses "transitional care," which is defined as a set of actions designed to ensure the coordination and continuity of health care as patients transfer between different locations or different levels of care in the same location. Transitional care is an emerging concept in geriatric medicine and is increasingly recognized as fundamental to

ensuring safe and effective management of both chronic and acute illness in older adults and necessitates the involvement of all members of the interdisciplinary team. This chapter will provide an introduction to care transitions as well as an understanding of effective approaches to improving the management of care transitions for older adult populations.

OVERVIEW ON TRANSITIONS IN CARE

Care System Fragmentation

Numerous factors have been identified that pose barriers to the provision of high-quality transitional care, but one of the most important is health system fragmentation. The higher rates of acute and chronic illness in older adults predispose them to require care across multiple settings or fragments within the US health system, yet the health system fragmentation they experience is a newer phenomenon which has emerged and evolved over the last half-century.

Decades ago, most health care was provided within just a few settings by a small provider team which accompanied the patient across all settings. However, following the implementation of US payment structures which incentivized services, settings, and practices that reduced acute care utilization and length of stay, there was substantial growth in subacute, postacute, hospice, and rehabilitative services. Concurrently, providers became more specialized, with clinical practice increasingly restricted to specific settings (eg, hospitalist, SNFist, emergency medicine physician, etc). While this ideally enabled more cost-effective use of resources at different stages in care, the rapid growth of single-site physician specialists and new service settings represented a fundamental change in the nature of care delivery in the United States.

In the mid-twentieth century, physicians commonly followed their patients across settings of care and specialist services were more often delivered following close communication with a patient's primary provider. It is now common for patients to travel between different settings of care and specialty providers without being accompanied by a consistent provider. For patients, this shift in care delivery has led to large gaps in care during times after discharge from one setting but prior to being seen in the next, where it is unclear who is responsible for the patient's care.

With a shift away from acute care delivery, patients are also discharged from hospital settings sooner and generally more ill, yet they are often not adequately prepared to follow increasingly complex posthospital care plans. These gaps are compounded by minimal and often inadequate communication between care teams across settings, leading to confusion and delays in necessary follow-up care. Additionally, systems have been slow to develop infrastructures capable of meeting patients' needs in this new fragmented care delivery model. However, the need for high-quality transitional care to support patients during these system gaps is increasingly recognized.

Consequences of Poor-Quality Care Transitions

The various adverse consequences associated with poor-quality transitions have been well documented and include a range of undesirable outcomes for patients as well as their caregivers. Communication failures during the posthospital period are common, and may involve the omission of vital elements of a care plan, such as information regarding mobility restrictions or diet orders. This may lead to inappropriate, disjointed, and/or harmful care in the next setting. For example, approximately one-third of patients are discharged with pending laboratory tests that are not communicated to the next setting of care, and at least 10% of these could have led to actionable changes in patient care plans. Medication errors and/or discrepancies, which may be the result of poor-quality medication reconciliation or insufficient patient/caregiver education or support, occur in 30% to 50% of patients in the posthospital period, and, when serious, can lead to a number of adverse events including avoidable rehospitalization, emergency department utilization, and death. Rehospitalization within 30 days of discharge occurs in 20% to 25% of Medicare beneficiaries and is more likely among certain vulnerable populations, such as older adults with cognitive impairment. Research suggests that nearly half of these rehospitalizations could be avoided if better care were provided during transition periods.

Policies Surrounding Transitions in Care

Policy makers in the United States have long recognized poor-quality care transitions as a dangerous and costly health delivery problem. The 2001 Institute of Medicine (IOM) report, *Crossing the Quality Chasm*, described the US health delivery system as complicated, poorly organized, and decentralized resulting in "layers of processes and handoffs that

patients and families find bewildering." The 2010 Patient Protection and Affordable Care Act includes multiple provisions aimed at improving care transitions including provisions that mandate financial penalties for hospitals with higher than projected rehospitalization rates. The legislation also includes financial incentives for the development of care models that enhance coordination, such as the Medicare Shared Savings Program for accountable care organizations (ACOs). ACOs consist of a group of providers who are responsible for providing care for a group of patients across settings. The law authorizes financial incentives for ACOs that successfully keep patients out of acute care while maintaining high-quality care. The legislation also permits payment for care transition services to providers operating as medical home practices, which aim to manage and coordinate care for patients with chronic conditions. Following these policy changes, health systems have shown increased interest in adopting programs, policies, and interventions which improve care transitions and decrease health system fragmentation.

Other Factors That Contribute to Gaps in Care

Limited clinician training in transitional care Transitional care is a relatively new concept that until recently has not been emphasized in clinical training programs. As a result, many clinicians are unprepared to successfully manage care transitions or to even recognize the consequences of health system fragmentation. Additionally, clinical training often takes place primarily in acute care settings. Many clinicians may have little to no exposure to other settings of care such as postacute care or home-based services. Postacute care services vary substantially in available resources, level of physician contact, and acuity of patient populations. **Table 15-1** provides an overview of a continuum of postacute care settings. A lack of exposure to these various settings may contribute to a limited understanding of the unique needs/resources outside of hospital settings, leading to inappropriate care plans and communication failures between hospital-based and postacute-based providers.

TABLE 15-1 POSTACUTE CARE CONTINUUM OF SERVICES

DOMAIN	CHARACTERISTICS OF SETTING	AVERAGE LENGTH OF STAY	MANDATED AVAILABILITY OF PROVIDER	QUALIFYING FEATURES FOR MEDICARE COVERAGE
Long-term care hospital (LTCH)	Extended multidisciplinary care for patients with clinically complex problems	27 d	Daily physician visits	Patient must be transferred directly from an acute care hospital, admitted within 60 d of being discharged from an inpatient hospital stay and require care with an average LOS of more than 25 d
Inpatient rehabilitation facility (IRF)	Intense rehabilitation therapy typically for acute orthopedic patients or neurologically injured patients	12 d	Physician visits at least 3 d/wk	Patient must require intensive rehabilitation at least 3 h/d, 5 d/wk
Skilled nursing facility (SNF)	Constant nursing care for patients with significant deficiencies with activities of daily living	< 100 d	Physician visits at least once every 30 d for the first 90 d after admission, and at least once every 60 d thereafter	Partial coverage if patient had prior hospital stay of at least 3 d, admitted to SNF within 30 d of prior hospital stay, and requires skilled care
Institutional long-term care	Health care and services (above the level of room and board) not available in the community,	26 mo	Varies by state	Most long-term care facilities perform custodial care and thus are not covered by

	needed regularly due to mental or physical impairment			Medicare
Home health agency (HHA)	Care services for homebound individuals including RN, PT, OT, ST, SW, aides	N/A	Physician or NPP visits no more than 90 d prior to home health start of care date	Short-term coverage if the following conditions are met: patient is homebound and requires intermittent skilled nursing care or other health services such as PT, OT, ST, SW
Assisted living	Communities of group living arrangements with minimal professional nursing staff; wide spectrum of care	28 mo	No physician on staff; physician/resident relationships are maintained independent of the facility	Medicare does not pay for assisted living facilities
Hospice	Palliative care for terminally ill; home or inpatient unit	72 d	Nursing and/or physician services available or on call on a 24-h basis, 7 d a week	Patient must be terminally ill and be expected to live <6 mo

LOS, average length of stay; NPP, nonphysician practitioner; OT, occupational therapy; PT, physical therapy; RN, registered nurse; ST, speech therapy; SW, social work.

Patient/caregiver underprepared for transitions Limited or inadequate preparation of patients and caregivers regarding what to expect at the next setting of care is also a common problem. Patients and their caregivers are often unaware of what to expect following hospital discharge or care transitions. They often are not empowered to sufficiently take part in their plan of care. Patients' and caregivers' sense of underpreparation may not necessarily be due to a lack of discharge information, but more so to the issue that the complexity and amount of information communicated is often overwhelming and challenging to retain in the short time frame for discharge teaching that is typically provided. It is also common for patients and their caregivers to not recognize that they are unprepared to succeed within their next setting of care, until they arrive and experience a care failure in that setting.

Poor-quality communication among provider teams High-quality communication between care teams at points of patient transition across settings is essential to patient safety, particularly at hospital discharge. More than half of all avoidable events following hospital discharge are related to poor communication among providers. Physicians have traditionally played the key role in communicating a patient's care plan to the next setting provider at hospital discharge, typically in the format of a discharge summary. The discharge summary is the only The Joint Commission (TJC)-mandated form of communication at hospital discharge and must be completed within 30 days of discharge, according to TJC standards. In this new era of health system fragmentation, most experts believe that this 30-day time frame is much too long. While TJC has minimal standards for the content of discharge summaries, these are widely considered by experts to be insufficient. Despite the importance of discharge summaries in facilitating coordinated care, physicians receive little to no training discharge summary creation and there is no mandated standard format for these documents. Perhaps unsurprisingly, research examining the quality and content of discharge summaries has found that important care plan components, such as code status, diet, warfarin instructions, and pending laboratory tests are routinely omitted.

While a physician has historically been the recipient of hospital discharge summaries, patients are now discharged to a range of postacute care facilities with varying multidisciplinary clinician teams who may require different information than what has been traditionally included within discharge summaries. Poor-quality discharge communication is particularly problematic for transitions to skilled nursing facilities (SNFs) where staffs rely heavily on written discharge communication which may serve as the only source informing a patient's care plan for up to 30-days postdischarge. In focus groups, SNF nurses have reported regularly receiving discharge information that is untimely, incomplete, inaccurate, or conflicting. Because discharge summaries often dictate a patient's plan of care for a significant period of time postdischarge and clarifying confusing information in discharge summaries often take several days, nurses in SNF settings have identified a list of discharge summary components that they require to safely

transition patients posthospitalization (**Table 15-2**).

TABLE 15-2 HOSPITAL DISCHARGE INFORMATION THAT SKILLED NURSING FACILITY NURSES NEED TO DEVELOP AND IMPLEMENT A SAFE PLAN OF CARE

- Contact information
  - Discharging unit and telephone number
  - Attending doctor and telephone number
  - Other providers who will manage specific conditions (eg, infectious disease, anticoagulation) and contact information
  - Registered nurse who cared for individual and telephone number
  - Spouse or partner and telephone number
  - Family member(s) involved in care and telephone number
  - Power of attorney, if activated, and telephone number
- Past medical history and hospital stay
  - Remarkable medical history
  - Remarkable events during hospital stay
  - Comorbidities
  - Code status
- Medications
  - Discharge medication list
    - Drug name
    - Dose
    - Diagnosis and rationale for every medication
    - Start and stop dates and last dose administered
  - Opioid prescriptions (signed hard copy)
  - Significant medication changes
    - Change in psychiatric medications during stay
    - Change in opioid medication at discharge
    - Withdrawal of medication because of side effects
- Allergies and intolerances
  - Medications
  - Food
  - Latex
- Functional status
  - Ability to perform and assistance required for activities of daily living
  - Sensory aids (dentures, glasses, hearing aids)
  - Mobility status
    - Level of assistance needed
    - Equipment requirements
    - Fall risk
- Psychosocial and behavioral concerns
  - Personal interests/communication preferences
  - Cognitive status
  - Behavioral symptoms related to dementia
    - Type and severity
    - Need for personal safety attendant during stay
    - Effective comforting and reorientation strategies
- Treatments
  - Wound care
    - Dressing type
    - Dressing schedule
  - Peripherally inserted central catheter line care
    - Dressing type
    - Dressing schedule
    - Flushing schedule
- Elimination status
  - Bladder or bowel incontinence and use of absorbent pads
  - Perineal skin concerns
  - Last bowel movement
    - Type and amount of medication administered for bowel-related problems before discharge
  - Use of indwelling urinary catheter and if and when discontinued
- Nutritional status
  - Swallowing or feeding concerns
  - Special eating devices
  - Appetite
  - Weight
  - Dentures
- Follow-up care
  - Scheduled appointments
    - Who
    - When
    - Where
    - Telephone number
  - Laboratory results
    - Pending results
    - Follow-up laboratory tests that need to be done
    - Name and number of insurance policy

Special Considerations for Care Transitions Among Older Adults

Older adults are heavy users of a range of health care services including acute care stays, postacute care, subacute care,

and home health care services. Those with one or more chronic condition see an average of eight different physicians annually. **Figure 15-1** depicts the experience of an older adult receiving care in a series of fragmented systems, where the patient often serves as the only connecting link between providers, and communication and integration between providers is commonly infrequent.

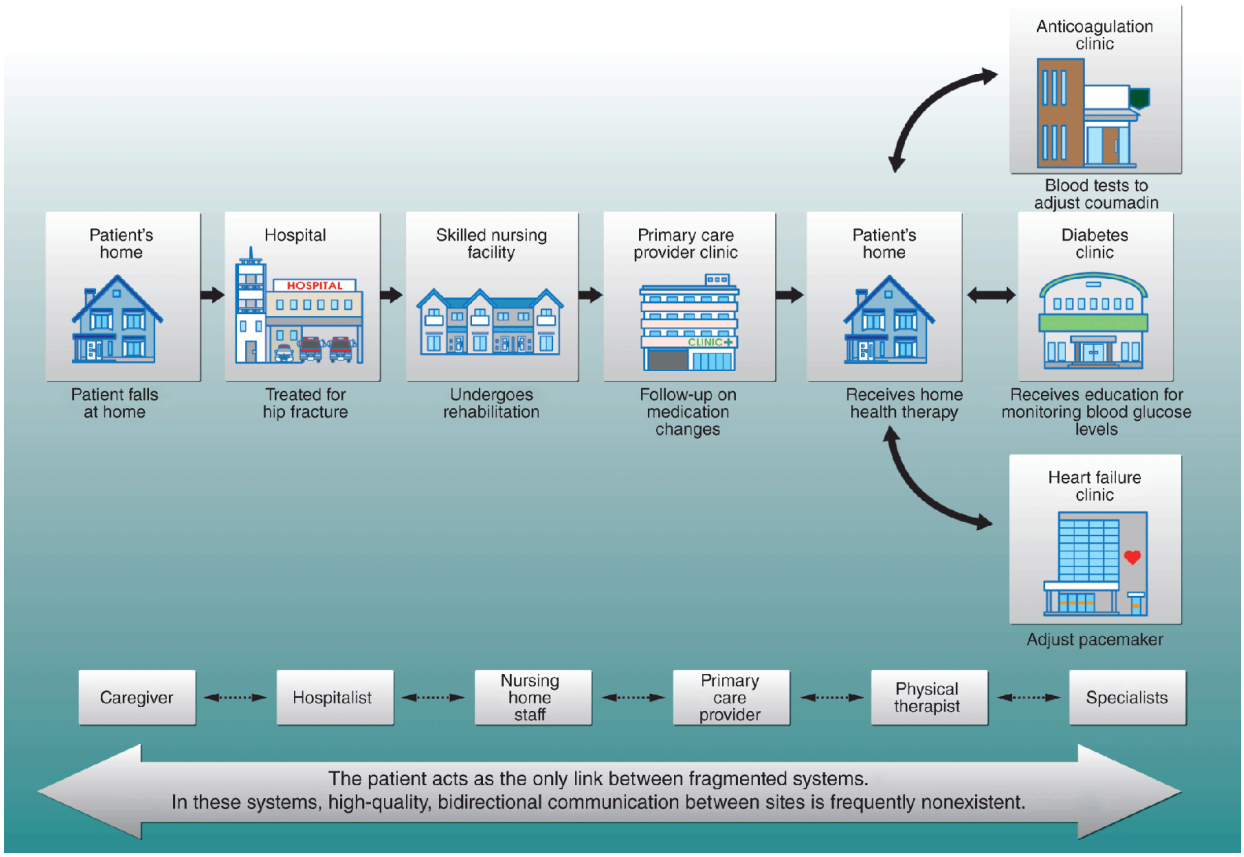


FIGURE 15-1. System fragmentation example.

Older adults experience a variety of transitions in care. Hospital discharge is a particularly vulnerable care transition for older adults, and results in an adverse event for approximately one in five adult medical patients within 3 weeks of discharge. Furthermore, nearly 20% of Medicare beneficiaries age 65 and older experience rehospitalization within 30 days of discharge accounting for over $17.4 billion in health care spending annually. Patients are increasingly discharged to a range of settings following hospitalization, with approximately 25% of older adults being discharged to a different institution and 12% being discharged to their homes with home health care services. **Table 15-3** includes examples of different types of transitions in the level of care or setting that may be experienced by older adults. Older adults who may be at increased risk for rehospitalization include those with difficulty with activities of daily living (ADLs), depression, substance abuse disorders, a history of previous hospitalization, difficulty with treatment adherence or medication compliance, or cognitive impairment.

TABLE 15-3 TYPES OF TRANSITIONS IN LEVEL OF CARE OR CARE SETTING COMMONLY EXPERIENCED BY OLDER ADULTS

Transitions Within Acute Care Setting
Emergency department to intensive care unit
Intensive care unit to medical unit
Transitions Out of Acute Care Setting
Medical/surgical unit to skilled nursing facility
Medical/surgical unit to community setting[a]

Medical/surgical unit to community setting[a] with home health services
Medical/surgical unit to inpatient hospice
Emergency room to community setting[a]
Transitions From Nursing Facilities
Skilled nursing facility to community setting[a]
Nursing facility[b] to emergency room
Nursing facility[b] to medical/surgical unit
Nursing facility[b] to urgent care office
Nursing facility[b] to primary care office
Nursing facility[b] to inpatient hospice

[a]Examples of community settings are home or assisted living facilities.
[b]Examples of nursing facilities are nursing homes or skilled nursing facilities.

While patients do not always transition between institutional settings, transitions to community settings may still include a range of other care provider teams including home health teams and primary care providers who may manage medical needs following hospitalization.

Patient and Caregiver Perspective on Care Transitions

Experiences of transitions for patients and families are often characterized by high levels of stress and dissatisfaction. In addition to poor communication between hospital providers, postacute providers, and primary care physicians (PCPs), ineffective physician-patient communication likely contributes to patients' underpreparation for managing their care following transitions, particularly after hospitalization. Various communication failures involving and surrounding patients during transitions also lead to the lack of appropriate follow-up care (eg, visit with PCP following hospitalization), which likely increases risk for rehospitalization. Failure to receive follow-up care and the resulting subsequent negative sequelae may be incorrectly attributed to the patient's noncompliance rather than other factors, such as inadequate preparation or education prior to discharge, leading patients and their caregivers to feel frustrated and unsupported.

Little research has examined patients' and caregivers' preferences surrounding transitional care. Some qualitative research has found that patients and caregivers struggle with hospital discharges. Patients report feeling anxious and reluctant to ask clarifying questions about posthospital care needs when hospital discharge occurs quickly or with little notice, leading to patients being discharged without a clear understanding of their posthospital care needs. Patients and caregivers also expressed insecurities about their ability to ask questions of the care team. **Table 15-4** includes quotations provided by patients and caregivers in research studies that illustrate their experiences surrounding transitions in care.

TABLE 15-4 ■ THE EXPERIENCE OF CARE TRANSITIONS FROM THE PERSPECTIVE OF PATIENTS AND THEIR CAREGIVERS

Patient Experience	
"They put it in their technical words and then they [primary care physicians] will understand what happened to me … I can't express what is written in this paper."[a]	Difficulty understanding discharge documentation, which is written for the PCP
"I needed some serious education about some things…I didn't know if they were not explaining things to me because I was not going to live much longer and it was just not worth it…how do I know?"[b]	Sense of underpreparation and inadequate education prior to discharge
"…to ask a question would be right but I have no clue what to ask…It's like you don't know what you don't know."[b]	Uncertainty regarding how to ask questions prior to discharge
Caregiver Experience	

"They prescribed her over $1000 in medicines…The discharge paper was blank…They didn't give her what she needed. They changed what was working to other medicines. It seemed like we had never spoken to those people at all…"[c]	Medication changes made during hospitalization that were poorly communicated with caregiver Lack of medication reconciliation
"Several times we didn't know what was out there to help us… She wanted to come home and we wanted to provide care for her at home…But we didn't know what other type of care there was…We finally got some of that information but…We had to struggle to search it out, and answers weren't readily available."[c]	Lack of involvement of caregiver in decision making surrounding transition
"The medical system, if you are not part of it, is a pretty foreign thing…If you find a person that will work with you, whether it be a doctor, a nurse…the scheduler…They are there to help guide you through the system. But finding them and really cultivating that relationship makes a huge difference."[c]	Difficulty connecting with clinical team to ask questions regarding transition

[a]Groene RO, Orrego C, Suñol R, Barach P, Groene O. It's like two worlds apart: an analysis of vulnerable patient handover practices at discharge from hospital. *BMJ Qual Saf*. 2012;21(suppl 1): i67–i75.

[b]Fuji KT, Abbott AA, Norris JF. Exploring care transitions from patient, caregiver and health-care provider perspectives. *Clin Nurs Res*. 2013;22(3):258–274.

[c]Benzar E, Hansen L, Kneitel AW, Fromme EK. Discharge planning for palliative care patients: a qualitative analysis. *J Palliat Med.* 2011;14(1):65–69.

HIGH-QUALITY TRANSITIONAL CARE

High-quality transitional care can combat system fragmentation to better support patients in bridging the gaps during transitions in care. One central component of effective transitional care is the importance of identifying and engaging caregivers for patients whenever possible. This is particularly important during hospitalization. Prior to experiencing a transition, such as hospital discharge, patients are often overwhelmed and acutely ill. Furthermore, navigating care needs following transitions often places patients in situations where they must rely on social supports and resources beyond themselves. These social supports (eg, caregivers' support) are more likely to be effective if they are engaged in and prepared for the posthospital period along with patients. This is critical for patients with cognitive impairments, such as dementia or delirium, who may struggle to retain information about the transition period. Effective transitional care also merits the involvement of the entire interdisciplinary team.

While most transitional care programs have focused on transitions from hospital to community settings, the common elements of these programs are applicable to supporting patients across any range of transitions. Multicomponent interventions which address more facets of a transition, have the ability to tailor their care responses to an individual patient's needs, and fully integrate with (ie, "bridge") both the sending and receiving setting are likely the most effective. Some specific elements of effective and high-quality transitional care include, but are not limited to, (1) involvement of the patient/caregiver in care plan decisions prior to and during the transition to ensure that their goals are addressed and that the plan is feasible, (2) patient and caregiver empowerment and preparation for necessary care in the posttransition period that is reinforced through a series of contacts over time before, during, and after the transition, (3) timely, complete, and accurate communication with the next care team with mechanisms for the receiving team to ask questions and obtain clarifications, and (4) high-quality medication reconciliation. Examples of activities that fulfill the definition of high-quality transitional care are provided in **Table 15-5**, as contrasted with typical, less-optimal care activities that may facilitate a discharge but do not necessarily support a high-quality, coordinated transition.

TABLE 15-5 HIGH-QUALITY TRANSITIONAL CARE AS COMPARED TO LESS-OPTIMAL TYPICAL CARE

Transitional care is defined as a set of actions designed to ensure the coordination and continuity of health care as patients transfer between different locations or different levels of care in the same location. The following list is not comprehensive, but is meant to provide examples of the intensity of activity necessary to support high-quality transitional care.

Example of Less-Optimal Typical Care Activities	*Example of High-Quality Transitional Care Activities*
Example of less-optimal discharge planning activity:	More optimal:

• Identify at least one nursing home that will accept the patient prior to hospital discharge to ensure a short hospital length of stay.	• Involve patient/caregiver in ongoing discharge planning throughout hospitalization to ensure that the posthospital plan for a site of care is acceptable, feasible, and optimal for the patient and caregiver.
Example of less-optimal discharge education: • On the day of discharge, provide the patient with an extensive and comprehensive paper binder which includes their medication list, recommended posthospital care, and information on all acute and chronic conditions. No limit to the number of pages offered.	More optimal: • Provide patient-tailored, reinforced, consistent, simple, goal-directed, education-based messaging over time (within and posthospitalization) for key care principles including medication management, follow-up care, and when/whom to contact with questions/problems. Actively engage the patient in care activities and observe performance over time (within and posthosptial) to ensure understanding. Engage caregivers in all teaching.
Example of less-optimal postdischarge support/contact: • Routine 1–5 min postdischarge phone calls made to all hospital patients that ask a few general yes/no questions about satisfaction or concerns, with little tailoring to the patient's condition or needs, or to their ability to recognize disease worsening.	More optimal: • Intensive postdischarge contacts that follow structured, evidence-based protocols and assess for medication discrepancies, signs of worsening condition, and presence of /adherence with follow-up care, typically with in-depth discussions and in-depth medication reconciliation. Depending on the program and patient, these contacts could be made via phone and/or home visit.

Patient/Caregiver Involvement in Decision Making

Involving patients and their caregivers in decisions about care plans prior to transitions addresses several important barriers to effective transitions. First, it enables patients to gain an idea of what to expect at the next setting of care, which may ultimately help them prepare for their needs. Early involvement in decision making also provides patients with the opportunity to express their goals and values, which may impact placement decisions.

Patient/Caregiver Empowerment, Preparation, and Support

Providing patients and their caregivers with the necessary empowerment, preparation, and support to successfully manage their needs in the next setting of care is critical. In successful transitional care programs, this preparation generally includes the following components: (1) education and empowerment in medication management, ideally using either in-person assessments or patient-/caregiver-led medication reconciliation techniques, (2) ensuring adequate follow-up care is in place and that the patient/caregiver is prepared to actively participate in that follow-up, (3) education of the patient/caregiver about signs of a worsening condition (often referred to as "red flags") and empowerment to recognize and act upon those signs, and (4) ensuring that patient/caregiver understands who to contact with follow-up questions and how to make these contacts. These core areas should be reinforced in the early discharge period through a series of contacts over time to best adhere to standard principles of adult learning.

High-Quality Communication Between Sending and Receiving Care Teams

High-quality communication is central to achieving safe transitions. While ongoing, bidirectional communication between the sending and receiving health care team would be ideal, typically most communication between care settings occurs in a written format at one point in time.

Written discharge communication, primarily the discharge summary, is the primary and often only form of communication that accompanies a patient following hospitalization. For patients discharged to nursing homes, the orders received either within or concurrently to the discharge summary can dictate a patient's care for up to 30 days; so high-quality written communication is especially key for these patients. Yet, as noted earlier in this chapter, the quality of written communication tends to be poor.

Several strategies can be adopted to improve the quality of written discharge communication. First, whenever possible, a provider who is familiar with the patient should create, complete, and sign, their discharge summary. In current practice discharge summaries are sometimes iteratively modified by multiple rotating providers until the time of discharge. In such cases, the posthospital care setting may receive several versions of discharge summaries with

conflicting information. It is important to recognize that many of these settings, such as SNFs, are not capable of implementing last-minute changes in orders and may face long delays in responding to medication changes or special equipment orders due to the lack of on-site pharmacies and central supply services. Consequentially, last-minute changes in discharge orders should be minimized and when they do occur, should be communicated to the admitting facility using another method (eg, phone) prior to patient transport. Because many postacute care settings require information about care plan elements that are not immediately available to the physician, engaging the interdisciplinary team in creating certain components of the document or providing recommendations for the document in the electronic medical record (EMR) may be advantageous. Some examples of these care plan elements may include information about behavioral symptoms in patients with dementia such as agitation, that are critical for staff in the next setting of care to be aware of in order to arrange appropriate staffing and supportive care. A care system can use a standard format for discharge summary creation to reduce omission of key information. A list of recommended discharge summary components required by nurses in SNF settings can be found in **Table 15-2**.

While written discharge communication is the primary form of communication for physician providers, other members of the care team should also consider verbal handoffs with providers in the next setting of care. Nurses in SNFs have identified high-quality verbal handoff with hospital nurses to be very helpful in preparing for patient transitions. This contact also provides an opportunity for both the sending and receiving end of the transition to identify and resolve relevant questions that may not have been recognized until patient transfer.

High-Quality Medication Reconciliation

Medication reconciliation is an essential component of transitional care programs in which the patient, members of the health care team, and other caregivers collaborate to improve medication safety as the patient transitions between health care settings (eg, hospital admission or discharge) or other care units. Medication reconciliation is the formal process recognized by TJC of creating the most accurate medication list by comparing, or reconciling, the patient's current list of medications with the medications ordered by providers upon admission, transfer, and discharge. TJC recommends five steps in the medication reconciliation process (**Table 15-6**). This process is intended to identify and resolve any medication discrepancies or errors such as omissions, additions, duplications, and frequency or dosing errors with the goal of preventing adverse drug events (ADEs) and subsequent patient harm. Since medication discrepancies are a major contributor to ADEs, TJC has made medication reconciliation a National Patient Safety Goal and requires all of its accredited institutions to have a process implemented at their site for reconciling medications. Despite these efforts, however, medication reconciliation processes have been challenging to perform effectively and consistently as evidenced by a continuing high prevalence of medication discrepancies for patients transitioning between health care settings and levels of care.

TABLE 15-6 PRIMARY COMPONENTS OF A MEDICATION RECONCILIATION

1. Develop a list of current medications (also known as the medication history).
2. Develop a list of medications to be prescribed.
3. Compare the medications on the two lists.
4. Make clinical decisions based on the comparison.
5. Communicate the new list to appropriate caregivers and to the patient.

The medication reconciliation process starts by obtaining the patient's medication history. Often, a physician, pharmacist, or nurse will obtain the patient's medication history by (1) interviewing the patient and their caregivers, (2) accessing the patient's past medical records, and (3) contacting other providers involved in the patient's care and the patient's community pharmacy for recently dispensed medications (**Table 15-7**). When creating the patient's list of current medications, it is important to include all medications the patient is taking including prescription, over-the-counter medications, herbals, and supplements. The patient's medication histories are then reconciled with medications to be ordered, to ensure that the new medications and doses are appropriate for the patient. Changes to the patient's medication regimen are documented in their medical chart, and a complete medication list is communicated to the patient, caregiver, and next provider/team. Reconciling medications applies to all health care settings including ambulatory care, inpatient services, emergency and urgent care, long-term care, and home care.

TABLE 15-7 INFORMATION FOR THE PREADMISSION MEDICATION HISTORY

Which medications taken at which times
Identities of prescribing providers
Identities of pharmacies dispensing medications
Nonoral medications used (eye drops, suppositories, patches, inhalers, creams, etc)
Assessment of patient's (or caregiver's) understanding of drug indications
OTCs and herbals/vitamins/supplements
Allergies and adverse drug reactions' history
Assessment of adherence (eg, number of doses missed per week)
How patient (or caregiver) manages the regimen at home (eg, use of pill box)

OTCs, over-the-counter medications.

EXAMPLES OF HIGH-QUALITY TRANSITIONAL CARE INTERVENTIONS

Transitional care interventions support patients as they move between different settings of care and generally emphasize medication management, empowerment/support with self-care management, and posthospital contact with a care provider. Many of these interventions recognize nurses as a clinical leader for supporting patients and their families as they navigate transitions **(Figure 15-2)**. They engage nurses as well as other members of the interdisciplinary team in developing care plans, performing medication reconciliation, and supporting medication adherence and self-care in the early discharge period. Most transitional care interventions focus on transitions from hospital to community settings, however, emerging care models continue to be developed to support patients during a range of unique transitions. As the field of transitional care continues to grow and mature, new interventions emerge. Some examples of specific transitional care interventions are noted below.



FIGURE 15-2. Transitional care nurse working with a patient and his family.

Interventions to Improve Hospital-to-Community Transitional Care Quality

Home visit–based transitional care interventions that have been tested in randomized controlled trials include Coleman's Care Transitions Intervention (CTI) and Naylor's Transitional Care Model (TCM). These interventions reduce rehospitalizations by about one-third. Both programs utilize posthospital in-home visits with a nurse practitioner to educate high-risk patients about their medications, medical follow-up, signs of condition worsening, and provider's contact information. While contact with patients in these programs only lasts for a few weeks, the effect on rehospitalization has been shown to last up to 180 days—likely due to improved self-care management. Both of these interventions, however, are limited to patients who agree to in-home supports and live within geographic reach of a home visit.

Emerging transitional care interventions utilizing similar steps as CTI and TCM have recently been developed to target vulnerable patients, including those with cognitive impairment, and those who refuse home visits or live too far from discharging hospitals to receive home visits. One of these, the Coordinated-Transitional Care (C-TraC) program, developed within the US Department of Veterans Affairs, is a low-cost, telephone-based program that uses a RN nurse case manager to coordinate the patient's transitional care through a series of protocol-driven in-hospital visits, intensive posthospital phone calls, and integration with in-hospital and posthospital clinical teams. In preliminary testing, the C-TraC intervention demonstrated one-third fewer rehospitalizations among enrollees than comparable patient groups, leading to a substantial cost avoidance. However, more rigorous testing is needed to better understand its impact.

Project Re-Engineered Discharge (RED) is an intervention based within the acute care setting, which involves enhanced in-hospital discharge processes and education. A randomized controlled trial of Project RED showed a decrease in 30-day emergency room visits, but no significant effect on rehospitalizations. The average age of the population tested in the study was 50 years, much younger than the typical older adult population at most risk for rehospitalization. Given this and the limited posthospital support available within this program, its role in high-risk and older patient populations remains unclear.

Interventions to Improve Nursing Home–to–Hospital Transition Quality

Nursing home patients experience a high degree of costly and avoidable transfers to the hospital setting that can be prevented through earlier recognition of changes in condition by nursing home staff. These transfers are both burdensome for nursing home residents, many of whom may be physically frail and have some degree of cognitive impairment. Interventions to Reduce Acute Care Transfers (INTERACT) is a program that was developed to reduce the frequency of transfers to acute care for nursing home patients by supporting nursing home staff's ability to identify, assess, and communicate changes in condition. The program consists of a toolkit composed of (1) A Situation Background Assessment or Appearance Request (SBAR) tool to support effective communication between nurses and physicians (2) an early warning tool designed to promote early recognition changes in condition, (3) a hospital transfer review tool to support review of hospitalizations and potentially avoidable causes, and (4) a standardized patient transfer form to communicate key patient information during transfer. INTERACT tools are available for no cost at http://interact.fau.edu and consist of a toolkit that supports both education for nursing home staff as well as implementation and data collection support. Early evaluation suggests that INTERACT decreased self-reported hospital admissions by 17% over a 6-month period, with a 24% reduction observed within the most engaged nursing homes in the assessment. Additional testing is under way.

SPECIAL POPULATIONS

Patients With Cognitive Impairment and/or Nearing End of Life

Older adults with cognitive impairments, such as dementia, are at increased risk for experiencing negative outcomes associated with transitions. Research suggests that dementia may increase rehospitalization risk by an alarming 40%. While little research has examined reasons for this increased risk, it is apparent that a person with dementia's limited capacity to learn, recall, and effectively communicate elements of their care plan may result in an inability to compensate for poor communication across clinical teams and may play a role in subsequent rehospitalizations. Persons with dementia also have difficulty adapting under stressors and responding to change, and generally benefit from consistency in caregiver teams and environment, making transitions across care settings particularly burdensome. Considerable changes in daily surroundings (eg, transitioning from nursing home–to–hospital setting) for a person with dementia may result in increased behavioral symptoms such as agitation or increased depressive symptoms. Despite the

considerable burden associated with transitions for persons with dementia, they experience more transitions within the last 3 months of life than those without dementia, including frequent transitions between different nursing settings into acute and intensive care. It is thought that such end-of-life transitions may not improve quality of life, but, instead add to suffering and burden, and that many of these transitions may be preventable.

While most people with dementia spend most of their life in community settings, they also experience transition into permanent care (eg, placement in a nursing home) more often than noncognitively impaired older adults. Transitions into permanent care represent considerable changes for both the individual with dementia and their family/caregivers. Persons with dementia have expressed a desire to be involved in the transition process as well as to have their family members engaged to offer support. However, research also suggests that persons with dementia may be excluded from the decision making surrounding transitions in care. The lack of inclusion of people with dementia in care decisions may result from the incorrect assumption that people with dementia are unable to contribute to decision-making conversations or that these conversations will result in distress due to a lack of comprehension. While some individuals with more advanced cognitive impairment may be unable to participate in their care at this level, many individuals with mild-moderate impairment may benefit from this opportunity as providing input into the decision to transition into a nursing home for permanent care has been shown to lead to a greater sense of acceptance with the decision.

Patients with dementia will also benefit from inclusion in transitional care interventions that emphasize empowerment and preparation of caregiver and adapt patient education strategies to meet the needs of individuals with cognitive impairment. The C-TraC program previously described is one example of a transitional care program that actively engages caregivers and uses methods of spaced retrieval to aid in information retention in persons with dementia.

Most community-dwelling older adults with dementia live with or receive frequent support from informal caregivers, who are often but not always family members. Because caregivers of people with dementia experience considerable burden and negative health outcomes related to the caregiving role, it behooves clinicians overseeing transitions in care for persons with dementia to also be responsive to the needs of their family/caregivers. Caregivers often experience guilt and frustration surrounding transitions into nursing home settings and are rarely prepared to manage these emotional conflicts and sense of bereavement during placement. Caregivers also generally express a desire to continue to participate in care following the transition. Enhanced support and counseling surrounding transitions to nursing home placement have been shown to have both short- and long-term benefits for caregivers. Providers may wish to refer caregivers to these or similar programs, and may also refer caregivers to website resources provided at end of this chapter (**Table 15-8**). **Table 15-9** illustrates a case example of the experience of transitional care for an older adult with dementia.

TABLE 15-8 EDUCATIONAL RESOURCES FOR PATIENTS AND FAMILIES DURING TRANSITIONS OF CARE

RESOURCE	DESCRIPTION
Family Caregiver Alliance, Hospital Discharge Planning: A Guide for Families and Caregivers (https://caregiver.org/hospital-discharge-planning-guide-families-and-caregivers)	Includes explanations of important transition elements, suggestions for improving the process, and provides checklists/questions to ask to ensure caregivers provide the best care for their loved ones in the transition process.
Centers for Medicare and Medicaid Services, Your Guide to Choosing a Nursing Home or Other Long-Term Care (http://www.medicare.gov/pubs/pdf/02174.pdf)	Includes resources on the following: how to find and compare nursing homes and other long-term care options, how to pay for nursing home care, your rights as a nursing home resident, and alternatives to nursing home care.
The National Consumer Voice for Quality Long-Term Care (http://theconsumervoice.org/uploads/files/general/Consumer-Voice-brochure.pdf)	A platform of resources to advocate for public policies that support quality care and quality of life in all long-term care settings. The Consumer Voice advocates for a strong, sufficient direct-care workforce and promotes best practices in delivering quality care.
Center for Advancing Health, Be a Prepared Patient (http://www.cfah.org/prepared-patient/plan-for-your-end-of-life-care/choosing-a-nursing-home)	A collection of trusted resources, tips, and stories from patients, caregivers, and health care experts about finding good care and making the most of it.

American Geriatrics Society's Health in Aging Foundation (http://www.healthinaging.org/)	Provides consumers and caregivers with up-to-date information on health and aging. Highlighted resources include easy-to-understand tip sheets on managing health and a series that provides practical questions to help direct conversations with health care providers.

TABLE 15-9 CASE EXAMPLE OF A POOR-QUALITY TRANSITION FROM HOSPITAL–TO–NURSING HOME FOR A PERSON WITH DEMENTIA

Genevieve is an 87-year-old woman with a history of Alzheimer disease who was recently hospitalized for pneumonia. According to family who accompanied Genevieve to the hospital, she has been struggling with managing at home alone ever since her husband of 60 y passed away 2 mo ago. Genevieve has had four hospital admissions for exacerbations of congestive heart failure and pneumonia in the last 2 y. During her hospital stay, she had dysphagia and she was placed on a thickened liquid diet to avoid further aspiration which likely contributed to her recurrent pneumonia. She had experienced functional decline during her hospital stay and was discharged to a skilled nursing facility for rehabilitation. The physician writing the hospital discharge orders did not include any information for her diet, and dietary information was also omitted from her discharge summary. Genevieve had a score of 23/30 on a global cognitive test (mild impairment). However, because she had a diagnosis of Alzheimer disease in her medical record, the discharging nurse decided that it was not necessary to review changes in her care plan with her prior to discharge as she thought it was unlikely that Genevieve would understand. Although he did discuss her antibiotics with her in detail, the physician did not review dietary changes with Genevieve under the assumption that others on the care team would perform that activity.
When sent to the nursing facility, Genevieve told the nurses there that her hospital doctors and nurses did not give her any special instructions regarding her diet, and that she was eating normally while at home. The nursing facility nurses did not have a diet order and could not reach any of Genevieve's hospital providers when they tried to call to clarify her diet, as the hospital providers had all rotated off-shift for the evening. When called, Genevieve's outpatient physician was surprised to hear that she had been in the hospital and had not yet received any information regarding Genevieve's hospital stay. Therefore, Genevieve was started on a regular diet at the nursing facility. While in the nursing facility, Genevieve seemed to tolerate her regular diet well, however, 5 d later she was noted to have a persistent cough, a low-grade fever, and to be short of breath. Genevieve was transported to the emergency department and ultimately was readmitted for recurrent aspiration pneumonia.

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Chapter 16

Acute Hospital Care

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Learning Objectives

- The reader will recognize advanced age as a risk factor for hospitalization and for hospital complications.
- The reader will understand the importance of a broad assessment of the hospitalized older patient, including medical comorbidities, functional status, cognitive status, caregiver and social support, living situation, and financial resources.
- The reader will be able to recognize and take measures to prevent common hospital problems in older patients, including delirium, immobility, falls, malnutrition, pressure ulcers, and nosocomial infections.
- The reader will understand the role of palliative and end-of-life care in the hospital care of elders.
- The reader will understand the key components of an effective hospital discharge, including thorough patient and caregiver education, robust communication with follow-up physicians, accurate medication reconciliation, an appropriate discharge level-of-care, and timely postdischarge follow-up.

Key Clinical Points

1. **Older patients are more likely to be hospitalized than their younger counterparts, and more likely to have complicated hospital courses.**
2. **Effective hospital management of an older adult requires an understanding of the patient's comorbidities, functional status, cognitive status, caregiver and social support, living situation, and financial resources.**
3. **In addition to treating the patient's principle problem, hospital providers must also be able to recognize and prevent problems that are common in the older population, including delirium, immobility, falls, malnutrition, pressure ulcers, and nosocomial infections.**
4. **The acute hospital care of elders often includes end-of-life care and palliative care.**
5. **The hospital discharge is a complex transition of care which depends on several key components, including thorough patient and caregiver education, robust communication with follow-up physicians, accurate medication reconciliation, an appropriate discharge level-of-care, and timely postdischarge follow-up.**

In 2003, patients who were 65 years or older accounted for one-third of all hospitalizations in the United States, despite representing only 12% of the population. According to the 2010 National Hospital Discharge Survey, an estimated 39% of the 35 million discharges from US nonfederal, short-stay hospitals involved patients 65 years or older. Perhaps even more impressive is the continued growth of this aging population. It is projected that, by 2030, one in five Americans will be 65 years or older. At the same time, the very old population (75 years or older) also continues to grow. A patient aged 85 or older is more than twice as likely to be admitted to the hospital as a patient aged between 65 and 74. Older patients are not only more likely to be admitted to the hospital, they also experience a greater number of complications, a longer length of stay, and a higher mortality rate than younger people (**Table 16-1**).

TABLE 16-1 CHARACTERISTICS OF HOSPITALIZATIONS AMONG YOUNGER AND OLDER POPULATIONS, 2003

	YOUNGER THAN 65	65 AND OLDER
Percentage of US population	88%	12%
Percentage of hospital stays	65.3%	34.7%
Mean length of stay (d)	4.0	5.7
Admitted through emergency department (%)	36.2%	57.4%
Died in hospital (%)	0.9%	4.7%

Data from AHRQ, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization project, Nationwide Inpatient Sample, 2003.

These data suggest that hospitalization is a different experience for older patients than younger ones. In fact, older hospitalized patients are more medically complex than young patients, with a larger number of comorbidities and medications. In addition, these patients are more likely to have health conditions or social circumstances that complicate their management, including functional decline, cognitive impairment, and dwindling social support.

Therefore, the hospital care of an older patient (from admission to discharge) is quite different than the care that would be provided to a younger patient. Indeed, the optimal delivery of hospital care to elders requires a unique conceptual framework. This framework includes not only an approach to the management of the "admission problem," but also an approach that prevents and recognizes common complications, and attends to the special needs of this often vulnerable population.

THE HOSPITAL ADMISSION

Reasons for Admission for Older Patients

Table 16-2 lists the 15 most common conditions leading to hospital admission in older patients. Also common and important to recognize, but less likely to be reported as the reason for admission, are conditions such as failure to thrive, falls, adverse drug effects, or change in mental status. In addition, older adults may be admitted with an atypical presentation of another condition, such as when a change in mental status is due to an underlying fluid and electrolyte disorder or infection.

TABLE 16-2 MOST FREQUENT CONDITIONS CAUSING HOSPITALIZATIONS AMONG OLDER PATIENTS, 2003

RANK	PRINCIPAL DIAGNOSIS	% OF ALL HOSPITALIZATIONS IN OLDER ADULTS
1	Heart failure	6.3
2	Pneumonia	5.8
3	Coronary atherosclerosis	5.1
4	Cardiac dysrhythmias	3.7
5	Acute myocardial infarction	3.4
6	Chronic obstructive pulmonary disease	3.1
7	Stroke	3.0
8	Osteoarthritis	2.8
9	Rehabilitation care, fitting prostheses, adjustment of devices	2.5
10	Fluid and electrolyte disorders	2.3
11	Chest pain	2.2
12	Urinary tract infection	2.1

13	Hip fracture	2.1
14	Complication of medical device, implant, or graft	2.0
15	Septicemia	1.9
Total admissions for top 15 conditions	6.4 million	48.3

Data from AHRQ, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization project, Nationwide Inpatient Sample, 2003.

Often, the reported discharge diagnosis for a hospitalized older patient may not capture all of the reasons for the admission, nor explain the hospital course and subsequent health status of the patient. While many of the 15 most frequent discharge diagnoses represent acute exacerbations of chronic diseases, the reasons for these "exacerbations" can often only be understood when viewed in the context of the many "nonmedical" domains of the patient's life, including functional status, cognitive status, caregiver and social support, and financial security.

The Complicated Context of the Older Hospitalized Patient

To successfully care for older hospitalized patients, it is necessary for providers to understand more than just the "reason for admission." A narrowly focused admission evaluation of an older patient may not provide the breadth of information needed to optimally manage the patient. Instead, the admission evaluation of an older patient must capture the whole context of the patient's condition, including several of the "nonmedical" domains. Even if the admitting practitioner accurately diagnoses and manages the patient's admission complaint, the treatment plan may fail if the health care team does not recognize that the patient is hard-of-hearing, cognitively impaired, financially insecure, or socially isolated. Geriatricians often make use of a comprehensive geriatric assessment (CGA), a multidisciplinary approach to the care of elders that is based on uncovering, describing, explaining, and intervening on *all* of a patient's problems, in a variety of different domains. This approach allows the provider to understand the full range of problems faced by the older patient, and the potential interactions between these problems. Although a full assessment of this type may not be necessary for most hospital admissions, it is clear that *some parts of this assessment are essential for understanding the often complicated context of the older patient*. **Table 16-3** lists several assessment domains that are particularly important in a hospital setting, and some of the tools and strategies to facilitate these assessments. All of these assessments need not be performed by physicians. Rather, many may be delegated to support staff. It is common for older patients to accrue problems in several of these domains, eventually reaching a point where they are labelled with poorly defined terms such as "fragile" or "vulnerable." Some of these complicating problems are especially important to identify and understand at the time of hospital admission. These include medical comorbidities, functional status and mobility, cognitive status, sensory issues, and the patient's and caregiver's capacity to provide care and make decisions.

TABLE 16-3 ■ IMPORTANT DOMAINS OF ASSESSMENT IN OLDER HOSPITALIZED PATIENTS

DOMAIN	RELATED ISSUES	ASSESSMENT TOOLS AND STRATEGIES
Medical	Admission: • What are the comorbid medical conditions? • Medication reconciliation Discharge: • What special medical needs does this patient have (eg, oxygen therapy, frequent suctioning, tube feeds, intravenous medications, wound care, palliative care, special equipment, etc)?	• Computer-based tools for medication reconciliation • Pharmacist assistance with medication reconciliation • Multidisciplinary discharge planning rounds
Functional/mobility/ sensory status	Admission through discharge: • Can this patient perform his ADLs, IADLs? • Does this patient have adequate mobility to function safely at his discharge destination? • Does this patient have sensory deficits that contribute to functional impairment?	• ADL and IADL scales • Physical therapy and occupational therapy evaluations

Cognitive status	Admission through discharge: • Does this patient have the cognitive capacity to understand his medical issues, make medical decisions, and manage his own care after discharge? • If the patient lacks decision capacity, who will make decisions for him?	• Mini-Cog • Mini-Mental State Examination • Psychiatric evaluation of decision-making capacity
Caregiver status and social support	Admission: • Who is this patient's caregiver? • Are there questions or concerns about the care that is being provided? Discharge: • Who can this patient rely on for help? • Will this patient be dependent on a caregiver after discharge? • Can this patient's caregiver(s) provide adequate care after discharge? Will he need additional support?	• Multidisciplinary discharge planning rounds
Mental health and substance abuse issues	Admission: • Did substance abuse or mental health issues contribute to the need for admission? Discharge: • Does this patient have mental health issues that impair his ability to care for himself? • Does this patient have substance abuse issues that impair his care or safety?	• Depression screening tools • Social work consultation • Psychiatric consultation
Living environment	Admission: • Did the patient's living environment contribute to the need for admission? Discharge: • Can this patient return to his preadmission living environment, or does he now have needs that cannot be met in that setting?	• Multidisciplinary discharge planning rounds
Financial/insurance resources	Discharge: • Can this patient afford his medications after discharge? • Does this patient have adequate insurance coverage, or will financial issues interfere with his care plan? • Does this patient have transportation to get to future appointments?	• Multidisciplinary discharge planning rounds

ADL, activities of daily living; IADL, instrumental activities of daily living.

Medical comorbidities In addition to the primary admission problem(s), hospital providers must have a complete understanding of a patient's comorbid illnesses. Over 60% of Medicare patients have two or more major chronic diseases and 24% have four or more. Comorbid chronic diseases have several consequences for hospitalized elders and their providers. Multiple diseases often equate to multiple outpatient physicians, complicating communication between inpatient and outpatient providers. Multiple diseases also lead to the use of multiple medications which can result in confusion about medications, difficulty with medication reconciliation and drug adherence, and adverse drug events

(ADEs). Also, a high burden of chronic disease can lead to self-care difficulties, patient and caregiver frustration and burnout, and physiologic instability for the patient.

Comorbidities directly impact the care that is provided in the hospital. For example, the recommendations of an evidence-based clinical practice guideline for a specific disease may be impractical, or even harmful, when considered in the context of a patient's comorbidities. Patients with multiple comorbidities must be carefully managed, recognizing that the treatment for one problem might exacerbate another problem. While there are no hard and fast rules for how to best manage this aspect of complexity, a successful approach is likely to emphasize the following points:

- Recognize and document the patient's comorbidities.
- Consider any proposed treatment in the context of these comorbidities.
- Communicate with the patient and family so that management decisions (often based more on judgement than evidence) will consider patient values and preferences.

At admission, the documentation of comorbidities can have important financial implications. Given the complexity of some older patients, it can actually be difficult to distinguish between admitting diagnoses, comorbidities, and complications of hospitalization. For example, a patient might be admitted for the treatment of an infected pressure ulcer. In this case, the ulcer is the admitting diagnosis. However, a patient with a chronic pressure ulcer might also be admitted for a different problem. In this case, the ulcer is an existing, comorbid condition. Similarly, a patient could develop a pressure ulcer while being treated in the hospital for a different condition. In this case, the ulcer would be considered a hospital complication. This same classification issue applies to several other conditions, including catheter-associated urinary tract infections (UTIs), traumatic injuries from falls, vascular catheter infections, diabetic ketoacidosis, or diabetic hyperosmolar states. Therefore, it is important that these conditions are documented as "present on admission," if they are noted during the admission process. When these diagnoses are noted to be present on admission, they add to the complexity of the patient, and increase the Medicare reimbursement to the hospital. However, if these conditions develop as complications, they warrant no such increases in reimbursement.

Functionality, mobility, cognition, and sensation Functional measures are stronger predictors of mortality and contribute more to prognosis in the hospitalized older patient than comorbid illness, disease severity, or admission diagnoses. As people age, they often experience functional decline. These declines might include limitations in mobility, cognition, or sensation, and can contribute to the need for the acute admission, and substantially influence the hospital course and discharge plans.

An individual's functionality can be screened by asking questions about the patient's activities of daily living (ADLs) and instrumental activities of daily living (IADLs). These questions provide a broad view of the patient's functionality.

An assessment of gait and mobility may also be appropriate. Direct observation of the patient's gait is the most helpful assessment tool, but questions about falls or gait stability can also be helpful. Any suspected mobility or ADL impairment should trigger physical therapy and/or occupational therapy assessments and should signal the need to institute early mobilization and early discharge planning.

A patient's cognitive status should also be considered during the functional screening. Cognitive impairment is a major risk for delirium. Recognition of dementia can facilitate the use of appropriate delirium preventative measures. In addition, cognitive impairment, even if stable, has profound implications on the delivery of care, impacting patient/family communication and education, and discharge planning. Screening for dementia is particularly important in the older patient who is losing weight, noncompliant with medications, admitted from a nursing home, or readmitted to the hospital. Although a health care provider may believe that the interview with the patient is an effective cognitive screen, this approach is an insensitive way of detecting cognitive dysfunction, and a specific cognitive screening tool such as the Mini-Cog or the Confusion Assessment Method (CAM) is preferred (see Chapters 47 and 66). Both tests have similar sensitivities, but the Mini-Mental State Examination (MMSE) is the only one to have been validated in the hospital setting, while the Mini-Cog is faster to perform.

Of course, it is important to recognize and accommodate sensory deficits in older patients. Often, hearing or visual impairments can be overcome, if they are recognized.

Patient and caregiver capacity to provide care and make decisions It is important for providers to assess a patient's functionality and cognition because these domains are so tightly linked to the patient's ability to provide self-care, and make medical decisions. The accumulation of functional limitations, as discussed earlier, can lead a patient to

a state of partial or complete dependence on others. For patients with functional limitations, the admitting provider must know who usually cares for the patient, and if that care is adequate. Inadequate care can lead to new medical problems, medication mismanagement, exacerbations of chronic diseases, malnutrition, and recurrent hospital admissions. And, at the extreme, inadequate care can be categorized as elder neglect or abuse. Similarly, patients with cognitive impairment may not be able to make their own medical decisions. In these cases, the hospital providers must urgently identify a surrogate decision maker for the patient, so that lines of communication can be established early. Of course, patient education and discharge planning also depend heavily on an understanding of who is ultimately responsible for the patient's care.

Key Aspects of the Hospital Admission Process

It is becoming increasingly rare for hospitalized patients to receive inpatient care from their primary care providers. Indeed, older patients are often "handed-off" at the time of admission. Hospital admission is often a time of intense relationship building and communication between a patient and new group of health care professionals. The start of the hospitalization depends on communication with the patient, the family, and the outpatient providers. In addition, hospital providers must quickly identify an accurate list of the patient's medications, a clear idea of who will make decisions for the patient, and the patient's wishes as they relate to the type and extent of medical care that might be provided in the hospital (eg, code status). Some key aspects of the hospital admission process are outlined below.

Communication with the patient Communication is a key component of taking a medical history and performing a physical examination. However, older patients may have special needs that can be addressed using thoughtful techniques. Patients who are hard-of-hearing will appreciate being interviewed in a quiet environment with hearing aids in place, with the interviewer speaking with appropriate volume. Patients with visual impairment may communicate more effectively if they wear their glasses, and if the interviewer situates himself close to the patient, with adequate lighting. Providers that *sit* when interviewing patients are hailed by patients as better listeners, even when they spend no more time with the patients. Of course, patients with cognitive impairment may not be able to provide accurate history at all, and providers must turn to other people for history in those circumstances.

Communication with family and primary care providers While many patients can provide accurate descriptions of their home situations and presenting symptoms, every effort should be made to discuss these issues with family members or caregivers, who can often provide additional information about the circumstances leading to the hospital admission. This additional historical information may also clarify the admitting diagnosis. Older patients often present with complex symptoms and atypical presentations of disease requiring increased attention to the factors that led to the admission. In many cases, the patient's primary care provider should also be contacted near the time of admission. Studies have shown that most primary care providers want to be contacted at admission. Primary providers can help clarify the acute problem and can provide a more complete medical history, including other comorbid conditions, previous diagnostic testing, and response to previous treatments. Depending on the reason for admission and the hospital course, communication with the patient's specialist physicians may also be appropriate.

Medication reconciliation Hospital admission is an important time for medication review. Clarification of the patient's medications, often prescribed by multiple physicians, and identification of potential ADEs are two important aspects of medication review. ADEs might include amplified side effects, drug-drug or drug-disease interactions, and errors in drug administration. ADEs may lead to hospital admission and are more common as the number of medications and comorbid illnesses increase. While age alone is not an independent predictor of ADEs, older patients are more likely to have multiple comorbid conditions and be on multiple medications. Regulatory bodies, such as the Joint Commission, require that all institutions have a process in place to reconcile medication lists. The medication reconciliation that occurs at the time of hospital admission is the first step in the management of multiple medications that will continue throughout the hospital stay (see more below). Aspects of medication reconciliation can be aided by computerized physician order entry systems and clinical pharmacists.

Establish and document surrogate decision makers and code status As discussed above, an assessment of the patient's decision-making capacity is a key part of the admission process. If a patient clearly lacks decision-making capacity, a surrogate decision maker should be identified as soon as possible, so they can speak to the patient's health care wishes. Even when patients are able to make their own decisions, they should be asked about surrogate decision makers in case they are needed in the future. If a patient has a durable power of attorney for health care document that identifies a surrogate, the written document should be added to the patient's medical record. Other health-related

documents (such as living wills) should also be added to the medical record, if available. Ideally, patients that lack these documents should be offered some assistance with advanced care planning.

Although a full assessment of a patient's health care wishes may not be necessary on hospital admission for most patients, the admission assessment should include, at least, a brief assessment of the patient's wishes regarding the application of emergency cardiopulmonary resuscitation measures. If patients have already made decisions about limiting health care interventions, these wishes should be documented and respected. However, this discussion at the time of hospital admission might be the first time that the patient has ever considered the concept of limiting medical care, and they may require guidance and education about the topic.

THE HOSPITAL STAY

Older hospitalized patients often experience syndromes that are uncommon in younger people, often referred to as "geriatric syndromes," such as delirium, malnutrition, immobility, falls, and pressure ulcers. Therefore, providers who care for older patients in the hospital must be skilled in recognizing, treating, and preventing these common problems.

In addition, older patients experience a fivefold increased risk of iatrogenic complications during hospitalization, compared to younger patients. These complications include infections, thrombosis, and ADEs, which can certainly contribute to posthospital institutionalization, functional decline, and hospital readmission. This high rate of complications has made the hospital care of elders a focal point of the patient safety movement over the last two decades, and has garnered the interest of researchers, payers, regulatory bodies, the federal government, patients, and their families.

Also, older patients commonly experience discomfort and face end-of-life circumstances while in the hospital. Therefore, hospital providers must be proficient in the areas of palliative and end-of-life care as well.

Common Problems in Hospitalized Older Patients

Delirium (see also Chapter 47) Delirium is an acute, fluctuating, alteration in mental status that frequently affects older hospitalized patients. Delirium is important because it is common and is associated with a long list of adverse outcomes. Although delirium occurs in about 25% of medical inpatients, the rates are much higher in surgical and critically ill patients. Delirium has been linked to increases in mortality, institutionalization, and length of stay, in addition to being a marker of future functional and cognitive decline. In the hospital, it is important to prevent delirium, and to recognize it when it occurs.

The prevention of delirium depends on the identification of high-risk patients, and the avoidance of factors that might precipitate delirium in these patients. The major risk factors for delirium include underlying cognitive dysfunction/dementia, bone fracture on admission, sensory impairment (vision and hearing), high severity of illness, low functional performance, and age. Patients with risk factors for delirium can be treated with proactive preventative strategies, and can be monitored closely for the development of delirium. Prevention of delirium is based on avoiding the precipitants of delirium, which include medications (polypharmacy, or the use of specific medications such as sedatives, analgesics, or psychoactive medications); use of physical restraints; and the presence of an indwelling urinary catheter. Also, avoidance of common complicating disorders is important (eg, electrolyte abnormalities, dehydration, constipation, urinary retention, or infection). In addition to avoiding known precipitants of delirium, proactive strategies such as frequent orientation and use of eye glasses and hearing aids can also help to prevent delirium. The hospital environment also seems to contribute to delirium, possibly via interruptions in normal patterns of sleep and mobility, so efforts to encourage regular ambulation (if possible) and preserve normal sleep patterns may also help prevent delirium. While attention to these issues by individual physicians is important, the case can also be made for a more systematic, interdisciplinary approach. Many institutions have put formal, nurse-driven delirium prevention programs into place. These programs are designed to provide cognitive stimulation and improve sensory inputs, and to avoid environmental factors that might precipitate delirium. The Hospital Elder Life Program (HELP) uses an orientation board and a program of cognitive stimulation to reduce the rate of delirium in at-risk patients.

Recognition of delirium can be difficult, as most patients with delirium have a "hypoactive" form of the disorder. These patients are not disruptive or aggressive, and their mental status changes can be easily missed. Recognition of delirium can be improved by understanding which patients are at highest risk for it, and by closely monitoring at-risk patients. Once suspected, a diagnostic tool such as the confusion assessment method can be used to help confirm the diagnosis. Additional information about the diagnosis and management of delirium can be found in Chapter 47.

Immobility and falls (see also Chapter 48) Older patients fall down frequently. This is evidenced by the fact that there were over 2.1 million emergency department visits for falls in this patient population in 2006. So, it is no surprise to learn that older patients are also at risk of falling when they are hospitalized. Estimates for inpatient falls among all hospitalized patients range from one to nine falls per 1000 patient-days, and the risk varies significantly among different hospital units. Inpatient falls are estimated to result in injury in one-third to almost one-half of cases. Most concerning is that an estimated 8% of falls result in moderate to severe injuries. Patients who suffer falls with injury have longer lengths of stay and higher costs than similar patients who do not fall. In addition to the in-hospital effects, a fall with injury may lead to serious long-term health outcomes as well. Falls among older patients are risk factors for increased use of health care resources in the future, functional decline, loss of independence, higher rates of discharge to extended care facilities, and even death.

In hospitalized patients, the risk of falls increases with age, and with the history of prior falls. While risk factors are not synonymous with causative factors, some of the known risk factors for falling might be "modifiable," which is to say that there may be a rational intervention that could mitigate the risk of falling that is related to that factor (**Table 16-4**). However, for the most part, strong evidence to support these interventions is lacking.

TABLE 16-4 POTENTIALLY MODIFIABLE RISK FACTORS FOR IN-HOSPITAL FALLS

RISK FACTORS	POSSIBLE INTERVENTIONS
Gait instability and muscle weakness	Physical therapy evaluation and treatment, including gait assistive devices, patient education about falls/prevention
Toileting issues (urinary incontinence, urinary frequency, need for assistance with toileting)	Scheduled toileting
Mental status issues (confusion, agitation, or impaired judgment)	Delirium prevention, recognition, and management
Medication-related (medications associated with sedation or delirium; polypharmacy)	Medication review, elimination or dose reduction of culprit medications, avoidance of unnecessary medications
Visual impairment	Provide adequate lighting, glasses
Postural hypotension or syncope	Elimination or dose reduction of culprit medications, attention to volume status, patient education about falls/prevention

Data from Olilver D, Healey F, Haines TP. Preventing falls and fall-related injuries in hospitals. Clin Geriatr Med. 2010;26:645–692.

Given the well-described risk factors for falls among hospitalized older patients, a tool for identifying those patients at highest risk would be useful. Several such tools have been developed and are easy to use, but are known to have significant limitations. First, existing tools do not predict falls with great accuracy. In fact, these tools typically fail to outperform the routine judgement of clinical staff in recognizing fall risk. Also, these tools present fall risk as a dichotomous variable (low-risk or high-risk) when the risk is, in fact, a continuous variable. In addition, global risk tools do not always lead to specific preventative actions (ie, they do not link a specific finding with a specific intervention). The use of these tools has never been proven to directly lead to decrease in falls or injury, and, although they continue to be used in many settings, they are unlikely to lead to dramatic improvements in fall prevention.

In fact, the majority of inpatient falls may not actually be preventable. Older patients fall down frequently—at home, in nursing homes, and in the hospital. Falls are not a problem that is unique to, or entirely caused by, hospitalization, and the goal of greatly reducing them is likely to be cost-prohibitive. Moreover, there are only limited data supporting the use of any intervention to reduce the risk of falls in the hospital. Most studies on single interventions have not demonstrated reductions, although there is some evidence that patient education about falls and how to avoid them may have a positive effect, as might computer-based interventions to reduce the use of culprit medications. In addition, although the use of multimodal interventions has led to modest effects in long-term care facilities, the study of these interventions in acute care hospitals is limited. A recent meta-analysis could only identify six randomized trials in the hospital setting. That study confirmed a statistically significant reduction in fall rates, but the effect size was small. In fact, the authors calculated a number-needed-to-treat of 1250 patient-days to prevent one fall. Moreover, it is impossible to understand which of the elements of the multimodal intervention might have had led to improvement. The authors also point out that the available studies are of limited quality, the strategies are complex, and compliance with interventions is often poor. A Cochrane meta-analysis of four randomized trials of fall prevention in hospitals only identified two programs that reduced fall rates, and one of those was a subacute facility (with benefit

most apparent after 45 days), and the other targeted a very specific population (a geriatric unit with hip fracture patients). These observations make it impossible to generalize to other populations.

Even more concerning in the race to prevent falls is the possibility that the wrong approach could actually hinder mobility in older patients. In 2008, the Centers for Medicare and Medicaid Services (CMS) announced that it would no longer pay for medical costs related to inpatient falls. The announcement was intended to be a stimulus for prevention of inpatient falls, and it resulted in widespread, intensive efforts to reduce these events. However, critics of this approach have noted the potential for unintended consequences. That is, hospitals might embrace strategies that will decrease inpatient falls by limiting patient mobility. These maladaptive strategies might include the use of restraints or sedative medications, which actually appear to increase rates of falling, and directly oppose the goal of improved mobility. There is a paradoxical relationship between falls and mobility. If a patient is totally immobile, he will have little opportunity to fall. However, immobilized patients will incur the adverse health consequences of immobility. Many patients need to be mobilized while in the hospital, as part of a strategy of increasing strength and well-being, and preserving dignity and autonomy. The best way to enhance mobility and preserve independence in older patients, while simultaneously reducing falls, is simply not known.

Currently, there is no widely accepted strategy to prevent older adults from falling in the hospital. Some experts suggest that the best approach to fall prevention may be an approach where modifiable risk factors for falling are recognized, and interventions targeting those risk factors are applied (see **Table 16-4**). Additional studies are needed to identify strategies that will balance the goals of mobility and independence in older patients with the goal of reducing the risk of falls.

Malnutrition (see also Chapter 35) Poor nutritional status is common among hospitalized older patients. Studies have estimated that up to 50% of all hospitalized older patients are nutritionally at risk and up to 25% meet criteria for malnutrition. Among hospitalized older patients, poor nutritional status is associated with worse clinical outcomes. During the hospitalization, nutritionally at-risk patients are more likely to suffer from hospital-acquired complications, particularly infection. Compared with patients with good nutritional status, poor nutritional status is associated with longer length of stay, higher readmission rates, increased likelihood of being discharged to an extended care facility, and higher mortality rates.

Given the prevalence and importance of poor nutritional status in the older hospitalized patient, the Joint Commission mandates nutritional screening in this population. Several screening tools have been developed including the Chandra scale, the Nutrition Screening Initiative, and the Mini Nutritional Assessment. The Mini Nutritional Assessment has been shown to be predictive for in-hospital mortality, longer length of stay, and greater likelihood of being discharged to a long-term care facility.

The causes of malnutrition are often multiple, and usually they relate to problems with the patient's appetite, ability to obtain or prepare food, or swallowing function. For example, poor appetite is a consequence of many chronic conditions, or the medications used to treat them. Also, poor functional status, cognitive impairment, or social and financial issues can limit an older patient's nutritional intake. Of course, some patients have conditions that impair their ability to chew or swallow as well, such as stroke-related deficits or poor-fitting dentures.

By far, the optimal approach to malnutrition in an older adult is to identify the major causes, and to intervene on those issues. Once that approach has been taken, other interventions are often added. These interventions include dietary counselling, oral supplementation, or enteral feeding in select populations. When possible, oral feeding is the optimal method for nutritional repletion and maintenance. Although most of the existing studies are of low quality, oral protein and energy supplements have been shown to reduce complications and mortality when given to hospitalized elders with malnutrition, and the use of these supplements is widespread.

At times, more aggressive feeding strategies, involving the use of feeding tubes, are considered in older patients. These strategies do have a role in patients who have reversible deficits in oral feeding ability (eg, postesophageal surgery) and in patients who are cognitively intact but with a long-term need for enteral feedings due to mechanical issues. However, hospital providers should also recognize the limitations of tube feeding strategies in the care of older patients. The preponderance of data suggests that tube feeding does not improve the quantity or quality of life in older patients with dementia who are no longer able to maintain adequate oral nutrition. It is important to recognize that a diminished nutritional intake is a marker of end-stage dementia, and that the placement of a feeding tube in this population carries the risk of complications without any apparent benefit. Families often need significant counselling around this question, and this discussion often leads to broader conversations about the goals of care for these patients.

Pressure ulcers (see also Chapter 52) Pressure ulcers are areas of skin damage that occur over bony prominences as a result of pressure, friction, and/or maceration (related to moisture) of the skin. Older patients often suffer from

conditions that are risk factors for the development of these ulcers, including immobility, malnutrition, and other comorbid health conditions.

The vast majority of pressure ulcers form, and are cared for, outside of the hospital. However, pressure ulcers are important in the acute care setting for two major reasons:

1. These ulcers can, infrequently, develop while a patient is in the hospital. When they do, they significantly increase the cost of the patient's care, and the hospital length of stay.
2. Since 2008, CMS does not reimburse hospitals for care related to a pressure ulcer that develops or worsens while the patient is in the hospital.

These reasons, taken together, suggest a need for vigilance regarding pressure ulcers in the acute care setting. Hospital providers should document pressure ulcers on admission, and engage the appropriate resources to stage and manage existing ulcers. In addition, the prevention of new ulcers is important, and hospitals should develop nursing protocols that aggressively employ the appropriate prevention measures. Chapter 52 covers the staging, diagnosis, treatment, and prevention of pressure ulcers in detail.

Preventing Adverse Events in Hospitalized Older Patients

In 1999, the Institute of Medicine published its landmark report demonstrating that hospitalized patients were often harmed by adverse events that occurred in the hospital. This led to the concept of patient safety—that is, the notion that some of these adverse events are preventable, and that it is the responsibility of the health care institution to minimize the occurrence of these events. Older patients are often disproportionately affected (either in incidence or morbidity) by these adverse effects of hospitalization, which include nosocomial infection, venous thrombosis, and adverse drug reactions (ADRs). Therefore, hospital care for older patients is now focused on the prevention of adverse events in the hospital. Geriatricians and other providers caring for older hospitalized patients should be actively involved with planning and implementing patient safety interventions in the acute hospital setting.

Preventing nosocomial infections A recent multistate survey by the US Centers for Disease Control and Prevention (CDC) estimates that there were over 700,000 health care–associated infections in 2011. These infections result in longer and more expensive hospital stays, and increased morbidity and mortality. The majority of hospital-acquired infections are due to UTIs, pneumonia, surgical site infections, gastrointestinal infections, and bloodstream infections. A full discussion of the management of all these infections is beyond the scope of this chapter, but older patients are disproportionately affected by UTIs, pneumonia, and increasingly, *Clostridium difficile* infections.

Hospital-Acquired Urinary Tract Infections Despite a rise in prevention efforts, UTIs are still common health care–associated infections. Most of these infections are catheter-associated urinary tract infections (CAUTIs), related to the use of indwelling urinary catheters. Women, older patients, and patients with severe underlying illness are at greatest risk. In 2012, the National Healthcare Safety Network reported an average rate of CAUTI of 1.4/1000 catheter days on an adult medical/surgical ward.

The prevention of health care–associated UTIs focuses on reducing the unnecessary use of urinary catheters. In addition to contributing to infection risk, catheters are known to increase the risk of delirium and falls and have been referred to as a "one-point restraint." Urinary catheters remain an important aspect of treatment when used for appropriate indications. Examples of appropriate and inappropriate indications for urinary catheters are listed in **Table 16-5**. Unfortunately, inappropriate use is common and underappreciated; some reports have suggested that up to 30% of hospital physicians are unaware that their patients have a catheter in place.

TABLE 16-5 EXAMPLES OF APPROPRIATE AND INAPPROPRIATE INDICATIONS FOR INDWELLING URETHRAL CATHETER USE

***Examples of Appropriate* Indications:**
Patient has acute urinary retention or bladder outlet obstruction
Need for accurate measurements of urinary output in critically ill patients
Perioperative use for selected surgical procedures: • Patients undergoing urologic surgery or other surgery on contiguous structures of the genitourinary tract

• Anticipated prolonged duration of surgery (catheters inserted for this reason should be removed in PACU) • Patients anticipated to receive large-volume infusions or diuretics during surgery • Need for intraoperative monitoring of urinary output
To assist in healing of open sacral or perineal wounds in incontinent patients
Patient requires prolonged immobilization (eg, potentially unstable thoracic or lumbar spine, multiple traumatic injuries such as pelvic fractures)
To improve comfort for end-of-life care if needed
***Examples of Inappropriate* Indications:**
As a substitute for nursing care of the patient or resident with incontinence
As a means of obtaining urine for culture or other diagnostic tests when the patient can voluntarily void
For prolonged postoperative duration without appropriate indications (eg, structural repair of urethra or contiguous structures, prolonged effect of epidural anesthesia, etc)

PACU, postanesthesia care unit.
Modified with permission from Healthcare Infection Control Practices Advisory Committee Guideline for Prevention of Catheter-Associated Urinary Tract Infections 2009. These recommendations are based primarily on expert opinion.

There are several alternatives to the use of urinary catheters in hospitalized elders. Urinary retention can sometimes be managed with the use of intermittent straight catheterization (ISC), instead of an indwelling catheter. For men requiring urinary management for indications other than urinary obstruction or retention, condom catheters may be an option. One small study demonstrated a lower occurrence of a composite endpoint of bacteriuria, symptomatic UTI, and death in men treated with a condom catheter, compared to those treated with an indwelling catheter. Condom catheters appear most useful in those men who can comply with the therapy, and who do not experience frequent accidental or purposeful removal of the catheter.

In institutions with computerized order entry, clinical decision support, electronic reminders, and automatic stop orders have been effective at reducing the overall use and duration of use of urinary catheters. Paper reminders are also effective in institutions lacking computerized order entry.

Hospital-Acquired Pneumonia Pneumonia is one of the most common nosocomial infections. The mortality attributable to nosocomial pneumonia is debated, but maybe as high as 30%. An episode of hospital-acquired pneumonia clearly increases hospital length of stay and costs.

Hospital-acquired pneumonia, also referred to as nosocomial pneumonia, includes both ventilator-associated pneumonia and nonventilator-associated pneumonia that develops 48 or more hours after hospitalization. Almost all of the data on prevention of hospital-acquired pneumonia comes from intensive care units (ICUs) and the study of ventilator-associated pneumonia. Extrapolation to the non-ICU population may not be appropriate. Prevention strategies for ventilator-associated pneumonia have been well-described elsewhere and are best directed at ICU physicians and staff.

Understanding the risk factors for developing nosocomial pneumonia (**Table 16-6**) is critical to implementing effective prevention strategies. Nosocomial pneumonia results from microbial invasion of sterile lung parenchyma as a result of microaspiration of contaminated oropharyngeal or gastric secretions. A defect in host defenses, aspiration of a large inoculum of organisms, or aspiration of a particularly virulent organism may contribute to parenchymal infection.

TABLE 16-6 RISK FACTORS FOR NOSOCOMIAL PNEUMONIA IN OLDER PATIENTS

Impaired host defenses/increased aspiration
Endotracheal tubes
Nasogastric tubes
Enteral feeding tubes
Supine positioning
Impaired mental status
Sedation

Large inoculum of organisms
Bacterial colonization
Gastric alkalinization (enteral feeds/H_2-receptor blockers, proton pump inhibitors)
Iatrogenic (forced hand ventilation)
Sinusitis
Malnutrition
Contaminated respiratory equipment
Overgrowth of virulent organisms
Prolonged antibiotic use
Iatrogenic (inadequate hand washing)
Central venous lines
Comorbid illness
Frequent hospitalizations
Prolonged hospital stays

There are important strategies to prevent nosocomial pneumonia for hospitalized elders in the non-ICU setting. One of the best strategies is to avoid intubation in patients with respiratory failure. Increasingly, the use of noninvasive ventilation has been effective in reducing the need for intubation. In selected patients with acute chronic obstructive pulmonary disease (COPD) or heart failure exacerbations, noninvasive ventilation can reduce the need for intubation and is associated with less pneumonia, shorter hospital length of stay, and in some studies, lower mortality. Another prevention strategy is to limit the use of medications that raise the gastric pH. Proton pump inhibitors and H_2-receptor antagonists are often used to prevent ulcers in hospitalized patients. However, the use of these medications appears to facilitate the colonization of the gastrointestinal tract with pathogenic organisms, and has been associated with increased rates of hospital-acquired pneumonia. In general, the only patients shown to benefit from stress ulcer prophylaxis using these medications are those with shock, respiratory failure, and coagulopathy. As a rule, these medications should be avoided in other hospitalized patients, unless there is a clear indication for their use.

Although there are limited data to support the use of other pneumonia-prevention strategies in noncritically ill hospitalized patients, extrapolation of data from other populations suggests that simple strategies such as elevating the head of the bed and attention to oral hygiene are also reasonable in most hospitalized elders.

***C difficile* Infection** *C difficile* has become one of the most common nosocomial infections. In 2009, over 336,000 hospital admissions involved *C difficile* infections (nearly 1% of all admissions). Patients over 65 years suffer the vast majority of the morbidity and mortality related to these infections.

The biggest risk factors for infection include antibiotic use and hospitalization. Additional risk factors relevant to the care of a geriatric population include advanced age, severity of illness, use of proton pump inhibitors, and use of tube feeding. While clindamycin and fluoroquinolones are commonly associated with *C difficile*, any antibiotic (including metronidazole and vancomycin, which are used to treat the disease) can cause infection. Prevention of *C difficile* requires both infection control measures and antibiotic stewardship. Infection control measures include patient isolation, implementation of contact precautions (gown and gloves), and liberal hand washing with soap and water for all persons entering and leaving the patient's room (*C difficile* spores are not effectively killed by alcohol-based hand rubs). There is evidence that formal antibiotic stewardship programs can also lead to decreased rates *of C difficile* infections in hospitals, by modulating the use of antibiotics. For example, the overuse of fluoroquinolones appears to have led to the development of fluoroquinolone resistance among highly virulent strains of *C difficile*, and the reduction in the use of fluoroquinolones specifically, and antibiotics more generally, is an important intervention in the prevention of *C difficile* infections. The use of probiotics for prevention of *C difficile* infection is somewhat more controversial. A large meta-analysis found that agents such as *Saccharomyces boulardii* or *Lactobacillus rhamnosus*, used as probiotics, prevent diarrhea associated with *C difficile*. However, it is less clear if these agents reduce the overall incidence of *C difficile* infections, and the most recent guidelines from the American College of Gastroenterology still recommend against the prophylactic use of probiotics to prevent this infection.

Preventing venous thromboembolism Prevention of venous thromboembolism (VTE), which includes deep venous

thrombosis (DVT) and pulmonary embolism (PE), is an important consideration in hospitalized patients. VTE is associated with increased morbidity and mortality in this population.

While there is no consensus on quantifying patient-specific risk factors, patients admitted with certain conditions (eg, heart failure, severe respiratory disease, or malignancy), patients confined to bed, and older patients are considered to be at increased risk for VTE. Multiple studies, including several meta-analyses, have demonstrated the efficacy of pharmacologic prophylaxis against VTE in high-risk hospitalized patients. Studies have shown that low-molecular-weight heparin (LMWH), unfractionated heparin, and fondaparinux all reduce the risk of both DVT and PE without a significant increased risk of major bleeding (minor bleeding episodes, including development of hematomas, may be more common in patients receiving pharmacologic prophylaxis). Prophylaxis has not been associated with a mortality benefit, and its cost-effectiveness has not been well-studied. For patients at high risk of bleeding, the use of intermittent pneumatic leg compression is a reasonable substitute for heparin products.

The use of standard order sets and reminders built into computerized order entry systems can facilitate routine use of VTE prophylaxis in high-risk patients.

Preventing adverse drug reactions (see also Chapter 64 on drug therapy) Older patients experience a greater number of ADEs than younger patients. This is in part due to the large number of medications prescribed to this population.

Assuring the appropriate use of medications in older patients is challenging for a number of reasons. First, it is worth noting that older patients are often excluded from clinical trials involving medications. This means that the conclusions of many medication studies might not apply to this population of patients. Also, pharmacokinetics and pharmacodynamics are different in older patients, with implications for dosing and response to medications in this population. In addition, older patients are prescribed more medications than their younger counterparts. This leads to more opportunity for side effects, and more drug-drug interactions. It can be very difficult for a provider to have a complete grasp of all of the concerning side effects and interactions for a patient taking 10 or 20 different medications. This difficulty is illustrated by the concept of prescribing cascades. A prescribing cascade occurs when one medication causes a side effect, and another medication is used to treat that side effect, without recognizing that the original symptom was a medication side effect itself. This cascade can lead to unnecessary polypharmacy, and very complicated medication regimens.

Unfortunately, there is no easy way to eliminate these prescribing problems in complex, older patients. However, attending to a few basic tenets can reduce the number of these adverse events:

- Drug side effects and interactions should always be considered in the differential diagnosis of problems in patients taking multiple medications. A trial of discontinuing suspect medication is often appropriate.
- High-risk medications should be avoided in older patients. Careful attention should be paid to medications most likely to lead to ADEs including analgesics, sedatives, cardiovascular medications, and psychoactive drugs. Although the use of any medication is dependent on an assessment of the risks and benefits of that medication, there are some medications for which the risk most often exceeds the benefit. The Beers list and the STOPP criteria have been created to increase the awareness of these high-risk medications, and help clinicians avoid their use in this population.
- Any new medication should be prescribed with great thoughtfulness, considering the likelihood of an adverse effect and the goals of care. Especially in older patients, newly prescribed medications should be considered therapeutic trials, and if the beneficial effects of the medication are not apparent, or adverse effects are seen, the patient may be better off without that medication, regardless of any theoretical benefit.

In addition, the use of clinical pharmacists and computerized systems can assist providers in appropriate medication prescribing in this population.

Palliative and End-of-Life Care (See Also Chapter 55)

There is a tremendous need for high-quality palliative and end-of-life care for older inpatients. In 2007, 32% of all deaths occurred in the hospital. Hospitalizations that end in death can be chaotic for patients and family members, and these hospitalizations cost 2.7 times as much as hospitalizations resulting in live discharges. Despite the fact that many people die in hospitals, there is evidence that end-of-life care in hospitals is often inadequate. Surveys of patients and families have shown that patients dying in hospitals believe they do not have enough contact with physicians, emotional support, or information about what to expect of the dying process. In addition, a substantial percentage

report moderate or severe pain in the last 3 days of life.

Although the terms “palliative care” and “end-of-life care” are sometimes used synonymously, they are better viewed as separate, but overlapping domains. Palliative care refers to care that aims to improve the quality of life through the relief of suffering. Palliative care focuses, primarily, on pain relief and symptom management. End-of-life care is the care provided to a patient who is nearing death. End-of-life care often includes palliative elements, but also incorporates specific interventions that are related to the impending death. Specifically, end-of-life care typically includes discussions about prognosis and patient wishes, and detailed planning of the patient’s care as he approaches death.

Delivering high-quality palliative and end-of-life care requires experience, a special set of skills, and a substantial investment in time. Central to the process is the need for extensive communication between the hospital providers, and the patient and family. End-of-life care in the hospital is based on the successful achievement of several goals:

- Assessing the patient’s understanding of the disease process and prognosis, current symptoms, and wishes, including goals of care.
- Determining the patient’s prognosis.
- Educating the patient and family about the disease process, the prognosis, and the types of care available.
- Negotiating realistic goals of care.
- Providing appropriate palliative care, including pain control, and control of other symptoms such as nausea, dyspnea, and others.
- Addressing spiritual and psychosocial needs of the patient and family.
- Planning for discharge and postdischarge care.

Accomplishing these goals can be very challenging, often requiring the work of a multidisciplinary team. As a result, many hospitals have developed formal palliative care programs to adequately address the needs of dying patients. As of 2011, 67% of all hospitals with more than 50 beds report having a palliative care program. While hospitals employ a variety of practitioners to staff their programs, geriatricians, hospitalists, and oncologists are well-represented in most programs. Board certification is now available in the area of hospice and palliative medicine. A full discussion of palliative and end-of-life care can be found in Chapter 55.

HOSPITAL DISCHARGE (SEE ALSO CHAPTER 15 [TRANSITIONS IN CARE])

The safe transition of elders from the inpatient to outpatient setting is a complex endeavor. At discharge, patients are routinely transitioned from the care of an inpatient physician to that of their primary care provider, one or more specialist physicians, or a health care provider at a nursing home or rehabilitation facility. At the same time, the patient moves from the care of hospital nurses, to that of themselves, family, personal caregivers, or nurses in other facilities. This “handoff” creates the opportunity for information to be lost or miscommunicated, resulting in the potential for adverse clinical consequences. The Institute of Medicine (IOM) report, “To Err Is Human” estimated that, after discharge, 49% of patients experience at least one medical error and 19% to 23% of patients suffer adverse events. These adverse events are associated with deficiencies in health literacy, patient education, communication among providers within and between systems, medical follow-up, and medication issues. The medication issues at discharge are well documented. Research has shown that 14% of patients experience one or more medication discrepancies after discharge, and that at 30 days, readmissions were twice as common in patients who had experienced a discrepancy. Other studies have shown an ADE rate of 11% at 3 weeks after discharge. While these transition problems are not unique to the geriatric population, older patients are disproportionately affected.

There is widespread agreement among health care professionals that improving safety during transitions of older patients from the inpatient to outpatient setting is a health system priority. Unfortunately, there are no national standards outlining criteria for assessing the adequacy of discharge planning for older adults and there is no consensus on the best strategy to optimize the discharge process. A systematic review of the literature indicated little evidence for the effectiveness of discharge planning as a means of reducing length of stay, mortality, or costs.

Much of the complexity of the hospital discharge process stems from the large number of changes that occur during a typical hospitalization. These changes include new medical diagnoses, alterations in the medical regimen, changes in the patient’s functional status, and changes in the level of care and support that the patient will require. Each of these changes requires an intervention. And these interventions must be clearly understood by the patient, the caregiver, and

the follow-up physician. The success of this complex discharge process depends, therefore, on assessing the patient, assuring that there is a plan for intervening on these changes, communicating about these interventions, and assuring that they carry forward, even after the patient leaves the hospital.

The first step in the discharge of a hospitalized elder is a need assessment. Although aimed at discharge, this assessment should ideally begin near the time of admission, and continue throughout the hospitalization. A hospital discharge cannot succeed unless the discharge team fully understands the medical plan, and the practical details of how it will be carried out after discharge. This requires an assessment of several domains of the patient's life, including functional status, cognitive status, caregiver and social support, home situation, and financial/insurance status (see **Table 16-3**). The predischarge assessment is complex, and it is usually accomplished by a multidisciplinary team that might include physicians, nurses, social workers, discharge planners, physical and occupational therapists, complex care managers, pharmacists, and others.

Once the patient has been fully assessed, the discharge process can proceed. Below is a discussion of some of the key elements of this process.

Patient and Caregiver Communication

Patients and caregivers need to understand the medical plan, and need to be given explicit discharge instructions. Discharge instructions must be simple, clear, and written or discussed at a level that is commensurate with the patient's health literacy. These instructions should inform patients of all the key actions that they must take to hasten recovery, including taking medications, participating in physical therapy, and attending follow-up appointments. These instructions should also cover physical limitations, warning symptoms that should prompt them to seek additional care, and a contact number in case of urgent needs. The importance of these instructions has led to the use of the "teach-back" method of instruction (having the patient repeat the instructions back to the teacher, to ensure comprehension). A simple set of instructions, written specifically for the patient, is also useful in the discharge education process.

Inpatient Provider and Follow-Up Provider Communication

The provider handoff at discharge depends on structured communication between the inpatient and outpatient providers. While a phone call at discharge to the primary care provider is sometimes appropriate, timely communication of a summary of the patient's hospital course, medication changes, and required follow-up can be automated and sent by e-mail or fax as well. The Society of Hospital Medicine has developed a checklist of the key components of a discharge summary (**Table 16-7**). In addition to this information, it is important that test results that are pending at the time of discharge are not lost in the transition. Hospitals and health systems should develop robust systems to assure that test results that become available after the hospital discharge are reviewed and managed appropriately.

TABLE 16-7 A HOSPITAL CHECKLIST FOR THE IDEAL DISCHARGE OF THE OLDER PATIENT

	PROCESS		
DATA ELEMENTS	DISCHARGE SUMMARY	PATIENT INSTRUCTIONS	COMMUNICATION TO FOLLOW-UP CLINICIAN ON DAY OF DISCHARGE
Presenting problem that precipitated hospitalization	x	x	x
Key findings and test results	x		x
Final primary and secondary diagnoses	x	x	x
Brief hospital course	x	x	x
Condition at discharge, including functional status and cognitive status if relevant	x—Functional status o—Cognitive status		
Discharge destination (and rationale if not obvious)	x		x

Discharge medications:			
Written schedule	x	x	x
Include purpose and cautions for each	o	x	o
Comparison with preadmission medications, (eg, new, changes in dose/frequency unchanged, medications that should no longer be taken)			x
	x	x	
Follow-up appointments with name of provider, date, address, phone number, visit purpose, suggested management plan	x	x	x
All pending labs or tests, responsible person to whom results will be sent	x		x
Recommendation of and sub-specialty consultants	x		o
Documentation of patient education and understanding	x		o
Any anticipated problems and suggested interventions	x	x	x
24/7 call back number	x	x	
Identify referring and receiving providers	x	x	
Resuscitation status and any other pertinent end-of-life issues	o		

x, required element; o, optional element.

Reprinted with permission from Halasyamani L, Kripilani S, Coleman E, et al. Transition of care for hospitalized elderly patients—development of a discharge checklist for hospitalists. J Hosp Med. 2006;1:354–360.

Medication Reconciliation

Just as medication reconciliation is important at the time of admission, it is critical to the discharge process. The reconciliation process must take into account the patient's new medical problems, comorbidities, the medications that were prescribed in the hospital, and the medications that the patient was taking before admission. The end product of the process is a list of medications that the patient will take at discharge, with unnecessary or inappropriate medications eliminated, drug interactions minimized, and doses and instructions correct. Regulatory agencies require that this occurs at discharge, and every hospital should develop a standardized system to ensure that this key task is accurately performed. The process can be automated or can involve the use of clinical pharmacists. Several studies have shown that involving clinical pharmacists in the medication reconciliation process at discharge leads to fewer ADEs after discharge and in some cases has reduced readmissions. Many of the more robust pharmacist-based programs also call patients by telephone after discharge to troubleshoot medication problems.

When reconciling medications, it is important to prospectively assess if patients will be able to obtain their medications after discharge. Some medications, especially novel or costly ones, might be freely available to the patient while hospitalized, but the patient may encounter a lack of insurance coverage, or a high copay, after discharge. These resource problems must be anticipated before discharge to avoid treatment interruptions. Some hospitals have partnered with local pharmacies to bring the patient's discharge prescriptions to the patient before hospital discharge.

Selection of Discharge Location and Level of Postdischarge Care

The discharge team must combine all of the information obtained from the discharge assessment, and formulate a plan to assure that the patient is discharged to a location that is safe, and with the appropriate level of care. Patients can be discharged to home with self-care, home with additional support (such as home care), or to care facilities which provide a spectrum of care (eg, long-term acute care, rehabilitation in a skilled nursing facility, hospice, etc). The appropriate assignment of the discharge location and postdischarge level of care requires a sophisticated understanding of the patient's needs, the medical plan, and the patient's financial/insurance and social resources. Most hospitals have specially trained staff to assist with these decisions.

Postdischarge Follow-Up

The postdischarge care of a patient depends on timely follow-up with outpatient providers, and there is some evidence that this follow-up improves outcomes and reduces unplanned readmissions to the hospital. Appropriate follow-up can be encouraged by providing the patient with a scheduled appointment at the time of discharge.

In summary, the process of discharging a patient from the hospital is complex and important, and hospitals should continue to develop and refine systems to assure that this transition occurs safely.

MODELS OF HOSPITAL CARE AND THE OLDER PATIENT

This section discusses several of the inpatient care models that are relevant to the care of hospitalized elders.

Hospitalist Care

Concurrent with the increased attention to the needs of hospitalized elders has been the emerging presence of hospitalists. The hospitalist physician, usually a general internist, focuses clinical activity almost exclusively on caring for hospitalized patients. Varied forces have driven the hospitalist movement, including improved efficiency of hospital care, physician ownership of inpatient quality and safety initiatives, and the many challenges of simultaneously managing patients in both the office and the hospital. Teaching hospitals also employ hospitalists to mitigate pressures resulting from resident work hour reductions. The rapid growth of the hospitalist field has been supported, in part, by direct financial support from physician group practices, hospitals, and academic medical centers.

It is estimated that there are over 40,000 hospitalists practicing in the United States in 2014, and that over 70% of hospitals utilize hospitalists in some capacity. As hospital medicine programs have grown, so have the roles of hospitalists in caring for older adults. This fact, along with the continued increase in the numbers of hospitalized elders, points to a need for continuing education in geriatric medicine for these providers. Although direct patient care remains the primary role of hospitalists, hospitalists also may fill a variety of other roles. Hospitalists often establish and run programs in palliative care, surgical comanagement, and quality and patient safety. And, with the hospital setting as their "office," hospitalists are often in leading administrative roles within hospitals and academic medical centers.

As the hospitalist model of care has spread, the field has changed the way clinical problems are approached and managed. New research questions have been raised regarding the clinical approach to hospitalized patients, implementation of best practices, care transitions, and how to improve patient safety. Many academic hospitalists have set their sights on improving quality and safety in several of the areas discussed in this chapter. As a site-defined specialty, hospitalists spend more time in the hospital than do many other physicians, and are perfectly poised to enhance the quality and safety of inpatient geriatric care.

Acute Care for Elders (ACE) Units

One model of care that incorporates many of the interventions that have been shown to improve hospital outcomes in older patients is the Acute Care for Elders (ACE) unit. In 1987, Bachman et al. published a description of a pilot experiment to create two medical units at Choate-Symmes Health Services that incorporated physical modifications and protocols designed to address functional impairment in geriatric patients. The physical modifications addressed safety issues such as low beds to decrease injury related to falls, while the protocols included nurse-initiated screening of geriatric syndromes and early discharge planning. Only one hospital (Symmes) demonstrated any improvement in geriatric patient outcomes, which in retrospect was most likely due to differences in implementation of the model.

However, subsequent reports in 1995 and 2000 by Landefeld et al. and Counsell et al. of randomized trials of care in ACE units versus usual care in a standard medical unit demonstrated several improvements in outcomes, including better maintenance of ADLs, fewer discharges to subacute care versus home, decreased falls, decreased length of stay, and improved patients' and families' satisfaction with the hospitalization. Over the subsequent 10 years, more ACE units were created in academic and community hospitals, some of which confirmed these results. Implementation was slow, however. A review in 2003 that surveyed hospitals associated with medical schools with a geriatrics program found that only 16 had ACE units. Adoption of the ACE model in community hospitals was also very slow.

One barrier to more widespread implementation of the concept was the variability of the results; however, this may have been due to variability in implementation of the model from one hospital to another. This included differences in how patients were placed in hospital beds (a physical unit vs scattered beds), a wide variety of different medical providers providing the core care (hospitalists, internists, community physicians, nurse practitioners, physician assistants), and variable training of staff in geriatric care. A meta-analysis that was performed in 2012 to address the discrepancies in outcomes between reports identified five key components that appeared to be essential for optimum results. These included the following features:

1. Environmental interventions (rugs, lighting, handrails, low beds).
2. A patient-centered care model that emphasizes independence and rehabilitation from the beginning of the hospital stay.
3. A multidisciplinary care team consisting of nurses, physicians, therapists, social workers, nutritionists, and pharmacists providing coordinated care within a dedicated inpatient unit.
4. Coordination of care, including a daily interdisciplinary round in which all members of the team share their findings.
5. Nurse-driven protocols that identify and treat geriatric syndromes (**Figure 16-1**).

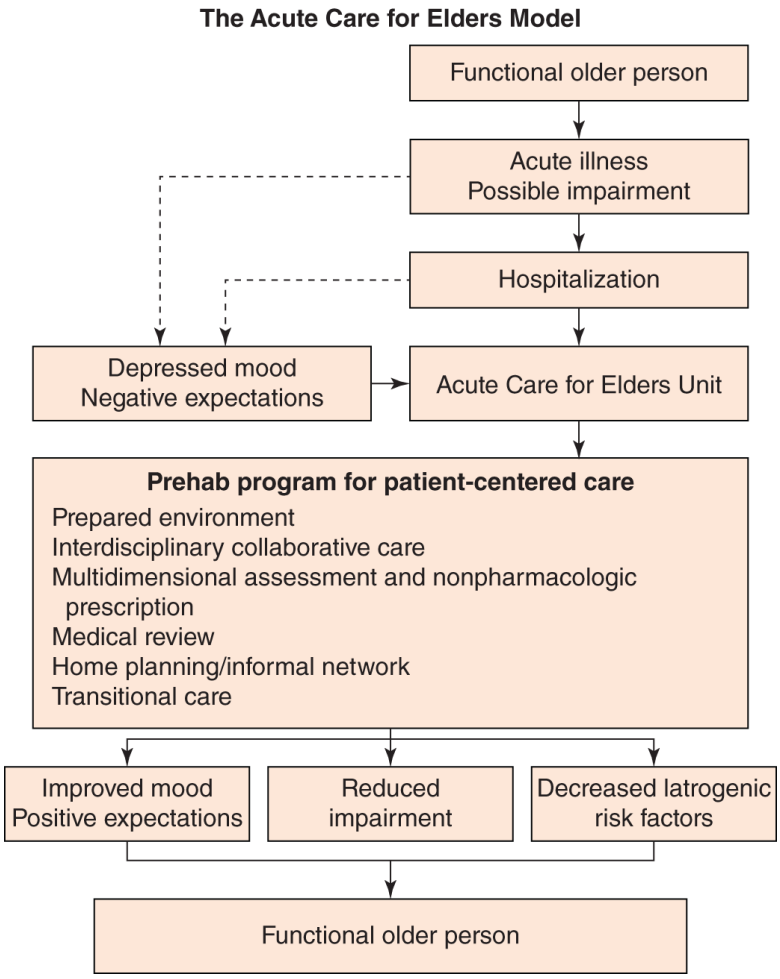


FIGURE 16-1. The Acute Care for Elders Model. (Adapted from Landefeld S. The story of ACE. In: Malone ML, Capezuti E, Palmer RM,

eds. *Acute Care for Elders—A Model for Interdisciplinary Care*. New York, NY: Humana Press/Springer Science and Business Media; 2014.)

ACE units incorporating all these components appear to be much more likely to achieve significant improvement in outcomes.

As additional positive reports have been published, adoption of the ACE model has increased rapidly during the past 5 years. Units have been opened in academic medical centers and community hospitals in every state in the United States, and are starting to appear in other countries, including Canada. The impetus for this increased adoption may be the recent reports of decreased hospital costs and lower readmission rates. In 2013, Flood et al. indicated that implementation of the ACE model in their institutions reduced costs of hospitalization and 30-day readmission rates in geriatric patients admitted to an ACE unit compared to controls matched for age and diagnosis treated in usual medical units. This is of particular interest as the majority of older adults have their health insurance coverage through Medicare, as Medicare has put in place several financial incentives to decrease the morbidity and costs associated with hospital readmission within 30 days.

There remain several barriers to creating a physical ACE unit, largely due to capital expenditures for environmental modifications, difficulty in recruiting qualified specialist leaders, and future concerns with not having enough room for the rapidly expanding patient population of adults aged 65 and older in such a space-defined unit. Some hospitals or academic medical centers have preferred to develop a virtual ACE team, rather than a dedicated ACE unit. The pioneering groundwork for this concept has been laid by Dr Michael Malone and his group at Aurora Health in Milwaukee, WI. Their virtual ACE team, outlined in a 2010 article in the *Journal of the American Geriatrics Society*, is a multidisciplinary geriatrics consult team involving physician, nurse, social work, pharmacy, and physical therapy that is designed to improve patients' hospital course and expedite discharge planning and transitional care. The tracking software developed for the Virtual ACE is compatible with several widely used electronic health care records. The Virtual ACE team model provides the expertise and systems approach to the care of the olderly hospitalized population, particularly the vulnerable and medically complex outside the confines of a defined unit. While less widely adopted, the Virtual ACE model has demonstrated some of the same benefits for geriatric patients as a physical ACE unit, including decreases in falls, rates of delirium, use of inappropriate medications, and readmissions.

Stroke Units

Stroke units use a care delivery model analogous to ACE unit models. A stroke unit is a geographic hospital unit dedicated to the care of patients with stroke. Physicians, nurses, and therapists are involved in a coordinated effort to support the care and rehabilitation of stroke patients. Cochrane reviews have concluded that stroke unit care, compared to usual care, is more likely to result in patients being alive, independent, and living at home 1 year after a stroke. Whether there are aspects of poststroke care that can be generalized and systematized to improve elder health care outcomes outside such a unit needs further investigation.

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Chapter 17

Emergency Department Care

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Learning Objectives

- Gain a perspective on the unique and essential role of the emergency department (ED) plays in the care of older people.
- Describe key aspects of guidelines for geriatric EDs.
- List differences in the evaluation of older versus younger patients in the ED.
- Recognize risk factors for functional decline in older people discharged from the ED.
- Summarize options to hospitalization for older patients evaluated in the ED.

Key Clinical Points

1. **Multiple organizations have endorsed guidelines for geriatric EDs that recognize that symptoms may be nonspecific and response to therapy difficult to predict in older ED patients, and the importance of the biopsychosocial model of care in evaluating and managing older ED patients.**
2. **The Geriatric Emergency Care Model encourages routine assessment of cognitive and functional status.**
3. **Adverse drug events account for more than 10% of ED visits among older patients.**
4. **Geriatric EDs are emerging as a new model of care that include environmental modifications and different approaches to evaluating the older patient.**
5. **Geriatric Emergency Medical Service trauma triage protocols can improve care for older adults who are injured.**
6. **EDs play an important role in managing older patients after natural disasters.**

INTRODUCTION

The Emergency Department (ED) plays a unique and essential role in the care of the older adult. The ED is open 24 hours a day, 7 days a week, 365 days a year. It provides access to the millions of people who have no other entry point for health care. It gives care to people who have no established community provider and acts as the gatekeeper between the community and the hospital. Older people use the ED at higher rates than other populations, present more often with urgent and emergent conditions, and are more frequently transported by ambulance. In addition, the ED is a major care provider for nursing home residents; one of four nursing home residents is transported to an ED yearly.

The prevailing model of care in EDs has been established for over 50 years but does not conform well to the needs of the older adult. Based on principles proposed in 1962 by the Committee on Trauma of the American College of Surgeons, EDs are designed for rapid evaluation and treatment of the emergent and urgent needs of acutely ill and injured patients. ED care differs from care delivered in other settings. Typically, there is no preexisting relationship between the patient and the physician. The process rewards speed, the time frame is immediate, and the focus is on the patient's complaint. It is not friendly to the older patient with complex needs who require thorough assessment and

evaluation and whose care process is slow moving.

In 2013, the American College of Emergency Physicians, the American Geriatrics Society (AGS), the Emergency Nurses Association, and the Society for Academic Emergency Medicine approved consensus-based Geriatric emergency department guidelines. These guidelines focus on specific geriatric needs and common complaints. They provide a template for focused training and policy development directed at this unique patient population. The Geriatric ED guidelines build upon the model of emergency care for older people developed by the Society for Academic Emergency Medicine (SAEM) Geriatric Task Force. This model appreciates differences in disorders and diagnoses by age, atypical presentation of disease, altered physiology of aging, the complexity of diagnosis and management of older patients, and the need to consider other issues beyond the presenting complaint (**Table 17-1**). The Geriatric Task Force recognized that symptoms may be nonspecific, comorbidities are common, and response to therapy is often difficult to predict. The Task Force proposed a biopsychosocial model of emergency care for older patients. The model upon which the guidelines are based has evolved over time and reflects the current thinking about basic principles for emergency care of the older patient. They recognize that the ED visit is an event in a continuum of care and that ED professionals must consider the discharge plan during the visit.

TABLE 17-1 GERIATRIC EMERGENCY CARE MODEL DEVELOPED BY THE SAEM GERIATRICS TASK FORCE

- The patient's presentation is frequently complex.
- Common diseases may present atypically.
- Comorbid conditions must be considered.
- Polypharmacy is common and may be a factor in presentation, diagnosis, and management.
- Cognitive impairment is possible and mental status should be evaluated.
- Standard values for diagnostic tests may not be applicable.
- With age comes decreased functional reserve and this must be anticipated.
- Social support systems are important in care of older patients and should be considered in planning for care.
- Knowledge of baseline functional status is essential in evaluating new complaints.
- Medical problems must be evaluated for psychosocial adjustment.
- The encounter is an opportunity to assess important conditions in the patient's personal life.

EPIDEMIOLOGY

The aging of the US population poses a challenge to health care delivery, as older patients consume a disproportionate share of health care resources. Population predictions project that by the year 2030, the percentage of Americans over the age of 65 will rise from 12.9% to 19%. Almost one in four of these older patients will visit the ED at least once a year. Additionally, of these older patients, ones that rate their health as "fair or poor" visit the ED twice as often as those that believe they are in "good or excellent" health. In the United States, 23% of residents 65 or older are in fair or poor health, compared to only 10% of younger residents. Emergency care is one area of heavy resource use by older patients. In 2010, approximately 15% of the ED visits were by patients aged 65 and older. More came by ambulance, 38%, than any other age group. Compared to younger patients, older patients have higher disease acuity and the probability of hospital admission from the ED is higher. Patients 65 to 74 years old have a 32% chance of hospital admission from an ED visit and patients 85 years and over have a 43% chance of admission, higher than any other group. Older adults were also more likely to be admitted to critical care units (4% vs <1%), more likely to undergo laboratory and radiographic testing, and had longer ED lengths of stay.

Given the high rate of ED use by older adults and the projected growth of the older populations, assuming stable visit rates, the proportion of ED visits that are by older patients will increase to approximately 25% by the year 2030. Increases in ED use rates could push the proportion of older adults in the ED even higher.

The presenting complaints of older patients differ from those of younger patients. The most common ED-presenting complaint for both older and younger patients is injury, though this complaint is even more common in younger patients (37%) than older patients (29%). The next four most common visit reasons in older patients were dyspnea, chest pain, abdominal pain, and weakness and fatigue.

PATHOPHYSIOLOGY AND PRESENTATIONS

Older patients have a higher probability of serious disease than do younger patients. The ED may provide the best place to accomplish diagnosis and treatment of potentially dangerous undifferentiated complaints with relative speed compared to traditional inpatient and outpatient settings.

Typical ED approaches to diagnosis may not work well with the older patient. Older patients may present with undifferentiated complaints that have a broad differential diagnosis encompassing numerous serious diseases. Common diseases may present atypically. Cognitive impairment may limit the ability to obtain an accurate history. Older patients may tend to minimize symptoms, attributing a symptom to a benign rather than a more serious condition. For example, an older ED patient may suggest that their chest pain is due to indigestion rather than heart attack or their abdominal pain is constipation rather than ischemic bowel. Typical presenting signs and symptoms may be absent, and diagnostic tests may be normal despite serious diseases. For these reasons, an extensive evaluation may be appropriate to sort out the complexities of the situation. While commonly considered a sign of poor judgment and derogatively described as “shotgunning,” with the complex older patient, extensive evaluation may be the most thoughtful approach.

Acute cardiac ischemia may be especially difficult to diagnose in the older patient. In the younger old (eg, 65–85 years), the majority of patients have chest pain, although atypical presentations can occur. After age 85, atypical presentations of cardiac ischemia outnumber typical presentations by a 2:1 margin. Common atypical presentations include altered mental status, abdominal pain, dyspnea, and arrhythmia. In fact, acute delirium or change in level of consciousness (stupor or coma) can sometimes be the single presenting symptom of what turns out to be acute cardiac ischemia. Conversely, altered mental status is only rarely due to acute cardiac ischemia; it is the cause of record in only 1% of patients who present to the ED with acute mental status changes.

Abdominal pain in the older adult also presents challenges in the ED. For example, among older patients with acute cholecystitis, most do not have epigastric or right upper quadrant pain, and 5% do not have any pain at all. Over half will be afebrile, and nearly half will have a normal white blood cell count. Only one in five older patients with appendicitis present classically, less than half have an elevated temperature, and a quarter have atypical tenderness on examination that is either diffuse or localized to an area other than the right lower quadrant. In contrast to younger patients with abdominal pain, lack of abnormal laboratory studies or a normal body temperature in an older patient would not help rule out the need for surgical intervention. The nonspecific presentation of serious abdominal disease in the older adults has led to increased reliance on the use of computed tomography, which has a much higher sensitivity and specificity than the clinical examination in the evaluation of the older patient with abdominal pain.

Generalized weakness and fatigue are common ED complaints in older patients that are seen in fewer than 1% of patients less than 65 years old. Common diagnoses after a workup for generalized weakness include pneumonia, urinary tract infection, congestive heart failure (CHF), dehydration, anemia, and gastrointestinal bleed. In younger patients these complaints tend to present with more obvious symptoms letting the provider obtain a more focused work-up. Older patients with generalized weakness receive more diagnostic tests and procedures while in the ED and are more likely to be admitted than older adults who do not have these symptoms.

Frailty is present in many older ED patients. It is a risk factor for falls, delirium, and functional decline. These may precipitate an ED visit or occur after a visit. Recognizing frailty and the heightened vulnerability to stress and post-ED decline is important. The cycle of frailty involves a spiral of fatigue, deceased energy expenditure, decreased appetite, and loss of muscle mass (see **Figure 46-3**). Frail patients are at an increased risk of death and further functional decline, so care must be taken with discharge planning.

EVALUATION

The Geriatric Emergency Care Model (see **Table 17-1**) outlines an approach to older ED patients that differs from the approach to younger patients. In addition to assessing the chief complaint, the care model encourages routine assessment of cognitive and functional status.

Older patients who present to the ED may have cognitive impairment. This impairment may limit the reliability of the medical history and reduce their understanding of and compliance with discharge instructions. Cognitive impairment may be previously diagnosed or unrecognized. Delirium is an important cause of cognitive impairment in older ED patients. About 10% of older ED patients have delirium, but is recognized as delirium in only 16% to 35% of

cases. The SAEM Geriatric Task Force recommends mental status screening for all older ED patients and considers it an indicator of quality (**Table 17-2**). The failure to diagnose delirium in ED patients can increase mortality threefold. Screening instruments for cognitive impairment that are useful in other settings may be of limited use in the ED. The Mini Mental Status Examination, for instance, takes up to 15 minutes to complete in ED patients and some tasks, such as writing, can be limited in patients with extremity injuries or IVs. These limitations make its use impractical for emergency physicians who must therefore use brief, sensitive tests to assess for cognitive dysfunction, leaving more in-depth assessment to primary care physicians and consultants. Examples of brief tests include the Orientation Memory Concentration Test, and the Six-Item Screener. Use of both the Delirium Triage Screen and the Brief Confusion Assessment Method has sensitivity of 82% and a specificity of 95% while taking less than 90 seconds to complete.

TABLE 17-2 ■ QUALITY INDICATORS FOR COGNITIVE ASSESSMENT FOR OLDER ED PATIENTS FROM THE SAEM GERIATRIC TASK FORCE, 2009

- ED providers should perform and document a cognitive assessment.
- Cognitive impairment should be assessed for a change from baseline and documented.
- Patients discharged with cognitive impairment should have a plan for follow-up and a supportive home environment.
- If the cognitive impairment is at baseline, but not previously diagnosed, it should be documented prior to discharge.

Functional status and the potential for functional decline after discharge are critical but rarely addressed issues in the ED. Factors that contribute to post-ED functional decline are listed in **Table 17-3**. People with subacute or chronic illnesses often visit the ED at a point where the illness has developed a significant impact on function, especially the ability to transfer and walk. Injuries can produce functional impairment either from the injury itself or from the treatments such as splints and slings. Patients whose basic activities of daily living are affected by their illness or injury require further evaluation or admission to the hospital, even if the treatment of the illness or injury would not require hospitalization. In the ED of the authors, mobility is assessed in older patients with a “Get Up and Go” test (assessing the ability to transfer and ambulate) with or without a walker as appropriate. Those who are unable to adequately complete the test should not be discharged home from the ED without intensive home support. If such support cannot be assured, it is essential to explore alternatives to discharge, such as hospitalization, a postacute care facility or admission to a skilled nursing facility. Other screening tools to predict functional decline include ISAR (Identification of Seniors at Risk—self-reported) and TRST (Triage Risk Screening Tool—completed by nurses) can be performed in the ED (**Table 17-4**). Patients who test positive with TRST, ISAR, or Get up and Go should have a detailed functional assessment arranged, if discharged home.

TABLE 17-3 ■ FACTORS ASSOCIATED WITH POST-ED FUNCTIONAL DECLINE AND ADVERSE OUTCOMES

- Cognitive impairment
- ADL/IADL impairment (walking, transferring, transportation)
- Requires assistance from caregivers or home nurses
- Recent (30-day) ED use
- Recent (3–6 month) hospitalization
- Multiple medications (> 3–5 meds)
- Lives alone, no caregiver
- Visual problems
- ED nursing recommendation

ADL, activities of daily living; IADL, instrumental activities of daily living; meds, medications.

TABLE 17-4 ■ TOOLS TO PREDICT FUNCTIONAL DECLINE

TRIAGE RISK SCREENING TOOL (TRST) COMPLETED BY NURSES, YES/NO RESPONSE	IDENTIFICATION OF SENIORS AT RISK (ISAR) SELF-REPORTED, YES/NO RESPONSE

• Presence of cognitive impairment?	• In general, do you have serious problems with your memory?
• Difficulty walking, transferring or recent fall?	• Since the illness or injury that brought you to the ED, have you needed more help than usual to take care of yourself?
• Lives alone with no available caregiver?	• Before the illness of injury that brought you to the ED, did you need someone to help you on a regular basis?
• Five or more prescription medications?	• Do you take more than 3 different medications every day?
• ED use in last 30 days or hospitalization in last 90 days?	• Have you been hospitalized for one or more nights during the past 6 months (excluding a stay in the ED)?
• Registered nurse concern?	• In general, do you see well?

MANAGEMENT

Medication

There are many aspects of geriatric pharmacotherapy that are important in the ED. Older adults use more prescription and over-the-counter drugs than any other age group. They consume a third of all prescription medications and half of the over-the-counter preparations. Adverse drug events including drug-drug interactions and adverse drug reactions are thought to account for more than 10% of ED visits and a quarter of hospital admissions for older patients. Drugs at higher risk for adverse events include anticoagulants, antineoplastic agents, opioids, nonsteroidal anti-inflammatory drugs, and anti-infective agents. Risk factors include polypharmacy and renal insufficiency.

Many patients receive new prescriptions when they are discharged from the ED. New medications can precipitate problems, such as unanticipated interactions with ongoing medications. The emergency physician may be unaware of the potential interactions or may not have complete information about ongoing medications. Only about 40% of community-dwelling older ED patients can either correctly identify their prescription medications or provide a written list. A third of the lists that are brought to the ED are not accurate.

Inappropriate prescribing can occur in the ED. Using the Beers criteria to identify potentially inappropriate medication (PIM) prescriptions, about 4% of ED prescriptions are considered inappropriate. PIMs were administered in almost 17% of ED visits by older patients. The Beers criteria have not been validated for use in the ED setting and it is possible that short-term use of selected medications deemed inappropriate in the Beers criteria would be acceptable, so these percentages may be an overestimate. Nevertheless, inappropriate prescribing is a correctable problem and system changes, like placing a pharmacist in the ED or using warnings as a part of computerized prescription order entry, might help minimize these problems.

Geriatric Emergency Departments

The first geriatric EDs appeared in 2008 and have increased in numbers. The 2013 Geriatric ED Guidelines strive to standardize care and environment so the designation Geriatric ED represents more than a marketing scheme. Geriatric EDs can be a whole unit or a physical space in a larger ED; but any hospital can implement these policies in their existing ED. The goal of these EDs is to improve allocation of health care resources, decrease nosocomial complications, transition patients to optimal inpatient or outpatient care, and positively affect staff satisfaction. Guidelines include recommendations on staffing, discharge protocols, quality improvement, equipment, and supplies. Recommendations are also given on developing policies and procedures to screen for seniors at risk, to use Foley catheters appropriately, to manage medications, to assess fall risk and cognition, and to provide palliative care. Policies aimed specifically at the geriatric population should be routine care and cover triage, safety, abuse/neglect, sedation, advanced directives, wound assessment, and patient death.

Teamwork is crucial for optimum emergency care of older patients. EDs can provide access to team members who can help with older adult care, such as geriatric nurse practitioners, social workers, pharmacists, and physical therapists. These team members are especially valuable for communication, coordination of care, and discharge planning. Nonprofessional or volunteer staff can help improve the patient's comfort by responding to requests for blankets, temperature control, and information.

Changes to the ED environment may also improve care to older patients. The hard gurneys used in EDs are helpful for patient transportation but can be painful for patients. Reclining chairs like those used for dialysis can reduce pain

and increase satisfaction for older patients. Other potential changes include sound-proof curtains between beds, nonskid surfaces on floors, handrails on walls, large print signage, and large-faced clocks. Since older patients can arrive at the ED without eyeglasses and hearing aids, the ED could have a standing supply of necessary items for sensory problems. A supply of magnifiers, reading glasses, and electronic sound amplifiers can promote communication and make the older patient feel more comfortable. The revolution in computerized medical records afforded by modern information technology holds great promise for improving the ED care of older patients. Reliable medical records could reduce the time needed to obtain the medical history. Medical errors might be reduced since important information would be available in the ED. Important information to be accessed should include past medical history, current diseases, recent imaging and laboratory studies, last known medications, allergies, dates of recent admissions, social history, and baseline cognitive and functional status.

PREVENTION

Accessing Vulnerable Populations

The ED provides a unique opportunity to see older patients who might not have regular health care providers or to evaluate seniors at risk. Fall prevention, identification of abuse or neglect, addressing substance abuse, and providing vaccinations are some examples.

ED-based pneumococcal vaccination programs have been evaluated. They do not affect patient's length of stay, and require only about 4 minutes of staff time. Studies have shown that offering influenza vaccine to older ED patients may be an effective approach to reducing influenza morbidity and mortality and also reduce ED crowding during the flu season.

Nearly 2 million people older than 65 years are treated in the ED for a fall each year. Acute skeletal muscle weakness is associated with functional decline and falls after an ED visit or with the acute physiologic insult that causes the patient to seek care (**Figure 17-1**). Falls prevention activities recommended by the US Preventive Services Task Force (USPSTF) include exercise (particularly training to improve balance), safety-related skills and behaviors, environmental hazard reduction, monitoring and adjusting medications, visual acuity testing, hormone replacement therapy, screening for dementia and osteoporosis, and postfall assessment and intervention. Given time constraints and the difficulty in evaluating acutely ill patients, most of these activities are unlikely to be conducted in the ED. However, the ED can educate older patients about falls and provide information and referral to reduce their risk of falling again. The ED visit might be a unique "teachable moment" for patients who have come to the ED because of falls. Patients who have fallen or are increased risk for falls may also be referred for geriatric assessment or falls prevention evaluation. While these activities have been recommended, it should be emphasized that there are few studies of their effectiveness.

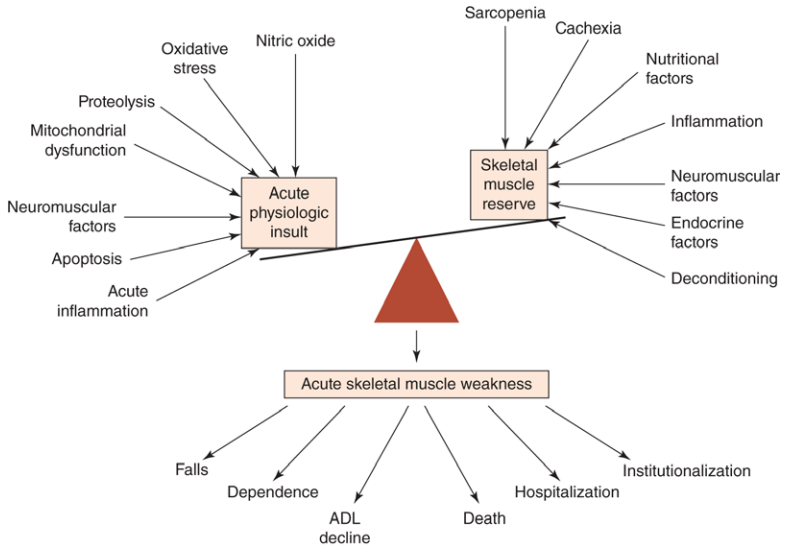


FIGURE 17-1. Causes and consequences of skeletal muscle weakness associated with ED visits for falls. ADL, activities of daily living.

Prevention of Post-ED Decline

Older ED visitors are susceptible to suffering health declines following an ED visit. Between 20% and 50% of older persons experience a significant deterioration in function after an ED visit. The vulnerability to decline in functional status after an ED visit is most likely due to a combination of chronic health conditions, acute illness or injury, coexisting medical and psychiatric problems, lack of social support, and iatrogenic issues such as medication errors. Factors associated with post-ED functional decline are listed in **Table 17-3**.

Regardless of the reasons for the decline, the ED would be ideal for community surveillance for older adults at risk for functional decline that could benefit from multidisciplinary, community-based care management programs. But results of studies in different countries and using different approaches have shown mixed results. One problem is that available ED-based screening instruments have a low specificity and thus find too many cases, resulting in a referral rate that overwhelms community services. Successful programs share three features: identifying patients most likely to benefit, clinical control of care, and long-term follow-up.

There are barriers to providing preventive care in the ED. Those who work in an ED have conflicting priorities and a different approach to patients compared to providers in geriatric inpatient or outpatient settings. While emergency physicians realize that older patients frequently have unique needs and complex clinical presentations, they are pressed by time and the need to prioritize to focus on the presenting complaint and the need to rule out emergent conditions. Linkages between ED and geriatric outpatient units may help reduce barriers to preventive care for older ED patients. These patients could be screened in the ED for suitability for a community program. Those who are suspected of being at high risk could be referred. This approach has been used with fall prevention programs and in the care management programs noted earlier.

While not always anticipated, the patients themselves may present barriers to referral to community agencies. Older ED patients are frequently unwilling to participate in community services. The authors attempted to link patients in their ED with a multidisciplinary Medicaid Waiver Program of the local Area Agency on Aging. The ED used the Agency's screening instrument to identify at-risk patients who were being discharged home. While many patients screened positive, few were willing to have the home-based assessment. It is possible that EDs with onsite geriatric nurses, care managers, or social workers could perform more focused screening. They might also help educate ED patients to encourage participation in the community agency programs and be directly involved in scheduling appointments.

SPECIAL ISSUES

Emergency Medical Services

Emergency medical services (EMS) use for older patients ranges between 100 and 167 per 1000 older adults per year. This rate exceeds for other age groups and has important implications for EMS operations. Patients 65 years and older are projected to compose 49% of all EMS transports by 2030. In the United States, EMS is generally provided by local communities and overseen by the state. However, the National Highway Traffic Safety Administration (NHTSA) created standard curricula, which have been adopted by many states. There are several levels of training for EMS providers. In the National Standard Curriculum for lower level providers (first responders and EMT-basic), there is a specific focus on children (who represent 4% of EMS patients), but no similar focus on older persons (who represent one-third of EMS patients). The curricula for higher-level providers (EMT-intermediate or EMT-paramedic) do have a specific focus on geriatrics. The curriculum for EMT-paramedic training includes comprehensive sections on physiology across the lifespan and geriatrics. Overall, this dedicated geriatrics training represents about 1% of the 1000- to 1200-hour curriculum.

The AGS and the National Council of State EMS Training Coordinators recognized the deficiency in geriatric training for EMTs and created a coalition of 13 national organizations, which developed a continuing education course, Geriatrics Education for EMS (www.gemssite.com). Future cooperation between the EMS community and geriatric professionals is essential to ensure that their training is appropriate and adequate.

EMS equipment and protocols must be adapted to the older patient. For instance, the standard approach to patients with potential neck injuries is to place them in a rigid cervical collar and a backboard with head immobilizing blocks. This approach may be difficult or impossible in older patients with kyphoscoliosis. Immobilization for prolonged periods can also lead to skin breakdown. An alternative is the use of long vacuum splints that can immobilize patients with kyphoscoliosis in a more comfortable position.

Providers of prehospital care have a rare opportunity among health care providers—the ability to assess patients in their homes during their acute illness. Programs have been developed to use EMTs to screen older adults for fall risk, social issues including abuse and neglect, and to assess the home environment. EMTs are trained to identify potential problems, refer at-risk patients to the appropriate agencies for assessment, and link the patient to community services. Evaluations of such programs have found a benefit to individual patients.

Geriatric EMS trauma triage protocols improve care for seniors. Adult EMS trauma triage guidelines were found to have poor sensitivity and specificity when applied to patients age 70 and older. Geriatric trauma triage guidelines use a higher systolic blood pressure and Glasgow Coma Scale (GCS) cutoffs, and contain anatomic and injury mechanisms that are not found on standard adult triage criteria. These include fall from any height with evidence of traumatic brain injury and motor vehicle crashes with fracture of a long bone (**Table 17-5**).

TABLE 17-5 GERIATRIC TRAUMA TRIAGE GUIDELINES

Glasgow Coma Score ≤ 14 with evidence of traumatic brain injury
Systolic blood pressure < 100 mm Hg
Falls from any height with evidence of traumatic brain injury
Pedestrian struck by motor vehicle
Multiple body regions injured
Known or suspected long bone fracture from a motor vehicle crash

Geriatricians and the ED

There are not enough geriatricians for the present population and prospects for reducing this shortfall seem unlikely. Other specialists must develop sufficient geriatric expertise to attend to the special needs of the older patient. There is increasing growth in the number of emergency physicians who identify with geriatric emergency medicine. Part of this growth is a result of the AGS initiative to increase geriatric expertise among surgical and related medical specialists. Emergency medicine has been an active participant in this project from its outset. The project's initial efforts were directed at increasing the geriatric content of residency education and improving the quantity and quality of research. This project, a collaboration between specialty societies developed a cadre of young leaders and improved the outlook for geriatric expertise in the surgical specialties, especially in emergency medicine.

Geriatricians can actively participate in increasing expertise among emergency physicians. They can contribute to the educational program for emergency physicians in training and in continuing education for board certified physicians. Geriatricians can participate in rounds and can give didactic material to those in training. The future of continuing education is likely to be in computer-based interactive educational modules. Geriatricians can participate in the development of these modules.

Geriatricians and advance practice nurses have been active and important consultants to emergency physicians. Emergency physicians appreciate the difficulty in diagnosis and management of older patients. A cooperative geriatric consulting service is of benefit to both the geriatrician and the emergency physician. Emergency physicians are responsive to service programs that will improve outcomes for their patients. Increasing interest in geriatric emergency care makes emergency physicians particularly amenable to programs that improve outcomes for older patients. Having a relationship of mutual respect further fosters willingness to cooperate. Geriatricians with an idea for a program that links the ED with a service, that is, a fall prevention or geriatric assessment, will find an ally if they wish to develop that program. Similarly, geriatricians should accept overtures from emergency physicians with ideas.

The Emergency Department's Relationship With Long-Term Care

Nearly a quarter of nursing home residents are transported at least once each year to the ED. Compared to community-dwelling older adults, nursing home residents tend to present to the ED with less information and are more likely to have a nonspecific chief complaint. Thus they are most likely to require special adaptation in ED care. Two-thirds of nursing home residents who present to the ED are cognitively impaired and cannot provide a clear medical history. Often, families are not immediately available or are unaware of recent changes in the patient's condition. For this reason, communication between the nursing home and ED is crucial. However, 10% of nursing home residents are transported to the ED without *any* written documentation and important patient information often is missing in the

90% who arrive with paperwork. If baseline cognitive and functional status is not reported, it is impossible to determine if changes have occurred. The ED is also often a poor communicator when older patients are discharged back to the nursing home. Nursing home personnel report that residents often return from the ED without notification, written documentation, or recommendations for care.

Nursing home to ED and ED to nursing home transfers are a frequent and important type of transition in care. Poor communication during these transitions increases the cost of care, leads to greater use of health care services, and jeopardizes the patient's safety. The interaction between nursing homes and EDs is one area where geriatricians, nursing home personnel, and emergency physicians can interact to improve the care of the older patient.

Alternatives to Hospitalization

The ED is a gatekeeper between the community and the hospital. The decision to admit a patient to the hospital or to discharge a patient is made in the ED. As noted above, this difficult decision must take into account medical, functional, and social issues. There are several potential alternatives to hospitalization following an ED evaluation. One is the "Hospital at Home" concept. "Hospital at Home" programs have been evaluated for a variety of medical conditions including pneumonia, CHF, cellulitis, and chronic obstructive pulmonary disease (COPD). These programs have demonstrated improved satisfaction, lower rates of depression, and lower rates of nursing home admissions, without a difference in functional status or mortality. Another alternative is direct ED admission to skilled nursing facilities. Currently, Medicare requires a 3-day inpatient hospital stay to qualify for Medicare skilled nursing facility coverage. Thus a Medicare patient can only be covered for a direct admission from the ED to a nursing home if they have had a qualifying hospital stay in the prior 30 days. For patients with private insurance or who belong to a Medicare health maintenance organization (HMO), the requirement for prior hospitalization may not be applicable. The requirement for prior hospitalization was created decades ago, prior to the many changes in inpatient, ED, and skilled nursing facility care. A change in this rule might lead to improved transitions and more efficient use of health care.

The Centers for Medicare and Medicaid Services 2-midnight rule affects many older patients who are not well enough for discharge from the hospital. Patients placed in observation may have large out-of-pocket expenses since Medicare part A does not cover that stay. Hospitals may lose money if patients are admitted with short inpatient stays that do not meet criteria. Patients can be placed in observation and changed to inpatient status if their condition changes or diagnoses become obvious, but the time spent in observation does not count toward their three midnight inpatient criteria for skilled nursing facilities. Patients must be in observation for at least 8 hours with care provided hourly by a registered nurse.

Cooperation between emergency physicians, primary care physicians, and geriatricians is essential to create successful alternatives to hospitalization. Guidelines could help match care settings with appropriate subsets of acutely ill older adults and treatment protocols to ensure patient and caregiver satisfaction, cost-effectiveness, low mortality, and good functional outcomes. Transitional care coordinators, hospital discharge planners, or social workers may be able to help arrange outpatient follow-up, safety assessments, medical equipment, home health, activities of daily living resources, and access to medical transportation.

Disaster Planning

Older people are at increased risk and have unique needs in natural and human-made disasters. However, they often are not recognized as a vulnerable group during disaster planning and response. Recent disasters demonstrate their vulnerability. In the 2004 Indian Ocean tsunami, there were more deaths in people older than 60 years than in any other age group. Nearly half of those who died in hurricane Katrina were 75 years or older and 70% were older than 60 years. Even power outages can be a significant problem for older adults who need oxygen or nebulizers or who depend on motorized wheelchairs or other electric devices.

Older adults, especially those with disabilities or chronic medical conditions, do not have the functional reserve to respond to a disaster. Social isolation, impaired mobility, economic constraints, functional dependence, and the need for specialized medical treatments such as dialysis affect the ability of older persons to cope with disasters. Geriatric specialists can help those involved in disaster planning and response to understand the unique needs of the older population.

Standard disaster shelters often are unable to accommodate older adults who are not functionally independent. Special needs shelters can be created to help care for chronically ill or functionally impaired patients, though these shelters may require patients to be accompanied by a caregiver. Special needs patients often present to hospital EDs

during a disaster, even without acute medical emergencies, because their needs cannot be met elsewhere. Unfortunately, they may spend considerable time in the ED or require hospitalization if no other location for care is identified. Since both EDs and hospitals may be functioning at or beyond capacity during a disaster, these limited resources are strained by the nonmedical demands of these special needs patients, and more appropriate settings are preferable for both the patient and the system.

CONCLUSION

The art and science of care for older ED patients is developing. We are now beginning to understand the complexities in caring for the growing number of older persons. The anticipated growth of older population makes it imperative that we increase the number of health care professionals with expertise in caring for older patients in the ED and that we develop systems of care that are older adult friendly. This requires the cooperation of researchers, educators, and clinicians to improve outcomes for our older patients.

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Chapter 18

Critical Care

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Learning Objectives

- Summarize the epidemiology of critical illness among older adults.
- Review age-related changes in physiology relevant to care of the older adult with a critical illness.
- Describe recent data on long-term physical, cognitive, and mental health outcomes among survivors of a critical illness.
- Explore the evidence-based ABCDE bundle as a means by which to improve clinical outcomes for older, critically ill adults.
- Describe the role of palliative care in modern intensive care unit (ICU) clinical practice.

Key Clinical Points

1. **Over half of all critically ill patients admitted to the ICU are 65 years and older.**
2. **The majority of patients admitted to an ICU survive. Yet survivorship from critical illness is often fraught with long-lasting physical disabilities, cognitive impairment, and other mental health problems.**
3. **Deep sedation and prolonged immobility, once mainstays of ICU care, are important contributors to poor short- and long-term outcomes.**
4. **The evidence-based ABCDE bundle that seeks to *A*ssess, prevent, and manage pain; perform *B*oth spontaneous awakening and breathing trials; *C*hoose proper analgesia and sedation; monitor, prevent, and manage *D*elirium; and perform *E*arly mobility and exercise is associated with improved short-term clinical outcomes.**
5. **The burden of physical and psychological symptoms in patients with a critical illness is high. Application of palliative care principles to address these symptoms, spiritual needs, medical treatment preferences and goals for care, inclusion of family members in decision-making discussions, and planning for transitional care when appropriate are important components of ICU care for older adults.**

INTRODUCTION

On average, Americans will be admitted to an ICU at least twice in their lives and will spend 4 days in the ICU during the last 6 months of their lives; one in five, in fact, will die in an ICU. These statistics are particularly relevant to older adults, their caregivers, and their clinicians given that well over half of all patients admitted to ICUs are 65 years or older. The age-specific incidence of mechanical ventilation for older adults is nearly five times greater than their younger counterparts **(Figure 18-1)**. The incidences of sepsis (ie, infection leading to organ dysfunction) and the acute respiratory distress syndrome (ie, severe respiratory failure)—the most common reasons for admission to an ICU—are highest among older adults, and mortality from these syndromes increases with age. Sepsis is the most common reason older adults are admitted to the hospital, with admission rates outpacing those for acute myocardial infarction nearly

fourfold.

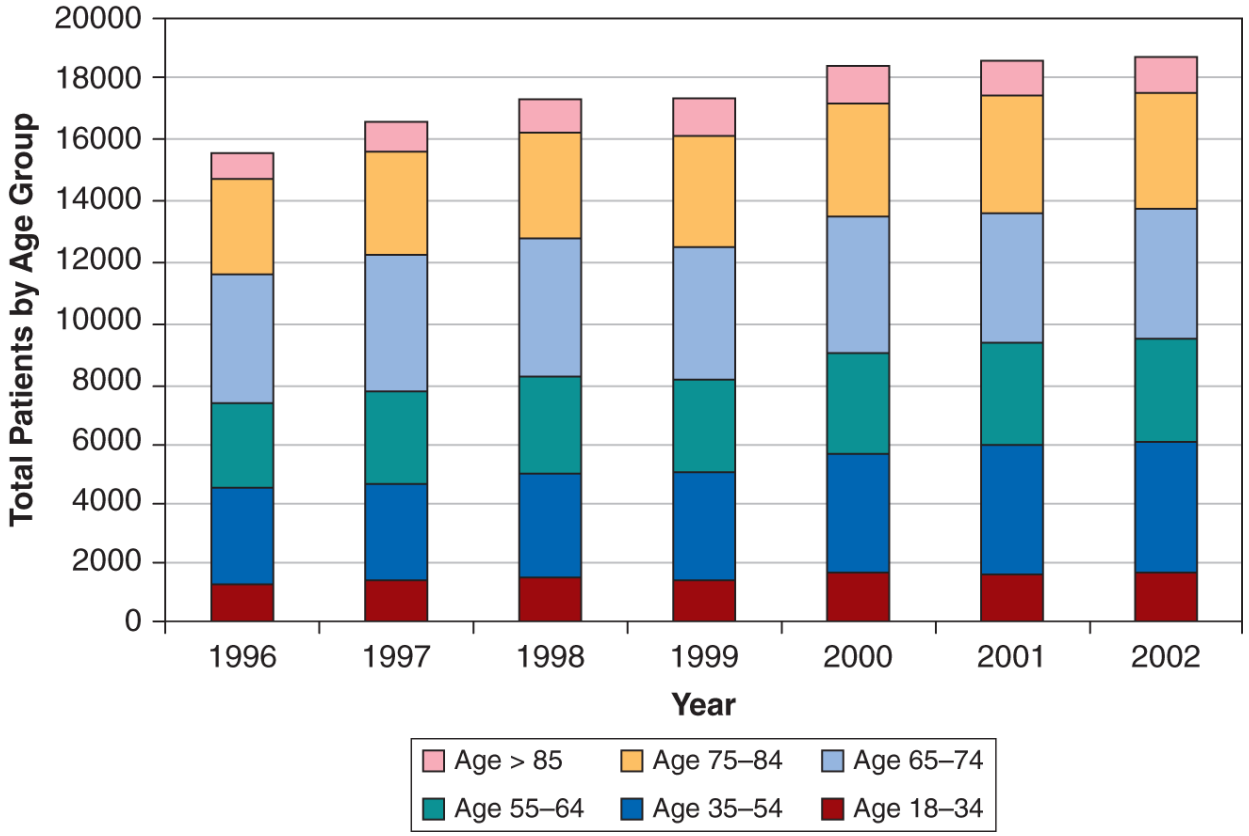


FIGURE 18-1. The incidence of mechanical ventilation and age. After adjusting for population growth, the number of patients who were mechanically ventilated increased by 11% from 1996 to 2002. While most of this increase was due to younger patients requiring mechanical ventilation, patients age 64 and older had a five times greater incidence of mechanical ventilation than their younger counterparts (937 episodes per 100,000 population in those 64 years or older versus 189 episodes per 100,000 population in those younger than 64 years in 2002). (From Carson SS, Cox CE, Holmes GM, Howard A, Carey TS. The changing epidemiology of mechanical ventilation: a population-based study. *J Intensive Care Med*. 2006;21:173–182.)

The observation that mortality from critical illness increases with age has led some to suggest that older adults should not be admitted to the ICU. Age in and of itself, however, does not predict mortality from critical illness. Indeed, ICU care may actually provide the greatest benefit to older adults given that differences in survival rates between patients with critical illness who are admitted to the ICU and those who are not are greatest among those 65 years and older. The last two decades have seen declines in mortality from critical illness, with the greatest improvements occurring for older adults. These improving outcomes as well as the aging of the US and worldwide population will lead the number of survivors of critical illness to increase appreciably in coming years. Yet, data describing new and worsened functional, cognitive, and mental health impairments temper this optimistic news.

Herein, we will review relevant age-related physiologic changes that affect the management of older adults in the ICU, discuss recent data on long-term outcomes for survivors of a critical illness, present the ABCDE bundle to address coexisting iatrogenic harms of sedation, delirium, and immobility and, finally, review the role of palliative care for older adults with critical illness.

Age-Related Changes to Organ Function

The specific reasons that the burdens of critical illness are predominantly borne by older adults remain unclear. Age-related conditions, such as a multimorbidity and dementia, increase the risk for hospitalization due to pneumonia and sepsis. In addition, the recent increase in admissions for sepsis is driven largely by an increase in organ failures suffered by patients hospitalized for infections rather than an increase in the overall number of infections. Thus, in the setting of the acute stress of critical illness, a lifetime of random molecular damage relating to chronic illness, injuries, environmental, and epigenetic factors in combination with the proinflammatory state of aging results in diminished physiologic reserves and capacity to maintain homeostasis, triggering organ failure requiring ICU-level care. Detailed descriptions of the physiology of aging and age-related organ system changes can be found elsewhere in this textbook.

We will focus our discussion on aging-related physiologic changes that are particularly relevant to patients with critical illness.

Respiratory failure, which often necessitates mechanical ventilation, is the most common reason for admission to an ICU. Age-related chest wall, parenchymal and vasculature changes reduce the ability to compensate for the increased respiratory demands common in critical illness. Chest wall efficiency is reduced in advanced age by narrowed intercostal spaces due to kyphosis and osteoporosis, rib cage calcification, and sarcopenic changes to intercostal muscles and diaphragm. Alveolar surface area declines and the composition of pulmonary surfactant changes decreasing parenchymal elasticity and reducing vital capacity and forced expiratory volume in 1 second (FEV_1). These parenchymal changes also result in premature closure of small airways at higher lung volumes, predominantly in the lower lung fields where blood flow is also greatest, causing mismatched ventilation and perfusion (ie, $\dot{V}$ / $\dot{Q}$ mismatching). $\dot{V}$ / $\dot{Q}$ mismatching and reduced alveolar surface result in diminished oxygen uptake. Finally, older adults may suffer from cervical spine disease, have a smaller incisor gap, reduced thyromental distance, and greater Mallampati scores, which may make endotracheal intubation more difficult.

A second common reason for ICU admission is cardiovascular failure (eg, shock). With age, both systolic and diastolic cardiac function decline, reducing stroke volume and ventricular filling. Ventricular hypertrophy increases ventricular size but results in an overall depletion of cardiac myocytes and functional myocardium. Thus, the ability to augment stroke volume in the face of acute stress is reduced for older adults. Hypertrophied and stiff ventricles are dependent on “atrial kick” for diastolic filling, and atrial arrhythmias are poorly tolerated. Age-related reduction in response to β-adrenergic stimuli lowers maximal heart rate and decreases the heart rate response to alterations in blood pressure (eg, tachycardic response to hypotension). Thus, in the setting of shock, whether hypovolemic or distributive, the aging heart maintains cardiac output by relying more on mechanisms that augment preload, such as increases in stroke volume and ventricular filling, than by increasing heart rate. Aggressive fluid resuscitation in the setting of stiff ventricles, however, may result in pulmonary edema, so careful attention to volume status is required.

Critically ill older adults are at increased risk of acute renal failure. An overall decrease in renal blood flow, structural changes to afferent and efferent arterioles that diminish renal autoregulation in hypotensive and hypertensive states, and loss of glomeruli and renal tubules lead to a decrease in the glomerular filtration rate by approximately 1.0 mL/min/1.73 m^2 per year beginning in the third decade of life. Age-related skeletal muscle loss, however, results in decreased creatinine production such that age-related declines in renal function are not typically accompanied by concomitant increases in serum creatinine. The ability to concentrate urine and maintain electrolyte homeostasis decreases with age, leading to potential volume status and electrolyte problems. Age-related declines in prostaglandin synthesis create augmented renin-angiotensin-aldosterone system–mediated vasoconstrictor responses to hypovolemia, shock, or medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs).

Sarcopenia increases with advanced age. Sarcopenic skeletal muscles are characterized by an overall diminished number of muscle fibers, including increased intramuscular lipid concentrations and remodeling of motor units leading to reduced muscle power and strength, easy fatigability, and slow gait speed. Critical illness, particularly in the setting of multiple organ failures, alters atrophy-hypertrophy signaling pathways and results in additional muscle breakdown. Ubiquitous immobility during critical illness contributes to muscle loss, declines in aerobic capacity, and reduced strength. Combined, these factors result in additional catabolic insults to aging muscles and may, in part, explain the greater incidence of ICU-acquired weakness among older adults.

Declines in cognitive function, especially in working memory, short-term memory, and in processing speed, occur with aging. Hormonal and immunologic feedback mechanisms weaken and are hypothesized to drive aberrant stress responses during the acute stress of critical illness, leading to neuroinflammation and neurodegeneration. In the appropriately vulnerable patient, the cycle of neuroinflammation and degeneration may result in neurotransmitter imbalances, metabolic abnormalities, and increased oxidative stress that disrupt neuronal networks. Clinically, this disruption may manifest as acute confusion, inattention, altered consciousness, and disorganized thinking, symptoms that characterize delirium, a geriatric syndrome affecting up to two out of every three critically ill patients. Following the acute stress of critical illness, the aging brain may become caught in a vicious cycle of neurodegeneration and neuroinflammation, resulting in significant neuronal loss and cognitive decline.

Long-Term Outcomes

The last two decades have seen major strides in the treatment of critical illness, which have led to significant reductions in mortality. The majority of survivors of critical illness, however, face life-altering physical, cognitive, and mental health impairments that result in disability and an increased risk of death in the months and years after

intensive care.

Disability in activities of daily living Acute illness requiring hospitalization is well known to be an important driver of disability in older adults. Severe sepsis dramatically increases that risk. In a nationally representative cohort of older adults from the Health and Retirement Study, hospitalization for severe sepsis was associated with greater odds of disability compared with hospitalization for other reasons and was associated with a 50% increase in the odds of new or worsened disability in activities of daily living (ADLs). Among those who survived for at least 3 years following their hospitalization for severe sepsis, 75% were disabled in at least one basic or instrumental ADL. This number is staggering, considering that the number of survivors of severe sepsis more than doubled between 1998 and 2008.

Acute respiratory failure requiring mechanical ventilation is also associated with worse disability in ADLs and in mobility. Data from the Medicare Current Beneficiaries Survey were used to classify patients into three mutually exclusive groups: those who were never hospitalized, those who were hospitalized but did not receive mechanical ventilation, and those who were hospitalized and received mechanical ventilation. At baseline, patients who were hospitalized (with or without mechanical ventilation) had worse disability scores compared with patients who were not hospitalized. In the year after hospitalization, patients who were hospitalized with mechanical ventilation suffered greater declines in functioning than those who were hospitalized without mechanical ventilation and those who were never hospitalized.

The trajectory of disability prior to critical illness has important implications for functioning and survivorship after critical illness. Data from the Precipitating Events Project explored the role of functional trajectories before and after critical illness in 291 patients who were admitted to an ICU. The majority of patients, regardless of preillness disability trajectory, either died or had significant declines in functional status during the first 30 days after ICU admission. The odds of having less disability after the ICU were essentially nil among patients who were mild to moderately or severely disabled prior to their illness. Strikingly, compared with patients with minimal preillness disability (ie, disability in one to two basic or instrumental ADLs), those with mild to moderate disability (ie, disability in three to four ADLs) before their critical illness were over two times more likely to die in the first year after ICU admission, and those who were severely disabled (ie, disability in 10 ADLs) were four times more likely to die. These data suggest that patients with greater levels of precritical illness disability face a limited likelihood of recovering even to their precritical illness functional status and a dramatic increase in the risk of death in the year afterwards.

The precipitants of disability present during hospitalization for critical illness are incompletely understood and in need of further study but likely are related to a combination of severity of illness, sedation, immobility, delirium, and polypharmacy.

Long-term cognitive impairment In addition to functional disability, critical illness precipitates cognitive decline in a high percentage of survivors. The effect of hospitalization with or without an ICU admission on the development of dementia was studied in nearly 3000 participants without significant cognitive impairment at baseline in the Adult Changes in Thought study. Compared with patients who were never hospitalized, those who were hospitalized but not admitted to an ICU were 1.4 times more likely to develop dementia, whereas those who were admitted to an ICU were 2.3 times more likely to develop dementia, suggesting that acute illness, especially that involving higher severity, contributes to the development of dementia.

Hospitalization for severe sepsis as a risk factor for cognitive impairment was also evaluated in the aforementioned Health and Retirement Study. Using patients' cognitive status in the years before developing sepsis as a control, hospitalization for severe sepsis was associated with a tripling of the odds of developing moderate to severe cognitive impairment that persisted for years afterwards. In contrast, patients who were hospitalized but did not have sepsis were not at increased risk of cognitive impairment afterwards. These studies highlight that critical illness hospitalization, particularly with severe sepsis, is an important risk factor for new or worsened cognitive impairment, though the mechanisms of this relationship remain poorly understood.

Important information about the risk factors for the development of new-onset cognitive impairment after critical illness was elucidated in a multicenter cohort study of 821 patients without dementia prior to becoming critically ill. Detailed physiologic, pharmacologic, and laboratory data were collected during the hospitalization, and in-depth neuropsychological testing was performed 3 and 12 months after hospital discharge. At 12-month follow-up, one out of four patients had cognitive impairment similar in severity to that caused by Alzheimer disease, and one in three had cognitive impairment on par with that due to moderate traumatic brain injury **(Figure 18-2)**. Independent of age, preillness cognitive functioning, the burden of comorbid medical conditions, and the severity of critical illness, the strongest predictor of lower cognitive scores 1 year after critical illness was the number of days that a patient suffered delirium while in the hospital. These results mirror those of an earlier, single-center study of critically ill patients and

are consistent with those that examined older, non-ICU patients hospitalized with acute illness, which have consistently shown delirium to be a key risk factor for persistent cognitive impairment after acute illness.

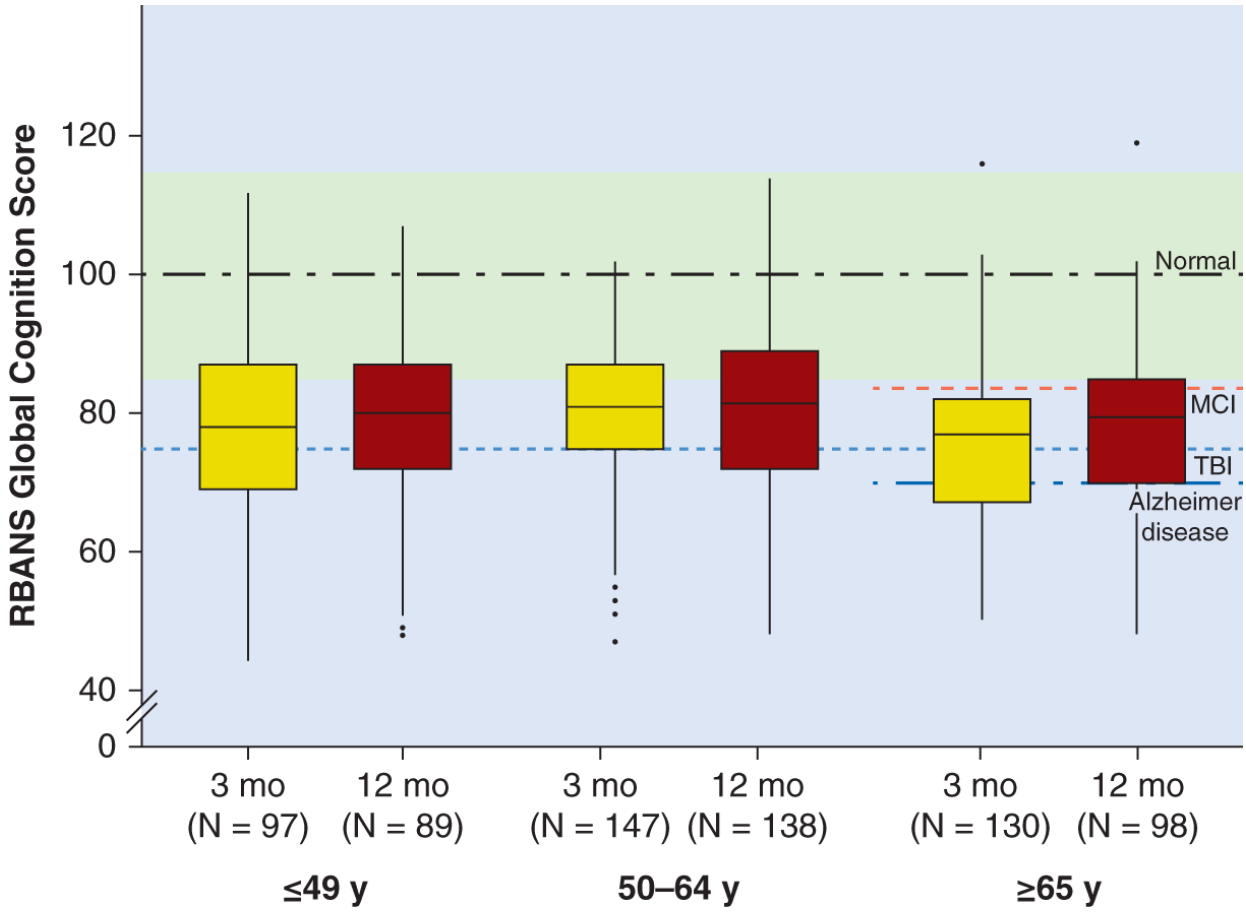


FIGURE 18-2. Long-term cognitive outcomes in survivors of a critical illness. Age-adjusted scores on a measure of global cognition, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), among survivors of a critical illness 3 and 12 months after ICU discharge, stratified by age. The mean age-adjusted RBANS score (± standard deviation) for the general population is 100 ± 15 and is represented by the black dashed line and green shading, respectively. The box and whisker plots show the median (black line) and the upper and lower ends of the boxes represent the interquartile ranges. Vertical bars represent 1.5 times the interquartile range and dots represent outliers. The green dotted line represents the mean RBANS score for patients with mild traumatic brain injury (TBI) and the blue dashed line represent the mean RBANS score for patients with mild to moderate Alzheimer disease. For survivors of a critical illness of all ages, median scores at 3 and 12 months were roughly 1.5 standard deviations below the population mean, nearly one in three had scores equivalent to or worse than patients with mild TBI and one in four had scores similar to patients with mild Alzheimer disease. (From Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369:1306–1316.)

Mental health impairments Symptoms of depression and posttraumatic stress disorder (PTSD), with the former being much more common, affect roughly one-third of critical illness survivors, regardless of age. Among survivors of a hospitalization for severe sepsis, however, the strongest predictor of depression was the presence of precritical illness depression, a finding that was also reported in several small studies. Interestingly, after adjusting for important potential confounders of mental health outcomes, age was associated with lower odds of both depression and PTSD after a critical illness. These data suggest that, whereas mental health impairments may be common after critical illness, older adults, particularly those without a prior history of depression or PTSD, may be less susceptible to developing these outcomes than younger adults. In addition, one large, multicenter investigation found that survivors of critical illness often had symptoms of depression during long-term follow-up but were primarily experiencing somatic rather than cognitive-affective symptoms. Thus, depression after critical illness is common but may be a manifestation of physical debility as much as mental health impairment.

Chronic critical illness An important subset of older adults with critical illness will survive the acute phase of their illness but will continue to have ongoing organ failures or severe infections that require prolonged ICU care and/or prolonged mechanical ventilation, a condition known as chronic critical illness. Ventilator dependency as well as

chronic brain dysfunction, neuromuscular weakness, endocrinopathy, malnutrition, anasarca, skin breakdown, and symptom distress are all common among patients with chronic critical illness. Older adults are the demographic most likely to develop chronic critical illness, often with dire consequences. A study of outcomes in patients who underwent tracheostomy for prolonged mechanical ventilation found substantial morbidity and mortality during the year after illness onset, such that fewer than 10% of patients were living independently at 1-year follow-up. Importantly, both physicians and patients' families had high expectations for survival and functional independence even among those patients who ended up dying or with significant disabilities.

Long-term mortality In addition to causing approximately one in five deaths, critical illness contributes to mortality in other settings, significantly increasing the risk of death in the years following admission to the ICU. In a study that compared long-term mortality among Medicare beneficiaries who were admitted to the ICU with that among those who were hospitalized but not admitted to the ICU and that of the general population, long-term mortality was greatest among those who were admitted to an ICU. In fact, ICU survivors who were mechanically ventilated were 1.5 times more likely to die than the general population during the 3 years after ICU discharge with the greatest risk of death coming in the first 6 months following ICU discharge. Conversely, there was no increase in long-term mortality among those who survived an ICU admission that did not involve mechanical ventilation.

Improving Short- and Long-Term Outcomes

Poor outcomes during and after critical illness may result from a patient's underlying preillness health and disability status and their vulnerability to the acute stressor of critical illness and its treatment in an ICU. Efforts to improve outcomes should focus on evidence-based treatment of the illness itself (the details of which are beyond the scope of this chapter) and on reducing iatrogenic sources of harm. In addition, appropriate symptom management and end-of-life care are key components of the care of critically ill older adults.

Although it was not always the case, ICU practice during recent decades was frequently characterized by deep sedation and immobility. Though these practices were well intended, a large and growing body of evidence has shown that the routine use of deep sedation and immobility is associated with significant harm. Moreover, data from clinical trials demonstrate that reducing exposure to sedatives and mobilizing patients are safe practices that improve outcomes. Efforts to reduce sedation and immobility in the ICU have resulted in the creation of the evidence-based approach to intensive care known as the ABCDE bundle.

The ABCDE bundle consists of *A*ssessing, preventing, and managing pain; performing *B*oth spontaneous awakening and breathing trials; *C*hoosing proper analgesia and sedation; *D*elirium monitoring, prevention, and management; and *E*arly mobility and exercise. Though the concepts behind many of these interventions will be familiar to those caring for older adults outside of the ICU, their application to critically ill patients may not. Thus, we will review these interventions and their ability to improve outcomes for older adults with critical illness.

Assessing, preventing, and managing pain Pain is common among patients with critical illness. Despite the wide availability of effective treatments for pain, assessing pain in critically ill patients can be challenging because factors such as delirium, endotracheal tubes, and sedation frequently prevent clear communication about pain. Thus, pain assessment tools have been developed and validated to overcome these barriers when patients are unable to self-report pain. The Critical Care Pain Observation Tool (CPOT) and the Behavioral Pain Scale (BPS) utilize nonverbal cues and patient behaviors such as facial expressions, body movements, and compliance with the mechanical ventilator to establish the presence of pain (**Table 18-1**). When in doubt about whether a patient is in pain, a trial of an analgesic medication may be effective in determining the presence of pain-related behavior.

TABLE 18-1 BEHAVIORAL PAIN SCALE

ITEM	DESCRIPTION	SCORE
Facial expression	Relaxed	1
	Partially tightened (eg, brow lowering)	2
	Fully tightened (eg, eyelid closing)	3
	Grimacing	4
Upper limb movements	No movement	1
	Partially bent	2

	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with mechanical ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

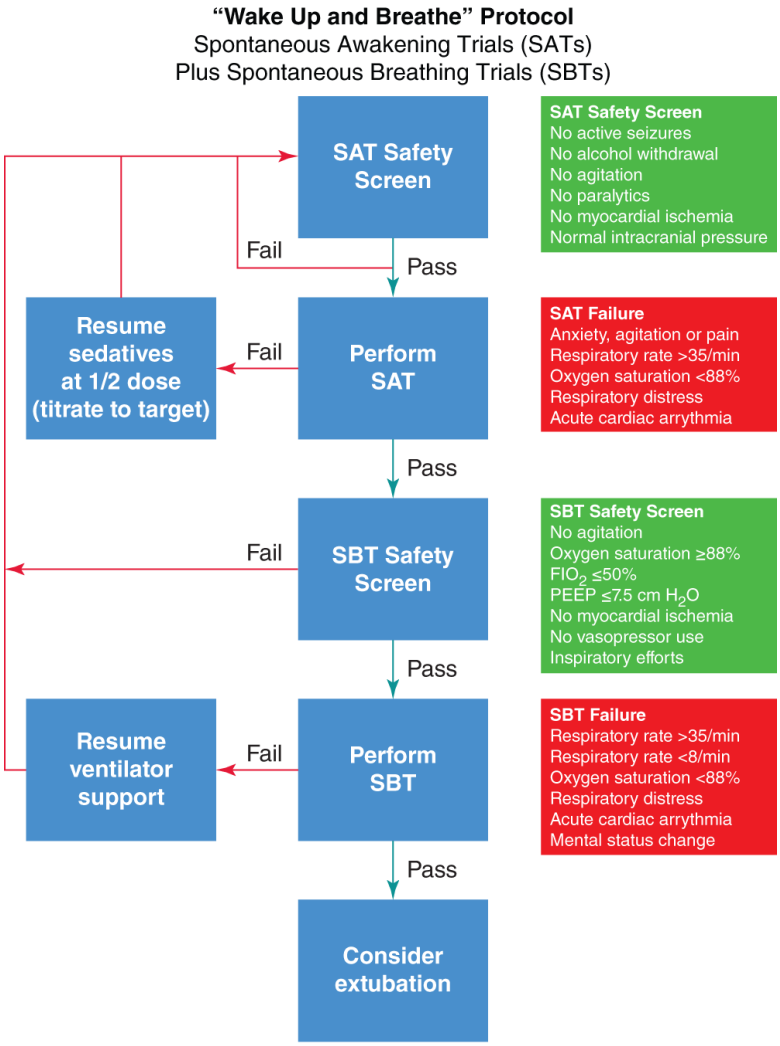
The Behavioral Pain Scale is a validated pain assessment tool for use in the critically ill. Patients are given points according to the presence and severity of symptoms, with higher scores indicating greater pain.
Adapted with permission from Payen JF, Bru O, Bosson JL, et al. Crit Care Med. 2001; 29:2258-63.

As with noncritically ill patients, pain management in the ICU consists of pharmacologic and nonpharmacologic approaches. First-line agents for acute, nonneuropathic pain management include intravenous opiates (eg, fentanyl and hydromorphone) with the choice of medication and dose determined by patient-specific factors, the characteristics and severity of pain, and drug profile. Adjuvant nonopioid medications may be used to reduce the exposure to opioids. Neuropathic pain may be managed with gabapentin or carbamazepine. Finally, nonpharmacologic interventions (eg, heat, ice, massage, relaxation techniques, or music therapy) may provide additional analgesic effects.

Agitation in critically ill patients is associated with adverse outcomes such as the removal of life support devices and other harms to patients and bedside staff. Agitated patients are frequently given sedation to reduce agitation. Nevertheless, it is important to note that agitation is not synonymous with sedation deficiency. Agitation may be due to a number of factors including developing or worsening organ failures, delirium, or withdrawal from alcohol or drugs. Perhaps the most common reason for agitation during critical illness, however, is pain. Thus, assessing for and treating pain may be sufficient to calm the patient. Current clinical practice guidelines recommend treating pain before administering sedatives.

A dramatic illustration of this approach comes from a randomized trial that compared a protocol of “no sedation” to a typical ICU sedation practice. Patients in the “no sedation” group first received morphine to treat agitation and, if they remained agitated, haloperidol. Only if these two medications failed to control agitation then they were given a 6-hour infusion of propofol. The usual care group was managed with an approach still common in many ICUs, receiving continuous infusions of propofol or midazolam for sedation. Patients who were treated with the protocol of “no sedation” were extubated earlier and discharged from ICU and hospital sooner than those managed with standard sedation.

Both spontaneous awakening and breathing trials Whenever analgesics and sedatives are given to critically ill patients, they should be held each day that basic safety criteria are met. This approach, known as a spontaneous awakening trial (SAT), allows clinicians to assess the need for, and optimal dosing, of these medications (**Figure 18-3**). In multiple randomized trials, management with daily SATs significantly reduced frequency of coma as well as days on mechanical ventilation, in the ICU, and in the hospital.



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FIGURE 18-3. Spontaneous awakening and spontaneous breathing trials.

Another advantage of daily SATs are that they facilitate performance of a ventilator weaning strategy known as a spontaneous breathing trial (SBT) (see **Figure 18-3**). An SBT consists of allowing an intubated patient who meets safety criteria to breathe on his or her own (or with only minimal ventilator assistance to overcome the resistance of breathing through the ventilator circuit tubing) to determine their need for ongoing mechanical ventilation. This highly effective ventilator weaning strategy led to shorter durations of mechanical ventilation in multiple randomized trials.

The effects of adding SATs to SBTs were tested in a multicenter randomized trial of 336 mechanically ventilated patients. Compared with patients managed with daily SBTs and sedation per usual case, those managed with the paired SAT plus SBT approach spent significantly more days off mechanical ventilation and were discharged from the ICU and hospital sooner. In addition, patients managed with the SAT plus SBT approach had a 14% increase in 1-year survival **(Figure 18-4)**.

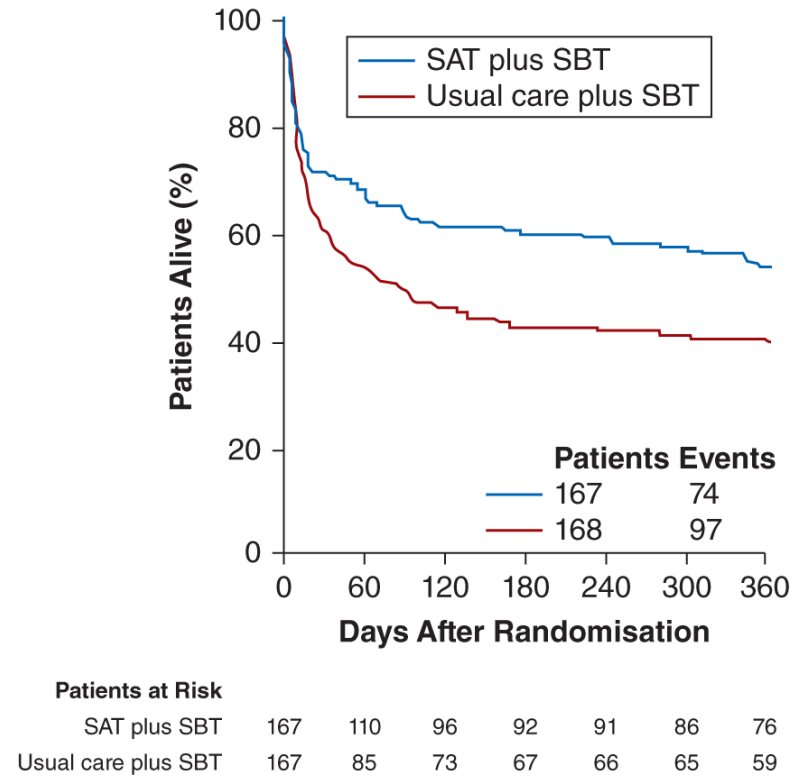


FIGURE 18-4. Mortality 1 year after ICU discharge in the awakening and breathing controlled trial. Patients who were managed with a coordinated daily interruption of sedatives (spontaneous awakening trial, SAT) plus a daily spontaneous breathing trial (SBT, blue line) were 32% less likely to die in the year after enrollment compared to patients managed with daily SBTs alone (red line). The absolute reduction in mortality at 1 year was 14%, indicating that for every seven patients managed with the combined SAT plus SBT approach, one life that otherwise would have been lost was saved. (From Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371:126–134.)

Choosing proper analgesia and sedation Despite assessing, preventing, and managing pain, some critically ill patients may require sedatives to maintain patient and clinician safety while an underlying cause for agitation is sought and treated. A growing body of evidence supports the concept that sedatives, when required, should be judiciously administered to maintain light rather than deep sedation. In addition to treating pain before administering sedatives and the combined SAT plus SBT approach described above, other techniques to reduce exposure to sedatives include intermittent dosing of sedatives (as opposed to continuous infusions), using validated sedation scales to target light (rather than deep) levels of sedation, and avoiding benzodiazepines.

Intermittent sedation has several benefits over continuous infusions to reduce sedative exposure in critically ill older adults. First, continuous infusions are more likely to facilitate accumulation and delayed clearance of the sedative, resulting in prolonged sedative effects. Second, from a practical perspective, continuous infusions are readily titrated up during periods of acute agitation, but rarely are titrated back down once the acute agitation has resolved. Both of these factors can result in greater sedative exposure with continuous infusions.

The targeting of light sedation to reduce overall sedative exposure is best accomplished when using a tool that reliably assesses a patient's level of consciousness. The two most widely used and well-validated level of consciousness tools are the Richmond Agitation-Sedation Scale (RASS) and the Riker Sedation-Agitation Scale (SAS). Using objective criteria to assign numeric scores to a patient's level of consciousness ranging from coma to extreme agitation, these tools facilitate communication between interdisciplinary health care providers regarding a patient's actual level of consciousness and his or her targeted level of consciousness (**Table 18-2**). If the actual level of consciousness differs from the target, analgesics and sedatives can be titrated up (in the case of agitation) or down (in the case of deep sedation).

TABLE 18-2 LEVEL OF CONSCIOUSNESS SCALES FOR CRITICALLY ILL PATIENTS: RICHMOND AGITATION-SEDATION SCALE AND THE RIKER SEDATION-AGITATION SCALE

RASS LEVEL	LABEL	DESCRIPTION	LABEL	SAS SCORE

+4	Combative	Combative, violent, immediate danger to staff, climbing over bedrail, thrashing side to side	Dangerous agitation	7
+3	Very agitated	Pulls to remove tubes or catheters, aggressive, requiring restraint and frequent reminder of limits	Very agitated	6
+2	Agitated	Frequent nonpurposeful movement; fights ventilator	Agitated	5
+1	Restless	Anxious, apprehensive, movements not aggressive; follows commands		
0	Alert and calm	Spontaneously pays attention to caregiver; follows commands	Calm and cooperative	4
–1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening and contact for >10 s)	Sedated	3
–2	Light sedation	Briefly awakens to voice (eyes open and contact for <10 s)		
–3	Moderate sedation	Movement or eye opening to voice (no eye contact)		
–4	Deep sedation	No response to voice, but movement or eye opening to physical stimuli	Very sedated	2
–5	Unarousable	No response to voice, physical or noxious stimulation	Unarousable	1

RASS, Richmond Agitation-Sedation Scale; SAS, Riker Sedation-Agitation Scale.
Higher (more positive) scores indicate greater agitation.
Data from Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166:1338; Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA. 2003;289:2983; Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med. 1999;27:1325.

The importance of using targeted sedation to achieve light (as opposed to deep) sedation is highlighted by two observational studies that examined over 500 patients. Patients who were deeply sedated (RASS –3 to –5) during the first 48 hours of their ICU stay spent significantly longer time on mechanical ventilation and in the ICU than patients who were not deeply sedated (RASS –2 or more alert). Strikingly, every 4 hours of deep sedation was independently associated with a nearly 10% increase in the risk of death at 6 months. These data suggest that deep sedation, a modifiable ICU practice, may be one way to reduce long-term mortality from critical illness. Though not powered to assess long-term mortality, two randomized trials showed that using validated sedation scales to target light sedation resulted in earlier extubation and ICU discharge than control strategies that allowed deep sedation.

Benzodiazepines, once the mainstay of sedation in the ICU, are now discouraged in clinical practice guidelines since numerous clinical trials have consistently demonstrated the superiority, safety, and cost-effectiveness of benzodiazepine-sparing regimens. Positive outcomes associated with avoiding benzodiazepines include shorter durations of mechanical ventilation, less delirium and coma, and reduced ICU and hospital lengths of stay. Compared with propofol, midazolam, and lorazepam, two commonly used benzodiazepines in the ICU were independently associated with increased mortality.

Delirium monitoring, prevention, and management Delirium affects up to two out of every three patients receiving mechanical ventilation in the ICU. A detailed discussion of delirium, including its diagnostic criteria, pathophysiology, risk factors, and management, is presented elsewhere in this text; thus, we will focus on aspects of delirium monitoring unique to the ICU as well as the long-term outcomes associated with delirium during critical illness.

A number of delirium screening tools have been developed for use in the ICU, where assessments for delirium can be complicated by sedation and/or a patient's inability to respond verbally during mechanical ventilation. The most rigorously evaluated and widely used tools—and thus the ones recommended by the Society of Critical Care Medicine in their clinical practice guidelines—are the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). As in noncritically ill patients, delirium screening in the critically ill is a two-step process that evaluates both the level of consciousness and content of consciousness.

The CAM-ICU is a categorical delirium screening tool that, during a 1- to 2-minute assessment, evaluates for four key features of delirium: (1) acute change or fluctuation in mental status, (2) inattention, (3) altered level of

consciousness, and (4) disorganized thinking. The CAM-ICU is positive and delirium is considered present if the patient exhibits features 1, 2, and either feature 3 or 4. Instructions for assessing each of the CAM-ICU features may be found in **Figure 18-5**.

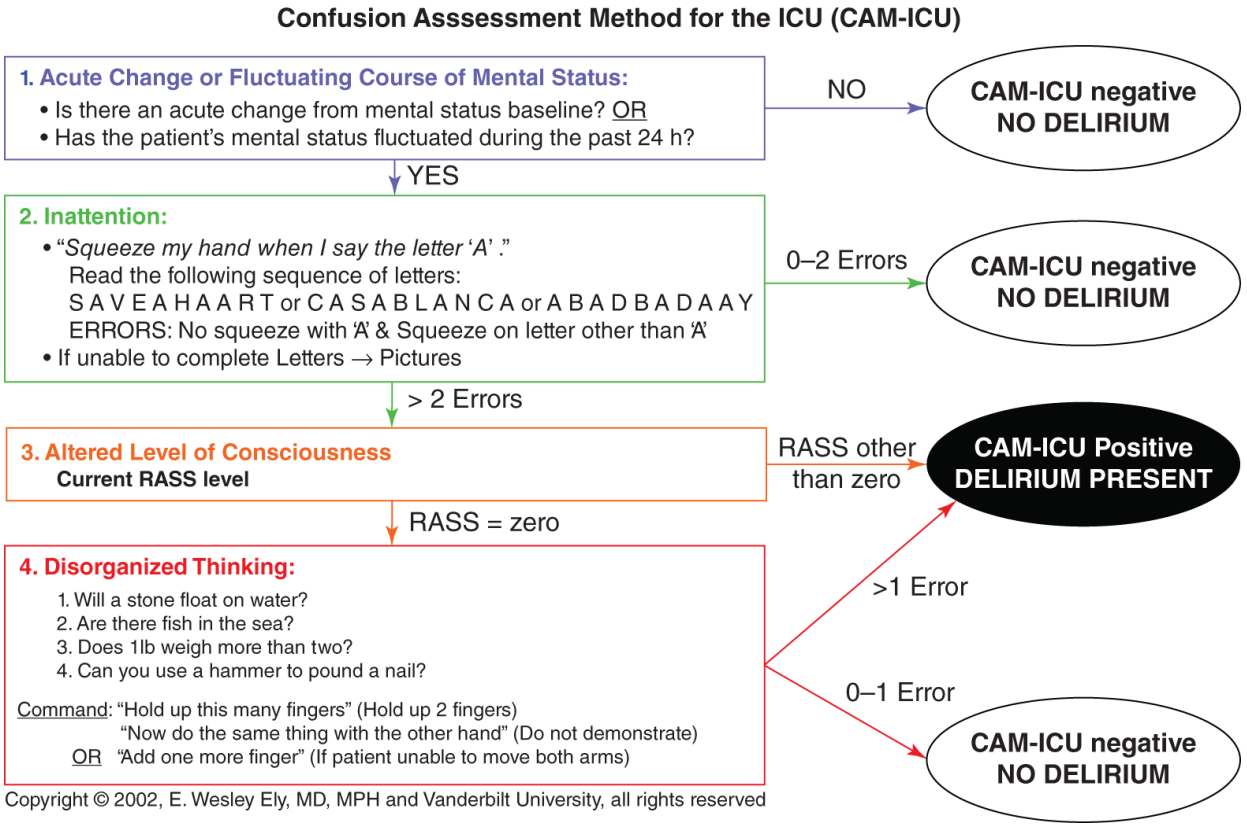


FIGURE 18-5. The CAM-ICU.

The ICDSC, in contrast to the CAM-ICU, is a delirium screening tool where eight delirium symptoms are assessed over the course of 8 to 24 hours (**Table 18-3**). The presence of each of the following symptoms result in one point, and a score of four or more indicates delirium: (1) altered level of consciousness, (2) inattention, (3) disorientation, (4) hallucinations, delusions, or psychosis, (5) psychomotor agitation or retardation, (6) inappropriate speech or mood, (7) sleep/wake disturbances, and (8) fluctuation of symptoms.

TABLE 18-3 THE INTENSIVE CARE UNIT DELIRIUM SCREENING CHECKLIST

1. Altered level of consciousness Choose *one* from A to E.		
Note: May need to reassess patient if recent administration of sedation therapy		
A. Exaggerated response to normal stimulation	Riker/SAS = 5, 6, or 7	Score 1 point
B. Normal wakefulness	Riker/SAS = 4	Score 0 point
C. Response to mild or moderate stimulation	Riker/SAS = 3	Score 1 point
(follows commands)	**Score 0 if LOC related to recent sedation/analgesia**	
D. Response only to intense and repeated stimulation (eg, loud voice and pain)	SAS = 2 ****Stop assessment**	
E. No response	SAS = 1 ****Stop assessment**	
2. Inattention Score *1 point* for any of the following abnormalities:		
A. Difficulty in following commands *or*		
B. Easily distracted by external stimuli *or*		
C. Difficulty in shifting focus		
Does the patient follow you with their eyes?		
3. Disorientation Score *1 point* for any one obvious abnormality:		

A. Mistake in either time, place, or person **Does the patient recognize ICU caregivers who have cared for him/her and not recognize those that have not? What kind of place are you in? (list examples)**
4. Hallucinations or delusions Score *1 point* for either: A. Equivocal evidence of hallucinations or a behavior due to hallucinations (*Hallucination* = perception of something that is not there with *no* stimulus) *or* B. Delusions or gross impairment of reality testing (*Delusion* = false belief that is fixed/unchanging) **Any hallucinations now or over past 24 h? Are you afraid of the people or things around you? (fear that is inappropriate to clinical situation)**
5. Psychomotor agitation or retardation Score *1 point* for either: A. Hyperactivity requiring the use of additional sedative drugs or restraints in order to control potential danger (eg, pulling IV lines out or hitting staff) *or* B. Hypoactive or clinically noticeable psychomotor slowing or retardation **Based on documentation and observation over shift by primary caregiver**
6. Inappropriate speech or mood Score *1 point* for either: A. Inappropriate, disorganized, or incoherent speech *or* B. Inappropriate mood related to events or situation **Is the patient apathetic to current clinical situation (ie, lack of emotion)?** **Any gross abnormalities in speech or mood? Is patient inappropriately demanding?**
7. Sleep/wake cycle disturbance Score *1 point* for: A. Sleeping less than 4 h at night *or* B. Waking frequently at night (do not include wakefulness initiated by medical staff or loud environment) *or* C. Sleep ≥4 h during day **Based on primary caregiver assessment**
8. Symptom fluctuation Score *1 point* for: fluctuation of any of the above items (ie, 1–7) over 24 h (eg, from one shift to another) **Based on primary caregiver assessment**
Total ICSDC score (add 1–8)

LOC, level of consciousness; SAS, Riker Sedation-Agitation Scale.

This eight-item checklist should be completed using clinical information gathered over the last 8 or 24 hours. First assess level of consciousness. If level of consciousness is A, B, or C proceed with the remaining items. Patients are given 1 point for having an obvious manifestation of the item. A score of 4 or greater is considered a positive delirium screen.

From Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27:869–864; Devlin JW, Marquis F, Riker RR, et al. Combined didactic and scenario-based education improves the ability of intensive care unit staff to recognize delirium at the bedside. Crit Care. 2008;12:R19.

Delirium in the critically ill portends a worse prognosis both in the hospital and afterwards. Patients with critical illness are more likely to remove life-support devices, require physical restraints and prolonged mechanical ventilation. Additionally, they suffer longer ICU and hospital lengths of stay, require greater health care resource utilization, and are less likely to be discharged home than similar patients who were never delirious. Following ICU discharge, each day of delirium during critical illness is independently associated with a 10% increase in the risk of death in the 6 to 12 months after ICU discharge. Moreover, more days of delirium during critical illness predict worse cognitive functioning and disability 1 year after ICU discharge.

Early mobility and exercise Critically ill patients were once believed to be too sick for physical activity and therefore were confined to bed. As survival from critical illness improved, however, it became evident that survivors were suffering tremendous neuromuscular weakness and disability. Concurrently, changes in sedation practice meant that critically ill patients were frequently alert rather than comatose. Thus, clinicians and researchers alike began to consider whether critically ill patients could safely undergo mobility beginning soon after ICU admission.

The largest randomized trial of early mobility to date compared disability outcomes in 104 patients without

disability prior to critical illness who were randomized to receive physical and occupational therapy (PT/OT) within 72 hours of ICU admission to usual care. At the time of hospital discharge, the proportion of patients who maintained independent functional status was significantly higher among those who received early mobility than among patients who began receiving physical and occupational therapy later (**Figure 18-6**). Additionally, patients in the intervention group were delirious only half as long as those randomized to usual care.

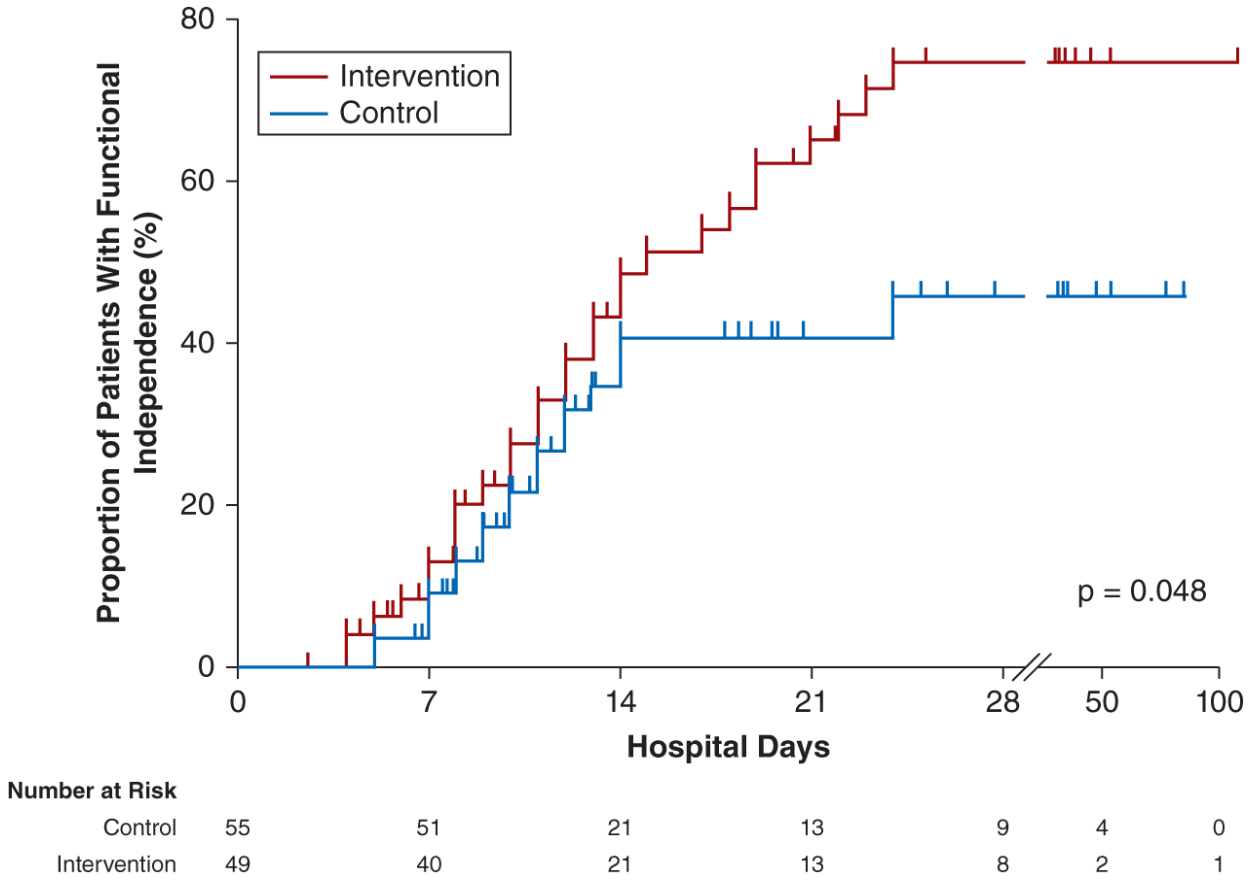


FIGURE 18-6. Effect of early physical and occupational therapy on functional independence among ICU survivors. A greater proportion of patients who were randomized to receive early physical and occupational therapy that began within 72 hours of mechanical ventilation (red line) were functionally independent at the time of hospital discharge compared to patients who were managed with traditional physical and occupational therapy that began after approximately 7 days of mechanical ventilation (blue line). (Data from Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373:1874–1882.)

Subsequent to that trial, a number of nonrandomized clinical trials and quality improvement projects reported the safety and feasibility of early mobility. They also suggested that patients mobilized early in their critical illness have shorter durations of mechanical ventilation and ICU and hospital lengths of stay. Though further study is needed to clarify the types of rehabilitation modalities that are most effective and the specific patient populations who will benefit most from this resource-intensive intervention, these data suggest that early mobility is a safe, efficacious way to improve outcomes for older adults.

Outcomes associated with the ABCDE bundle A prepost implementation study evaluated the combined ABCDE bundle in 296 patients admitted to medical and surgical ICUs at a single center. Patients treated with the ABCDE bundle spent 3 more days alive and breathing without mechanical ventilation than did patients who did not receive the bundle. Use of the ABCDE bundle was independently associated with a near halving of the odds of developing delirium and a doubling of the odds of being mobilized out of bed. These outcomes were achieved without an increase in adverse events.

Nutritional support during critical illness Compared with their younger counterparts, older critically ill patients are at greater risk for under- or malnutrition. Emerging data suggest that delayed nutritional support and iatrogenic underfeeding, which are common during intensive care, may be harmful. Because many critically ill patients are unable to maintain adequate oral intake on their own, nutrition is often provided enterally or, in some case, parentally. The

risk-benefit ratio for parenteral nutrition, however, is narrow, so its use should be reserved for patients who are severely malnourished or in whom enteral nutrition is not expected to be feasible for a number of days.

A recent randomized trial compared trophic enteral feeding (ie, ~ 25% of daily caloric needs) compared with full caloric feeding during the first 6 days of mechanical ventilation in patients with the acute respiratory distress syndrome did not find differences in clinical outcomes. These data suggest that meeting the full caloric needs of critically ill patients during the early phases of a critical illness may not be necessary. It should be noted, however, that this study enrolled a relatively young population (mean age of 52) and excluded those who were undernourished. Whether similar outcomes would be observed in older adults and/or those with poor nutritional status is unknown.

The majority of critically ill older patients, therefore, should be fed enterally via naso- or orogastric tube, with the latter being preferred in mechanically ventilated patients since nasogastric tubes increase the risk of sinusitis. Typically, standard 1 to 1.5 kcal/mL tube feed formulas should be used at rates that deliver 25 to 30 kcal/kg/day and 1.2 to 2.0 g of protein/kg/day. Since the typical ICU patient receives only 50% of the recommended daily intake of calories and protein, strategies to ensure adequate feeding are recommended. These strategies may include minimizing interruptions of tube feedings for tests, nursing care, and procedures; setting targets at approximately 120% of the suggested caloric intake; and/or eliminating use of the gastric residual volume as a clinical indicator in nonsurgical patients.

Symptom management and end-of-life care Nearly one in seven patients with a critical illness, regardless of age, meet criteria for receiving palliative care while in the ICU. Surrogate decision makers, who are under tremendous stress, have difficulty understanding issues relating to patient prognosis and medical treatments, and they often have trouble expressing patient's values and goals. Patients, families, and clinicians often hold unrealistic views of prognosis and efficacy of ICU treatments. Busy clinical ICU practice frequently results in delayed and fragmented communication, which contributes to inadequate planning for care that might be better delivered in another setting. Palliative care in the ICU is actually associated with improved patient outcomes such as more patients completing advanced directives, decreases in nonbeneficial ICU treatments, reductions in ICU lengths of stay, and fewer ICU readmissions. Despite these data, the number of patients who receive any type of palliative care in the ICU is low.

Palliative care in the ICU can be delivered via several models. First, ICU clinicians, either with formal or informal training, integrate palliative care principles into routine ICU care. Second, palliative care consultants can be used to facilitate palliative care in the ICU. Finally, a mixed model that combines elements of the integration and consultative model can also be applied.

Because the demand for palliative care in the ICU vastly outstrips the supply of clinicians trained in palliative care, research is ongoing to identify patients who will benefit most from palliative care in the ICU, as well as appropriate triggers for palliative care consultation and the most effective palliative care interventions. Additionally, some are advocating for providing formalized palliative care training for ICU clinicians. Whether implemented by formally trained palliative care providers or by intensivists without training in palliative care, the palliative care principles of effectively managing physical, psychological, and spiritual needs; communicating about prognosis, goals, and preferences in a clear, timely manner; ensuring that treatments are in line with patient preferences; including family members in decision making discussions; and planning for transitional care when appropriate are important pieces of ICU care for older adults.

CONCLUSION

The number of older adults who develop critical illness is large and growing. Modern ICU care has resulted in an increasing number of patients surviving critical illness. These survivors face physical, cognitive, and mental health impairments and an increased risk of death in the months and years after ICU discharge. Interventions, such as the ABCDE bundle, that reduce sedation, delirium, and immobility can improve short-term outcomes and may reduce the burdens of ICU survivorship. The symptom burden for critically ill patients and those who survive is high; thus palliative care is an increasingly important component of ICU care.

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Chapter 19

Subacute Care

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Learning Objectives

- Improve understanding of how the affordable care act and the creation of accountable care organizations (ACOs) is impacting postacute care.
- Understand the types of postacute settings and what differentiates them.
- Define the role of physicians and other medical care providers (nurse practitioners [NPs], physician assistants) in subacute care.
- Identify the key issues that need to be addressed in order to have high-quality care transitions from the hospital to skilled nursing facility (SNF) setting.

Key Clinical Points

1. **Patients in the subacute care setting have diverse needs ranging from short-term orthopedic rehabilitation to complex medical management to end-of-life care.**
2. **Clinicians in the subacute setting must be skilled in using systems that enable them to collaborate effectively with hospital-based and the primary care physician.**
3. **Clinicians in the subacute setting must be highly skilled in managing geriatric syndromes as well as having expertise in pain and symptom management.**
4. **Advance care planning must be integrated into the overall care of patients in the subacute setting.**

OVERVIEW

The Affordable Care Act has provided a tremendous incentive to stimulate innovation in the postacute care setting. Newspapers, television news shows, blogs, and podcasts discuss the impact of health care reform on how health care is delivered. The mantra of controlling cost and improving quality of care is heard incessantly and has started a wave of initiatives that are impacting all areas of health care including postacute care. The Institute of Health Care Improvement has developed a vision to meet three goals that in the past were targeted separately, but now are being addressed under a single unifying vision, the Triple Aim. The Triple Aim is attempting to improve care and costs by addressing simultaneously three essential components of health care:

- Improving the patient experience of care (including quality and satisfaction)
- Improving the health of populations
- Reducing the per capita cost of health care

The philosophy delineated by the Triple Aim is impacting many local health care markets in a dramatic fashion by aligning hospital systems, multidisciplinary group practices, skilled nursing facilities, and home care agencies to better coordinate care and to provide that care in the most appropriate setting from both a quality and a cost perspective.

We are now seeing partnerships and collaborations evolving that are both formal and informal, among primary care practices, insurers, and hospitals with the postacute facilities they use. The care continuum is being coordinated in

many regions in what is sometimes called a vertically integrated system. Postacute provider networks that include hospitals, nursing facilities, and home health agencies are being created. Care managers that can work for insurers, medical practices, or hospitals are being assigned to facilitate and monitor the patient's journey through the care continuum.

Some medical groups and hospitals are taking on global risk for quality and cost outcomes of their patients' populations. The impact on postacute care facilities is efforts to improve including care transitions and reduce readmissions. This has also lead to increased efforts to partners with not just skilled nursing facilities but also with clinicians who provide the care in these settings.

The postacute setting is composed of three types of inpatient facilities and two types of home care agencies. Of the three types of inpatient facilities, two of these facilities are licensed as hospitals. They are long-term acute care hospitals (LTACHs) and inpatient rehabilitations facilities (IRFs). The third type of inpatient facility is a SNF.

The two hospital-level inpatient facilities are similar in that the patients they care for must meet Medicare criteria for hospital-level of care. LTACHs generally meet this criteria by caring for medically complex individuals while IRFs care for patients with extensive, multidisciplinary rehabilitation needs. Each of these settings has its own system of reimbursement from Medicare. Examples of an LTACH patient could include patients requiring ventilator management, individuals needing frequent blood products, and those with complex wound or intravenous medication needs needing extensive nursing care and daily on-site physician oversight. LTACH patients typically are not able to participate in extensive rehabilitation programs because of their medical acuity. IRF patients typically are able to participate in rehabilitation programs that usually include 3 or more hours of occupational and physical therapy and often speech therapy. Examples of individuals who qualify for care in an IRF include those with new spinal cord injuries, brain injuries, strokes, and multiple traumas. A physiatrist is often overseeing the care of patients in the IRF setting.

Skilled nursing facilities typically care for two populations of patients. The first population is the traditional nursing home patient. This population includes individuals who are generally living long term at the facility. These individuals often have significant physical and/or cognitive deficit that compromise their ability to perform their activities of daily living (ADLs) and care for themselves. Typically Medicare and commercial insurance do not pay for long-term care in nursing facilities. The care may be covered by Medicaid, the patient's own money, or a long-term care insurance policy. Care of these patients is a major focus of Chapter 20.

The second population of patients in SNFs is often referred to as SNF patients. This population also comprises the subacute population. While subacute care can be delivered in both free-standing SNFs and in hospital-based transitional care units, the former has come to dominate the industry. The term subacute care typically describes SNF patients who may have more complex medical and/or rehabilitative needs than the typical SNF patient. These patients may typically require physician and/or advanced practice clinician (APC) (either a nurse practitioner or a physician's assistant) visits one or more times a week. Subacute care is an important component of the continuum of care for older patients, and care in this setting is frequently provided by geriatricians and geriatric nurse practitioners. In fact, subacute care is an important clinical niche of geriatric medicine. These individuals have medical and/or rehabilitation needs that meet the Medicare criteria for inpatient skilled care. These patients may meet these criteria by some combination of rehabilitation needs such as physical, occupational, or speech therapy, generally for up to 3 hours/day. They may also meet Medicare criteria based on nursing needs such as daily wound care, the need for intravenous medications, or daily monitoring of a medical condition that is not well controlled such as diabetes. Some patients with end-of-life care needs may also qualify for care in a SNF. In the Medicare fee-for-service system, to qualify for care in a skilled nursing facility, a three-night inpatient hospital stay is needed in order to activate the skilled nursing facility benefit. With health care reform some hospital systems, managed care programs, and group practices are applying for a "SNF waiver" whereby patients can be admitted to a SNF without a qualifying three-night hospital stay.

The types of home care agencies that provide postacute care and visiting nurse agencies (VNAs) are hospices. Again, criteria must be met for Medicare to provide this coverage. To qualify for VNA services two criteria that need to be met are that the patient must be "homebound" and have skilled needs which can include nursing or rehabilitation services. A hospice agency is a home care agency that can provide care in any setting but most commonly is provided in the home setting. Patients qualifying for hospice must have physician certification of a life expectancy of less than 6 months and the patient generally must choose to focus on treatments geared toward optimizing comfort and quality of life rather than curative treatments. Patients on hospice do not need to be homebound or have a skilled need.

Care in the LTACH and IRF settings is typically significantly more costly per day than in a SNF, and care at home is less expensive than in any inpatient setting. In an era focused more and more on managing costs, in many regions IRFs and LTACHs are seeing lower patient volume. This has increased the volume for some SNFs but on the other

side of the coin the proliferation of assisted livings and enhanced home care services has reduced volume in some SNFs. The result is a dynamic postacute care marketplace that is undergoing rapid change.

The remainder of this chapter discusses the fundamentals of subacute care from the perspective of clinicians delivering care in this setting within the context of the dramatic changes that are taking place in terms of the heightened perspective of improved care transitions and reduction in readmissions. One area that will be repeatedly stressed is the focus on how care for patients approaching the end of life should be done in a manner that honors their values and care preferences. At times this may require procedure-oriented medical care in higher-intensity settings and at other times striving to minimize the use of treatments that may actually prove counter to patients having their care goals met. The chapter follows the timeline of subacute care, beginning at the hospital, to subacute admission, assessment, care planning, medical management, and discharge planning. The chapter also briefly touches on the financial and medicolegal aspects of providing care in this setting and highlights aspects of medical management and decision making that may be unique in the subacute setting.

DEFINITION OF SUBACUTE CARE

There is some debate about the exact definition of subacute care. In fact, there is a great deal of variation in the settings, patients, and providers encompassed within subacute care. In this chapter, subacute care is defined as the management of discrete episodes of illness requiring medical management and/or functional rehabilitation within the SNF. The intensity of the medical management is generally less than that provided on a general medical/surgical unit in an acute care hospital or LTACH, but greater than what can be provided in the traditional nursing home setting, or at home. The level of functional rehabilitation provided is less intense than in an IRF, but greater than that provided at home. Usually, but not always, subacute care provides a continuation of a treatment plan initiated in the hospital. The frequency of medical encounters and the costs of care are also intermediate between the hospital and long-term care settings.

A major distinction between acute care and subacute care is a focus on function. This makes it an ideal setting for geriatricians. Acute care in hospitals is focused on diagnosis and targeted aggressive treatment of acute medical problems. Unfortunately, as a result of hospitalization, many older persons suffer nosocomial complications and functional decline that persist well after the acute problem is corrected. In addition, many of the interventions provided in acute care hospitals impact a moment in time but do not have an overall impact on the trajectory of illness for a given older individual. Innovative models have been developed to reduce the risk of delirium and functional decline in acute care hospitals including the use of geriatricians to help comanage the care of some patient populations. Nonetheless, these problems remain rampant, particularly in frail individuals with underlying dementia or chronic medical illnesses. Add to this the continuing pressure to shorten length of stay, and many acutely hospitalized older persons are unable to return to their residences at discharge. Subacute care has filled the need for a place where these patients can receive ongoing medical and nursing care, in addition to skilled rehabilitation, discharge planning, and more commonly advance care planning for eventual return to the community. Length of stay in subacute care varies widely, from less than 1 week to up to 100 days (the Medicare limit), but the average is generally 10 to 21 days.

Subacute care has played a particularly important role in managed care for many years, and now with the health care reform for many of the same reasons there is increased focus on the Medicare system as well. First, the cost pressures continue to place the focus on treating patients in the least costly environment that meets their needs. Second, the Medicare diagnosis-related group (DRG) system incents hospitals to discharge patients. Third, while for a number of years managed care plans have been exempt from the “3-day” hospital rule (in traditional Medicare, patients must be hospitalized for at least three nights to qualify for a skilled nursing benefit), the formation of ACOs has resulted in new 3-day waiver policies for some Medicare beneficiaries, so that more patients can access their SNF benefit with a shorter hospital stay, or even can be directly admitted from the community (often via the doctor’s office or emergency department). For many years managed care plans have been leaders in the ongoing trend to admit sicker patients to SNFs for shorter lengths of stay. Managed care providers have been the leaders in developing innovations to improve the systems for the provision delivery of subacute care. This expertise is now impacting the traditional Medicare population as well, especially those patients who are part of an ACOs or other Medicare shared risk reimbursement systems. With the national shortage of primary care physicians and the increased acuity of subacute patients, it is less common for office-based internists and family practitioners to be able to provide care in nursing facilities. Foremost in these innovations has been the establishment of teams of physicians and nurse practitioners who spend most or all of their professional lives delivering subacute care. These teams have developed protocols for facilitating hospital

transfers to SNFs, assessing patients, delivering sophisticated medical care, addressing acute medical problems, minimizing rehospitalizations, providing case management, and proactive discharge planning. Each of these is discussed in greater detail later in this chapter.

SUBACUTE CARE PATIENTS

Compared to the usual nursing home population, subacute patients tend to be younger (average age in seventies rather than late eighties), more acutely ill, but less likely to have dementia or major chronic functional limitations. Most patients admitted for subacute care come directly from hospitals and are expected to return to their homes after a specific, planned treatment course. However, a small but significant fraction of subacute patients (10%–33%) never achieve discharge goals and "convert" to long-stay nursing home patients. Another significant fraction of patients become medically unstable in the subacute setting and need to be rehospitalized (up to 25%). A third group of patients present with advanced illness and receive end-of-life care and die in the subacute setting. These figures depend on the acuity of illness and underlying frailty of the population, as well as on the quality of care provided at the facilities. Each of these three groups has different care needs require specialized supports. Having more physician and nurse practitioner presence on site in the SNF with better care coordination with hospitals and emergency rooms (ERs) can reduce rehospitalization rates. Frailer patients can be cared for in the community with enhanced home supports such as those provided in assisted living facilities, by specialized programs such as Program for All-Inclusive Care for the Elderly (PACE) and by innovative home nurse practitioner–led home visit programs. Finally, identifying patients approaching the end of life and the care goals may allow some to return home with the support of hospice services. Typical subacute diagnoses include hip and knee replacements, hip fracture, other fractures (upper extremity or vertebral), stroke, cardiac and pulmonary conditions (including pneumonia), pressure and vascular ulcers, postoperative care, and deconditioning. Subacute patients may need intensive medical management, functional rehabilitation, or a combination of both. As noted earlier, some may also receive hospice-like services in the subacute setting by clinicians skilled in palliative and end-of-life care. Formal hospice may be difficult to provide in the subacute setting because room and board costs are typically not covered by hospice and patients therefore often elect to use their SNF benefit (which does include room and board) whenever possible to defray costs that they would otherwise be responsible for.

SUBACUTE CARE PHYSICIANS

Delivering effective care to the subacute population requires a much greater physician presence than traditional long-term care. Just as the term *hospitalist* denotes physicians working primarily in the hospital, *SNFist* and *subacutist* are terms occasionally used to describe clinicians practicing primarily in the subacute environment. Practicing as a long-term care and subacute care clinician requires a special set of skills. Physicians working in SNFs and subacute units are usually geriatricians or other clinicians with strong geriatric skills such as internists, osteopathic physicians, and family practitioners.

A number of clinical, administrative, and interpersonal skills are important for a physician to achieve success in the area of subacute care. To properly manage this challenging patient population, the nursing facility clinician must have *clinical expertise* in managing conditions that are a blend of office, hospital, and geriatric practice (**Table 19-1**).

TABLE 19-1 AREAS OF CLINICAL EXPERTISE IN SUBACUTE CARE

Geriatric syndromes including delirium, dementia, and urinary incontinence
Postoperative orthopedic and surgical patients
Pressure ulcer prevention and management
Postoperative pain and management
Non-ICU hospital conditions such as congestive heart failure and infections
Medication administration and dosing in an older population
Wound care
Geriatric rehabilitation

Palliative care

ICU, intensive care unit.

Leadership skills are highly desirable in the physicians practicing in this setting. The physician is often a leader of the facility interdisciplinary team whose members include rehabilitation specialists, nurses, social service, and case management. The subacute setting is an environment that benefits greatly from a physician leading the geriatric care team.

Administrative skills are also important for the subacute care practitioner. Nursing facilities have a relatively simple administrative structure. The administrator and director of nursing are the primary salaried personnel that run the facility. There is a facility medical director as well. Attending physicians have the opportunity to work closely with these three individuals in a facility. Attending physicians, even if they are not the medical director, can make significant contributions to the quality of care of subacute patients (**Table 19-2**). The American Medical Directors Association (AMDA)—the Society for Post-Acute and Long-Term Care Medicine is a national leader in advocacy for clinicians who practice in nursing facilities, provides training and certification in nursing home medical direction, and is developing competencies for physicians who practice in this setting.

TABLE 19-2 AREAS OF ADMINISTRATIVE EXPERTISE IN SUBACUTE CARE

Improving care transitions from hospital to subacute facility
Improving facility systems regarding ancillary supports (especially lab, x-ray, and pharmacy), training staff, documentation, and communication
Knowledge regarding OBRA[a] and other federal and state regulations
Working effectively within the constraints of the reimbursement system for nursing facilities under Medicare and managed care

[a]OBRA, Omnibus Budget Reconciliation Act of 1987.

Interpersonal skills are the third key area for subacute care practitioners. The ability to form trusting collaborative relationships with patients and families quickly is critical to effective care in nursing facilities. Patients currently entering nursing facilities are often critically ill, are more dependent than previously, fear loss of independence, have caregivers under great stress, and often have financial and housing pressures. They may also be suspicious of nursing facilities and may not understand all of the medical issues. Just as important is the ability of the subacute care practitioner to collaborate with hospital-based specialists and primary care clinicians. Many patients have ongoing clinical needs that need to be comanaged. This can include patients receiving wound care, oncologic care, or ongoing management of advanced medical conditions such as congestive heart failure. **Table 19-3** summarizes the interpersonal skills needed in a subacute care provider in order to handle these issues.

TABLE 19-3 INTERPERSONAL SKILLS NEEDED TO PROVIDE EFFECTIVE SUBACUTE CARE

Understand and appreciate the nursing home culture
Be a skilled leader of the interdisciplinary team
Work well with families regarding discharge planning and end-of-life care
Teach staff within the facility
Interface effectively with hospital and outpatient clinicians
Be a good listener and a good communicator
Effective leader of family meetings

ROLE OF ADVANCED PRACTICE CLINICIANS

Daily rounding by a clinician with round-the-clock phone availability is essential to providing effective subacute care. To provide this enhanced clinical coverage, physicians may collaborate with APCs such as nurse practitioners and physician's assistants. APCs play a major role in providing care in many subacute units. States and facilities vary regarding the scope of practice for APCs. In some locales, nurse practitioners practice as independent clinicians, while

in others, direct physician supervision is required. Many facilities require written guidelines that describe the scope of practice of the APC as well as the manner by which physician supervision will be provided.

The physician working in a subacute care setting may find tremendous benefit from working with an APC. Many APCs have specialized areas of expertise that complement the skills and knowledge of the physician. **Table 19-4** lists the roles and duties an APC can assume in a subacute unit. A physician practicing with an APC has the opportunity to form a team that can improve the quality of care provided and can improve job satisfaction for both providers. As in other teams, excellent communication, trust, availability, and support are essential.

TABLE 19-4 ROLES OF ADVANCED PRACTICE CLINICIANS IN SUBACUTE CARE

Specialized areas of expertise including management of dementia, pressure ulcers, wounds, gynecologic issues, and congestive heart failure
Patient/family education regarding diabetes, home safety, medication administration, medication simplification, and other topics
Training facility staff
Working out problems with nurses, nurses' aides, patient, and family
Provide overall clinical care and obtain physician consultation appropriately
Participate in all call coverage

The model of physician-APC collaboration in the subacute setting has many similarities to an inpatient hospital model. The APC may operate much like a first-year resident, managing day-to-day issues, identifying new issues, educating patients and their families, and requesting support from the physician when needed. By rounding together on a regular basis the MD-APC care team have the opportunity to assess patients together. Patients and families can be reassured seeing their care team together. There is no substitute for a bedside evaluation in assessing issues such as pain control, cognitive status, anxiety, and medical stability. APCs are able to participate in night and weekend on-call duties. It is essential that if an APC is taking "first call" that there always be a physician available for consultative support.

Unlike hospitals there is no onsite physician or APC during overnight hours. Phone management is an important aspect of subacute care. It is preferable to have a model of on-call coverage that uses clinicians who not only know the patient but also the capabilities of the facility. When it is not possible to have a clinician who is a direct caregiver providing on-call coverage, effective signouts are important. Key clinical information can be transmitted by direct verbal communication or, with Health Insurance Portability and Accountability Act (HIPAA) appropriate safeguards to ensure patients' confidentiality, by written summaries that can be faxed or e-mailed to the covering clinician. Effective phone management can reduce avoidable ER visits and hospital readmissions.

SUBACUTE CARE REGULATIONS

Subacute care units are licensed and regulated under the same regulations as nursing homes. In 1987, a set of regulations regarding patient care in nursing facilities was enacted in the Omnibus Budget Reconciliation Act (OBRA). These regulations laid out a number of principles that were used to standardize care in nursing facilities. In 1995, the nursing home certification and enforcement regulations took effect. Unless nursing facilities were found to comply with the standards laid out in OBRA, they would not be allowed to participate in the Medicare and Medicaid programs. **Table 19-5** summarizes key aspects of the OBRA regulations. These principles provide a framework for providing appropriate clinical care. Physicians must work collaboratively with nursing facility staff to maintain compliance with OBRA regulations. It is particularly challenging managing a high turnover, higher acuity population under these regulations. Excellent assessment skills, complete and accurate documentation, and a well-functioning interdisciplinary team are necessary to meet regulatory requirements, and are also the cornerstone of good subacute care.

TABLE 19-5 KEY ASPECTS OF THE OBRA[a] REGULATIONS

The medical regimen must be comprehensive and part of an interdisciplinary care plan
A decline in the resident's physical, mental, and psychosocial well-being must be demonstrably unavoidable

Restraint use requires rigorous individual clinical assessment
The resident's drug regimen must be justifiable

[a]OBRA, Omnibus Budget Reconciliation Act of 1987.

DEFINING QUALITY IN SUBACUTE CARE

Quality in subacute care goes beyond traditional medical process and outcome measures emphasized in hospitals. Perhaps most important is the quality and availability of the nursing staff. Because of the stress of managing high-acuity patients in the nursing home setting, many subacute facilities are chronically understaffed, or experience high staff turnover, especially of licensed nurses and nursing aides. Significant use of "agency" personnel, with little knowledge of the facility or its patients, can have a major negative impact on quality. Additional issues that are of great importance in the subacute setting include the quality of the rehabilitation services for patients with medical conditions that are likely to improve, and palliative care services for patients whose clinical status is likely to deteriorate. Subacute facilities are also judged on their hotel services in addition to their medical services. Good food, pleasant ambience, television, and clean rooms are all part of the reasonable expectations of patients and their families. Subjective measures, such as patient and family satisfaction and the facility's reputation in the community, can be good overall measures of quality. Medicare has a rating system for nursing facilities that consumers often use as a guide (http://www.medicare.gov/nursinghomecompare/search.html).

ADMITTING A SUBACUTE PATIENT: THE HOSPITAL PERSPECTIVE

The vast majority of subacute patients are transferred from acute care hospitals. The providers at the hospitals have a critical role in ensuring the success of the subacute stay. We often think of hospital clinicians as "senders" and SNF clinicians as "receivers." Often the senders, hospital providers, operate with little knowledge of the facilities to which they are sending their patients. This can lead to management issues since the clinical capabilities between LTACHs, IRFs, and SNFs differ. Even among SNFs clinical capabilities may differ. One wants to avoid a mismatch between patient care needs and facility capabilities. While the screening process for admission can help with this, there is also value to having a brief communication that is bidirectional and interactive between the hospital and subacute clinicians can help to answer questions about appropriateness, timing of transfer, specific treatments, and overall goals of care. This communication can be from physician to physician as well as nurse to nurse. Some hospitals are piloting a "warm handoff" process where the discharging nurse at the hospital calls the receiving nurse at the nursing facility prior to hospital discharge. Unfortunately, this type of communication is more the exception than the rule. Most communication is via "cold handoffs" typified by the written information contained in discharge summary which is unidirectional and not interactive. In general, if the acute care hospital providers have any questions or concerns about transfer of a patient, it is best to ask before acting.

The first question to be asked is who should be sent to subacute care, and who should not? Subacute facilities vary widely in terms of their capabilities, so there is no general answer. Hospital physicians often make the naïve assumption that the nurses "screening" patients for facilities have intimate knowledge of them and can make appropriate referrals. Often, these screeners work for large corporations that may have several facilities in a large urban area. The screeners focus more on "filling beds," and leave it up to the clinicians to determine appropriateness. It is also important to note that once a patient is accepted by a facility, the actual transfer may not take place for 1 to 2 days. During that time period, the patient may change clinically and the treatment plan may change, so it is important to reassess for clinical appropriateness at the time of transfer.

A few rules of thumb hold: in general, a patient requiring care that is typically delivered in an intensive care unit (ICU) is *not* appropriate for subacute care. The rare exception is a stable ventilated patient who is being transferred from an ICU to a specialized pulmonary subacute facility. In addition to ICU care, few subacute facilities have sophisticated cardiac monitoring, and so patients with active cardiac issues such as unstable angina, poorly controlled congestive heart failure needing day-to-day assessment for intravenous diuretics, or arrhythmias requiring continuous monitoring are rarely good candidates for subacute care.

Nursing care in subacute facilities is less intensive than in acute care hospitals. While hospitals rarely have more than seven patients per nurse, subacute units may have from 12 to 20 or more patients per nurse—in an 8-hour shift, this averages to as little as 20 minutes per patient. Therefore, patients with hemodynamic instability, on multiple

intravenous medications, or other situations requiring close nursing monitoring, may be poor candidates for subacute care. It is therefore critical that an assessment is made to be sure that the needs of the patient can be met with the staffing available. In general, patients with a relatively straightforward treatment plan for acute illness that has shown evidence of improvement, combined with established treatment of chronic illnesses and functional rehabilitation needs, are appropriate for the subacute setting.

On the opposite end of the spectrum is a patient who will likely be able to go home within a few days. For these patients, an additional facility transfer is probably not worthwhile or necessary, and runs the risk of introducing further discontinuity and iatrogenic problems. In general, subacute stays substantially shorter than 1 week should be avoided in favor of direct discharge to home.

Another issue is selecting the best facility for the patient. This is a complex issue that involves both clinical and psychosocial factors. Screeners and hospital case managers often need to be focused on getting a bed quickly rather than finding the best facility for the patient. In addition, bed availability can at times be an issue. Facilities vary widely in their capabilities, and some have specialized programs in specific areas, such as orthopedics and stroke care. In general, knowledge of a proven track record of success handling a particular kind of patient is the best proof of the wisdom of transfer. Some facilities have evolved close collaborative relationships with hospitals and primary care practices. In some sites the SNF attending is able to communicate electronically with key hospital-based and outpatient clinicians and have access to electronic medical record information. This can improve care efficiency and quality. In addition to these clinical issues, patients and family members may prefer a facility close to home, which can facilitate family visits and the like. These preferences should be honored if all else is equal. However, it should be explained to patients and family members that because only a short-term stay is anticipated, established medical care linkages and proven clinical excellence should outweigh geographic convenience to ensure the best possible outcome.

The optimal time for transfer can be defined as the point when the patient's needs can be met as well or better at the subacute facility as in the hospital. In practice, this is often hard to define, and discharge is often dictated by bed availability or "critical pathways" that predetermine length of stay. Multiple clinicians may have input into the decision to discharge a hospitalized patient including the physician, care manager, nurse, and rehabilitation therapists, as well as the insurer. Ultimately, it is the attending physician's responsibility to determine whether the patient is clinically ready for transfer, and for ensuring adequate transfer of information with the patient for continued implementation of the plan of care. It is better to keep the patient for an extra day in the hospital than to risk a rapid readmission for medical instability or a poorly coordinated transfer.

When the time for transfer comes, it is crucial that the appropriate information accompany the patient. **Table 19-6** describes the key information required by the SNF. In addition, the physicians at the hospital should review the discharge summary and other key transfer documents to ensure that there are no discrepancies—if so, these should be remedied. Checklists are being used by some hospitals to help ensure that the needed paperwork accompanies the patient on transfer. Examples of such a list and a transfer form can be found on the INTERACT program website (http://interact.fau.edu).

TABLE 19-6 KEY DATA NEEDED FOR TRANSFER TO A SUBACUTE UNIT

A list of clinical problems
Complete medication list matched with the clinical diagnosis
Identification of medications that are new and discontinued
Summary of hospital course
Code status/advance directives
Name of health care proxy/guardian
Wound care instructions
Identification of and contact information for physicians who are providing ongoing care, ie, surgeon, oncologist, cardiologist, infectious disease specialist when appropriate
Weight-bearing instructions
Recent significant laboratory test results
Key health care providers involved in care and how to contact them
Diet including consistency of food/liquids if swallowing is impaired
If on tube feeding, type of tube, rate/time of feeding, amount/time of water flushes

Recent focused physical examination findings
Goals for the subacute stay
Pending tests and how to follow up
Follow-up appointments
Clear anticoagulation orders with recent PT/INR results, INR goals
Indications for urinary catheter if present and when it can be removed
Last bowel movement
Family contacts with accurate names, phone numbers, and addresses
Type of intravenous access with x-ray report confirming correct location of central lines

INR, international normalized ratio; PT, prothrombin time.

Developing better systems whereby receiving facilities and sending hospitals coordinate the transitions of care is crucial to improving patient care and optimizing outcomes. One approach can be achieved through sharing information via computer systems. Clearly, this is easiest for onsite transitional care units (which are much less common). However, even free-standing subacute facilities can now have computer links with sending hospitals so that medical information can be accessed. Only certain members of the subacute staff (particularly the physicians, who may also be on staff at the sending hospital) will generally have access to key elements of the patient's electronic outpatient and hospital-based medical record, as well as the ability to e-mail hospital providers.

Understanding the capabilities and limitations of subacute care facilities can help hospital providers better manage the transfer of care. First, consider the timing of transfer. Unfortunately, many patients arrive for admission to SNFs between 4 and 7 PM However, staffing at most SNFs is best on the day (7 AM–3 PM) shift. In addition, physicians and advance practice clinicians are much more likely to be on site during the day shift. Therefore, hospitals should attempt to transfer the patient as early as possible during the day, preferably before noon. Before sending the patient, hospital providers should ensure that all patient needs, including nutritional, are met for the next several hours. Second, consider that most SNFs do not have onsite pharmacies and that it may take several hours for some ordered medications to be delivered to the patient. Therefore, all medications, particularly pain medications that the patient will need over the next 4 to 6 hours, should be administered prior to transfer. Finally, SNFs may have difficulty inserting intravenous access in a timely fashion. Therefore, stable access should be ensured prior to transfer. If the patient will need more than 1 to 2 days of treatment, a more permanent "long-line" catheter is advisable.

One special case deserves mention: direct admissions from the community to subacute care. While many patients are not able to be direct admitted to a SNF because of Medicare's "3-day rule," direct admissions are more common as a way of reducing costs, readmissions, and getting patients the care they need in the appropriate setting. These direct admissions are allowable if they are for managed care patients (who are exempt from this rule), patients who are part of a previously described Medicare "SNF waiver" program, or patients who have had a 3-day hospital admission in the previous 30 days. Direct admissions should be medically stable and should not require immediate diagnostic or therapeutic intervention. In the United States, systems for sending patients to a SNF are well developed for hospital inpatients but not for patients being sent to a SNF from the ER, direct from home or the physician's office. Thus, it is crucial that appropriate information, including reason for admission, medical history, physical examination, medications and their clinical indications, treatments, allergies, and the like, be transmitted from the emergency department or doctor's office. A warm handoff between the sending and receiving physician is often required. Ideally SNFs should have processes in place for streamlining and coordinating the admission of patients not coming from the hospital setting before accepting such patients.

ADMITTING A SUBACUTE PATIENT: THE FACILITY PERSPECTIVE

Those who work in a subacute environment need to understand the crucial role played by the first 24 hours postadmission. From a clinical outcome, patient satisfaction, and a risk management perspective, the first day and night in the facility is the key. Case 1 illustrates some of the perils of the hospital-subacute transfer.

Case 1: Transition of Care Issues in the First 24 Hours

An 85-year-old male retired professor is admitted with a hip fracture, hypertension, and diabetes. Here are some

common issues that arise that can impact outcomes in a subacute setting:

1. *Family communication:* The patient's daughter does not know if and when her father is going to the subacute facility and does not know how to get to the subacute facility.
2. *Timing of admission:* The patient is scheduled for a 2 PM arrival, but arrives at 6 PM because the hospital nurse had another sick patient and did not get the paperwork done. The patient left the hospital before dinner was served and arrived at the subacute facility after dinner was over.
3. *Avoidable complications:* His blood glucose was 40 mg/dL and he was lethargic by the time his dinner arrived.
4. *Missing information:* The weight-bearing status is not given on the hospital referral. The page 1 referral had a "titrate Coumadin to international normalized ratio (INR) of 2.0" order but no dose and no INRs. The discharge summary did not arrive with the patient. The hospital was not aware that the patient took glaucoma drops, and therefore, these medications were not noted on the referral form.
5. *Facility issues:* Physical therapy had left by the time the patient arrived and nursing was not comfortable transferring the patient out of bed to the toilet. Diapers were placed on the patient irrespective of continence status. The room smelled because the patient was incontinent. Pain medicine was ordered but was not delivered for 8 hours.

The daughter arrives, sees her father in diapers, in pain, more confused, and the nurses unsure about his medications, and wants to send the patient back to the hospital and says she is going to write a complaint letter to the Department of Public Health. The patient in the next bed is upset because the room smells and the daughter has gotten him upset as well.

The issues that arise in Case 1 are not unusual. Patients arrive unexpectedly, sometimes with medical issues requiring prompt attention, and the information transmitted is inadequate and sometimes contradictory. Interagency referral forms may be done at different times than discharge summaries and can contain conflicting information.

Nursing home physicians and advance practice clinicians often manage new SNF admissions telephonically for the first 24 to 48 hours. Accurate, complete nursing assessments are important to the SNF clinician who is attempting to manage a patient he or she has never met over the phone. Nurses who work on subacute units need to work effectively with their offsite physician colleagues. An important aspect of this collaboration is judgment as to when to page the physician/APC and what information to have available. Nurses need to perform an appropriate assessment of the patient based on the clinical situation. In addition, it is important to have information on medications being given, as well as recent laboratory results. There are tools that being used by many SNFs that help with these assessments. The **INTERACT** program is one such example. INTERACT is an acronym for "**Inter**ventions to **R**educe **A**cute **C**are **T**ransfers" and is a quality improvement program that was first designed in a project supported by the Centers for Medicare and Medicaid Services (CMS) to improve the identification, evaluation, and communication about changes in resident status. Many nursing homes across the country are using INTERACT. The tools and related resources are free for clinical use at http://interact.fau.edu.

A comprehensive history and physical examination is required within 48 hours of subacute admission. It is a best practice if this can be performed within the first 24 hours. In addition to understanding the medical problems identified at the hospital, key issues for the subacute clinician to consider when admitting a new patient include understanding the goals for the SNF stay, making sure medications are appropriately dosed, and assessing pain, bowel status, and cognition. If the patient has an indwelling bladder catheter, the reason it was placed and the ongoing need for it should be assessed and the catheter should be removed as soon as possible.

In addition to the history and physical by the physician-APC team, the newly admitted subacute patient must have a number of assessments performed by many disciplines. The physician or APC, as leader of the interdisciplinary team, needs to be aware of key findings from these team members and integrate them into the initial treatment plan. **Table 19-7** provides examples of the assessments that need to be done and the disciplines that do them.

TABLE 19-7 INITIAL ASSESSMENT OF THE NEW PATIENTS BY SUBACUTE STAFF

Rehabilitation team	Screens by physical and occupational therapy and speech
Nursing	Skin, cognition, fall risk, pain, bowel/bladder, medication review, and reconciliation
Dietary	Nutritional needs/diet

Kitchen	Food preferences
Social service	Psychosocial evaluation, end-of-life preferences
Case management	Discharge planning including equipment and home care
Administration	Valuables assessment

Patients not only have medical issues identified by the hospital, but may arrive with unidentified issues, such as fever, delirium, skin breakdown, constipation, pain, and urinary retention, which may require immediate attention. The subacute clinician has to organize this information and prioritize issues that need immediate attention. The admitting physician must also be on the alert for errors in the hospital discharge medication list which can include missing medications, inaccurate lists based on older inaccurate medication lists and unnecessary medications. Careful medication reconciliation is an essential aspect of admitting patients to the subacute care setting.

Nursing facilities generally do not have onsite pharmacies. Delivery of medications can take several hours. To help with this issue, facilities have drug "emergency boxes" that contain dozens of frequently used medications including intravenous antibiotics and a small selection of opioids. Familiarity with the contents of these boxes is important for the subacute care provider to practice effectively. At times, short-term substitutions must be made until the exact medication can be delivered. In addition, like hospitals, many facilities have formularies. Medications may need to be changed to meet formulary requirements.

PATIENT/FAMILY/STAFF INTERACTIONS

In addition to being astute and thorough when assessing a new patient, the subacute clinician must be skilled at establishing trusting relationships with the patient and key family members as soon as possible after admission. Any time a patient changes setting and new caregivers assume care, there are opportunities and dangers. The initial hours after admission are therefore an important window period in which the receiving clinicians can form a strong collaborative relationship with the patient and the family.

Family members provide important clinical and functional information that may otherwise be unavailable. Speaking with family members may help to identify areas of concern related to past care and can point to special issues on which to focus immediately on admission. The physician can establish themselves as a patient advocate and a problem solver. A best practice is to connect with the sending physician and the primary care physician early in the admission to review the plan of care and have any questions answered. It is often very reassuring to patients and families to know that the nursing facility physician is collaborating with physicians with whom the patient and family have a preexisting and trusting relationship. This connection can often be done by e-mail using secure systems that are compliant with HIPAA. By establishing an early, strong family connection, the subacute clinician is better able to identify and ultimately meet the goals of care, and overcome barriers to discharge.

PHYSICIAN'S ROLE IN REHABILITATION

In the subacute setting, an interdisciplinary team meeting plays a crucial role in formulating and assessing the plan of care. At the team meeting, key issues of function, medical condition, cognition, mood, and interactions between family, patient, and staff can be shared. The interdisciplinary team needs to gather and communicate information regarding medical condition, treatment and prognosis, rehabilitation potential and level of function, psychosocial needs, financial options, and family/patient teaching needs. Most internists, primary care physicians, family practitioners, and general practitioners do not receive formal training in rehabilitation or in how to work on or oversee an interdisciplinary team meeting. There is a vital role that a subacute physician can play in this regard which benefits the facility and the patients, as well as the patients' families.

The team meeting can serve several purposes. It is a way for the physician to hear firsthand from nursing and therapy how the patient is doing. The physician may be made aware of issues not previously recognized such as inadequate pain control, incontinence, anorexia, and constipation. The physician plays an important role in sharing clinical information with the team. The physician understands the pathophysiology of disease processes better than any other member of the interdisciplinary care team. Therefore, the physician has a critical role to play in leading the team in identifying realistic functional goals for patients, understanding, and explaining the impact of intercurrent medical illnesses on patient function, and communicating with patients, staff, and families regarding realistic goals and

expected level of function. The physician does not need to know how best to identify weakness in a particular muscle group and what exercises to do to strengthen it, nor what the best assistive device will be for a patient. However, the physician does need to understand whether the goals of treatment outlined by the therapy team are realistic based on the patient's physical ability, cognitive capacity, as well as their home environment and supports. The physician or APC may also have leaned key information speaking with family members that is important for the rest of the team to know. This can include information on caregivers and other home supports. Although some physicians working in nursing facilities do not take an active role in team meetings and in assessing the patient's rehabilitation needs, goals, and progress this is a missed opportunity that can be very rewarding to the physician and beneficial to the patient and the team as whole.

How to get the patient walking safely as well as managing ADLs as independently as possible are often the major challenges to face nursing facility staff. Generally, physical and occupational therapists are able to provide 1 to 3 hours of therapy per day, 5 to 6 days per week, in the subacute setting. It is essential that other members of the care team provide an environment that encourages patients to get out of bed and ambulate when the therapists are not working with the patient. Nurses and aides need to be taught by the therapists how best to transfer the patient, to observe any weight-bearing restrictions, and to learn which assistive devices need to be used. Often schedules need to be set up to get the patient washed, fed, dressed, and out of bed. Identifying what is not working well and brainstorming with other members of the care team to identify solutions is an important role for the physician. There are a number of roles that the physician maybe required to fill in the interdisciplinary team (**Table 19-8**).

TABLE 19-8 PHYSICIAN'S ROLES IN THE INTERDISCIPLINARY TEAM

Provide medical expertise on prognosis
Determine realistic, achievable functional goals
Determine whether medical improvement is likely, resulting in improved function, or whether medical status has plateaued or will deteriorate with stable or reduced function
Adjust treatment based on input from team members (pain/bowel/anxiety, etc)
Gather input from specialists and share with team members
Participate in brainstorming to identify solutions
Guide discussions around ethical issues
Determine when skilled care is not beneficial or needed
Facilitate family communication
Determine when discharge to another setting is appropriate
Provide constructive feedback
Assess/improve teamwork between rehabilitation/nurses/nurses' aides

Clear communication between all members of the interdisciplinary team is essential (see Chapter 26). The physician, nurse practitioner, and physician assistant play an important role in helping set realistic goals and making sure that each member of the care team is providing care that is geared toward achieving those goals. They also play a key role in communicating with family members.

Case 2 outlines the key role of physicians in communicating between providers and altering the plan of care to optimize patient outcomes.

Case 2: Importance of Communication in Subacute Care

A 78-year-old woman with a left hip fracture repair and a history of mild dementia presents to the nursing facility for rehabilitation. The patient arrives with a non–weight-bearing status order for her left leg. The physician sees the patient and finds she has poor memory and impaired judgment. She lives with her frail but independent husband in a home with eight stairs separating the bedroom and kitchen. The physician orders occupational and physical therapy evaluations.

On day 2 of the admission, the physician realizes that the patient's functional and cognitive deficits will likely prevent her from keeping weight off the operated leg. Furthermore, it is clear that very few 78-year-olds can ambulate safely on one leg using a walker or crutches. In such situations, the end result is often that until the weight-bearing restriction is removed, which generally takes 1 to 2 months, the patient will not be able to ambulate She will require a

wheelchair for locomotion and will be dependent on others for transfers to and from the bed, the chair, and the toilet, likely requiring a prolonged nursing home stay. This places the patient at high risk for becoming further deconditioned and depressed and at higher risk for skin breakdown from prolonged sitting and ultimately needing permanent long-term care. The physician calls the operating surgeon and explains the dilemma. Upon further reflection, the surgeon states that the fracture was minimally displaced, the alignment was good, the repair was reasonably strong, and in conjunction with being reminded that the patient is only 105 lb and advances her to a weight-bearing as tolerated status. The treatment plan for this patient has now changed dramatically. Achieving independence with transfers now becomes a realistic possibility. She may be able to negotiate stairs. The plan is now for a 1- to 2-week stay with discharge to a home setting with community supports and the family paying for extra assistance, and if needed, bringing a bed to the first floor.

Some individuals have cognitive and physical limitations that may impact their ability to have successful rehabilitation outcomes. The physician plays a vital role in identifying patients who have such limitations and for helping brainstorm ways to overcome them. Patients with advanced dementia or delirium may have great difficulty learning new strategies or compensatory techniques. Conditions such as depression which may impact motivation, inadequately managed pain, preexisting physical issues related to neurologic conditions such as Parkinson disease or stroke, as well as cardiac or respiratory conditions may result in individuals having difficulty participating in and benefiting from a rehabilitation program. The physician must play an active role in identifying and treating the depression, pain, or congestive heart failure that is limiting participation in and benefit from the rehabilitation program.

It is often appropriate and necessary to teach nursing facility staff such as nurses' aides how best to feed, transfer, and ambulate patients. The goal is to provide for the patient's safety while maximizing their autonomy. There is a tension at times between getting things done quickly by helping the patient and having the same task be done more slowly but with the patient doing all or most of it. The patient may take 20 minutes to get dressed, needing periodic verbal cues from the nurses' aide during the process. If the nurses' aide did more of the work the job might be done in 10 minutes. The patient may even prefer to have the aide do more of the work. However, a cornerstone of care for the older patient is to encourage as much independence as possible, and this is even more important in the subacute setting when the goal is often to improve and return home.

PHYSICIAN'S ROLE IN FAMILY MEETINGS

Family meetings are an invaluable means of sharing information, reviewing care goals, making decisions, and identifying action steps. Family meetings should generally take place after there has been an interdisciplinary team meeting without the family's presence so that all team members can be on the same page. At the family meeting complex information needs to be presented in an organized manner that allows time for questions, discussion, and identifying action steps. Ideally, all this needs to be done in fewer than 45 minutes, so that staff can resume other duties and patients and family members are not overwhelmed. Family meetings can include the patient; key family members and caregivers; the physician/nurse practitioner/physician's assistant; case manager; social service; the rehabilitation team, including physical, occupational, and speech therapy; nursing; and even aides. Formulating an agenda and goals for the meeting ahead of time helps identify who needs to be present. **Table 19-9** summarizes common goals for family meetings.

TABLE 19-9 GOALS OF FAMILY MEETINGS

Information gathering regarding:
Previous function
Caregiver supports
Financial resources
Home environment
Goals of care
Decision making regarding:
End-of-life care
Rehabilitation goals that need to be attained

Discharge site, eg, home, long-term care, assisted living
Setting a discharge date
Resolving areas of conflict:
Between family members
Between family and patient
Regarding facility services

A staff member such as the physician, case manager, or social worker should run the meeting. It is often very helpful for the senior clinician to provide a brief update regarding the medical issues and prognosis. Knowing what different team members are going to recommend is essential for family meetings to go well. Major differences in the treatment plan between team members should be addressed before the family meeting. For example, the therapist may find the confused patient with a resolving pneumonia is not participating in rehabilitation. However, the physician may be able to explain that the confusion is likely related to a delirium and may improve quickly as the pneumonia responds to antibiotics. Without the physician present to provide this input, the facility caregivers and family members may not have an accurate picture regarding disease progression, clinical improvement, and overall prognosis. Providing a clear, realistic picture of function and medical prognosis is also a critical part of the discharge planning process.

Several conditions are especially common among subacute patients. Key aspects of these conditions relevant to subacute care are discussed below. Other chapters in this text discuss these conditions in more detail including management and decision making near the end of life.

MEDICAL MANAGEMENT IN THE SUBACUTE SETTING

Pain Management

It is well recognized that pain, especially in individuals with cognitive impairment, is often unrecognized and undertreated. Effective pain relief is an essential aspect of subacute care. **Table 19-10** outlines some of the negative consequences of untreated pain.

TABLE 19-10 IMPACT OF PAIN IN SUBACUTE PATIENTS

Decreased mobility
Reduced participation in rehabilitation program
Incontinence
Longer length of stay
Constipation/impaction
Pressure ulcers
Delirium
Depression
Anxiety
Anorexia
Pneumonia
Increased risk of needing long-term care
Family stress

Recognizing and relieving pain are critical skills for the subacute clinician. It is beyond the scope of this chapter to review the broad area of pain relief. However, opioid use in the subacute setting merits special mention.

Opioids play an important role in pain control. Whether for postoperative pain or end-stage cancer, a sound knowledge of principles of pain control and an understanding of nursing facility regulations regarding opioid use is essential. Opioids can be delivered in several different forms. Familiarity with the different routes of administration

for opioids is an important aspect of providing pain management. **Table 19-11** summarizes routes of administration. Patients arriving from hospitals may have orders written for intravenous "push" opioids. Nurses in nursing facilities do not generally give opioids, or other medications, in this manner. However there are many other options. The clinician in the nursing facility needs to reorder these medications in a form that is appropriate for the facility which can include oral, sublingual, transdermal, subcutaneous, or intravenous methods of delivery.

TABLE 19-11 ROUTES OF OPIOID ADMINISTRATION

Oral tablets in both short- and long-acting form
Oral liquids
Sublingual liquids in concentrated form
Disintegrating lozenges
Rectal suppositories
Transdermal patches
Subcutaneous injections
Subcutaneous infusions
Intravenous infusions

The regulatory issues in nursing facilities can, at times, complicate and impair the provision of good pain control. Unlike the hospital setting, nursing facilities' regulations require a handwritten prescription for each opioid order. The physician generally must either fax a prescription to the pharmacy or call the pharmacy to obtain an emergency 72-hour supply of the medication which needs to be followed by a faxed prescription. In nursing facilities, exact doses and parameters for "as needed" indications are required, for instance: "Percocet (5/325 mg) one tablet orally q4h PRN for moderate hip pain (4–7 on pain scale) and two tablets orally q4h PRN for severe hip pain (8–10 on pain scale)." Sliding scale dosing orders without specific parameters, such as "morphine sulfate 1 to 4 mg subcutaneously q1–4h PRN," are not allowed.

Many patients may experience a roller coaster effect when given PRN doses of short-acting pain medications. The result is many hours of discomfort with just a few hours of pain relief. Familiarity with and use of sustained-release oral opioids is an essential aspect to being able to provide successful pain control in the nursing facility. It should also be noted that most extended-release medications should not be crushed. If the patient is not able to swallow a long-acting opioid tablet, then an alternate dosing route needs to be considered, such as a transdermal patch.

Finally, a standing bowel program needs to be ordered along with the opioids. Orders for "milk of magnesia PRN" or routine stool softeners are inadequate for most patients on opioids. **Table 19-12** summarizes key points regarding opioid use in subacute care.

TABLE 19-12 KEY ISSUES REGARDING OPIOID USE IN SUBACUTE CARE

Be specific regarding dosing/frequency when ordering opioids
Know the contents of the facility's "emergency box"
Prompt faxing/phoning reduces delays in getting opioids
Order a bowel program with opioids
Evaluate whether a sustained-release product is needed with PRN "rescue" doses
For new admissions, consider developing a system where it is known what the medications (including opioids) will be before the patients arrive and *preorder* them so there will not be delays
Encourage hospital clinicians to include written prescriptions when patients are discharged

Some best practices include modifying the limited contents of emergency kits to meet the common opioids that are used by a particulate high-volume referring hospital, preordering opioids so that they are immediately available when the patient arrives at the skilled nursing facility and working with hospitals to create systems whereby hard copies of opioid prescriptions are sent with the patient on transfer. These practices can reduce wait times for obtaining pain medications for new admissions.

Urinary Incontinence and Catheters

Many patients arriving at subacute facilities have indwelling catheters or were incontinent at the hospital. Urinary catheters are most commonly used to monitor urine output when patients are first admitted to the hospital. Most patients arriving with catheters from the hospital can have them removed immediately. Efforts to reduce the incidence of catheter-associated urinary tract infections (CAUTI) begin with removing the catheters as soon as it is clinically appropriate. From both an infection control and a nursing home regulatory perspective, urinary catheters should be used in very limited situations. The two main ones are in the setting of urinary retention when intermittent catheterization is not practical and in the case of severe skin wounds when healing would be impaired by urine from an incontinent patient. Before committing a patient to permanent catheterization for urinary retention, it is important to determine whether there is a reversible cause for the retention, such as stool impaction or a medication side effect. Anticholinergic medications are particularly likely to inhibit proper bladder emptying. When indications for a urinary catheter are not clearly stated it is a best practice to contact the sending clinicians or specialists to get clarification on whether the catheter is needed.

The hospitalized patient with new incontinence often has an etiology that can be diagnosed and treated in the nursing facility without sophisticated studies. It is important to determine the prehospitalization continence status and the etiology for the incontinence. Infections, medications (diuretics), delirium, immobility, fecal impaction, urinary retention, and deconditioning are common causes of incontinence that are readily treated. Nurses' aides, nurses, and therapists are very important to the clinician as a source of information regarding continence. An interdisciplinary meeting is an excellent way to obtain information on continence and to develop a plan to manage it. **Table 19-13** summarizes some ways of rapidly assessing and managing incontinence in the nursing facility (see also Chapter 53, Incontinence).

TABLE 19-13 ■ ASSESSING AND MANAGING INCONTINENCE

Treat a diaper as a red flag: ask why it is on and if not needed make sure it stays off
Consider performing a rectal examination: stool impaction is commonly overlooked and is very treatable
Consider a bedside commode if the patient is slow transferring and ambulating
Make sure there is no problem with delays answering call lights; if there are delays, involve the director of nursing in formulating a solution
Avoid anticholinergics, especially in men, as they may cause urinary retention or confusion
Get a good history from the patient/family regarding prehospitalization continence
Consider obtaining a postvoid residual volume to rule out urinary retention; this is particularly noninvasive if facility has a bladder scanner
Review medications and lab work for causes of incontinence

Swallowing Issues

An appropriate diet and feeding plan can be crucial in the subacute setting. Hospitals may not always supply detailed information on food and beverage consistencies for patients at the time of admission to the nursing facility. Patients with strokes, impaired cognition, and other neuromuscular disorders require special types of diets because of dysphagia. The subacute clinician should be familiar with these diets. Solid foods can be ground or pureed to facilitate swallowing. Liquids can be thickened to nectar- or honey-thick consistencies to reduce aspiration risk. Contacting the sending hospital prior to feeding the patient may be necessary to determine the proper diet in a patient with dysphagia. Speech therapists are important members of the rehabilitation team in nursing facilities. Speech therapists have a dual role. They work on communication techniques and strategies and also screen for and evaluate swallowing difficulties. Speech therapists can assess whether food consistencies are appropriate and whether other interventions are needed such as elevation of the head of the bed, tucking the chin, or turning the head with swallowing. Speech therapist can also work with patients who have cognitive and problem-solving impairments. They have a key role in teaching staff how to best meet a patient's needs regarding eating, drinking, and communicating.

Swallowing difficulties can develop in the setting of an acute or a chronic illness. Delirium and dementia contribute to swallowing problems, especially if an acute medical illness develops. Stroke, neuromuscular illnesses, anatomic abnormalities, and infections may also cause dysphagia. Thrush and xerostomia are common issues in patients that can be alleviated if they are identified. Coupled with swallowing problems is the fact that older patients

entering nursing facilities often have poor dentition, ill-fitting, or missing dentures. Dentures are often used by patients at home and their use should be continued in the nursing facility. Every effort should be made to locate missing dentures that may still be at home, at the sending hospital, or in a drawer next to the patient's bed. The role of the speech therapist in reducing aspiration risk includes items listed in **Table 19-14**. **Table 19-15** summarizes the physician's role in helping to manage the patient with swallowing difficulties.

TABLE 19-14 SPEECH THERAPIST'S ROLE IN ASPIRATION MANAGEMENT

Screening new admissions for swallowing difficulties
Assessing swallowing capabilities
Recommending food and liquid consistency
Ensure that food from kitchen is at the proper consistency
Coordinate the interdisciplinary team to ensure that the proper food and liquid consistency is provided at all times
Teaching the patient compensatory swallowing strategies, eg, chin tuck
Recommend when diet can be advanced
Recommend whether further diagnostic studies are needed, eg, modified barium swallow
Determine how medications should be taken, such as crushed or with applesauce
Training facility staff and family members on proper techniques

TABLE 19-15 PHYSICIAN'S ROLE IN ASPIRATION MANAGEMENT

Order appropriate food and fluid consistencies with input from speech therapist
Order aspiration precautions when appropriate with input from speech therapist
Order further diagnostic studies if needed, eg, modified barium swallow
Assess whether a feeding tube might be indicated
Identify reversible medical causes of dysphagia

Falls

A significant challenge in managing patients in nursing facilities is the tension between safety and autonomy. Many patients in nursing facilities have cognitive impairment as well as a functional deficit that hinders transfers or ambulation. The physician plays a vital role in helping families understand this and in working with facility staff in identifying risk factors for falls and reducing those risks. Many facilities have fall committees that meet regularly to strategize on how to prevent falls. Medication reviews should be a part of this review and often pharmacy consultants can be utilized to assist. There are specific definitions of what constitutes a fall that are generally standardized within the nursing home industry. **Table 19-16** identifies some of the common causes of falls in a subacute setting. Falls are discussed in detail in Chapter 48.

TABLE 19-16 CAUSES OF FALLS IN SUBACUTE SETTINGS

Medication-related postural hypotension
Medication-related confusion
Medical condition causing weakness or orthostasis, eg, pneumonia, anemia
Pain
Poorly fitting footwear
Inadequate lighting
Delays in answering call lights
Incontinence causing a slip and fall
Lack of familiarity with environment
Environmental hazards such as oxygen tubing, bedside trays that roll when leaned on

New stroke or fracture causing weakness in a limb(s)

If a patient falls, a review of the above issues needs to be undertaken to determine why the fall occurred and to take corrective measures. The use of restraints, whether physical or chemical, to prevent activities or behaviors that increase the risk of falls needs to be carefully scrutinized. Physical restraints are rarely needed and may result in injury or even death if improperly used or monitored. Chemical restraints (eg, sedating psychotropic drugs) have significant morbidity associated with them as well and need to be used with great care with attempts at dose reduction and discontinuation made on a regular basis. Finding ways to manage problematic behaviors to decrease the risk of falls or to keep patients safer is especially challenging in patients with cognitive impairments (**Table 19-17**). Training of staff and family in techniques that can prevent or reduce agitation can involve environmental adaptations (avoiding busy, loud areas) and identifying sources of physical as well as emotional discomfort.

TABLE 19-17 ■ FALL/INJURY REDUCING INTERVENTIONS IN SUBACUTE SETTINGS

Identifying the high-risk patient
Consider using a bell instead of a call button—better for some demented patients
Physical/occupational therapy evaluation
Bed or chair alarm—although these often go off after the patient is on the ground
Implement a toileting schedule—this needs to work on all 21 shifts per week
Low beds or putting mattress on the floor
Placing a pad next to the bed
Reminders, eg, “call don’t fall”
Encourage time spent in group activities
Use half instead of full bed rails
Identify correlating events, eg, postprandial hypotension

Having a clear, well-documented interdisciplinary plan on how to manage the patient who is at risk for falls can be very helpful in this situation in preventing litigation, citations, or even monetary penalties for the facility.

Pressure Ulcers

Clinicians practicing in nursing facilities must have a good understanding of preventing and managing pressure ulcers. Pressure ulcers can result in pain, immobility, catheter use, infections, malnutrition, prolonged SNF stays, and hospital admissions. While some pressure ulcers are avoidable, many others are unavoidable. Similar to falls, clinicians and facilities must realize that these ulcers are potential areas for litigation. Excellent documentation and a thorough knowledge of techniques for preventing and treating pressure ulcers are areas with which the subacute clinician must be familiar.

Nursing facilities do skin assessments as part of the admitting process, and again periodically during the stay. It is worthwhile to familiarize yourself with the screening tool used in your facility and to review it once it is completed on new admissions. High-risk patients can be identified in this manner. Good communication with nursing staff is essential since, changes can occur in which a low-risk patient can quickly become high risk. For instance, a patient may develop diarrhea and weakness. The physician-APC team must recognize a new increased risk for skin breakdown. **Table 19-18** identifies the patients at highest risk for skin breakdown.

TABLE 19-18 ■ CONDITIONS PLACING PATIENTS AT HIGH RISK FOR SKIN BREAKDOWN

End-stage diseases
Poor nutritional status
Cognitive impairment
Immobility from fracture or neurologic deficit
Incontinence of urine and stool
Dehydration

Infections
Sensory impairment
Improper fit of orthotics or casts
Pain

By recognizing the at-risk patient population, steps can be implemented that can reduce the likelihood of skin breakdown (see Chapter 53). Even if pressure ulcers develop, demonstrating that preventive measures were in place and being monitored can protect the facility and the clinician from censure by local health departments and from litigation (**Table 19-19**).

TABLE 19-19 GENERAL MEASURES THAT MAY AVOID OR MINIMIZE PRESSURE ULCERS

Pressure-reducing mattresses
Turning schedules
Optimizing nutrition
Short-term vitamin supplements such as zinc and vitamin C
Maintaining hydration
Controlling moisture and soiling from incontinence
Avoiding prolonged sitting
Pressure-relieving devices on chairs
Managing other medical conditions
Using protective devices such as multipodous boots for heel protection if fit properly

Medication Issues

A growing awareness of the impact of medication-related morbidity has taken place in recent years (**Table 19-20**). The subacute practitioner needs to have a good understanding of the medication delivery and administration systems. Nursing facilities have emergency kits that contain common medications including a limited supply of opioids. Very few nursing facilities have an in-house pharmacy. Medications are delivered after being called or faxed in to an outside pharmacy. It generally takes several hours to deliver medications. In certain situations (high-dose opioids, frequent intravenous antibiotics), medications should be preordered so that they are available to the patient immediately on admission.

TABLE 19-20 COMMON MEDICATION ISSUES IN NURSING FACILITIES

Late doses
Missed doses
Giving medications to the wrong patient
Wrong dose or medication administered
Patient refused medication and physician not informed
Mislabeled medication from pharmacy
Wrong dose of medication sent from pharmacy
Medications ordered that should be avoided in the older population (eg, anticholinergics, long-acting benzodiazepines)

Physicians in nursing facilities must be aware of medications that should be avoided or dose adjusted in older patients. Patients may arrive from hospitals on medications that have a high risk of side effects in this population. It is incumbent on the subacute clinician to carefully review each medicine for necessity, proper dosing, and potential interactions with other medication being administered. Adjusting doses for reduced creatinine clearance is another important aspect of medication management in the subacute setting. Medication reconciliation has become a standard practice at any care transition. Identifying home medications, new medications, and medications that have been eliminated on admission to the skilled nursing facility is a best practice.

It is also important to know that medication lists that arrive with patients may not be accurate. Sometimes they are based on old medication lists and contain medications not being taken or have incorrect dosages or they may be incomplete. The process of medication reconciliation needs to be a standard step in the admission process. Case 3 illustrates a useful example on medication ordering.

Case 3: Issues in How Medications Are Ordered

An 80-year-old woman with a history of hypertension, angina, and atrial fibrillation is on metoprolol 50 mg bid. The admitting physician is asked by the nurse to provide parameters for the order so "metoprolol 50 mg bid, hold if blood pressure is under 100 systolic or pulse under 55" is written. Two days later, the patient is sent to the emergency department complaining of chest pain and is found to be in atrial fibrillation with a ventricular response of 140 beats/min.

On review of the medical record, it is found that the patient had a blood pressure in the 90s and metoprolol was held for three doses. The initial parameters for the metoprolol were written to avoid hypotension or bradycardia. However, the medication was needed for rate control and angina treatment. As in most other aspects of nursing home care, excellent communication is the key to success. Modifying the original order to read "metoprolol 50 mg bid, hold *and call MD* if blood pressure under 100 systolic or pulse under 55" could have alerted the physician to the fact that multiple doses were being missed. The dose could be reduced or another medication used that could ultimately have avoided a hospitalization.

DEALING WITH COMPLICATIONS OF THE ACUTE HOSPITAL

Subacute providers must often treat complications of hospitalization. In fact, the necessity for postacute care maybe determined more by these complications than by the primary diagnosis itself. Both the principles of geriatrics and empiric research suggest that the most effective approach for dealing with these complications is to prevent them. Unfortunately, subacute providers are not traditionally in a preventive position and must effectively manage problems that develop in the hospital. However, there are models of medical care in the subacute setting whereby subacute physicians work closely with hospitalists and other specialists. This provides an opportunity for constructive feedback and suggestions. With hospital now at financial risk for some readmissions there is an opportunity to collaborate with hospital-based colleagues in addressing some of the issues described below.

Foremost among hospital-acquired complications is delirium, or acute confusion, which affects up to one-third of hospitalized patients aged 70 or older. While some delirious patients clear quickly in the hospital, others remain confused for weeks to months. Because patients with persistent confusion are usually unable to return home, a large percentage of these patients are discharged to subacute facilities. In subacute care, residual delirium may profoundly impact the medical or rehabilitation plan, so that these patients are at high risk of "bouncing back" to the acute hospital, or failing to meet their rehabilitation goals. These patients are at higher risk for a variety of issues including falls, polypharmacy, and incontinence.

Patients with delirium must be identified promptly and evaluated to ensure that all medical problems or medications that perpetuate delirium are eliminated. Probably the most common error among subacute practitioners is to attribute symptoms of delirium to an underlying dementia, and therefore neglecting potential opportunities to restore a patient's cognitive and functional status. To combat this, a brief but structured mental status assessment should be performed on all new admissions to subacute care, with particular focus on identifying key symptoms of delirium as described in the Confusion Assessment Method. Once delirium is recognized, in addition to identifying and treating its causes, a comprehensive cognitive and functional rehabilitation program that recognizes and abates the effect of delirium should be put into place. Key steps in the management of delirium in subacute care are described in **Table 19-21**.

TABLE 19-21 ■ STRATEGY TO MANAGE PERSISTENT DELIRIUM IN POSTACUTE CARE

Structured mental status assessment on admission with application of the Confusion Assessment Method to detect delirium
If delirium detected, contact the physician/APC
Work up to identify and treat reversible causes and contributors to delirium
Institute measure to prevent or manage common complications of delirium

Avoid physical and chemical restraints, and sedatives at night if possible

Create an environmental milieu conducive to recovery from delirium, including provision of appropriate sensory aids, orientating devices such as clocks, calendars, and an orientation board, consistency of staff (if possible), cognitive and physical rehabilitation

Educate family members about delirium, and engage them to help reorient the patient

Another major problem inherited from hospitals is deconditioning. Patients at bed rest lose muscle strength (and bone mineral density) rapidly, so that after a prolonged hospitalization, many frail individuals are unable to walk, even though their primary disease process had nothing to do with ambulation (eg, pneumonia). Cardiovascular deconditioning may lead to severe orthostatic hypotension that may take months to resolve. Prolonged muscle and cardiovascular reconditioning may be required to restore these patients to their preillness status.

Depression is also very common in older patients after acute hospitalization. The presence of significant depressive symptoms, even in the absence of clinical depression, exerts a powerful negative influence on functional recovery in the weeks to months following acute illness. Subacute patients should be evaluated for depression or depressive symptoms using both informal staff observations and a structured assessment tool such as the Geriatric Depression Scale. Those with evidence of depression should be referred for appropriate mental health consultation and/or initiated on antidepressant medication. Because antidepressant medication may take weeks to become effective, psychostimulants such as methylphenidate can be quite useful as a short-term “bridge” in severely depressed postacute patients.

Finally, a mundane but serious consequence of hospitalization is the loss of glasses, dentures, hearing aids, or other assistive devices that many individuals need for communication, eating, and the like. Often, these are not brought in to the hospital; in this case, the family should be asked to bring these into the subacute facility as part of the patient’s rehabilitative plan. If the devices are indeed lost, prompt replacement maybe required, often at financial hardship to the patient. An old pair of glasses or pocket amplifier hearing devices may serve as a temporary substitute while a permanent replacement is obtained.

ACUTE MEDICAL PROBLEMS IN SUBACUTE CARE

The subacute population comprises individuals unable to return home after a hospitalization. These are sick, frail, and medically complex patients, which places them at higher risk for the development of an acute medical problem and hospital readmission.

The rate of “bounce backs” varies widely among facilities and practitioners. As discussed earlier in this chapter, reducing hospital readmission is the focus of a variety of efforts. While some acutely ill patients clearly need to go back to the hospital, we will briefly discuss some of the most common acute problems in subacute care, and some of the key issues in determining whether they can be managed at the facility or transferred back to the hospital. The aforementioned INTERACT program focuses on providing clinicians tools to identify and manage various changes in condition in the facility without hospital transfer when safe and feasible.

Fever is perhaps the most common acute problem in this setting. The first step is to determine whether the patient is clinically and hemodynamically stable. A critical factor in managing the patient is whether a physician or APC is on site or not. There of course is no substitute for being at the bedside. However, it is common for issues such as a fever to arise when a physician or advance practice nurse is on site and management decisions are made based on telephone assessments. The collaboration between the nurse on duty and the clinician on call is a unique aspect regarding how care is delivered in the subacute setting. There needs to be excellent timely communication and confidence that the nursing assessment is complete and accurate. Whether the MD or APC is on site or on the phone, the ability to perform a prompt diagnostic work-up is a key issue in determining the need for transfer. In addition to the ubiquitously ordered urinalysis and culture, a targeted physical examination, chest x-ray, and appropriate blood tests should be part of a basic fever work-up. The facility needs to have a reliable vendor such that results can be available in hours, not days. Facilities that can administer prompt intravenous therapy, either for antibiotics and/or fluids to treat concomitant dehydration, are more apt to be successful in managing patient without hospital transfer.

Shortness of breath is another common presenting acute problem in subacute care, with many possible etiologies. Prompt work-up will include examination of the lungs and heart, testing for oxygen saturation, and possible electrocardiogram, or chest x-ray. Treatment may include oxygen, bronchodilator treatments, diuretics, and respiratory therapy. In addition to clinical severity, facility capabilities, and advance directives may determine whether the patient needs to be transferred.

Perhaps the most vexing issue in subacute care is acute mental status change, or incident delirium. This should be distinguished from prevalent or residual delirium that was present at the time of hospital transfer. Proactive measures, such as careful documentation of a baseline mental status examination, are key to the proper management of this problem. If new acute mental status change is detected, prompt and thorough evaluation for adverse drug effects and acute medical problems by a physician or APC is required. Often, medical management is relatively straightforward and should be attempted in the nursing facility when possible. At times, the patient's behavior and inability to cooperate with the staff rather than the medical condition necessitate transfer.

ADVANCE DIRECTIVES AND END-OF-LIFE ISSUES

Every subacute patient should have advance directives reviewed and discussed, including identifying a substitute decision maker and describing advance care wishes. If not already in place, a health care proxy should be completed. Resuscitation status, transfer back to the hospital, and any limits to care, including use of artificial hydration or feeding, should be discussed with the patient and/or family and carefully documented in the medical record and appropriate forms completed based on the specific state regulations. Several stays have implemented documents a process for creating medical orders honored in all-care settings within that state. Two examples are the medical orders for life-sustaining treatment (MOLST) and physician orders for life-sustaining treatment (POLST).

While most of this chapter has focused on patients whose goal is to return home and to premorbid functioning, subacute care is also being increasingly used as a place for the dying. In the past, hospitals would care for patients during the dying process, which may extend from a few days to weeks. Now, however, hospitals face intense pressure to discharge these patients as soon as the decision is made to no longer pursue aggressive medical care. Subacute care facilities have filled a niche for such patients who are unable to go home and can provide a comfortable, supportive environment for the dying patient and the patient's family.

Effectively managing the dying process in the subacute setting requires expertise as well as a team approach. Some facilities have developed palliative care teams to help with pain and symptom management, advance care planning discussions, and to provide spiritual and psychosocial support to the patient and loved ones. Many facilities have affiliations with one or more hospice programs which can be very helpful. Hospice can be challenging in the subacute setting because many of these patients are using their Medicare SNF benefit which includes room and board. Patients may have to forego their SNF benefit to enroll in hospice. Hospice typically does not cover room and board costs and therefore for some patients this can be a barrier to hospice initiation. Effectively integrating a formal hospice program into a subacute setting requires strong leadership and commitment, as well as intensive collaboration and education support between hospice and subacute facility staff. Palliative care is discussed in several chapters in this book, and is the focus of Chapter 55.

DISCHARGE PLANNING IN SUBACUTE CARE

Discharge planning from the subacute setting needs to be individualized; however, a number of basic principles and concepts can be applied to all individuals. Discharge planning should begin on or before admission. Patients should be sent to a subacute facility with clear goals for the stay. Often these goals involve rehabilitation to improve mobility, working toward independence with ADLs, and stabilizing ongoing medical problems. Identifying these goals and the available home supports is helpful in establishing a treatment plan that will reduce barriers to discharge.

A common problem faced by the subacute interdisciplinary team is whether the patient will be safe at home. Common issues are how well someone needs to walk or transfer to be allowed to go home. Autonomy must be balanced with safety. Enlisting extra home supports from family members, friends, and home care agencies, or getting a personal safety alarm, can increase the comfort level of the care team to attempt a discharge to a home setting. Equipment such as walkers, bedside commodes, and wheelchairs may need to be ordered. These require living spaces without excess clutter and adequate doorways. Stairs, railings, and bathrooms may need to be assessed as well. Home modifications such as ramps, grab bars, raised toilet seats, and railings are sometimes needed.

Many people have input into when a patient should be discharged. While the physician has ultimate responsibility for the discharge order, therapists, social workers, insurers, family members, and of course the patient may play a major role in the discharge decision. The physician needs to be skilled at assessing the input received from team members in making this decision. Independence in the ability to transfer, ambulate, perform ADLs, and take

medications properly is not essential if proper supports are in place. The time spent in a subacute setting is an opportunity to clearly discuss, identify, and document end-of-life goals of care.

There is an opportunity when discharging a patient to do a complete review of all medications and treatments. Ideally, this review should be performed by a physician or APC because a facility registered nurse cannot make medication or treatment changes. Removing unnecessary PRN medications, simplifying dosing schedules, writing out prescriptions, and educating on medication taken are just some of the issues that need to be addressed. The facility case manager needs to work with the physician-APC in deciding on the appropriate home care services and ordering them. Communicating with primary care teams who will assume care upon discharge is a critical part of the process. Generating a discharge summary, which is given in a hospital setting, can prove challenging in nursing facilities. Discharge information should be sent to the physician assuming responsibility for the patients' care on discharge and appropriate follow-up appointments should be made.

Sometimes, despite the best efforts of subacute clinicians and facilities, a patient fails to recover sufficiently to return home and needs to be placed in long-term care. This may require discharge to a new nursing home, moving to a different unit within the same facility, or merely "decertification" of a bed. Regardless of the physical arrangement, this change has major financial ramifications because the cost of care must now be borne by the patient, Medicaid, or if this has been purchased, a long-term care insurance provider. At times, it is determined that the patient no longer has skilled medical or rehabilitative needs which terminates the room and board coverage provided by Medicare or another insurer. This process can sometimes be contentious and often requires input from multiple members of the care team including the attending physician. It is best to give the patient and family as much advance notice as possible in these situations, especially if transfer to another facility may be required. Many SNFs provide outpatient rehabilitation and partner with home health agencies to provide continuity at the time of transition back to the community.

RISK MANAGEMENT IN SUBACUTE CARE

There are a number of areas of risk management in nursing facilities that are quite different from those of the ambulatory setting. Practitioners need to educate themselves about these areas of increased risk. As in any clinical situation, documentation is critical to demonstrate that appropriate care has been provided. When there is a lawsuit related to the care of a nursing home patient, the facility is often named as a defendant. The physician might also be named. **Table 19-22** describes common causes of lawsuits against nursing facilities.

TABLE 19-22 COMMON CAUSES OF LITIGATION IN NURSING FACILITIES

Falls with injury
Pressure ulcers
Elopement
Restraints
Weight loss
Physical, emotional, or sexual abuse
Medication errors
Aspiration

SUBACUTE FACILITY REIMBURSEMENT

Beginning in 1999, a dramatic change occurred regarding Medicare nursing home reimbursement, which has driven many individually owned and large national for-profit nursing home chains into bankruptcy. This change in reimbursement is called prospective payment system (PPS). Under PPS, nursing facilities must categorize and group each patient into one of several dozen categories. These categories, or resource utilization groups (RUGs), have different daily rates of reimbursement for the facility from Medicare. The medical, rehabilitation, and nursing needs of each patient must be properly and accurately identified in order to obtain the proper RUG classification. The RUG classification is determined by the minimum data set (MDS). The MDS is an assessment tool used for all nursing home patients, including those receiving subacute care. The MDS assists the facility in developing a plan of care for the

patient, and also identifies the appropriate RUG category.

The reimbursement that the facility receives from Medicare covers essentially all aspects of care, including rehabilitation, laboratory, x-ray, supplies, and pharmacy. Only by effectively managing these ancillary costs can facilities cover their costs. Achieving success under PPS requires excellent identification and documentation of patient needs and function, cost-effective use of x-ray, laboratory, and pharmacy services, including those services provided outside of the facility, such as ambulance, emergency room, and diagnostic services. Managed care contracts, for the most part, are similar to PPS in that the per diem rate covers rehabilitation, x-ray, laboratory, and pharmacy services. Medicaid and private payments are used primarily for long-term institutional care rather than for subacute care.

Subacute physicians and APCs are instrumental in helping nursing facilities succeed under PPS and managed care. The clinical expertise provided by these practitioners enables facilities to better evaluate the scope and severity of clinical conditions for each patient. Having enhanced clinical presence in the nursing facility can help to identify and treat new illnesses sooner, thereby implementing less-costly interventions and avoiding complications and rehospitalizations. For example, identifying and treating pneumonia before the patient becomes delirious, dehydrated, and septic is certainly better for the patient and can lead to a reduced need for intravenous therapies, emergency department visits, ambulance services, and hospitalization. The result is a better financial outcome for the facility, as well as a better clinical outcome for the patient.

REIMBURSEMENT FOR PHYSICIANS

A nursing home practice has some distinct advantages over an office practice. For instance, a nursing home practice can have lower overhead costs. A physician who only practices in SNFs does not have to pay rent on a large office with multiple examination rooms, needs less nursing and administrative staff, and does not have to pay for as much equipment and other office supplies.

Physician billing in nursing facilities is currently based on codes organized into three categories. The first two categories are codes related to discharges and follow-up visits. The third category relates to the performance of a full history and physical examination on admission, or at a yearly physical. Nurse practitioners and physician's assistants can bill Medicare for the care they provide in nursing facilities. At present, the Medicare fee schedule is 85% of the physician payment for the same level of service code. Individual states and insurance carriers may not view coding similarly. It is suggested that physicians learn about coding guidelines in their specific geographic regions. The American Medical Directors Association is an excellent resource for obtaining up-to-date billing information (www.amda.com).

SUBACUTE CARE AS A SAFETY NET

Subacute care is an important setting to provide medical and rehabilitative services, as well as end-of-life and palliative care. The interdisciplinary approach on which subacute care is based should benefit patients and society from both quality of care and cost perspectives. Hospitals are discharging increasingly complex patients just getting over a critical illness, often on new medications, and with functional decline. Many of these patients have conditions that are continuing to evolve in the days immediately posthospital discharge. By providing enhanced clinical support services, the subacute site serves as a safety net in the continuum of care for older persons. A large cadre of physicians and APCs with expertise in managing complex illnesses, as well as strong skills in geriatrics and palliative care, are needed to care for the growing numbers of patients who can benefit from subacute care.

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Chapter 20

Nursing Home Care

Joseph G. Ouslander, Jill Shutes

Learning Objectives

- List the goals of nursing home (NH) care.
- Understand the complexity of caring for residents/patients in NHs, including the differences between short and long stayers.
- Identify the roles and responsibilities of different disciplines in NH care.
- Describe strategies to improve nursing care.
- Summarize key ethical issues in NH care.

Key Clinical Points

1. **The goals of NH care are different than traditional medical care in other settings.**
2. **NH care is provided by a team of health professionals, all of whom have critical input into the resident/patient's care plan.**
3. **Screening and preventive practices are relevant for many long-stay NH residents.**
4. **Several strategies, including collaborative practice among physicians and nurse practitioners (or physician assistants) and innovative use of health information technology, can help improve NH care.**
5. **Determination of decision-making capacity, appropriate utilization of advance directives, and proxy decision makers are critical aspects of NH care.**

The focus of this chapter is the clinical care of nursing home (NH) residents. Many older people who would have otherwise been in NHs are now residing in assisted living facilities or in their own homes. Management of older people with multiple medical problems and geriatric conditions in the NH setting is challenging for a number of reasons. Although many NHs provide excellent care, the poor quality of care provided in many other NHs has been recognized for decades. Since the Institute of Medicine issued its critical report in 1986 and the mandating of the Resident Assessment Instrument in 1987, the overall quality of care has improved. The Centers for Medicare and Medicaid Services (CMS) has instituted several strategies that are designed to improve the quality of NH care. These include the NH Compare website (http://www.medicare.gov/nhcompare/home.asp), which shows consumers (and NHs) how individual homes perform on surveys and specific quality indicators; the new federal survey process employing the Quality Indicator Survey (QIS; http://www.cms.gov); the Five-Star rating system (www.Medicare.gov); and the new requirement in the Affordable Care Act that all NHs must have a Quality Assurance and Performance Improvement (QAPI) program. Despite all of these efforts, the US Office of Inspector General issued a report documenting the high frequency of adverse events among NH residents during the first 1 to 2 months of admission. The report documented that about one in three residents suffer an adverse events (including medication-related side effects; the quality of care such conditions as falls, electrolyte disturbances; and infections) take place. Thus, much remains to be done to improve NH care in the United States.

Because typical older NH residents suffer from multiple underlying diseases, good medical care is especially

important. Despite the logistical and economic barriers that can foster inadequate medical care in the NH, many straightforward principles and strategies can improve the quality of medical care for NH residents. Fundamental to achieving these improvements is a clear perspective on the goals of NH care, which differ in many respects from the goals of medical care in other settings and patient populations.

THE GOALS OF NURSING HOME CARE

The modern NH serves multiple roles. **Table 20-1** lists the key goals of NH care. While the prevention, identification, and treatment of chronic, subacute, and acute medical conditions are important, most of these goals focus on the functional independence, autonomy, quality of life, comfort, and dignity of the residents. Physicians and other clinicians who care for NH residents must consider these goals while the more traditional goals of medical care are being addressed.

TABLE 20-1 GOALS OF NURSING HOME CARE

1. Provide a safe and supportive environment for chronically ill and dependent people.
2. Restore and maintain the highest possible level of functional independence.
3. Preserve individual autonomy.
4. Maximize quality of life, perceived well-being, and life satisfaction.
5. Provide effective rehabilitative, medical, nursing, and psychosocial care to individuals discharged from an acute hospital in order to facilitate their transition to their previous living environment.
6. Provide comfort and dignity for terminally ill patients and their loved ones.
7. Stabilize and delay progression of chronic medical conditions.
8. Prevent acute medical and iatrogenic illnesses, and identify and treat them rapidly when they do occur.

The heterogeneity of the NH population results in a diversity of goals for NH care. NH residents can be subgrouped into five basic types (**Figure 20-1**). While it is not always possible or desirable to isolate these different types of residents geographically, and although residents often overlap or change between the types described, subgrouping NH residents in this manner will help the clinician and interdisciplinary team to focus the care-planning process on the most critical and realistic goals for individual residents. The "short-stay" patient population is largely in the NH for subacute care. Subacute care is discussed in great detail in Chapter 19.

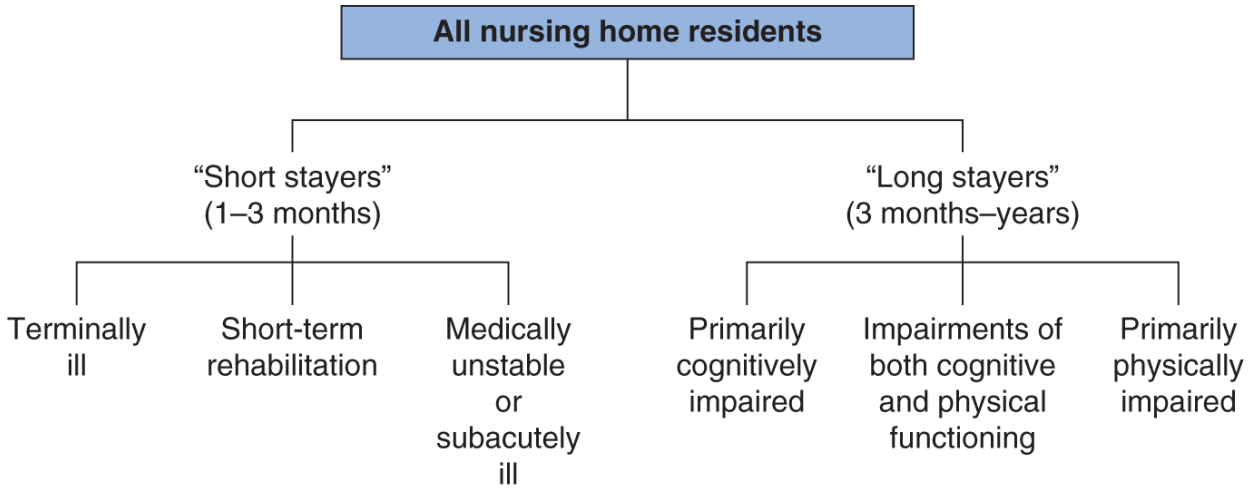


FIGURE 20-1. Basic types of nursing home residents.

The underlying social contract implied by NH admission is quite different for each of the five groups of NH residents illustrated in the figure. In some cases, access to treatment takes precedence over the living environment; in other circumstances, the environment may be the most critical element of care. Those admitted to a NH with the intent of active treatment and discharge home may be willing to accept a living situation akin to that of a hospital in the

expectation that the benefit they receive from treatment will offset any discomfort or inconvenience. For terminally ill persons under the hospice model, the living environment is made as flexible and supportive as possible. Efforts are directed toward making these patients comfortable and permitting them to enjoy, to the extent possible, their last days. For the other groups in the middle of this distribution, attention to making their living situation comfortable and providing active primary care are important. Ideally, a NH should be able to provide what the name implies: high-quality nursing (and medical) care, in a homelike environment.

CLINICAL ASPECTS OF CARE FOR NURSING HOME RESIDENTS

In addition to the different goals for care in the NH, several factors make the assessment and treatment of NH residents different from those in other settings (**Table 20-2**). Many of these factors relate to the process of care and are discussed in the following section. A fundamental difference in NH care compared to care in other settings is that medical evaluation and treatment must be complemented by an assessment and care-planning process involving staff from multiple disciplines. The integral involvement of nurses' aides in the development and implementation of care plans is crucial to high-quality NH care. Data on medical conditions and their treatment are integrated with assessments of the functional, mental, and behavioral status of the resident in order to develop a comprehensive database and individualized plan of care.

TABLE 20-2 ■ FACTORS THAT DISTINGUISH ASSESSMENT AND TREATMENT IN THE NURSING HOME DIFFERENT FROM THAT IN OTHER SETTINGS

1. The goals of care are often different (see **Table 20-1**).
2. Specific clinical disorders are prevalent among nursing home residents (see **Table 20-3**).
3. The approach to health maintenance and prevention differs (see **Table 20-6**).
4. Mental and functional status are just as important, if not more so, than medical diagnoses.
5. Assessment must be interdisciplinary, including:
   a. Nursing
   b. Psychosocial
   c. Rehabilitation
   d. Nutritional
   e. Pharmacy
   f. Other (eg, dental, podiatry, audiology, ophthalmology, spiritual)
6. Sources of information are variable:
   a. Residents often cannot give a precise history.
   b. Family members and nurses' aides with limited assessment skills may provide the most important information.
   c. Information is often obtained over the telephone.
7. Administrative procedures for record keeping in both nursing homes and acute care hospitals can result in inadequate and disjointed information.
8. Clinical decision making is complicated for several reasons:
   a. Many diagnostic and therapeutic procedures are expensive, unavailable, or difficult to obtain and involve higher risks of iatrogenic illness and discomfort than are warranted by the potential outcome.
   b. The potential long-term benefits of "tight" control of certain chronic illnesses (eg, diabetes mellitus, congestive heart failure, hypertension) may be outweighed by the risks of iatrogenic illness in many very old and functionally disabled residents.
   c. Many residents are not capable (or are questionably capable) of participating in medical decision making, and their personal preferences based on previous decisions are often unknown (see **Table 20-7**).
9. The appropriate site for and intensity of treatment are often difficult decisions involving medical, emotional, ethical, economic, and legal considerations that may be in conflict with each other in the nursing home setting.
10. Logistic considerations, resource constraints, and restrictive reimbursement policies may limit the ability of and incentives for physicians to carry out optimal medical care of nursing home residents.

Medical evaluation and clinical decision making for NH residents are complicated for several reasons. Unless the physician has cared for the resident before NH admission, it may be difficult to obtain a comprehensive medical database. Residents may be unable to relate their medical histories accurately or to describe their symptoms, and medical records are frequently unavailable or incomplete, especially for residents who have been transferred between NHs and acute care hospitals. When acute changes in condition occur, initial assessments are often performed by NH staff with limited skills and are communicated to clinicians (physicians, nurse practitioners, physician assistants) by telephone. Even when the diagnoses are known or strongly suspected, many diagnostic procedures and treatments among NH residents are associated with an unacceptably high risk-benefit ratio. For example, an imaging study may require sedation with its attendant risks; nitrates and other cardiovascular drugs may precipitate syncope or disabling falls in frail ambulatory residents with baseline postural hypotension; and adequate control of blood sugar may be extremely difficult to achieve without a high risk for hypoglycemia among cognitively impaired diabetic residents with marginal or fluctuating nutritional intake, who may not recognize or complain of hypoglycemic symptoms.

Further compounding these challenges is the inability of many NH residents to participate effectively in important decisions regarding their medical care. Their previously expressed wishes are often not known, and an appropriate or legal surrogate decision maker has often not been appointed. These issues are further discussed in Chapter 30.

Table 20-3 lists the most commonly encountered clinical disorders in the NH population. They represent a broad spectrum of chronic medical illnesses; neurologic, psychiatric, and behavioral disorders; and problems that are especially prevalent in frail older adults (eg, incontinence, falls, nutritional disorders, chronic pain syndromes). The management of many of the conditions listed in **Table 20-3** is discussed in some detail in other chapters of this book.

TABLE 20-3 COMMON CLINICAL DISORDERS IN THE NURSING HOME POPULATION

Medical conditions
Congestive heart failure
Degenerative joint disease
Diabetes mellitus
Gastrointestinal disorders
Reflux esophagitis
Constipation
Diarrhea
Gastroenteritis
Infections
Respiratory
Urinary
Skin
Conjunctivitis
Kidney disease (chronic kidney disease, renal failure)
Lung disease (chronic obstructive, emphysema, asthma)
Malignancies
Neuropsychiatric conditions
Dementia
Depression
Behavioral disorders associated with dementia
Agitation
Aggression
Depression
Neurologic disorders other than dementia
Stroke
Parkinsonism

- Multiple sclerosis
- Brain or spinal cord injury
- Pain: musculoskeletal conditions, neuropathies, malignancy
- Geriatric conditions and syndromes
  - Delirium
  - Incontinence
  - Gait disturbances, instability, falls
  - Malnutrition, feeding difficulties, dehydration
  - Pressure sores
  - Insomnia
- Functional disabilities necessitating rehabilitation
  - Stroke
  - Hip fracture
  - Joint replacement
  - Amputation
- Iatrogenic disorders
  - Adverse drug reactions
  - Falls
  - Nosocomial infections
  - Induced disabilities
  - Restraints and immobility, catheters, unnecessary help with basic activities of daily living
- Palliative care and end-of-life care

PROCESS OF CARE IN THE NURSING HOME

The process of care in NHs is strongly influenced by numerous state and federal regulations, the highly interdisciplinary nature of NH residents' problems, and the training and skills of the staff that delivers most of the hands-on care. Federal rules and regulations contained in the Omnibus Budget Reconciliation Act of 1987 (OBRA, 1987) and implemented in 1991 place heavy emphasis on assessment and care planning as a means of achieving the highest practicable level of functioning for each resident and the use of the Resident Assessment Instrument. The minimum data set (MDS), recently updated to version 3.0, is the foundation of clinical assessment and care planning for individual residents. In addition to the MDS, each resident or responsible health care proxy should be assisted in articulating the goal for their NH care (ie, short-term rehabilitation and/or medical and nursing management of unstable medical conditions with the goal of returning home; long-term care of chronic conditions; or palliative or hospice care). Detailed guidance for state and federal surveyors has been developed for several clinical care areas, such as unnecessary drugs and urinary incontinence. Failure to adhere to the clinical recommendations contained in the regulations and related surveyor guidance can result in citations and, in some instances, financial penalties for the NH. Failure to appropriately manage medical conditions in the NH puts the facility and physician at risk for lawsuits.

Physician involvement in NH care and the nature of medical assessment and treatment offered to NH residents are often limited by logistic and economic factors. Few physicians have offices based either inside the NH or in close proximity to the facility. Many physicians who do visit NHs care for relatively small numbers of residents, often in several different facilities. Many NHs, therefore, have numerous physicians who make rounds once or twice per month, who are not generally present to evaluate acute changes in resident status, and who attempt to assess these changes over the telephone. Practice patterns are shifting to a model of physician-nurse practitioner practices caring for large numbers of residents in several NHs. Such physician-nurse practitioner teams have been shown to improve care and reduce hospitalization rates.

Many NHs do not have ready availability of laboratory, radiologic, and pharmacy services with the capability of rapid response, further compounding the logistics of evaluating and treating acute changes in medical status. Thus, NH

residents are often sent to hospital emergency rooms, where they are evaluated by personnel who are generally not familiar with their baseline status and who frequently lack training and interest in the care of frail and dependent residents patients.

Medicare and Medicaid reimbursement policies also dictate certain patterns of NH care. While physicians are required to visit NH residents only every 30 to 60 days, many residents require more frequent evaluation and monitoring of treatment, especially with the shorter acute care hospital stays brought about by the prospective payment system. While Medicare reimbursement for physician visits in NHs has improved, reimbursement for a routine visit is sometimes inadequate for the time that is required to provide good medical care in the NH, including travel to and from the facility; assessment and treatment planning for residents with multiple problems; communication with members of the interdisciplinary team and the resident's family; and proper documentation in the medical record. Activities often essential to good care in the NH, such as attendance at interdisciplinary conferences, family meetings, complex assessments of decision-making capacity, and counseling residents and proxy decision makers on treatment plans in the event of terminal illness, are often not reimbursable at all. Medicare intermediaries sometimes restrict reimbursement for rehabilitative services for residents not covered under Part A skilled care, thus limiting the treatment options for many residents. Although Medicaid programs vary considerably, many provide minimal coverage for ancillary services that are critical for optimum medical care, and may restrict reimbursement for several types of drugs that may be especially helpful for NH residents.

Amid these logistic and economic constraints, expectations for the care of NH residents are high. **Table 20-4** outlines the various types of assessment generally recommended for the optimal care of NH residents. Physicians are responsible for completing an initial assessment within 1 week of admission and for monthly visits thereafter for the next 90 days. More frequent visits are often necessary for residents admitted on a Medicare Part A skilled nursing benefit. Licensed nurses assess new residents as soon as they are admitted, on a daily basis, and generally summarize the status of each resident weekly. The nationally mandated MDS must be completed within 14 days of admission and updated when a major change in status occurs; several sections must be routinely updated on a quarterly basis. The MDS is intended to assist NH staff in identifying important clinical problems that need further evaluation, management, and monitoring. It is also used as the basis for calculating daily reimbursement rates for residents on the Medicare Part A skilled benefit by generating a Resource Utilization Group (RUG) that reflects case mix and needed staffing levels, and as the basis for calculating various quality measures, including those on the NH Compare website and those used for the Five-Star rating system.

TABLE 20-4 IMPORTANT ASPECTS OF VARIOUS TYPES OF ASSESSMENT IN THE NURSING HOME

TYPE OF ASSESSMENT	TIMING	MAJOR OBJECTIVES	IMPORTANT ASPECTS
Medical initial	Within 72 h to 1 wk after admission	Verify medical diagnoses Medication reconciliation Document baseline physical findings, mental and functional status, vital signs, and skin condition Attempt to identify potentially remediable, previously unrecognized medical conditions Get to know the resident and family (if this is a new resident) Establish goals for the admission and a medical treatment plan	A thorough review of medical records and physical examinations is necessary Relevant medical diagnoses and baseline findings should be clearly and concisely documented in the patient's record Medication lists should be carefully reviewed and only essential medications continued Request for specific types of assessment and input from other disciplines should be made A database should be established (see example in Figure 20-2)
Periodic	Monthly or every other month	Monitor progress of active medical conditions Update medical orders Communicate with patient and	Progress notes should include clinical data relevant to active medical conditions and focus on changes in status

		nursing home staff	Unnecessary medications, orders for care, and laboratory tests should be discontinued Mental, functional, and psychosocial status should be reviewed with nursing home staff and changes from baseline noted The medical problem list should be updated
As needed	When acute changes in status occur	Identify and treat causes of acute changes	Onsite clinical assessment by the physician (or nurse practitioner or physician's assistant), as opposed to telephonic consultations, will result in more accurate diagnoses, more appropriate treatment, and fewer unnecessary emergency room visits and hospitalization Vital signs, food and fluid intake, and mental status often provide essential information Infection, dehydration, and adverse drug effects should be at the top of the differential diagnosis for acute changes in status
Major reassessment	Annual	Identify and document any significant changes in status and new potentially remediable conditions	Targeted physical examination and assessment of mental, functional, and psychosocial status and selected laboratory tests should be done (see Table 20-6)
Nursing	On admission, and then routinely with monitoring of daily and weekly progress Minimum data set on admission; update when major change in status occurs and annually; update selected sections quarterly	Identify biopsychosocial and functional status, strengths, and weaknesses Develop an individualized care plan Document baseline data for ongoing assessments	Particular attention should be given to emotional state, personal preferences, and sensory function Careful observation during the first few days of admission is important to detect effects of relocation Potential problems related to other disciplines should be recorded and communicated to appropriate members of the interdisciplinary care team
Psychosocial	Within 1–2 wk of admission and as needed thereafter	Identify any potentially serious psychosocial signs and symptoms and refer to mental health professional if appropriate Determine past social history, family relationships, and social resources Become familiar with personal preferences regarding living arrangements	Getting to know the family and their preferences and concerns is critical to good nursing home care Relevant psychosocial data should be communicated to the interdisciplinary team Discharge potential should be assessed
Rehabilitation (physical and occupational therapy)	On admission and daily or weekly thereafter (depending on the rehabilitation care plan)	Determine functional status as it relates to basic activities of daily living Identify specific goals and time frame	Small gains in functional status can improve chances for discharge as well as quality of life Not all residents have areas in which

		for improving specific areas of function Monitor progress toward goals Assess progress in relation to potential discharge	they can reasonably be expected to improve; strategies to maintain function should be developed for these residents Assessment of and recommendation for modifying the environment can be critically important for improving function and discharge planning
Nutritional	Within days of admission and then periodically thereafter	Determine nutritional status and needs Identify dietary preferences Plan an appropriate diet	Restrictive diets may not be medically necessary and can be unappetizing Weight loss should be identified and reported to nursing and medical staff
Pharmacy	Within days of admission and periodically	Medication reconciliation and drug regimen review	Check for high-risk medications, appropriate indications, drug-drug and drug-disease interactions, stop dates, monitoring parameters
Interdisciplinary care plan	Within 1–2 wk of admission and every 3 mo thereafter	Identify interdisciplinary problems Establish goals and treatment plans Determine when maximum progress toward goals has been reached	Each discipline should prepare specific plans for communication to other team members based on their own assessment
Capacity for medical decision making	Within days of admission and then whenever changes in status occur	Determine which types of medical decisions the resident is capable of participating in A resident who is still capable of making decisions independently should be encouraged to identify a surrogate decision maker in the event the resident later loses this decision-making capacity If the resident lacks capacity for many or all decisions, appropriate surrogate decision makers should be identified (if not already done)	Residents with varying degrees of dementia may still be capable of participating in many decisions regarding their medical care Attention should be given to potentially reversible factors that can interfere with decision-making capacity (eg, depression, fear, delirium, metabolic and drug effects) Concerns of the family and health professional should be considered, but the resident's desires should be paramount The resident's capacity may fluctuate over time because of physical and emotional conditions
Preferences regarding treatment intensity and nursing home routines	Within days of admission and periodically thereafter	Determine residents' wishes as to the intensity of treatment they would want in the event of acute or chronic progressive illness	Attempt to identify specific procedures the resident would or would not want This assessment is often made by ascertaining the resident's prior-expressed wishes (if known), or through surrogate decision makers (legal guardian, durable power of attorney for health care, family)

The extent of involvement of other disciplines in the assessment and care-planning process varies depending on the residents' problems, the availability of various professionals, and state regulations. Representatives from nursing, social services, dietary activities, and rehabilitation therapy (physical and/or occupational) participate in an interdisciplinary care-planning meeting. Residents are generally discussed at this meeting within 2 weeks of admission and quarterly thereafter. The product of these meetings is an interdisciplinary care plan that separately lists interdisciplinary problems (eg, restricted mobility, incontinence, wandering, diminished food intake, poor social interaction), goals for the resident related to the problem, approaches to achieving these goals, target dates for

achieving the goals, and assignment of responsibilities for working toward the goals among the various disciplines. These care plans are an important force in driving nursing staff behavior and expectations and should be reviewed by the primary physician.

STRATEGIES TO IMPROVE MEDICAL CARE IN NURSING HOMES

Better medical care of NH residents should lead to fewer exacerbations of chronic illnesses, iatrogenic conditions, and other adverse events, and hence lower use of emergency rooms and hospitals. Several strategies might improve the process of medical care delivered to NH residents. Four strategies are briefly described: (1) improved documentation practices; (2) a systematic approach to screening, health maintenance, and preventive practices for the frail, dependent NH population; (3) use of nurse practitioners or physicians' assistants; and (4) practice guidelines and related quality improvement activities.

In addition to these strategies, strong leadership of a medical director who is appropriately trained and dedicated to improving the facilities' quality of medical care is essential in order to develop, implement, and monitor policies and procedures for medical services. Certification through the American Medical Directors Association (AMDA)—the Society for Post-Acute and Long-Term Care Medicine should be encouraged (http://www.amda.com). The medical director should set standards for medical care and serve as an example to the medical staff by caring for some of the residents in the facility. He/she should also be involved in various committees (eg, quality, infection control), and should try to involve interested medical staff in these committees, as well as in educational efforts through formal in-service presentations, teaching rounds, and appropriate documentation procedures. Federal quality measures, as well as other quality indicators, developed through literature review and expert consensus can be used to track improvements in medical and overall care in the NH setting. Medical directors should use these indicators and other approaches in their quality improvement programs.

Documentation Practices

Electronic health records specific for NHs are now widely available, and when used properly can greatly improve clinical documentation. Critical aspects of a NH resident's health status should be recorded on a face sheet of the medical record. **Figure 20-2** shows an example of a format for a face sheet. Additional standardized documentation should contain social information, such as individuals to contact at critical times and information about the resident's treatment status in the event of acute illness. These data are essential to the care of the resident and should be readily available in one place in the record, so that when emergencies arise, when medical consultants see the resident, or when members of the interdisciplinary team need an overall perspective, they are easy to locate. The face sheet should be copied and sent to the hospital or other health care facilities to which the resident might be transferred. Time and effort are required in order to keep the face sheet updated. Electronic health records can facilitate incorporating the face sheet into a database and updating it periodically.

Health Summary for Long-Stay Nursing Home Residents

Active Medical Problems

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____

Hospitalizations (last 12 months)

1. _____
2. _____
3. _____
4. _____

Major Past Surgical Procedures

Year

1. _____
2. _____
3. _____
4. _____

Allergies

1. _____
2. _____

Cognitive Status

1. Dementia? ____ **Yes** ____ **No**

a. If yes, type:

____ Alzheimer's ____ Lewy Body
____ Multi-infarct ____ Other
____ Parkinson's ____ Uncertain

b. If yes, behavioral symptoms?

____ **Yes** ____ **No**

If yes, describe:

_____
_____
_____
_____

2. Usual mental status

___ Alert, oriented, follows simple instructions
___ Alert, *dis*oriented, but *can* follow simple directions
___ Alert, *dis*oriented, *cannot* follow simple directions
___ Not alert (lethargic, comatose)

3. Most recent mental status test score if available:

Test _____ **Score** _____

Functional Status

A. Ambulation

__ Independent
__ With cane
__ With Walker
__ Unable

Transfer: __ Ind __ Dep

B. Continence

	Cont	Inc
Urine	___	___
Stool	___	___

C. Vision

__ Adequate for regular print
__ Impaired, can see large print
__ Severely impaired

D. Hearing

__ Adequate
__ Minimal Difficulty
__ Hears only with amplifier or aid

Date Updated	Name of updating clinician
___/___/_____	_____
___/___/_____	_____
___/___/_____	_____
___/___/_____	_____

Advanced Care Planning/Directives

1. Date of most recent relevant progress note, if available __/__/____

2. Decision Making Status

___ Capable of making health decisions
___ Can participate with proxy involvement
___ Proxy makes decisions

3. Care limiting orders

a. Refer to POLST, MOLST, POST if available

b. Specific orders

__ DNR __ Do not hospitalize
__ Other _____

4. Proxy Health Care Decision Maker

Name _____
Relationship _____
Contact No. _____

FIGURE 20-2. Example of a face sheet for a nursing home medical record. (From Kane RL, Ouslander J, Abrass I, Resnick B. *Essentials of*

Clinical Geriatrics. 7th ed. New York, NY: McGraw-Hill Education; 2013, Figure 16-2.)

Handwritten medical documentation in progress notes for routine visits and assessments of acute changes is frequently scanty, uninformative, and/or illegible. Statements such as "stable" or "no change" are too frequently the only documentation for routine visits. While time constraints may preclude extensive notes, certain standard information should be documented. The SOAP (*s*ubjective, *o*bjective, *a*ssessment, *p*lan) format for charting routine notes is especially appropriate for NH residents (**Table 20-5**). Simple forms, flow sheets, or databases with word-processing capabilities can be used to enable physicians to efficiently produce legible, concise, yet comprehensive progress notes.

TABLE 20-5 SOAP FORMAT FOR MEDICAL PROGRESS NOTES ON NURSING HOME RESIDENTS

Subjective	New complaints
	Symptoms related to active medical conditions
Objective	General appearance and mood
	Weight
	Vital signs
	Physical findings relevant to new complaints and active medical conditions
	Laboratory data
	Reports from nursing staff
	Progress in rehabilitative therapy (if applicable)
	Reports of other interdisciplinary team members
	Consultant reports
Assessment	Presumptive diagnosis(es) for new complaints or changes in status
	Stability of active medical conditions
	Responses to psychotropic medications (if applicable)
Plans	Changes in medications or diet
	Nursing interventions (eg, monitoring of vital signs, skin care)
	Assessments by other disciplines
	Consultants
	Laboratory studies
	Discharge planning (if relevant)

Another area where medical documentation is often inadequate relates to the residents' decision-making capacity and treatment preferences. These issues are discussed briefly at the end of this chapter as well as in Chapter 30. In addition to placing critical information in a standardized format in readily accessible locations, it is essential that physicians thoroughly and legibly document all discussions they have had with the resident, family, or legal guardians; they must also document any durable power of attorney for health care about these issues. Failure to do so may result not only in poor communication and inappropriate treatment, but also in substantial legal liability. Notes about these issues should not be removed from the medical record and are probably best kept on a separate page behind the face sheet.

All of these recommendations can and should be incorporated into electronic medical records as NHs increasingly begin to utilize health information technology. AMDA (http://www.amda.com) and the Interventions to Reduce Acute Care Transfers (INTERACT) quality improvement program (http://interact.fau.edu) have examples of tools that can help improve documentation of clinical care in the NH and that can be integrated into electronic health records.

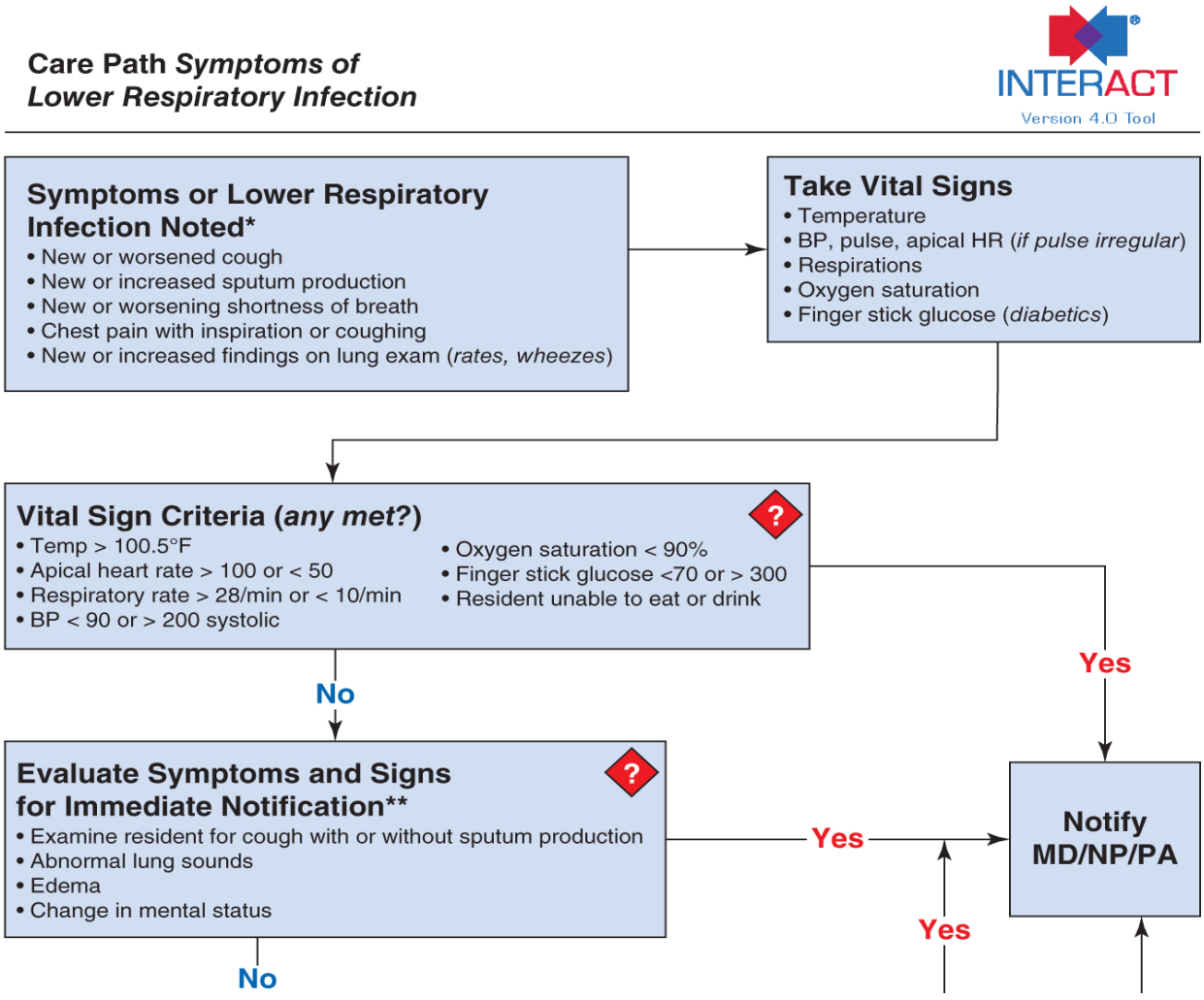
Screening, Health Maintenance, and Preventive Practices

A second approach to improving medical care in NHs is developing and implementing selected screening, health maintenance, and preventive practices in order to delay or prevent exacerbations of chronic medical conditions. **Table**

20-6 lists examples of such practices. With few exceptions, the efficacy of these practices has not been well studied in the NH setting. In addition, not all the practices listed in this table are relevant for every NH resident. For example, some of the annual screening examinations are inappropriate for short-stayers or for many long-stay residents with end-stage dementia or other end-stage diseases. Thus, the practices outlined in **Table 20-6** must be tailored to the specific NH population, as well as for the individual resident, and must be creatively incorporated into routine care procedures as much as possible in order to be time-efficient, cost-effective, and reimbursable by Medicare.

Nurse Practitioners and Physician Assistants

A third strategy that may help to improve medical care in NHs is making greater use of nurse practitioners and physician assistants. This approach appears to be cost-effective in both managed care and fee-for-service settings. These health professionals may be especially helpful in carrying out specific functions in the NH setting. Physician assistants and nurse practitioners can bill for services under fee-for-service Medicare and individual facilities and/or physician groups can hire them on a salaried basis. Nurse practitioners may have an especially helpful perspective in interacting with nursing staff about the nonmedical aspects of care for NH residents. Nurse practitioners and physician's assistants can be very helpful in implementing some of the screening, monitoring, and preventive practices outlined in **Table 20-6**, and in communicating with interdisciplinary staff, families, and residents at times when the physician is not in the facility. One of the most appropriate roles for nurse practitioners and physicians' assistants is in the initial assessment of acute or subacute changes in resident condition. They can perform a focused history and physical examination, and can order appropriate diagnostic studies. The INTERACT quality improvement program has several care paths for this purpose that address 10 of the most common conditions associated with hospital transfers, one of which is shown in **Figure 20-3**. Use of such care paths and other tools available through the INTERACT website (http://interact.fau.edu), as well as through AMDA, enables the onsite assessment of acute change, the detection and treatment of new problems early in their course, more appropriate utilization of acute care hospital emergency rooms, and the rapid identification of residents who need to be hospitalized.



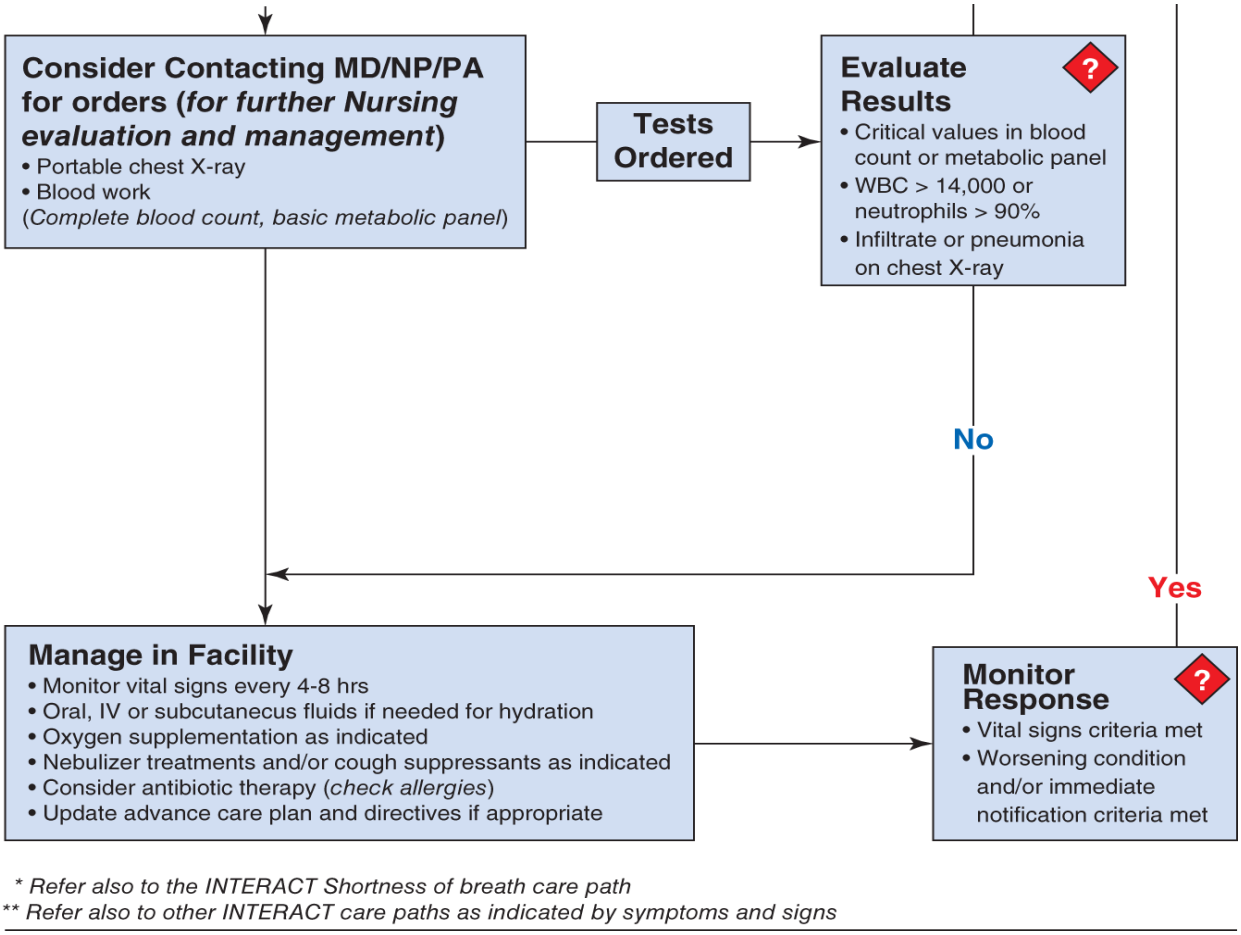


FIGURE 20-3. Example of 1 of 10 INTERACT (Interventions to Reduce Acute Care Transfers) program care paths for managing acute change in condition in a nursing home. (Reproduced from http://interact.fau.edu, with permission.)

TABLE 20-6 ■ SCREENING, HEALTH MAINTENANCE, AND PREVENTIVE PRACTICES IN THE NURSING HOME FOR LONG-STAY RESIDENTS

PRACTICE	RECOMMENDED FREQUENCY[a]	COMMENT
SCREENING		
History and physical examination	Yearly	Focused examination including rectal, breast, and, in some women, pelvic examination
Weight	Monthly	Generally required Persistent weight loss should prompt a search for treatable medical, psychiatric, and functional conditions
Functional status assessment, including gait and mental status testing and screening for depression	Yearly	Functional status assessed periodically by nursing staff using the minimum data set (MDS) Systematic global functional assessment done at least yearly using MDS to detect potentially treatable conditions (or prevent complications) such as early dementia, depression, gait disturbances, urinary incontinence
Visual screening	Yearly	Assess acuity, intraocular pressure, identify correctable problems
Auditory	Yearly	Identify correctable problems
Dental	Yearly	Assess status of any remaining teeth, fit of dentures, and identify any pathology
Podiatry	Yearly	More frequently in diabetics and residents with peripheral

		vascular disease Identify correctable problems and ensure appropriateness of shoes
Tuberculosis	On admission and yearly (may vary by state)	All residents and staff should be tested Booster testing recommended for nursing home residents
Laboratory tests Stool for occult blood Complete blood count Fasting glucose Electrolytes Renal function tests Albumin, calcium, phosphorus Thyroid function tests	Yearly	Not all tests are appropriate for individual residents
MONITORING IN SELECTED RESIDENTS		
All residents		
Vital signs, including weight	Monthly	More often if unstable or subacutely ill
Diabetes Fasting and postprandial glucose, glycosylated hemoglobin ($HgbA_{1C}$)	Every 1–2 mo when stable (fasting) Every 4–6 mo ($HgbA_{1C}$)	Sliding scale insulin should be avoided. Periodic glucometer testing can be useful, but should not be overused for stable residents
Residents on diuretics or with renal insufficiency: electrolytes, BUN, creatinine	Every 2–3 mo	Nursing home residents are more prone to dehydration, azotemia, hyponatremia, and hypokalemia
Anemic residents who are on iron replacement or who have hemoglobin <10: hemoglobin/hematocrit	Monthly until stable, then every 2–3 mo	Iron replacement and/or erythropoietin should be discontinued once hemoglobin value stabilizes
Blood level of drug for residents on specific drugs, for example: Anticonvulsants Digoxin Lithium	Every 3–6 mo	More frequently if drug treatment has just been initiated
PREVENTION		
Influenza vaccine	Yearly	All residents and staff with close resident contact should be vaccinated
Oseltamivir, zanamivir	Within 24–48 h of outbreak of suspected influenza	Residents and staff should be treated throughout outbreak
Zoster vaccination	Once	Selected residents
Pneumococcal vaccine	Once	All residents who have not had the vaccine
Tetanus booster	Every 10 y, or every 5 y with tetanus-prone wounds	Many older people have not received primary vaccinations; they require tetanus toxoid, 250–500 units of tetanus immune globulin, and completion of the immunization series with toxoid injection 4–6 wk later and then 6–12 mo after the second injection
Tuberculosis Isoniazid 300 mg/d for 9–12 mo	Skin-test conversion in selected residents	Residents with abnormal chest film (more than granuloma), diabetes, end-stage renal disease, hematologic malignancies,

		steroid or immunosuppressive therapy, or malnutrition should be treated
Antimicrobial prophylaxis for residents at risk	Generally recommended for dental procedures, genitourinary procedures, and most operative procedures	Chronically catheterized residents should not be treated with continuous prophylaxis
Body positioning and range of motion for immobile residents	Ongoing	Frequent turning of very immobile residents is necessary to prevent pressure sores Semiupright position is necessary for residents with swallowing disorders or enteral feeding to help prevent aspiration Range of motion to immobile limbs and joints is necessary to prevent contractures
Infection-control procedures and surveillance	Ongoing	Policies and protocols should be in effect in all nursing homes Surveillance of all infections should be continuous to identify outbreaks and resistance patterns
Environmental safety	Ongoing	Appropriate lighting, colors, and the removal of hazards for falling are essential in order to prevent accidents Routine monitoring of potential safety hazards and accidents may lead to alterations that may prevent further accidents

[a]Frequency may vary depending on resident's condition. Not all recommendations are relevant to every resident.

Clinical Practice Guidelines and Quality Improvement Activities

Several clinical practice guidelines relevant to NH care have been developed by the AMDA (http://www.amda.com). In addition, quality indicators for a number of conditions have been developed. While these guidelines and quality indicators are largely based on expert opinion rather than on controlled clinical trials, they are helpful as a basis for standards of practice that will improve care. Implementation and maintenance of clinical practice guidelines can be challenging in NHs, as it is in other practice settings. NHs are required to have an ongoing quality assurance committee, and as mentioned above, new federal regulations require an active QAPI program. Principles of continuous quality improvement (CQI) engage front-line staff to monitor objective outcomes (such as the frequency of falls, severity of incontinence, adverse drug reactions, and skin problems) and to identify work processes that can be modified to continuously improve these outcomes. NH administrators, directors of nursing, and medical directors must create an environment that provides incentives for ongoing CQI activities in order to maintain these programs over time. The Medicare Quality Improvement Organization (QIO) program as well as AMDA and its journal have substantial resources for assisting NH providers with quality improvement initiatives. In addition, CMS provides educational resources and tools for NHs to help them meet the QAPI requirement (http://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/QAPI/nhqapi.html).

POSTACUTE CARE AND THE NURSING HOME–ACUTE CARE HOSPITAL INTERFACE

The increasing acuity of NH residents, a high incidence of acute conditions, and the need for high levels of skilled postacute care will continue to place increased demands on NHs. Medicare-managed care and new reimbursement approaches such as bundled payments and accountable care organizations are incentivizing NHs to provide more and more high-level skilled care. The term *postacute care* has many connotations; for the purposes of this chapter, it refers to skilled care reimbursed by Medicare Part A (or by a capitated system) in a free-standing NH. Caring for patients in a free-standing NH who are recovering from an acute illness and hospitalization intensifies many of the challenges already alluded to in this chapter (see **Table 20-2**). This level of care requires greater involvement of physicians, nurse practitioners, and physician assistants; nursing staff trained for more acute patients; ready availability of ancillary services such as laboratory, x-ray, physical and respiratory therapy; and more intensive discharge planning. Moreover, Medicare reimbursement for Part A services is "bundled," so that NHs will be at financial risk for services that are

ordered by medical staff, including drugs, laboratory tests, x-rays, and therapies. This reimbursement structure requires close cooperation between physicians and NH administrators in order to make this form of subacute care economically viable. Subacute care is discussed in detail in Chapter 19.

As a result of the increasing acuity and frailty of the NH resident population, transfer back and forth between the NH and one or more acute care hospitals is common. About one in five NH residents admitted from a hospital are readmitted to the hospital within 30 days. Transfer to an acute care hospital is often a disruptive process for a chronically or subacutely ill NH resident, and is especially hazardous for NH residents with dementia. In addition to the effects of the acute illness, NH residents are subject to acute mental status changes and a myriad of potential iatrogenic problems. The most prevalent of these iatrogenic problems are related to immobility, including deconditioning with resulting difficulty regaining ambulation and/or transfer capabilities, hospital-acquired infections, incontinence and catheter use, polypharmacy and adverse drug effects, delirium, and the development of pressure ulcers.

Because of the risks of acute care hospitalization, the decision to transfer a resident to the emergency room or hospitalize a resident must carefully balance a number of factors. A variety of medical, administrative, logistic, economic, and ethical issues can influence decisions to hospitalize NH residents. Decisions regarding hospitalization often boil down to the capabilities of medical care providers and the NH staff to provide services in the NH, the preferences of the resident and the family, and the logistic and administrative arrangements for acute hospital care. If, for example, the NH staff has been trained and has the personnel to institute intravenous therapy without detracting from the care of the other residents, or if it has arranged for an outside agency to oversee intravenous therapy and there is a nurse practitioner or physician's assistant to perform follow-up assessments, the resident with an acute infection who is otherwise medically stable may best be managed in the NH. Better advance care planning and advance directive use can also help to avoid unnecessary hospitalization of severely impaired NH residents when the palliative or hospice care may be more appropriate than hospital transfer.

As a result of the Affordable Care Act, multiple health care reform initiatives are under way in the United States to reduce unnecessary transfers of NH residents to hospitals, with a particular focus on potentially avoidable emergency department visits, hospitalizations, and hospital readmissions. The changes in Medicare payment mentioned earlier will provide potent financial incentives for better coordinated care at the NH hospital interface. Savings from such programs can be shared with providers to make further improvements in care. Expansion of the Program of All-Inclusive Care for the Elderly (PACE) or statewide programs for dually eligible Medicare and Medicaid beneficiaries will also incentivize better transitional care and will address the problematic cost-shifting that currently occurs between the Medicare and Medicaid programs.

AMDA has developed a clinical practice guideline and related tools on care transitions (http://www.amda.com/tools/clinical/TOCCPG/index.html). The INTERACT program includes educational resources and tools that have been developed and have shown promise in reducing unnecessary hospital transfers (http://interact.fau.edu). The INTERACT program uses several basic strategies to improve the management of acute changes in condition and prevent unnecessary hospital transfers: (1) proactive identification of conditions before they become severe enough to require hospital care (eg, dehydration, delirium); (2) management of some conditions (eg, pneumonia, congestive heart failure) without transfer when safe and feasible; (3) improving advance care planning in order to consider palliative or comfort care as an alternative when the risks of hospitalization may outweigh the benefits; (4) improved documentation practices; (5) improved communication within the NH and between the NH and the hospital; and (6) embedding these strategies within everyday care, including within electronic health records.

ETHICAL ISSUES IN NURSING HOME CARE

Ethical issues arise as much or more in the day-to-day care of NH residents as in the care of patients in any other setting. These issues are discussed in Part IV of this textbook. **Table 20-7** outlines several common ethical dilemmas that occur in the NH. Although most attention has been directed toward those marginally able to express their preferences, important daily ethical dilemmas also face those who are capable of decision making. These more subtle problems are easily overlooked. Physicians, nurse practitioners, and physicians' assistants providing primary care must serve as strong advocates for the autonomy and quality of life for NH residents.

TABLE 20-7 COMMON ETHICAL ISSUES IN THE NURSING HOME[a]

ETHICAL ISSUE	EXAMPLES
Preservation of autonomy	Choices in many areas are limited in most nursing homes (eg, mealtimes, sleeping hours)
	Families, physicians, and nursing home staff tend to be paternalistic
Decision-making capacity	Many nursing home residents are incapable or are questionably capable of participating in decisions about their care
	There are no standard methods of assessing decision-making capacity in this population
Surrogate decision making	Many nursing home residents have not clearly stated their preferences or appointed a surrogate before becoming unable to decide for themselves
	Family members may be in conflict, have hidden agendas, or be incapable of or unwilling to make decisions
Quality of life	This concept is often entered into decision making, but it is difficult to measure, especially among those with dementia
	Ageist biases can influence perceptions of nursing home residents' quality of life
Intensity of treatment	A range of options must be considered, including cardiopulmonary resuscitation and mechanical ventilation, hospitalization, treatment of specific conditions (eg, infection) in the nursing home without hospitalization, enteral feeding, comfort, or supportive care only

[a]See Part IV of this text for further information.

NHs care for a high concentration of individuals who are unable or are questionably capable of participating in decisions concerning their current and future health care. Among these same individuals, severe functional disabilities and terminal illnesses are prevalent. Thus, questions regarding individual autonomy, decision-making capacity, surrogate decision makers, and the intensity of treatment that should be given at the end of life arise on a daily basis. These questions are both troublesome and complex, but must be dealt with in a straightforward and systematic manner in order to provide optimal medical care to NH residents within the context of ethical principles and state and federal laws. NHs should be encouraged to develop their own ethics committees or to participate in a local existing committee in another facility. Ethics committees can be helpful in educating staff; developing, implementing, and monitoring policies and procedures; and providing consultation in difficult cases.

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The American Medical Directors Association (http://www.amda.com)
Interventions to Reduce Acute Care Transfers (INTERACT) (http://interact.fau.edu)
Long-Term Care Focus (http://ltcfocus.org)
National Association of Directors of Nursing Administration (http://www.nadona.org)
NH Regulations Plus (http://www.hpm.umn.edu/nhregsplus)

Chapter 21

Community-Based Long-Term Services and Support and Home Care

Jennifer Hayashi, Jessica Colburn, Bruce Leff

Learning Objectives

- Recognize the scope, nature, and heterogeneity of community-based long-term services and support (CBLTSS) in the United States.
- Describe the semantic challenges to evaluating CBLTSS due to heterogeneity of descriptive terms and delivery models.
- Identify common models of CBLTSS delivery and reimbursement.
- Recognize emerging trends in CBLTSS with the implementation of the Affordable Care Act of 2010.

Key Clinical Points

1. **The vast majority of care for older people at home is provided by friends and family as unpaid informal caregivers, at enormous indirect cost to society in the form of lost wages, lost productivity, and future social insurance costs.**
2. **There is a substantial body of evidence suggesting that various models of CBLTSS are effective; cost-effectiveness and outcomes associated with these models depend substantially on targeting of services to appropriate populations.**
3. **Innovative care delivery models funded by the Center for Medicare and Medicaid Innovation (CMMI) hold promise for improving health outcomes and controlling costs over the next several years.**

In 2012, an estimated 11 million older Americans needed long-term care (LTC) due to functional impairment, usually as a result of chronic medical conditions and illnesses. Over half (57%) of these people are 65 years or older. Most choose to remain in the community, and require services to help them stay in their homes rather than enter an institution. These services constitute what is generally known as community-based long-term services and support (CBLTSS). As the population ages and the number of functionally impaired older adults increases, so will the need for CBLTSS. Unfortunately, no coherent national policy drives CBLTSS in the United States, which leaves a "system" that is inconsistent, decentralized, difficult to access, bewildering to navigate, and unable to fully meet the needs of many patients. Much of what is actually done to meet these needs is provided by unpaid family caregivers at great personal and economic cost. This chapter addresses CBLTSS for older adults in the United States. We outline the semantic challenges in understanding the scope and nature of CBLTSS and the heterogeneity of care models that comprise it; describe who receives, provides, and pays for it; and review the evidence for its effectiveness. We also discuss important public policy issues and identify emerging innovations and trends in CBLTSS delivery.

SEMANTIC CHALLENGES OF CBLTSS

The term "community-based long-term services and support" overlaps with several other terms in the medical and

social sciences literature, including *home care, personal care services, home- and community-based services, home visits, house calls*, and others. In general, these terms refer to nursing, personal care, or social services provided to older persons, with an explicit goal of filling unmet needs or maintaining them in the community. Most of this kind of care is provided by unpaid family members or friends, sometimes with support from a variety of formal caregivers. Home care may mean home-based rehabilitation or disease management after hospital discharge, transitional care interventions, preventive health interventions, geriatric assessment, primary care physician visits, community-based social services, or highly technological care provided in individual patient homes. These services often overlap to such an extent that important aspects of a given intervention are not accurately reflected in a single label. For example, a program in which an interdisciplinary team provides comprehensive geriatric assessment followed by primary care home visits, inpatient management as needed, and continuing longitudinal care after hospital discharge does not fit neatly into any one category. Several forms of CBLTSS integrate housing arrangements with personal and medical care, further blurring the distinction between community-based and institutional long-term services and support. **Table 21-1** depicts the heterogeneity and scope of services and settings that fall under the rubric of CBLTSS.

TABLE 21-1 ■ COMMUNITY-BASED LONG-TERM SERVICES AND SUPPORTS

TYPE OF CBLTSS	DESCRIPTION/SERVICES	FUNDING
Home health care Formal (agency or consumer-directed) Skilled care Personal care Community resources Informal	Home health agency or client provides and pays personnel Nursing, occupational and physical therapy ADL assistance Meals on Wheels, Department of Social Services, Agency on Aging case management, pastoral care ADL/IADL assistance as needed	Medicare/Medicaid or private long-term care insurance/private pay (if no skilled care need) Community agencies, local jurisdictions, local faith-based groups None/opportunity cost of caregivers
Physician house calls	Medical visits in patient's home	Medicare, private insurance, private pay
Hospital at home	Acute-level care at home with daily nurse/physician visits	Variable depending on system implementing the model
Preventive home visits	Health maintenance visits by health care providers (physicians, nurses, social workers) or trained "health visitors"	National insurance (Europe/United Kingdom), research grants (United States)
Home-based geriatric assessment	Multidisciplinary evaluation of medical, social, functional, and cognitive issues	Variable depending on evaluator and context
Case management	Disease-specific teaching and support provided by nurses	Medicare (as part of skilled care) or private insurance
Program of All-Inclusive Care for the Elderly (PACE)	Comprehensive medical, functional, and social care for dually eligible, nursing home–eligible patients	Medicare- and Medicaid-capitated payments
Adult day care Medical Social	Supervised congregate activities, 1–7 d/wk for several hours a day Includes medication administration and basic monitoring Limited to social interaction	Private pay
Assisted living	Apartment-style living with unskilled and/or skilled services available on site	Long-term care insurance, private pay
Sheltered housing	"Senior apartments" with varying	Private pay, subsidized by federal and

	social services on site (eg, friendly visitors, congregate meals, transportation)	local governments
Adult foster care	Older adult who needs assistance or supervision moves in with "foster" family	Private pay, subsidized by federal and local governments
Group home	Group of adults who needs assistance or supervision lives in one building with unskilled and/or skilled services available on site (can be similar to assisted living)	Subsidized by federal and local governments
Continuing care retirement communities (CCRCs)	Geographically localized and self-contained spectrum of living arrangements from independent housing to nursing home care	Private pay
Life care at home	Spectrum of care from minimal assistance to nursing home–level care provided in patient's own home	Private pay

ADL, activities of daily living, IADL, instrumental activities of daily living.

Home health care usually comes in two forms: unskilled and skilled care. Unskilled care refers to services provided by unpaid caregivers, usually female family members. The estimated 43 million informal caregivers in the United States provide 66% to 92% of all home care and CBLTSS services at an estimated economic value of $234 billion—far greater than national spending on formal home care ($58 billion) and nursing home care ($134 billion). Skilled home health care refers to formal services delivered by professional providers, such as nurses or physical, occupational, or speech therapists. Medicare certifies and reimburses home health care agencies (HHAs) to provide this type of care when a patient is homebound and has a skilled need (see "Who Provides and Pays for CBLTSS" later in the chapter). HHAs may also provide formal personal care services (bathing, dressing, etc) under the Medicare home health care benefit while a patient is receiving skilled care. There is growing awareness of Medicare skilled home health care, and an increasing number of referrals are originating in the community. For example, an older patient who suffers an acute exacerbation of chronic obstructive pulmonary disease may spend several days in bed (at home or in the hospital), and may need nursing to monitor her respiratory status and physical therapy to help her regain her baseline functional mobility. It is important to note that the effectiveness of skilled home care often relies on services provided by an informal caregiver who, if available, can implement a home exercise program, clean and dress pressure ulcers, or bathe, dress, and toilet a dependent patient.

Two related models of formal home-based medical care include home-based primary care provided by physicians who make house calls and hospital-at-home model. Home-based primary care, in which physicians (and, increasingly, nurse practitioners and physician assistants) provide ongoing longitudinal medical care at home, can play an important role in providing access to routine and urgent care for older adults who have difficulty getting to a medical office. Home-based primary care programs have been increasing in prevalence in recent years and have been shown to be effective (see below). In 2012, there were over 10,000 individual providers (MD, DO, NP, or PA) making home visits in the United States. Hospital-at-home is an emerging care model that provides hospital-level care in a patient's home as a substitute for an acute hospital admission that has been shown to be associated with better care quality and lower costs than typical hospital care. Other forms of CBLTSS involve intermittent assessment and monitoring over time. Preventive home visits and home-based geriatric assessment typically aim to identify older adults in the community who have hidden risks for developing illness or functional decline, and modify those risks to prevent poor outcomes. Disease management targets patients known to have specific diseases or conditions that require significant care coordination, such as diabetes or heart failure, for formal support in managing those conditions, with the goal of delaying disease progression and avoiding hospitalization.

Still other forms of CBLTSS entail temporary or permanent changes in location of care. Adult day care generally includes transportation to a day care center, and can provide both structured social activities and basic medical monitoring and treatment. The Program of All-Inclusive Care for the Elderly (PACE) relies heavily on a "day health center" in which dually eligible (ie, Medicare and Medicaid eligible) nursing home–eligible participants receive

comprehensive medical, hygienic, social, and rehabilitative care. For patients who cannot continue to live in their own homes, assisted living, sheltered housing (also known as senior apartments), adult foster care, and group homes all provide varying levels of functional assistance and access to some medical services. Continuing care retirement communities (CCRCs), as the name suggests, are self-contained organizations that allow people to move within the community to increasing levels of care as their needs dictate. At one end of the continuing care spectrum, a fully independent older adult lives in a single-family home or apartment, but over time may transition first to an assisted-living apartment, then to the skilled nursing facility within the same CCRC. There are several variations on this model, but most charge an entrance and monthly fee that provides lifelong care in the event that the participant develops some kind of functional impairment. Finally, some continuing care models, called life care at home, provide a similar range of care but do not require purchasers to move from their own homes.

This array of services and settings can be framed as a quasicontinuum of care services for older adults, as shown in **Figure 21-1**. While some forms of CBLTSS are designed to address the needs of older adults through a variety of health or disease states, such as home health care, CCRCs or postacute disease management programs, others are targeted to specific populations based on levels of impairment or disability, such as preventive home visits or PACE. Again, many patients and programs do not fit neatly into a single category and patients do not usually move across the continuum in a straight line, as the use of services depends not only on the fit between the needs of an older adult and the care model, but also on the preferences of older adults and local availability of care models. For example, skilled home health care may be used by a healthy older adult after elective joint replacement surgery, or by a frail chronically ill patient recovering from a recent episode of community-acquired pneumonia treated at home by a physician house call program. However, the concept of a continuum is a useful construct for organizing categories of CBLTSS.

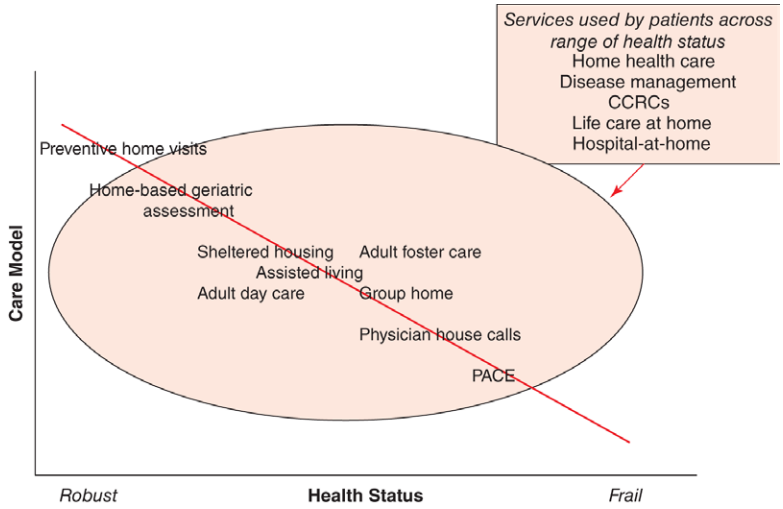


FIGURE 21-1. CBLTSS continuum of care.

WHO RECEIVES CBLTSS?

As **Figure 21-1** demonstrates, CBLTSS may be used by older adults over a wide range of health status. Health maintenance strategies such as preventive home visits and geriatric assessment tend to target patients who are relatively robust and functionally independent, while PACE and physician house calls address the needs of patients who are more frail and impaired. CCRCs and life care at home explicitly transition patients from the robust state through functional decline. Postacute home health care, physician house calls, and hospital at home may be used by both robust and frail older adults in specific circumstances, but the primary intended users of most CBLTSS remain those who have chronic and complex medical illness accompanied by some level of functional disability, and thus require care for a prolonged or even indefinite time. The likelihood of receiving formal care is lower for men, minorities, married individuals, those with lower socioeconomic status, and those who are less dependent for assistance with activities and instrumental activities of daily living (ADLs).

WHO PROVIDES AND PAYS FOR CBLTSS?

The role of unpaid informal caregivers cannot be overemphasized. The work they perform is not directly reimbursed or financially rewarded by the health care system. The indirect costs are enormous when lost wages, lost productivity, and future social insurance losses are calculated for caregivers who may sacrifice paid employment to provide informal care for a parent or other relative. For formal care, the provider varies with the type of CBLTSS. In the most common model of home health care, an HHA certified to provide care under Medicare reimbursement rules employs nurses, therapists, aides, and social workers, and assigns them to individual patient cases. A physician must certify that the patient is homebound and has a skilled need in order for a Medicare-certified HHA to provide care for a 60-day "certification period." This certification must be based on a face-to-face encounter by the physician or associated nurse practitioner within the 90 days before or the 30 days after the start date of home health services. By definition, a skilled need requires care that is part-time, intermittent, and must be provided by a person with special training (eg, a nurse or therapist). Personal care assistance with ADLs such as bathing and dressing is covered during the certification period, but Medicare does not pay for it in the absence of a skilled need. The settlement of the *Jimmo v Sebelius* case, in 2013, clarified that Medicare reimbursement for skilled home health services is allowed for people whose potential to improve may be limited, as long as there is a skilled need focused on preventing further deterioration or maintaining current level of function.

The HHA must catalog each patient's medical, functional, and socioeconomic characteristics in the Outcome and Assessment Information Set (OASIS), which then determines in the prospective payment system (PPS) the Medicare reimbursement the agency will receive for the certification period. PPS was implemented in 2000 in response to a period of extraordinary growth in medical home health care expenditures in the 1990s, which was unfortunately accompanied by inefficient or even fraudulent fee-for-service (FFS) billing. A patient can be "recertified" for multiple 60-day periods as long as a skilled need exists. HHAs can also be privately paid by the care recipients. Additionally, a "consumer-directed" or "cash and counseling" model allows selected patients to choose, train, and pay their personal care providers directly with designated state funds (usually from Medicaid programs), instead of using an agency as an intermediary. In these programs, care providers can be family members or other previously unpaid caregivers. This model has had positive results, showing increased patient empowerment and satisfaction, and fewer unmet needs.

Interdisciplinary teams are critical in coordinating and delivering care in home health care, home-based geriatric assessment, PACE, home-based primary care, and hospital at home (see Chapter 26). Such teams typically include physicians, although the physician role may vary in different settings depending on the medical complexity of the patient and the setting. For example, in PACE, the physician provides primary care services, manages acute illness during hospitalization, and coordinates the activities of the interdisciplinary team. In postacute and home rehabilitation care, the interdisciplinary team drives most of the management with a focus on restoring function and following up medical issues, with the physician acting largely in an administrative role. In hospital-at-home interventions, the physician actively manages acute illness at home, so that physician house calls complemented by close coordination of the interdisciplinary team are crucial in this setting. Improvements in Medicare reimbursement for physician house calls have contributed to a recent growth in academic and private sector house call programs.

Other forms of CBLTSS rely less on physicians and more on specialized nurses or trained lay visitors. Disease management, postacute home health care, and medical day care are often based on protocols driven by nurses. Home-based geriatric assessment is usually performed by geriatric nurses or nurse practitioners and then discussed as needed with physicians, while preventive home visits have been successful in using "health visitors," or specially trained community residents, in screening for health risks. Medical care in assisted living facilities (ALFs), sheltered housing, and group homes is generally limited to medication administration and vital signs monitoring and may include relatively easy access to physicians when needed, such as domiciliary care visits or a clinic housed within a senior apartment building. A small number of older adults carry privately funded LTC insurance, and in recent years, some businesses have added this option to their employee benefit packages. Ultimately, many people exhaust their retirement savings and home equity to pay for LTSS, becoming eligible for Medicaid through this "spend-down" process.

IS CBLTSS EFFECTIVE?

Studies of CBLTSS are challenging to interpret because of the semantic difficulties outlined above, the heterogeneity of home care interventions, difficulties in controlling for severity of disability or illness of patients, patient attrition issues, changes in regulation over time, and examination of a disparate range of outcome measures. However, key studies and their findings are summarized in **Table 21-2**. The National Long-Term Care Demonstration project (also

known as the Channeling Demonstration) in the early 1980s was a large study that evaluated the effect of adding comprehensive case management and a broad array of other purchased services to existing community care networks. It served an extremely frail population with unmet service needs, but did not show overall cost savings or decrease hospitalization, nursing home placement, or functional decline. However, it did improve in-home care, unmet needs, and quality of life of patients and caregivers. This landmark study set a pessimistic tone for home care research: that home care may be preferred by patients and caregivers, but difficult to justify in terms of clinical and economic effectiveness. Similarly, the Social Health Maintenance Organization demonstration projects (SHMO I and II) that expanded case management services within Medicare managed care organizations (MCOs) failed to demonstrate any patient care or cost advantages over usual managed care practices, and in 2003 reverted to standard Medicare MCOs. The Patient Protection and Affordable Care Act of 2010 reduced funding for Medicare MCOs due to their higher costs and lack of health outcome benefit.

TABLE 21-2 ■ EVIDENCE FOR EFFECTIVENESS OF CBLTSS

AUTHOR/YEAR	STUDY	SETTING	TARGETED POPULATION	MAJOR FINDINGS
Kemper 1986	National Channeling Demonstration	United States	Frail older adults at risk of nursing home placement	Improved patient/caregiver quality of life, in-home care, and unmet needs No decrease in costs, hospitalization, nursing home placement, or functional decline
Thompson 2002	SHMO I and II	US Medicare HMOs	Frail older adults	No improvement in quality of care, institutionalization, or hospital utilization compared with usual capitated care
Shaughnessy 2002	OBQI	Medicare-certified home health agencies	Homebound older adults with skilled needs	Reduced hospitalization and improved other targeted outcomes
Eng 1997	PACE	Eleven PACE sites in 9 US states across United States	Dually eligible, nursing home–eligible frail older adults	Decreased hospital length of stay Fewer nursing home days Less outpatient subspecialist utilization Decreased polypharmacy No increase in mortality Cost savings of 5%–15% relative to nursing home
Abt Associates 2001	PACE	Eleven PACE sites in 8 US states	Dually eligible, nursing home—eligible frail older adults	Increased life expectancy Decreased use of NH/hospital Improved (self-rated) health status Improved satisfaction with care and with life in general Decreased Medicare costs Increased Medicaid costs
Naylor 1999	Posthospital disease management	Two urban US academic hospitals	Older adults hospitalized for 1 of 8 medical or surgical diagnoses	Decreased readmission rate Lengthened time between discharge and readmission Decreased Medicare costs
Shepperd 2009	Hospital at home	Systematic review	Acutely ill adults >18 y	Hospital-at-home models that substituted for inpatient admission reduced 6-mo mortality and cost, despite a nonsignificant increase in hospital transfer or readmission within 3 mo
Caplan 2012	Hospital at home	Meta-analysis	Acutely ill patients >16 y randomized to	Significantly reduced mortality, readmission rates, and cost Significantly increased patient and caregiver satisfaction

			hospital admission or hospital-at-home services	
Weissert 1988	Home care	Systematic review	N/A	Targeting was “uneven and best accomplished” when accompanied by a mandatory nursing home preadmission-screening program Cost savings on institutional care did not offset costs of intervention Hospital use increased in some studies
Stuck 2002	Preventive home visits	Meta-analysis	N/A	Functional decline reduced in trials using multidimensional assessment with follow-up and in trials with control group mortality in lowest tertile Nursing home placement reduced in trials with >9 home visits during follow-up Mortality reduced in younger (<77.5 y) but not older populations (>80 y)
Hughes 2000	Team-managed home-based primary care	Veterans Administration	Older veterans with CHF, COPD, terminal illness, or impairments in 2 or more ADLs	Increased patient and caregiver satisfaction but also increased overall costs
Huss 2008	Preventive home visits	Meta-analysis	Community dwelling older adults	Functional decline reduced in trials with multidimensional assessment including clinical examination Mortality reduced in younger (<77 y) but not older (>80 y) populations Favorable but nonsignificant heterogenous effects on nursing home placement
Stall 2014	Home-based primary care	Systematic review	Homebound community-dwelling older adults	Decreased utilization (emergency department visits, hospital admissions/days of care, long-term care admissions/days of care) Positive influence of interprofessional team with regular team meetings and after-hours support

ADLs, activities of daily living; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

Other interventions have been more successful at controlling costs and improving health outcomes. Two outcome-based quality improvement (OBQI) Medicare demonstration programs collected, encoded, and transmitted patient-level health status information to provide a risk-adjusted outcome report, which was then used to implement action plans to change Medicare-certified home health care agency behaviors. Each demonstration agency focused on reducing rehospitalization rates and one other targeted outcome (eg, functional status or medication self-management) based on its performance report. With over 260,000 patients in 73 home care agencies in 28 states, the OBQI intervention achieved a more than 20% reduction in hospitalization and a 5% to 7% improvement in other targeted outcomes. In addition, the comprehensive management strategies of PACE programs are effective at reducing institutionalization of at-risk patients, and targeted postacute hospital disease management programs for specific conditions such as congestive heart failure, deep venous thrombosis, and diabetes mellitus improve patient outcomes such as hospital readmissions and self-management skills. Finally, hospital-at-home experiments, especially those that substitute entirely for an acute hospital admission, have reduced total days in care and geriatric clinical complications such as confusion and incontinence, with health outcomes and health-related quality-of-life measures comparable to usual care.

The evidence on the effects of other CBLTSS interventions is less consistent and may result from issues related to

model design and targeting of models to the appropriate patient population. A meta-regression analysis on the effects of home visits to prevent adverse outcomes found a 24% risk reduction in mortality for "young-old" (younger than 80 years) rather than "old-old" (older than 80 years) populations, while multidimensional assessment was associated with better functional outcomes compared with single-clinician assessment (relative risk 0.76), and risk of nursing home placement decreased by 34% as the number of follow-up visits increased from fewer than 4 to more than 9.

Similarly, some physician house call programs have been shown to reduce hospital or emergency department utilization, and a large Veterans Administration (VA) study demonstrated significant improvements in patient health-related quality of life and caregiver satisfaction for patients receiving team-managed home-based primary care. A more recent study of VA home-based primary care demonstrates the provision of high-quality care that is associated with reductions in both VA and Medicare costs. Evidence for cost savings associated with non-VA home-based primary care is also growing. As **Table 21-2** indicates, an extensive home care literature includes a wide variety of interventions and target populations. While this heterogeneity creates significant difficulty in drawing conclusions about the effectiveness and cost-effectiveness of home care, the overall body of evidence suggests that specific models when appropriately targeted are probably effective.

This issue of targeting care to appropriate patient populations is a major determinant of the cost-effectiveness of specific interventions. A related factor that complicates discussions of cost-effectiveness is the notion of paid care inappropriately substituting for informal care at a cost to society, or the "moral hazard" or "woodwork" effect. In theory, if CBLTSS services are made widely available, functionally impaired patients will "come out of the woodwork" to utilize them, even though most of these patients would never enter an institution even without using CBLTSS. Thus, the cost of providing care will overwhelm the potential savings of avoiding institutionalization. Targeting services to patients who are at high risk for institutionalization is generally accepted as an important way to optimize cost-effectiveness, but no practical, precise, and accurate targeting tools have been developed and tested. Recent reviews have demonstrated associations between greater state expenditures on CBLTSS and lower rates of institutionalization of older adults who do not have significant impairment in "late-loss" ADLs (bed mobility, toileting, transferring, and eating). Cost-effectiveness also depends on the economic features of the health systems in which various forms of CBLTSS have been studied; findings from European programs in which the government is the payer for CBLTSS, institutional LTC, and acute care are difficult to apply to the US FFS environment with multiple public and private payers and complex cost-shifting pressures.

INNOVATIONS

Recent technological and social advances have the potential to improve access to care, quality of care, and coordination of care for medically complex community-dwelling older adults. Telemedicine is a small but growing field with particular relevance to rural or homebound populations with chronic diseases that cannot otherwise access specialized care; dermatology, ophthalmology, and wound care have been widely studied in small clinical trials and appear to allow accurate diagnosis and management through both real-time interactions and "store-and-forward" applications in which clinical data including video images are collected and stored for later review by a clinician. Other specialties relying heavily on verbal interactions, such as psychiatry and neurology, appear to effectively diagnose and treat patients via interactive video conferencing. Similarly, home-based telemedicine interventions in chronic diseases probably enhance communication between patients and providers and facilitate closer monitoring of overall health when conducted in settings with specialized equipment and dedicated staff. Although the evidence is limited by methodologic variability, lack of comparison with in-person evaluation, and absence of clinical outcome measures, a 2006 systematic review by the Agency for Healthcare Research and Quality (AHRQ) concluded that in some situations, the use of telemedicine might be warranted even if the evidence is inconclusive, including "remote rural areas or other locations where medical care is not available locally and the patient is for whatever reason unable to travel to a setting where it can be obtained." More recent systematic reviews confirmed that additional small or methodologically weak trials did not improve the evidence base for telemedicine, and larger, well-designed comprehensive trials that include clinically meaningful outcome measures are needed in light of the increasing advocacy for health care payers to cover its use. However, these later reviews also noted that interest and commercial development of telemedicine continues to grow, and suggest that it is "an ongoing intervention where users influence its development and hence that effectiveness of outcome is a complex collaborative achievement." Like telemedicine, point-of-care diagnostic and therapeutic technology including electrocardiography, ultrasound, blood analysis, and intravenous treatment holds promise for health care delivery in home care and house calls. Wireless telephone and

Internet applications that allow secure, high-speed broadband connections between portable electronic medical records (EMR) systems and acute care or office information systems can provide safe and seamless continuity of care with immediate data access and entry for providers caring for complex older patients with multiple medical issues, medications, sites of care, and consultants.

A third important innovation in caring for community-dwelling functionally impaired older adults is not based on technology, but on social, medical, and financial support. Medicaid waiver programs, authorized in section 1915(c) of the Social Security Act, allow states to shift funds for extensive home-based services for older or disabled people. Since much nursing home care is paid for by state-administered Medicaid programs, Medicaid has a major stake in financing LTSS that can substitute for nursing home care without increasing costs, unmet needs, or adverse outcomes. Hence, 1915(c) waiver programs lower the income and asset thresholds for Medicaid, and provide a combination of traditional medical services (ie, dental services, skilled nursing services) and nonmedical services (ie, respite, case management, environmental modifications) with the goal of avoiding relatively expensive institutionalization for at-risk older adults with functional disabilities. Family members and friends may be providers of waiver services if they meet standard provider qualifications. Approximately 287 waiver programs are currently active in 48 states and the District of Columbia as government struggles to mitigate the costs of institutional care. A recent analysis showed that 58% of patients in these programs were older or disabled. A relatively small proportion of Medicaid waiver spending went toward this group (23.8% or $3.4 billion) compared with the amount expended on patients with mental retardation or developmental disability (74% or $10.5 billion).

Finally, a 2005 Medicare demonstration project, Care Management for High-Cost Beneficiaries (CMHCB), awarded 3-year contracts to several health care provider organizations across the nation to “test the ability of intensive management for high-cost beneficiaries with various medical conditions to reduce cost as well as improve quality of care and quality of life.” These organizations are using a variety of care management tools such as increased provider availability (including physician house calls), structured chronic care programs, restructured physician practices, and expanded flexibility in care settings in an attempt to demonstrate overall cost savings and care improvement. Remarkably promising outcomes from some of these programs are fueling increased interest in this model of chronic care management, with cost savings of up to 19% in high-utilizing patients at Massachusetts General Hospital followed from 2006 to 2012. Similarly, the CMMI (http://innovation.cms.gov/) has funded more than 50 smaller initiatives across the country aimed at developing new payment and service delivery models in accordance with the Affordable Care Act and the Social Security Act. These models are organized under seven general categories ranging from “primary care transformation” to “bundled payments for care improvement,” with the underlying premise that aligning financial and clinical incentives will improve the care of medically complex patients, including older Medicare beneficiaries.

TRENDS

Several emerging trends in CBLTSS will undoubtedly affect the future health care of the aging US population. Interdisciplinary team-based models of care providing medical care, nursing, and social work at home for older adults with multiple chronic illnesses, once seen only in academic medical centers, are being developed by private sector companies and hospitals. These teams focus not on single-disease management, but on coordination of care, integration of patient goals and preferences, and improvement of patient outcomes relevant to this particularly frail and vulnerable group. At the same time, an increasing number of physicians are withdrawing from the current Medicare FFS system as the reimbursement schedule continues to decline relative to the costs and risks of medical practice. This “opting out” trend, combined with the already grave shortage of primary care physicians including geriatricians, may, over time, drive a demand-based shift toward private insurance, health savings accounts, and concierge practices, further depleting the supply of physicians. The current interest in “pay-for-performance” (P4P) is aimed primarily at discrete, disease-specific measures such as hemoglobin A_{1C} levels, which are not consistently applicable to a frail geriatric population. Currently, efforts are underway to develop a quality-of-care framework, quality indicators, and a national registry for home-based primary and palliative care practices to facilitate practice-based quality improvement, performance reporting, and comparative effectiveness research. The care of medically complex older adults will also require evaluation of events such as hospital admissions, intensive care stays, or nursing home placement for high-cost populations. The Affordable Care Act established the Medicare Shared Savings Program to promote the formation of “accountable care organizations (ACOs),” groups of providers and suppliers that agree to work together to coordinate care for the defined population of Medicare beneficiaries they serve. ACOs emphasize value-based care over volume-

driven care. In this context, CBLTSS will be better integrated into health service delivery. Finally, the growing recognition that patient empowerment and involvement improves quality and satisfaction will ideally translate into systems that value, support, and pay informal family caregivers for their essential and indispensable work.

CONCLUSION

CBLTSS is a varied collection of services aimed at allowing functionally impaired older adults to age in place according to their wishes. Although decades of research have resulted in some evidence of cost-effective benefit, this evidence is limited by semantic and methodological issues. Overall, CBLTSS is effective when appropriately targeted; older adults continue to prefer living in the community to living in institutions, and social pressures from an aging generation will only increase demand for CBLTSS in the future. The current fragmented system of CBLTSS will be untenable in the coming years as the number of older adults with complex multimorbidity and functional disability increases. Emerging models of CBLTSS including physician house calls, team-based primary care coordination, and population-based pay-for-performance hold promise for improving health care for these patients, although systematic barriers exist to their widespread implementation. Creative economic, technological, and clinical solutions that focus on quality and cost-effectiveness will be critical in reforming the system to affirm and fulfill the public trust.

FURTHER READING

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Chapter 22

Rural Aging

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Learning Objectives

- Describe the demographics of the rural aging population.
- Describe three common problems that affect rural elders in ways different from their urban counterparts.
- Describe the special health service programs designed to improve care to rural elders.

Key Clinical Points

1. **Rural elders have high rates of disability and poverty, thereby increasing their risk for adverse health outcomes.**
2. **The need for geriatric health care providers in rural areas is very great. This is especially true for those with multiple chronic conditions.**
3. **The federal government, to increase access to care for rural elders, has created a number of special programs. Geriatric care providers should make use of these programs.**

Approximately 60 million Americans of all ages live in areas classified by the US Office of Management and Budget (OMB) as nonmetropolitan, or "rural." They comprise one-fifth of the US population. The "rural life" holds great value in the history of the United States, though there are many stereotypes about rural elders **(Table 22-1)**. For most of our country's history, rural living was practically the only way of life. The majority of Americans lived in rural areas up until the early 1900s. Throughout the years, rural living has been seen as a noble and pure form of existence. Getting "back to the land" has long been viewed as a dream for many city dwellers.

TABLE 22-1 COMMON STEREOTYPES OF RURAL ELDERS

- They live on farms and are a homogenous group.
- They are in better physical and mental shape because of hard work, good food, and living in the country.
- They are more active.
- They are better able to take care of themselves and make ends meet.
- They are not homeless and have better housing.
- They are surrounded by large families who are available and willing to help.
- They have less need for health and social services.
- They can get what they need in the local stores.

Rural life is also connected to prominent American values—the dual values of self-reliance and interdependence with one's neighbors, freedom from governmental control, a slower pace of living, and the back to nature philosophy. As will be discussed, a significant movement, or "in-migration" of older people back to rural areas is occurring in part because of these values. However, the long trend of younger people moving away or "out-migration" from rural areas and the poorer and sicker older people remaining also continues. What society may be facing in the next few decades

is a population of primarily older people living in large portions of the country—a population made of two subgroups, healthy active and politically motivated baby boomers who have returned to the land, and a larger group of frail elders who have lived all their lives in that environment. This development will challenge health care service providers, as well as Medicare and Medicaid.

Rural aging engenders the same attitudes held toward older people in our society with a geographic twist. For instance, when viewed from an economic perspective, rural residence is expensive for both society and individuals. The costs of distance, inefficiencies of spatial dispersion, and absence of economies of scale mean that patients have difficulty accessing and providers have difficulty delivering care locally. Yet the fact is older people make up a large percentage of the population of people living in rural settings.

DEMOGRAPHY OF RURAL AGING

One of the problems in discussing rural aging is the definition of "rural." The two most frequently used definitions of rural used in research and policy development are those of the US Census Bureau and the OMB. The US Census Bureau defines as "urban" any incorporated city, town, village, or borough with a population of at least 2500 people. Any area not defined as urban is rural. The OMB identifies counties as metropolitan, micropolitan, and nonmetropolitan. Micropolitan and nonmetropolitan counties are considered rural. OMB definitions are used to assign eligibility and reimbursement for a number of federal programs, including Medicare. Finally, the two definitions (Census and OMB) do not completely overlap, creating difficulties in planning. As it is, most counties contain a mixture of rural and urban living.

Older Americans made up 13.3% (41.4 million people) of the US population in 2011. Among the population that lives in a nonmetropolitan area, 20% are older than 65 years, a higher proportion of older people than in metropolitan and micropolitan areas. Further, the population living in rural America ages 55 to 75 is predicted to increase by 30% by 2020, representing a doubling of the population of people 55 to 75 years living in rural and small towns from 2000 to 2020. The greater concentration of older adults in rural areas is largely a function of three factors: (1) aging in place, (2) younger persons migrating out for better jobs, and (3) in-migration of older adults after retirement. The percentage of women and those who are widowed reflects numbers similar to the general population of metropolitan areas.

Ethnic diversity among older Americans living in rural areas is increasing, but varies by region. However, rural America remains less diverse than urban America. The poverty rate overall for nonmetropolitan (nonmetro) is higher than for metropolitan areas (metro) of country, although the differences, like racial/ethnic minority population, vary by region. The rate of poverty in nonmetro areas has always been the highest in the South. Persistent poverty (PP), defined as poverty rates greater than 20% of the population, is predominantly a rural problem. Of the 353 PP counties in the United States, 85.3% are nonmetro, accounting for 11.2% of all counties in the United States, and 15.2% of all nonmetro counties. Approximately 84% of PP counties are in the South. Socioeconomic status is probably the strongest factor affecting health and health care services, so the implications of this fact cannot be overstated.

Another important aspect of aging that affects health care is the availability of caregivers. Nationally, one out of four families is providing assistance to an older family member. Informal caregiving is the primary source of long-term care in this country, and that is certainly true for the rural population. Unfortunately, rural elders appear to be trapped between their higher expectations for care from a family member, and the decreasing availability of younger family members. A larger percentage of rural elders receive assistance from "fictive kin"—friends and others in the rural community. Studies of rural caregiving indicate that caretakers and patients use more informal supports than those in urban areas and that informal caretakers (ie, unpaid) provide services about 26 hours per week and are dealing with increasingly complex care needs. This and the relative dearth of home- and community-based services in rural communities are probably major contributors to the fact that long-term institutional care is more common in rural areas than urban areas.

Finally, an important dynamic in the demographics of rural aging is the resettlement of rural areas by retirees, termed "in-migration." In the 1970s, a net in-migration to rural areas followed decades of out-migration. This was caused by a combination of some manufacturing jobs moving to more rural areas for cheaper land and labor and a "back-to-the-earth" movement following the tumultuous 1960s. Some of these residents are now the rural elders who have aged in place. However, this in-migration was short-lived, and in the 1980s, almost 2 million persons aged 20 to 29 moved away from rural areas. More recently, wealthier and healthier elders have been moving back into rural areas after retirement, in order to seek a lower cost of living and the amenities afforded by recreational and cultural opportunities (**Table 22-2**).

TABLE 22-2 ■ RESULTS OF IN-MIGRATION TO RURAL AREAS

- Although in-migration encourages job growth, it does not increase per capita income or contribute to economic stability in host communities.
- Retired migrants contribute their fair share of taxes but they also bring added costs to rural governments with increased demands for public and health care services.
- Rural in-migration is likely to accelerate with the retirement of the baby boomers.

HEALTH STATUS OF RURAL ELDERS

Rural populations lag behind metropolitan populations in many health status indicators. These include higher rates of heart disease, respiratory disease, diabetes, stroke, mental diseases, malnutrition, obesity, substance abuse, and cancer, as well as reduced rates of having insurance and access to primary care. Some studies have shown diabetes to be 17% higher in rural areas. Compounding these high rates is the difficulties older adults experience trying to access specialist care and even primary care providers in some areas, resulting in poorly managed chronic illness and preventable hospitalizations. In addition, recommended screening practices (eg, colorectal screening) also occur at lower rates than in urban areas. Rural populations also have higher rates of risky healthy behaviors, including smoking, alcohol consumption, and sedentary lifestyle. Taken together these issues may account for recent disturbing findings that life expectancy in many, predominantly rural, counties has decreased between 2000 and 2007, and that female mortality in particular has increased in 42.8% of counties (3.4% increase among males).

Disability

While recent studies have documented a declining rate of disability among older Americans, the rate of frailty and dependency in activities of daily living (ADLs) and instrumental activities of daily living (IADLs) continues to be high in rural communities. Almost three-quarters (73%) of the rural older population has activity limitations, compared to approximately 50% in those living in metropolitan areas, complicated by the relative lack of services, especially for rehabilitation. In addition, access to personal care by physical and occupational therapists or to in-home services is limited as well.

Mental Illness

Higher rates of mental illness and substance abuse are particularly problematic in rural areas, where providers are few and special services are limited. The MoVIES Project, a 10-year prospective study of dementia in rural older people showed that the incidence rates of Alzheimer and other dementia was higher in rural areas than in urban population, with particularly high rates in men. Older people in the National Health Interview Survey reported self-reported hopelessness, helplessness, worthlessness, and lethargy at higher rates. Depression rates have been reported as high as 40% in women in rural areas, compared to 13% to 20% in urban older women. Rural Hispanic women have been found to have rates of depression two times higher than white women. Suicide rates are also higher in rural areas than urban. Finally, utilization of mental health services, where available, is lower in rural areas.

Nutrition

Nutritional problems are very common among rural elders. Both overnutrition (obesity and overweight) and undernutrition are common (**Table 22-3**). In addition, older women in rural areas consume lower amounts of recommended protein, vitamins A, C, E, B_6, B_{12}, riboflavin, and folate, as well as some minerals (calcium, phosphorus, and magnesium). Many rural elders consume a diet of low-nutrient value, including a high intake of bread, cereal, rice, pasta, fats, oils, and sweets. This pattern leads to high calorie consumption and low intake of essential vitamins and minerals. In addition, many older rural residents consume limited amounts of fruits and vegetables. Substantial numbers of rural elders report not having enough to eat or not having enough money to purchase quality foods. Rural minorities are at substantially increased risk for food insecurity.

TABLE 22-3 ■ PERCENTAGE OF OVERWEIGHT AND OBESE RURAL ELDERS (>65 Y) BY SELECTED STATES AND REGIONS

	OVERWEIGHT	OBESE
West Virginia	34	20
Pennsylvania	44	35
North Carolina	31	34.5
Mississippi Delta	Not available	42.6

Options for improvement in nutrition for elders are food stamps and home-delivered meals. Unfortunately, a smaller percentage of rural elders participate in the food stamp program than urban elders (7.9% vs 9.4%) and the majority of elders get the minimum benefit (US Department of Agriculture Web site). Similarly, home-delivered meals, such as Meals on Wheels Programs, are much less commonly located in rural areas.

ETHNIC AND MINORITY RURAL AGING

Over 80% of the population growth in nonmetro areas between 2000 and 2010 consisted of racial/ethnic minorities, that is, everyone who was not a non-Hispanic white, although minorities account for only 21% of the nonmetro population. The nature of the rural racial/ethnic population varies significantly by region, eg, African-Americans in the South, Hispanics in the South and the West, and American Indians (AI) and Alaskan Natives (AN) predominantly in Alaska, Arizona, New Mexico, North Carolina, and Oklahoma. About 50% of AI/AN live in three states—Oklahoma, California, and Arizona. The well-known presence of health care disparities among ethnic groups exists, and in some cases, is magnified in rural areas. For instance, African-Americans in rural areas are less likely to receive specialized medical care, to adhere to long-term preventive drug regimens, and to use more complex health care services.

Over 90% of rural African-Americans live in the South, three-quarters of these live in just seven states (Louisiana, Mississippi, Alabama, Georgia, South Carolina, North Carolina, and Virginia). There are fewer home- and community-based services available to them, and consequently the rate of nursing home utilization is higher among rural African-Americans than those in urban areas.

Rural Hispanic elders have a higher prevalence of ADL and IADL deficits and cognitive impairments than comparable non-Hispanic white elders. Rural Hispanics are twice as likely as nonrural Hispanics to use nursing home care. Still, because over 60% of rural Hispanic elders were born outside the United States, their access to care is limited and they are often underserved. In part, this is due to lack of Medicare, lack of knowledge of available services, and language barriers. In addition, Hispanic elders have high expectations that their children will provide assistance when needed.

There are over 200,000 American Indians and Alaskan Natives age 65+, according to the 2010 US Census. There are 562 federally recognized tribes and over 200 languages. Older American Indians have often lived their whole lives in one community. According to the Indian Health Service (IHS), the incidence of chronic diseases is increasing rapidly, substantially raising health care costs. Disability is extremely common among AI/AN elders with 30% having at least one ADL deficit (compared to 17% of whites).

Although there has been a movement toward independent and self-administered health care for many AI/AN tribes, the IHS continues to provide care to many older persons. However, funds have never been appropriated to the IHS for long-term care (LTC). Hence, most elders in need of LTC use tribal support, Medicaid, and Administration on Aging–funded services. Many go without services. There are only 20 tribally funded nursing homes in the United States. Many providers involved in caring for older American Indians and Alaskan Natives have been advocating for expansion of home- and community-based waivers through the state's Medicaid programs or funding at a national level.

ACCESS

Rural Providers

Fewer than 11% of the nation's physicians are practicing in rural areas. Over 20 million rural residents live in areas that have a shortage of physicians to meet their basic needs. The majority of physicians (54%) in rural areas are in the primary care specialties of family or general practice, general internal medicine, pediatrics, and obstetrics/gynecology,

compared with 38% of metropolitan physicians. Among the primary care specialties noted, family physicians are the most likely to practice in rural areas. Unfortunately, not only is there a geographic maldistribution of physicians, as evidenced by 11% serving 20% of the population, an additional concern is the aging of the current rural health care workforce and the anticipated retirement, without replacement, of that workforce.

The maintenance of a rural practice is difficult. As is the case with rural hospitals, patients are older, suffer from multiple chronic illnesses, and are more likely to have public insurance coverage. To address the latter, Medicare offers a 10% bonus payment to physicians practicing in Health Professions Shortage Areas, 65% of which are rural. Recently, the Affordable Care Act (ACA) increased Medicaid reimbursement to primary care physicians to the Medicare level, although for a time-limited period. Yet many physicians do not make use of the bonus and some who are not eligible have used it extensively. A study of rural physicians in Florida revealed that many were considering dropping Medicare or some services because of reimbursement problems.

Rural Health Clinics

The federal government authorized Public Law 95-210, the Rural Health Clinic Services Act, in 1997, which assures Medicare and Medicaid reimbursement to certified clinics staffed by physician assistants (PAs) and nurse practitioners (NPs) working with physician supervision. The purpose of the rural health clinic (RHC) program is to increase primary care medical services in rural, physician-shortage areas by utilizing PAs and NPs. Financial stability was promoted by providing cost-based compensation for care of Medicare and Medicaid patients. RHCs are now paid under a special prospective payment system designed for them. The program failed to thrive during its first 10 years until Congress made a series of changes that reduced burdensome paperwork, increased payment levels, and enhanced technical assistance and awareness. Modifications to state PA and NP laws, such as relaxation of onsite supervision requirements and the delegation of prescriptive authority, have also contributed to the program's success. As a result, the number of certified RHCs has grown from less than 600 in 1990 to over 4000 in 2013.

RHCs care for large numbers of Medicare, Medicaid, and uninsured patients. A 2003 national survey revealed that Medicare or Medicaid covers approximately 56% of patient visits in RHCs and approximately 15% are uninsured. Unlike a fee-for-service practice where Medicare and Medicaid payment is based on the cumulative charges for all services provided, a RHC is paid on a clinic-specific, all-inclusive rate that is adjusted annually and, in a majority of cases, subject to a limit set by the government. Challenges continue including questions about reimbursement models, the requirement for use of PAs and NPs, and the impact of managed care programs.

Federally Qualified Health Centers

Federally qualified health centers (FQHCs) include all organizations receiving grants under section 330 of the Public Health Service Act, certain tribal organizations, and FQHC look-alikes. Look-alikes are those organizations that meet the eligibility requirements noted below but do not receive Section 330 grant funds. There are approximately 1200 FQHCs with more than 9000 sites that receive grants under Section 330. In 2012 they served 21,102,391 patients. There are about 100 FQHC look-alikes that served 951,242 patients. Over 7% of patients served in FQHC were age 65 and over (**Table 22-4**).

TABLE 22-4 REQUIREMENTS FOR FEDERALLY QUALIFIED HEALTH CENTERS

- Serve an underserved area or population (Medically Underserved Area or Medically Underserved Population designation).
- Offer a sliding fee scale.
- Provide comprehensive services, including primary care services for all ages, preventive health services, dental services, mental health and substance abuse services, and transportation services necessary for adequate patient care. Hospital and specialty care must be provided on site or through an arrangement with another provider.
- Have an ongoing quality assurance program.
- Have a governing board of directors (www.raconline.org/topics/federally-qualified-health-centers).

There have been some studies comparing RHCs with FQHCs. The North Carolina Rural Research Center compared the distribution of RHCs and nonmetro FQHCs. They found that there are three times as many RHCs (hospital based and independent) than nonmetropolitan FQHCs, even though they are not evenly distributed around the country. RHCs see more Medicare beneficiaries than do nonmetro FQHCs, although a greater percentage of the

provider fee is paid by the patient at a RHC than at a nonmetro FQHC. RHCs see higher percentages of older adults between the ages of 75 to 84 (27% vs 21%) and the oldest old (13% vs 8%) than nonmetro FQHCs, and the RHC clientele is predominantly white (91% vs 81%). Medicare beneficiaries travel shorter distances for care at a RHC (median distance 7 mi) compared to a nonmetro FQHC (median distance 8.7 mi).

Pharmacy Services

Over a 10-year period, 2003 to 2013, 12.1% of independent pharmacies located in rural America closed their doors. The loss of the local pharmacy hits hardest those rural elders with limited mobility and those without a support network that can pick up their prescriptions. Moreover, the local pharmacy has played an important role in rural communities with a limited primary care workforce in that they have been a source for a variety of clinical services including blood pressure checks, diabetes counseling, and immunizations. It is likely that the 340b Drug Pricing Program, which is afforded to FQHCs and rural safety net hospitals (eg, critical access, sole community, etc), mitigates some of the problem by providing discounts on outpatient drugs.

Rural Hospitals

Rural hospitals serve nearly 72 million people, of whom about 20% are Medicare beneficiaries. Rural hospitals face significant pressures—continued shortages of trained staff, rising health care liability premiums, and access to capital for investments in new technology or information systems. Rural hospitals are financially more at risk due to their small size, modest assets, and limited financial reserves. They also serve a higher percentage of Medicare patients since rural populations are typically older than average urban populations. Hence, Medicare margins are the lowest for rural hospitals, with the smallest hospitals having the lowest margins. For all these reasons, there has been a dramatic increase in the closure of rural hospitals, with more rural hospitals closing in 2014 alone than in the previous 15 years. The loss of a rural hospital represents a sea change in the economic health of a community, representing as it does a major employer, as well as a key factor in a community successfully bringing in and/or retaining health care providers and new businesses.

Older age and higher rates of poverty among its service population contribute greatly to rural hospital dependence on public programs, that is, Medicare and Medicaid, and the impact of policy changes in those programs on their financial bottom lines. For example, the advent of prospective payment in the 1980s and managed care in the 1990s led to the closure of many rural hospitals. Those that survived diversified their offerings by developing a variety of postacute services. These included in-hospital skilled nursing facilities and home health programs. Some also developed assistive living facilities and adult day care programs. However, the Balanced Budget Act (BBA) of 1997 decreased payments to rural hospitals for skilled nursing and home health services, leading many of the hospitals to subsequently reduce or discontinue these programs.

The federal government has developed some special categories of hospitals to better meet the constraints posed by being in a rural setting. In 1997 Congress passed the Medicare Rural Hospital Flexibility Program allowing small hospitals, that is, fewer than 25 beds, to apply to be certified as Critical Access Hospitals (CAHs), a special category of rural hospital that receives cost-based reimbursement. To be designated a CAH, a rural hospital must meet defined criteria. As of June 2014, there are 1326 certified CAHs located throughout the United States. CAHs account for almost 50% of all rural hospitals. A list of CAH can be viewed online at http://www.flexmonitoring.org/data/critical-access-hospital-locations/.

The Medicare Modernization Act of 2003 created the Rural Community Hospital Demonstration Program to test the advisability and feasibility of establishing a different category of RCHs to provide Medicare-covered inpatient hospital services in rural areas. In order to participate in the demonstration, the hospital must be located in a rural area, have fewer than 51 acute care beds, have 24-hour emergency care services available, and not be eligible for CAH designation. Medicare inpatient services are paid based on reasonable costs of providing such services to Medicare beneficiaries. After a period of time, the reimbursement process is modified to account for increased costs. For this demonstration, hospitals had to be located in one of the 10 least densely populated states: Alaska, Idaho, Montana, Nebraska, Nevada, New Mexico, North Dakota, South Dakota, Utah, or Wyoming. Thirteen small rural hospitals in seven sparsely populated states were among the initial program participants. Twenty additional hospitals were added in 2010. A bill to extend the Demonstration Program was introduced in Congress in May 2014 in order to add new hospitals to the demonstration in response to the loss of facilities due to closure or a change to CAH status.

Congress has also created other designations to try and protect rural hospitals including the Sole Community Hospital, the Medicare Dependent Hospital, and the Rural Referral Center. Each of these designations must meet

certain criteria (eg, number of beds, geographic isolation, and Medicare load) and receives reimbursement based on criteria specific to the designation. Along with the CAH designation together these account for 87% of all rural hospitals. The remaining 13% are paid under Medicare's standard inpatient and outpatient prospective payment system.

LONG-TERM CARE

The Social Security Act permits certain small, rural hospitals to enter into a swing bed agreement, under which the hospital can use its beds, as needed, to provide either acute or skilled nursing facility (SNF) care. Approximately 95% of rural hospitals operate swing beds. As defined in the regulations, a swing bed hospital is a hospital or CAH participating in Medicare that has Centers for Medicare and Medicaid Services (CMS) approval to provide posthospital SNF care and meets certain requirements. Medicare Part A covers posthospital extended-care services furnished in a swing bed hospital. Swing bed facilities must be incorporated into the SNF prospective payment system by the end of a statutory transition period. CAHs with swing beds are exempt from the SNF prospective payment system (PPS) under more recent legislation. To qualify for SNF-level services, a beneficiary is required to receive acute care as a hospital inpatient for a medically necessary stay of at least 3 consecutive calendar days.

Nursing home care is the mainstay of LTC services in rural areas. Nearly 40% of the nation's nursing homes are in rural areas, and nursing home beds per 1000 population are higher than urban areas. However, skilled beds and special care units are less common. A large number of rural hospitals still offer a variety of postacute and long-term services. Approximately 50% of rural hospitals operate an SNF.

Rural hospitals are involved in operating home health agencies, though the number has been declining. Approximately 35% of CAHs have home health programs. However, after the BBA of 1997, home health care in rural areas dropped by 26%, compared to a 19% decline in urban areas. Many rural hospitals are finding it difficult to maintain these programs and 52% of programs are operating at a loss. Those units that are part of a multihospital system tend to offer both skilled nursing unit services and home health at a higher rate than independent hospitals.

Integration of acute and long-term services has been promoted as a method to improve quality, reduce errors in transitions in care, and lead to reduced costs. Care integration is more difficult in rural areas for a number of reasons. Limited financial resources are the main hindrance. Rural hospitals do not operate high-volume, high-reimbursement business lines, such as transplant or cardiac surgery programs. They also serve a larger proportion of Medicare and Medicaid clients. However, some states such as Wisconsin and Minnesota have developed successful integrated rural programs. Perhaps the quintessential integrated program is the Program of All-Inclusive Care of the Elderly (PACE). This model uses capitated Medicare and Medicaid funding to provide services to nursing home–eligible clients. In 2005, the CMS announced $7.5 million in competitive grants to 15 rural health care provider organizations to support development of PACE across rural America. Since that time all but one have been successfully launched. More on rural PACE programs can be found at www.npaonline.org.

Residential care facilities (which operate under a variety of names, such as assisted living facilities, boarding homes, community residencies, or personal care homes) tend to have older, but less disabled residents than their urban counterparts. They are also more likely to offer a variety of services, such as respite care, social services counseling, and transportation. In addition, they more often serve elders with developmental needs and mental illness.

TECHNOLOGY AND RURAL AGING

Because of the problems of distance, and the lack of providers, facilities, and economies of scale, technology holds great promise to expand the services provided to older adults living in rural areas. A wide variety of technologies exist for this use, and the technology is rapidly changing and becoming less expensive. Medicare now covers telemedicine, which has greatly expanded access.

Telemedicine may be particularly useful when using interdisciplinary teams in rural geriatric care. NPs, PAs, and rehabilitation therapists can communicate with one another and a physician to optimize care for frail older persons. Kansas University has been using telemedicine to enable speech and language pathologists to conduct swallowing evaluations from remote sites. It has also been used in rural nursing homes for monitoring and directing wound care. Comprehensive geriatric assessment has been conducted in rural areas using telemedicine to link with a geriatrician at a remote area. It is particularly useful in home care, where a wide variety of health assessments, such as blood pressure, temperature, monitoring of heart and lung sounds, oximeters, spirometers, and laboratory determinations can

be made. Patients of family caregivers can be trained to administer the assessments and transmit the results to treatment of team members. This is particularly useful in chronic disease management programs.

The challenges of instituting widespread use of interactive televideo medicine are numerous. They include limitations of reimbursement in some states, the absence of or antiquated technical infrastructure, interstate telemedicine license questions, privacy concerns, and the fact that the present cohort of elders and particularly those in rural areas are not particularly technologically savvy. However, in spite of these barriers, rural physicians who recognize the benefits to both themselves and to their patients are likely to implement a telemedicine strategy when offered.

THE AFFORDABLE CARE ACT AND RURAL AGING

A number of provisions of the ACA affect rural aging health care. The elimination of cost sharing for preventive care is likely to disproportionally benefit elders in rural areas, as out-of-pocket spending is generally higher there. The expansion of the Money Follows the Person program will likely increase home- and community-based services. The 10% bonus payments to physicians and surgeons help to stabilize the primary care environment. In 2011, over $76 million in bonus payments were made to rural primary care providers. Medicaid payment parity also helps rural providers. Some outpatient and hospital protections were implemented. The ACA authorized $11 billion for community health centers (CHCs). Nearly one-half of CHCs are located in rural areas. Unfortunately, only a few of the innovative models being tested by the Center for Medicare and Medicaid Innovation are focused on rural health care.

HIV, RURAL LIFE, AND AGING

Due to treatment advances many HIV patients are now living a normal life span. Ultimate longevity does vary slightly depending on CD4 count at initiation of treatment and the achievement of long-term viral suppression. Because of these advances, geriatricians are beginning to see the first generation of older HIV patients, and many live in rural areas. Rural populations comprise 5% to 8% of all US HIV cases. Regionally, the southern rural areas are the hardest hit, with 68% of all AIDS cases. The infection rate in these areas is 320/100,000. Minority communities make up the majority of those infected. African-Americans compose more than 50% of the rural AIDS cases. Latinos and American Indians/Alaskan Natives make up 9% and 2%, respectively. Caucasians make up the remaining 37%.

In many cases of those with a lifelong HIV infection, friends and family with HIV are their major support system. The loss of those supports is particularly difficult for the older person. In addition, in rural areas, there may be a greater perception of the stigma related to the diagnosis. There are still many misconceptions that HIV can be transmitted through simple touch, kisses, and sharing drinks. More importantly, there are those who firmly believe that those infected somehow “got what they deserved,” for the lives they have chosen to lead. Because of this, patients are very skeptical of disclosing their status.

In many small communities, the church acts as the primary support system to many patients. Congregations provide meals, social/recreational activities, and financial assistance. In many rural communities, churches have begun nonprofit church-based health clinics. Many of these clinics are not specifically set up for HIV patients, but still meet their needs collaterally in terms of overall medical health. The confounding factor in many cases is that the views of the church are in direct contradiction to the views of the patient in regard to lifestyle choices (especially in the case of men who have sex with men). This can make it very difficult for these patients to ask for help, even if it may be a last resort.

SUMMARY

Rural aging provides both significant challenges and special opportunities. The number of elders in rural settings is not likely to decline soon. Primary care physicians will always provide the bulk of care to older persons in rural areas. The advent of new technologies should allow expansion of services and greater access to high-quality geriatric care.

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Additional Resources

National Rural Health Association: www.nrharural.org

National PACE Association: www.npaonline.org

National Association of Rural Health Clinics: www.narhc.org/

USDA Economic Research Service. Rural Poverty and Well-Being: http://www.ers.usda.gov/topics/rural-economy-population/rural-poverty-well-being/geography-of-poverty.aspx#.U9FQMeNdWSo

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FQHC FAQ: http://www.raconline.org/topics/federally-qualified-health-centers/faqs#location
National Association of Community Health Centers: http://www.nachc.com/about-nachc.cfm

Chapter 23

Quality of Care

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Learning Objectives

- Identify the different ways that quality of care can be assessed.
- Discuss the quality-of-care issues particular to older adults.
- Explain which patient safety practices are most relevant for older adults.
- Understand the basic elements of quality improvement.

Key Clinical Points

1. **Quality can be measured as structure, process, and outcome. Most quality measurement schemes have used process measures, but outcome measures are becoming more common, and will likely continue to do so into the future.**
2. **There are a great many existing US quality measurement efforts. Particularly prominent examples are those led by the Centers for Medicare and Medicaid Services (CMS), the National Committee for Quality Assurance (NCQA), the Consumer Assessment of Healthcare Providers and Systems, and The Joint Commission (TJC).**
3. **There is no cookbook that can be followed for quality improvement initiatives. Success depends on many factors, and context is important.**

DEFINING QUALITY OF CARE—THE DONABEDIAN STRUCTURE-PROCESS-OUTCOME MODEL

The traditional framework for understanding how quality of care can be measured is one proposed by Donabedian (**Figure 23-1**). The underpinning of this framework is that high-quality medical care is defined as care which is expected to achieve the best balance of health benefits and risks, in other words medical care that does the best job at improving health or preventing health decline. Within this framework, quality is conceptualized as pertaining to technical and interpersonal care, each of which may influence the other.

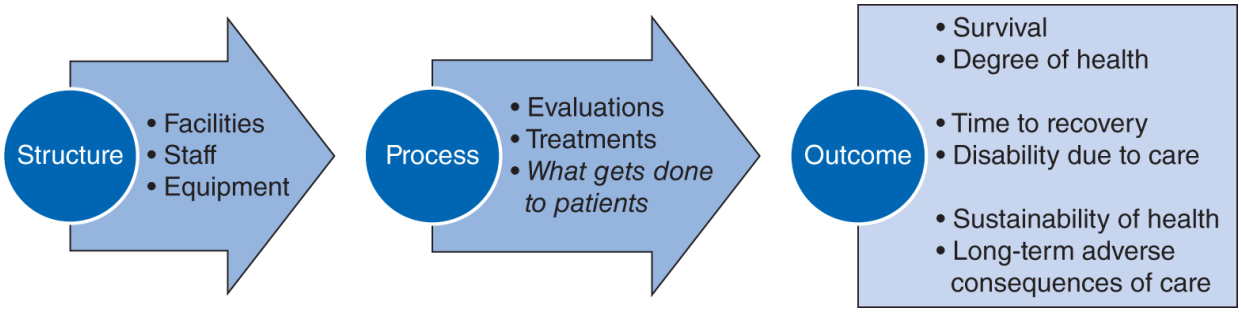


FIGURE 23-1. Donabedian frame work. (Adapted from Donabedian A. *The Definition of Quality and Approaches to Its Management, Vol 1:*

Technical Care

Technical care can be measured in three domains: structure, process, and outcomes. *Structure* refers to the relatively stable characteristics of the providers, the tools and resources available to them, and the physical environment and organizational characteristics of the health system. Examples of structural measures of quality include board certification of physicians and accreditation of health organizations such as hospitals and health plans; the use of electronic health records or computerized provider order entry; and designation as a level 1 trauma center, which requires several structural requirements be met, including but not limited to, 24-hour in-house coverage by general surgeons, a minimal annual volume of severely injured patients and a comprehensive quality assessment program. The validity of structural measures depends on the evidence to support a relationship between the structure and a health outcome. An advantage of structural measures is that they are relatively easy to measure. However, given the stability of most health care structures, structural measures are generally not suitable for continuous quality assessment/improvement activities, but rather for periodic assessment.

Process refers to what health care providers do for patients. Examples of process measures include the prescription of β-blocker medications to patients following an acute myocardial infarction, the offering of annual influenza vaccinations for certain classes of patients, screening for colorectal cancer with a fecal occult blood test or colonoscopy, and providing yearly examinations of the feet in patients with diabetes. As with structural measures, the validity of process measures depends on demonstrated evidence that the process is associated with a favorable health outcome. For example, there is good evidence that β-blockers given after a myocardial infarction will reduce future myocardial infarctions, cardiac arrhythmias including sudden death, and mortality. An advantage of process measures is that they can be used in real time, or over relatively short periods of time, to identify and correct process of care gaps that can be closed to improve health outcomes. While data for some process measures can be collected with relative ease from health plan administrative data, many process measures require detailed clinical data available only from medical records' abstraction or clinical registries designed specifically to capture those data.

Outcome refers to a person's health state, and is commonly divided into two categories: *indirect* (or *intermediate* or *proxy) outcomes*, and *patient health outcomes* (or sometimes *patient-centered outcomes*). Patient health outcomes include specific clinical events that are ascertained or diagnosed by clinicians such as myocardial infarction, stroke, or death. Patient health outcomes also include "patient-reported outcomes" or "PROs," which are things patients can feel or observe for themselves such as pain, function, or urinary incontinence. Indirect outcomes refer to outcomes that lead to, or act as a proxy for, patient health outcomes that are otherwise difficult to measure. Indirect outcomes include measures of *clinical parameters* such as blood pressure, blood sugar, and lipid levels, and of *utilization* such as hospital admissions, readmissions, and emergency room visits. Blood pressure is one of the most well-known clinical parameters used as an indirect outcome. The vast majority of patients with elevated blood pressure have no symptoms attributable to it, but the presence of persistent high blood pressure is known to be a contributing cause to many patient health outcomes, such as stroke, myocardial infarction, and kidney failure. It takes many years for these outcomes to develop, and it is proven that lowering elevated blood pressure can reduce the risk of stroke, myocardial infarction, etc. Thus, we accept that the control of blood pressure—a condition most patients can't feel—is a valid indirect measure of patient outcome. Other examples of commonly used indirect clinical measures of patient outcome include the value of hemoglobin A_{1c} in patients with diabetes and various lipid measurements in patients with (or at risk for) cardiovascular disease. Similarly, certain types of health care utilization are used as proxies for poor or worsened health. For example, it is presumed that the health of a patient with asthma had declined if the patient visited an emergency room (ER). Likewise, it is presumed that the health of patient is poor if the patient requires a readmission to a hospital within 30 days of discharge.

Of course, the degree to which an indirect measure of outcome is considered valid rests on the strength of the evidence supporting the relationship between the measure and the outcome it represents. Much of the controversy surrounding some indirect measures is because of disagreements about the interpretation of the evidence supporting this linkage. For example, although the utilization metric for hospital length of stay is sometimes used as an indirect outcome measure, there is concern that reducing length of stay too much will worsen health outcomes. Determination of the optimal length of stay to achieve the best health outcomes for various conditions is needed to inform the use of this metric as an indirect outcome measure.

Outcome measures are often considered the "gold standard" of quality measures as they directly measure the health that the medical system is intended to improve. However, many other factors outside the control of the health system

may also impact health outcomes. Additionally, underlying patient health status may impact achievable outcomes. Hence, outcome measures must be risk-adjusted as appropriate for factors beyond the health system that may impact the outcome.

Interpersonal Care

Interpersonal care describes the "goodness" of interactions between patients and the health care system, and includes patient experience or patient satisfaction. Patients are the ultimate authority on which aspects of interpersonal care are important and in determining whether some defined level of interpersonal care was delivered. While interpersonal care may impact technical care—a satisfied patient may be more likely to comply with care recommendations—the two measure fundamentally different constructs and may be incongruent. Technically perfect care delivered by providers who seem uncaring to a patient, or from within a system that is difficult for a patient to navigate may not be associated with high patient satisfaction.

These measures of quality are viewed differently by different stakeholders. Process measures are often viewed by clinicians as the best measure of quality, since process measures define doing the right thing, for the right patient, at the right time. As such, they are under the control of the provider, and are "actionable"—meaning that if quality is judged to be low based on the proportion of patients receiving an annual influenza examination, for example, providers know that to remedy this requires delivering more vaccinations. Outcomes are often viewed by patients as being the best measure of quality, since outcomes are what patients value most—"Did I get better?" Clinicians view much of the outcome of a health condition as being outside their control, and can all relate stories about patients who got the right care at the right time and still had bad outcomes, as well as stories about patients (cared for by other providers) who did not get the right care at the right time yet still recovered. Recent advances in risk adjustment has increased clinicians' acceptance of some outcomes as valid measures of quality.

HOW QUALITY IS MEASURED

Quality measures operationalize the concepts of interpersonal and technical care quality for measurement in different settings. Quality measures specify in great detail the specific structures, processes, outcomes, or consumer experiences to be measured, the specific population in which these should be measured, and the time frame over which measurement should occur. Types of data (eg, patient report, medical records, administrative data from health plans or other sources) are also explicitly defined for a quality measure. Quality measures in the United States are developed by a number of different types of entities with interest in the health care quality including accreditation organizations, government, provider organizations, health delivery systems, specialty societies, and academic institutions. The same quality concept could be developed into several different measures, generally in order to measure quality at different levels within the health care system. For example, NCQA, an accreditation organization, and the American Medical Association's Physician Consortium for Performance Improvement (AMA PCPI), which represents physicians, have developed measures to determine whether diabetics obtain appropriate screening for retinopathy. The AMA measure is focused on the population within a physician practice; the NCQA Healthcare Effectiveness Data and Information Set (HEDIS) measure on the population within a health plan. The National Quality Forum (NQF), an independent not-for-profit entity established in 1999 based on recommendations by the President's Advisory Commission on Consumer Protection and Quality in Health Care, is the national overseer of quality measures in the United States. NQF does not develop measures, but defines areas of national importance and reviews measures developed by others within those priority areas for endorsement. NQF regularly reviews new and existing measures in priority areas, using a standard process that is open to the public. All measure developers can submit measures to NQF for review and endorsement if the measure meets NQF standards. One of NQFs' priorities is to align and streamline related quality measures, which it does through its Measures Application Process (MAP). Many quality measurement entities in the United States seek to utilize only NQF-endorsed quality measures in their measurement systems, unless NQF has not evaluated measures in a topic area.

Some Existing US Quality Measurement Schemes

There are numerous existing schemes for measuring quality of care, each with a different focus dependent on the interests of the sponsoring organization. Hence, the unit of analysis (eg, health plan, patients treated within a single hospital, etc) and the combination of individual measures within each system differ. Each of these systems has an

underlying quality theme/measurement objective and reaches into the pool of available individual quality measures to build a measurement system. Consequently many of the same individual measures are used in different measurement systems. If the measures needed to assess quality concepts of interest do not exist, an entity may develop the needed measures. Developing quality measures is very challenging, especially in the geriatric population. Lack of evidence, validity of applying existing evidence to complex and vulnerable older patients, the need for carefully constructed risk-adjustment methodology that can be confusing to physicians and patients, and the potential for unintended consequences of quality measures to do harm in older patients combine to make the development of valid measures of quality that can be used to fairly judge the quality of geriatric care an extremely time-consuming and challenging endeavor.

Current reporting schemes and programs use a variety of different measures applied to different populations, which are of varying importance to different stakeholders. For example, the measures in the Physician Quality Reporting System (PQRS) are applicable to individual and groups of physicians, while measures in the Medicare Advantage Stars Program are applicable to health plans. These different measurement schemes have varying utility for different end users. For patients seeking information on the quality-of-care delivery, reporting at the level of the individual provider, provider group, or hospital is most relevant. However, reporting at this level is currently somewhat limited. Quality reported at the health plan level provides useful information to consumers in differentiating health plans, particularly with regard to plan-specific constructs such as the impact of plan benefits on access to care and medications. The applicability of clinical quality reported at the plan level to individual consumers will vary from plan to plan depending on the size, geographic range, and degree to which the provider network is integrated. For example, clinical quality scores for health plans that have an exclusive relationship with a specific provider group, such as the relationship between Kaiser and the Permanente Medical Group, likely represent well the quality that an individual plan beneficiary is likely to receive. However, the scores for plans with large, geographically disperse networks of independent providers may not represent well the quality that individual beneficiaries will receive as it is likely to vary across providers and geographies.

QUALITY MEASURE SETS

In the United States, probably one of the best known measure sets is the HEDIS, developed by the NCQA. Begun more than two decades ago (as the Health Plan Employer Data and Information Set), HEDIS started out as a handful of process measures and today has grown to over 80 measures (of structure, process, and outcome) that encompass effectiveness of care, access/availability of care, experience of care, and utilization/relative resource use (http://www.ncqa.org/HEDISQualityMeasurement.aspx). HEDIS measures are assessed at the level of the health plan. Health issues addressed in HEDIS include asthma medication management, controlling high blood pressure, breast cancer screening, antidepressant medication management, childhood and adolescent immunization status, and diabetes care. HEDIS measures are used for public reporting of health plan quality by NCQA, as one component of NCQA health plan accreditation scoring and as one component of NCQA's national health plan ranking system. State Medicaid programs and the federal Medicare Advantage program also use plan-level HEDIS scores in transparency programs and to determine health plan payment.

The AMA's PCPI has worked with individual medical specialty societies over the last decade to develop performance measures that can be assessed at the point of care (https://www.ama-assn.org/ama/pub/physician-resources/physician-consortium-performance-improvement.page). The measures developed by the PCPI are based on recommendations in existing clinical practice guidelines. The PCPI measure set includes over 300 primarily process measures that span 47 clinical topics. These can be measured through paper or electronic medical records review or through the use of Common Procedural Terminology-II (CPT II) codes. In contrast to CPT codes, which detail medical services provided for the purposes of billing, CPT II codes are developed for specific quality measures and describe whether certain care processes or clinical characteristics defined in the measure have been completed. Some AMA PCPI measures are used in the CMS PQRS, described below.

Another key measure set, which is used by many quality assessment systems is the group of Consumer Assessment of Healthcare Providers and Systems (CAHPS) surveys. CAHPS surveys ask patients to report on their experiences with a range of health care services at multiple levels of the delivery system. In addition to items on patient experience, the CAHPS survey includes some items that relate to technical care, for example, whether a consumer received a flu shot. Separate surveys are available to assess consumers satisfaction at the levels of health plans, mental health plans, hospitals, dialysis centers, nursing homes, and physicians' offices. The CAHPS surveys are developed and

maintained by Agency for Healthcare Research and Quality (AHRQ). They are in the public domain and available for use free of charge. CAHPS measures are used in many quality programs including NCQA health plan accreditation, The Joint Commission (TJC) health organization accreditation, the CMS Hospital Compare Program, and the CMS Medicare Advantage Stars Program.

A variety of other organizations also develop quality measures including medical specialty societies, state or other local quality collaborative groups or coalitions, and academic centers. In many cases, medical specialty society–developed measures have been developed for and are measured through clinical registries run by the society. The Society of Thoracic Surgeons (STS), the American Society of Clinical Oncology (ASCO), and the American College of Gastroenterology are such examples. State-wide quality improvement organizations such as Minnesota Community Measurement and the Wisconsin Collaborative for Healthcare Quality may likewise develop measures to support local quality improvement efforts.

Quality Assessment Programs

Building on individual quality measures, quality assessment programs are used to measure and report quality more comprehensively. Many of these programs assess quality within a specific clinical area (eg, cardiovascular or surgical care) or for a specific care structure or process (eg, case management or health information technology). Quality programs are specific to different parts of the delivery system including health plans, health systems, and individual health providers. The scope of the programs can range from national to very local. The purpose of the programs may range from quality improvement, to transparency, to accountability. These programs may be used to determine participation in networks or payment for care delivery. We describe below some of the larger quality assessment programs in the United States.

In addition to developing the HEDIS quality measures, the NCQA maintains a number of other quality programs, many of which utilize HEDIS measures. NCQA was born out of employer interest in understanding the quality of care that was being delivered by managed care organization from whom they were purchasing health insurance for their employees. NQCA's quality assessment activities were initially focused on health maintenance organizations (HMOs) but have expanded over the years to include accreditation for HMO and preferred provider organization (PPO) health plans, case management, disease management, and accountable care organizations; certification for health information products, credentials verification organizations, and physician organizations; and physician recognition programs for back pain, diabetes, and patient-centered medical homes. A complete list of the quality assessment programs offered by NCQA can be found at http://www.ncqa.org/HEDISQualityMeasurement/QualityMeasurementProducts.aspx. Participation or achievement of set targets in these programs by one stakeholder may be required by another stakeholder. For example, certain employer-purchasers may require health plans to achieve accreditation; health plans may require provider groups to achieve patient-centered medical home recognition.

Another well-known US organization measuring quality of care is TJC. With roots in the American College of Surgeons and its Minimum Standards for Hospitals program dating back to 1917, TJC is the oldest quality standards setting and measurement organization in the United States. Initially focused on hospital quality, the Joint Commission on Accreditation of Hospitals (JCAH) expanded its scope to include other health care organizations such as psychiatric and long-term care facilities and became the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), which is now known simply as "The Joint Commission." TJC accredits hospitals, health organizations, and programs. In many instances TJC accreditation is a requirement for participation in the networks of health insurers including CMS. TJC has a number of core measure sets for conditions such as stroke, tobacco treatment, venous thromboembolism, heart failure, pneumonia, and acute myocardial infarction. These sets may include structure, process, and outcome measures. They are assessed using all-payer data at the level of the health organization, which is accredited (eg, hospital, long-term care facility).

The CMS measures quality at the physician, hospital, skilled nursing facility (SNF), home health care, and health plan levels. The Physician Compare, Hospital Compare, Nursing Home Compare, Home Health Compare and Medicare Advantage Stars Programs report quality information on the internet at the levels of the physician, hospital, nursing home, home health agency and health plan, respectively. The quality reported at Physician Compare for individual physicians is currently limited to board certification and whether a physician participates in any CMS quality programs. At the group level, performance scores are reported on five different process and intermediary outcome measures for those who participate in the Medicare Group Practice Reporting Option, which at this writing numbered some 138 groups. Under Section 10331(a) of the Affordable Care Act, CMS is required to "make publicly available information on physician performance that provides comparable information on quality and patient

experience measures." However, the date by which performance reporting on individual doctors must be available has not been defined. Hospital Compare displays the performance of hospitals who accept payment from Medicare on over 100 individual structure, process, outcome, and patient experience measures. The Medicare Advantage Stars Program reports both quality and cost information for Medicare Advantage Health Plans. Originally developed as a consumer shopping tool to assist Medicare beneficiaries in comparing and selecting Medicare Advantage Health Plans, the program has evolved to include a payment component; health plans may earn up to an additional 5% of revenue based on performance in the Stars program. Similar to the Medicare Advantage Stars Program, the Physician Value-Based Payment Modifier and Hospital Value-Based Payment Programs link payment to physicians and hospitals to performance on quality measures. A subset of the quality measures reported in hospital care is used to determine the quality payment in the Hospital Value-Based Payment Program. Currently the physician program is based only on participation, that is, reporting, in the Physician Quality Reporting System Program quality reporting, but will move to performance in the future. Both programs are designed to be budget neutral. Funding for the hospital funding comes from a current 1% reduction in the "base-operating diagnosis-related group (DRG)" payments that the hospital receives from Medicare. This amount will increase to 2% by 2017. About half of hospitals will receive a quality bonus from this pool. In the physician program, payments to physicians will increase for those who deliver higher-quality more cost-effective care, and will decrease for those who provide lower-quality less cost-efficient care.

The CMS has a particular focus on measuring quality of care in SNFs, largely because of repeated reports in medical literature, governmental and Institute of Medicine reports, and the lay press of poor quality of care in this setting over the past four decades. For example, in 2014 the Office of Inspector General (OIG) issued a report documenting that 22% of SNF patients experienced an adverse event in the first 35 days of their SNF stay, and that 59% of these events were rated as preventable by a panel of experienced physicians. The CMS has an extensive set of rules and regulations intended to address the quality of care in SNFs, which are being extensively updated in 2015 "since their last update in 1991." The CMS posts quality measures for SNFs on the Nursing Home Compare website (https://www.medicare.gov/nursinghomecompare/search.html). These measures are derived from the minimum data set (MDS), and many of them are controversial (see below). Based on these and other measures, US SNFs are rated on a five-star system (http://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/CertificationandComplianc/FSQRS.html). The derivation of this rating system is very complicated and is very controversial in the SNF industry.

The comprehensiveness of quality programs sponsored by medical specialty societies varies greatly from essentially no organized quality measurement activities to the development of robust measures which can be used at the point of service to improve clinical care. Some specialty societies strike a middle ground by reviewing and endorsing/rejecting measures developed by other organizations that are relevant to their particular specialty. Both the American Geriatrics Society (http://www.americangeriatrics.org/health_care_professionals/clinical_practice/clinical_guidelines_recommendations/) and the American Medical Directors Association/Society for Post-Acute and Long-Term Care Medicine (http://www.amda.com/tools/guidelines.cfm) have developed numerous clinical practice guidelines, and have participated actively in the American Board of Internal Medicine Foundation's Choosing Wisely Campaign. As of 2015 these two organizations have each identified 10 interventions that should be avoided or carefully considered in older patients, with substantial overlap in their recommendations (http://www.choosingwisely.org/societies/american-geriatrics-society/ and http://www.amda.com/tools/choosingwisely.cfm). However, neither organization develops or endorses quality measures.

MEASURING QUALITY OF CARE IN OLDER ADULTS

Measuring the quality of care in older adults has many similarities, but also some important differences, to measuring quality of care in younger adults. Many health conditions—pneumonia, myocardial infarction, stroke, diabetes, etc—occur with equal or greater frequency in older adults, and have similar or identical process and outcome measures that are relevant to assessing quality of care. However, there are a number of health care conditions that are far more common in older adults than in younger adults, and for which (in the past) many existing quality measurement schemes had few or no measures. Dementia, falls, urinary incontinency, hearing impairment, and end-of-life care are a few such conditions. In addition, even for conditions like acute myocardial infarction, stroke, and diabetes, the goals of care may not be the same in older adults as in younger adults. One of the best known examples of this is in tight control of glucose in patients with diabetes. The benefits of tight control only manifest themselves after many years of

treatment, and while this may make sense for a patient aged 50, with 25+ years or more of life expectancy, it may make less sense for patient aged 75, for whom the benefits of tight control in terms of fewer complications in 5 to 10 years may be offset by the immediate risks of hypoglycemia as a result of tight control. Lastly, younger adults have fewer health care conditions than do older adults, and multimorbidity is the rule in older adults. Determining what constitutes quality care may be very different when it occurs as a single condition, such as diabetes or heart failure, than when it occurs in a patient who also has many other health conditions like osteoporosis, osteoarthritis, ischemic heart disease, and mild cognitive impairment. Attention has to be given to interactions between drugs and diseases, drug-drug interactions, and the potential for recommending multiple nonpharmacologic interventions that may be impractical in a vulnerable older person.

THE ASSESSING CARE OF VULNERABLE ELDERS QUALITY ASSESSMENT SET

One of the first attempts to develop a set of quality measures specific for older adults was begun in 1998 by investigators at RAND Health and the University of California, Los Angeles. The goal of this effort was to develop a set of measures that was reasonably comprehensive and included processes of care that, if followed, could be expected to improve morbidity and mortality in older adults. This required defining a group of older adults who were particularly vulnerable to functional decline or death, with the expectation that better health care could make an important difference in delaying these outcomes. Using data from the Medicare Current Beneficiary Survey, a small set of factors, including age, self-rated health, and functional disabilities and limitations was able to identify a group of persons who had four times the risk of functional decline or death over a 2-year period, when compared to older adults without these factors. These patients were called “vulnerable elders” and were the focus of the quality measurement set, as “nonvulnerable elders” were believed to be adequately covered by existing quality measurement sets such as HEDIS. Using a process of literature review and structured expert opinion, 21 target conditions were selected based on their prevalence in older adults, their importance to health care outcomes, the effectiveness of medical care at improving outcomes, and the feasibility to measure care. These 21 diseases, geriatric syndromes, physiologic impairments, and clinical situations included targets such as diabetes and heart failure, hearing and vision impairment, falls and urinary incontinence, and hospital care and end-of-life care (since updated to 26 conditions, see **Table 23-1**). Through a formal process of literature review and structured multidisciplinary group judgment, 236 quality indicators were developed across these 21 targets, with 9% of indicators dealing with screening, 17% of indicators dealing with prevention, 21% of indicators concerning diagnosis, 36% of indicators assessing treatment, and 9% and 8%, respectively, dealing with follow-up and continuity. Each quality indicator was structured in an If-Then-Because format, which specified the target population, the process to be given, and why. For example: **If** a vulnerable elder reported two or more falls in the past year, or a single fall with injury requiring treatment, **Then** there should be documentation that a basic fall evaluation was performed that resulted in specific diagnostic and therapeutic recommendations, **Because** many causes of falls can be detected and treated, detection and treatment will reduce the likelihood of future falls and associated complications.

TABLE 23-1 TARGET CONDITIONS FOR WHICH QUALITY INDICATORS WERE DEVELOPED FOR THE ASSESSING CARE OF VULNERABLE ELDERS PROJECT

Benign prostatic hypertrophy[a]
Breast cancer[a]
Chronic obstructive pulmonary disease[a]
Colorectal cancer[a]
Continuity and coordination of care
Dementia
Depression
Diabetes
End-of-life care
Falls and mobility disorders
Hearing impairment

Heart failure
Hospital care and surgery
Hypertension
Ischemic heart disease
Medication use
Osteoarthritis
Osteoporosis
Pain management
Pressure ulcers
Screening and prevention
Sleep disorders[a]
Stroke and atrial fibrillation
Undernutrition
Urinary incontinence
Vision impairment

[a]Conditions developed for ACOVE-3.

Modified with permission from Wenger NS, Roth CP, Shekelle P. Introduction to the assessing care of vulnerable elders-3 quality indicator measurement set. J Am Geriatr Soc. 2007;55(suppl 2): S247–S252.

Subsequent evaluations of care in two US managed care organizations found that among 420 vulnerable elders eligible for 10,711 quality indicators the overall adherence rate was 55%, and that this varies by condition, with care for general medical care (heart failure, diabetes, etc) being better than geriatric conditions (dementia, falls, urinary incontinence, etc; 83% vs 41% for acute care indicators, 51% vs 29% for chronic care indicators). Supporting the validity of the Assessing Care of Vulnerable Elders (ACOVE), process measures have been studies assessing their association with outcomes. For each 10% increase in adherence to the ACOVE quality indicators, there was a hazard ratio for better survival of 0.64 (95% confidence interval 0.49–0.84). For conditions where mortality is not the primary outcome, such as falls and urinary incontinence, observational studies also supported the validity of the ACOVE measures. For each 10% increment in receipt of recommended care there was an associated 1.4 point improvement in the Incontinence Quality of Life Scale or a 0.4 point improvement in the Falls Efficacy Scale. The original ACOVE set has since been updated, and there have been developed various quality improvement programs based on ACOVE measures. These interventions have involved case-finding and a multicomponent practice change intervention: efficient collection of condition-specific clinical data, medical record prompts to encourage the performance of essential care processes, patient education and activation, and physician decision-support and education. When implemented in two community medical groups, overall care for three ACOVE conditions (falls, urinary incontinence, and cognitive impairment) increased from 25% to 41%, although cognitive impairment care did not improve. A second assessment, of a similar intervention in five practices, also increased quality of care for falls and urinary incontinence (about 20%). ACOVE quality measures have also been developed for the nursing home setting, but have not been as extensively tested as those for community-dwelling vulnerable older adults.

PATIENT SAFETY AND OLDER ADULTS

Improving patient safety is an important goal of health care. It is the first of six priorities identified by the CMS in the US National Quality Strategy: making care safer by reducing harm caused in the delivery of care. The OIG estimated that 13.5% of hospitalized Medicare beneficiaries experienced adverse events during their hospital stay: 0.6% of beneficiaries had a serious reportable event as defined by the NQF, 1.0% had a hospital-acquired condition, and 13.1% had an adverse event in the four most serious categories of patient harm (a prolonged hospital stay, permanent harm, need for a life-sustaining intervention, or death). As discussed above, the OIG has also estimated that 22% of Medicare beneficiaries experienced adverse events during their stay in a SNF.

Partly in response to these data, the CMS decided they will no longer pay for a group of complications termed “Never Events”—originally eight complications, such as retained foreign bodies after surgery and transfusing incompatible blood products, but also including two conditions of particular relevance to older adults: catheter-

associated urinary tract infections and pressure ulcers. (The term "Never Events" is also used by the NQF to apply to a much larger list [more than 20] that includes things like wrong-site surgery and artificial insemination with the wrong donor sperm or donor egg). Many other insurers have followed suit. Additionally, the AHRQ commissioned a review of the evidence for a large number of patient safety practices, Making Health Care Safer II. Two practices were specifically designated as being "aimed primarily at hospitalized elders" (preventing in-facility falls and in-facility delirium), and the report included many other patient safety practices relevant to older adults: reducing adverse drug events by increased use of clinical pharmacists, medication reconciliation, reducing catheter-associated urinary tract infection, reducing pressure ulcers, and ensuring documentation of patient's preferences for life-sustaining treatment. **Table 23-2** presents the summary from that report for each of these topics. The referenced publications review the evidence for specific interventions intended to improve patient safety outcomes. Some concern has been voiced over the "Never Events." For example penalizing hospitals for fall-related injuries could have the unintended consequence of increasing the use of physical and chemical restraints.

TABLE 23-2 ■ PATIENT SAFETY PRACTICES OF IMPORTANCE FOR OLDER ADULTS

PATIENT SAFETY PRACTICE	SCOPE OF THE PROBLEM TARGETED BY THE PSP (FREQUENCY/ SEVERITY)	STRENGTH OF EVIDENCE FOR EFFECTIVENESS OF THE PSP	EVIDENCE OR POTENTIAL FOR HARMFUL UNINTENDED CONSEQUENCES	ESTIMATE OF COST	IMPLEMENTATION ISSUES: HOW MUCH DO WE KNOW?/HOW HARD IS IT?
Safety Practices for Hospitalized Elders					
Multicomponent interventions to prevent in-facility falls[a]	Common/Low	High	Moderate (increased use of restraints and/or sedation)	Moderate	Moderate/moderate
Multicomponent interventions to prevent in-facility delirium; in-depth review[b]	Common/Low	Moderate	Low	Moderate	Moderate/moderate
Other Patient Safety Practices of Particular Relevance to Older Adults					
Use of clinical pharmacists to prevent adverse drug events[c]	Common/low	Moderate-to-high	Low	High	Little/moderate
Medication reconciliation supported by clinical pharmacists[d]	Common/low	Moderate	Low	Moderate	Moderate/moderate
Reducing unnecessary urinary catheter use and other strategies to prevent catheter-associated urinary tract infections[e]	Common/moderate	Moderate-to-high	Low	Low	Moderate/moderate
Multicomponent initiatives to prevent pressure ulcers; in-depth review[f]	Common/moderate	Moderate	Negligible	Moderate	Moderate/moderate
Ensuring documentation of patient preferences for life-sustaining treatment, such as advanced directives[g]	Common/moderate	Moderate	Low	Low	Moderate/moderate

Agency for Healthcare Research and Quality. Making Health Care Safer II: An Updated Critical Analysis of the Evidence for Patient Safety Practices. Rockville, MD: Agency for Healthcare Research and Quality. http://www.ahrq.gov/research/findings/evidence-based-reports/ptsafetyuptp.html. Accessed March 2013.

[a]Miake-Lye I, Hempel S, Ganz D, Shekelle P. Inpatient fall prevention programs as a patient safety strategy: a systematic review. *Ann Intern Med*. 2013;158(5 pt 2):390.

[b]Reston J, Schoelles K. In-facility delirium prevention programs as a patient safety strategy: a systematic review. *Ann Intern Med*.

2013;158(5 pt 2):375.

[c]Glassman P *Clinical Pharmacist's Role in Preventing Adverse Drug Events: Brief Update Review in Making Health Care Safer II: An Updated Critical Analysis of the Evidence for Patient Safety Practices*. Rockville, MD: Agency for Healthcare Research and Quality. http://www.ahrq.gov/research/findings/evidence-based-reports/ptsafetyuptp.html. Accessed March 2013.

[d]Kwan J, Lo L, Sampson M, Shojania K. Medication reconciliation during transitions of care as a patient safety strategy: a systematic review. *Ann Intern Med*. 2013;158(5 pt 2):397.

[e]Meddings J, Rogers MA, Krein SL, Fakih MG, Olmsted RN, Saint S. Reducing unnecessary urinary catheter use and other strategies to prevent catheter-associated urinary tract infection: an integrative review. *BMJ Qual Saf*. 2014;23(4):277.

[f]Sullivan N, Schoelles KM. Preventing in-facility pressure ulcers as a patient safety strategy: a systematic review. *Ann Intern Med*. 2013;158(5 pt 2):410.

[g]Dy S. *Ensuring Documentation of Patients' Preferences for Life-Sustaining Treatment: Brief Update Review in Making Health Care Safer II: An Updated Critical Analysis of the Evidence for Patient Safety Practices*. Rockville, MD: Agency for Healthcare Research and Quality. http://www.ahrq.gov/research/findings/evidence-based-reports/ptsafetyuptp.html. Accessed March 2013.

THE MINIMUM DATA SET

The MDS was originally designed as a comprehensive, standardized geriatric assessment and care planning tool (the Resident Assessment Instrument) and was mandated by the US Congress as a strategy to improve care in US SNFs. Conceptually, the MDS standard assessments of multiple clinical domains can result in triggers for further assessment and changes to the patient's care plan when indicated. The original MDS has gone through two major revisions, and in the process of revision, the focus remained on its use as an assessment and care planning tool. The MDS has, however, been used by CMS for two additional purposes. First, it is used for case-mix adjusted reimbursement for patients on the Medicare SNF benefit (resource utilization groups or "RUGs"). Second, it is used to derive quality measures. A tool originally designed for geriatric assessment has serious limitations when attempts are made to make valid determinations of the costs of care as well as care quality. In the most recent update of the MDS (MDS 3.0) attempts were made to structure several of the items in a way that might result in more valid quality measures. In addition, over the last few years the CMS has recognized that relevant quality measures for short-stay patients may be different than those for long-stay patients, and has added several short-stay measures. Despite these changes, use of MDS-derived quality measures remains challenging and fraught with pitfalls, controversies about risk adjustment and whether to use process as well as outcome measures, and the potential for unintended consequences. Nevertheless, the CMS uses MDS-derived quality measures for public reporting of quality on the Nursing Home Compare website and in calculating SNF five-star ratings. While these measures are developed and tested by experienced clinicians on technical expert panels convened by the CMS, they remain imperfect. Intense and ongoing efforts are underway to make MDS-derived quality measures better—more valid, less subject to reporting bias, focused on important outcomes as well as care processes, and less likely to result in unintended consequences for the quality of care to the vulnerable population in SNFs.

The MDS has also served as the basis for the development of an international collaboration ("InterRAI") with the goal of improving the quality of life of vulnerable persons through a seamless comprehensive assessment system (http://www.interrai.org).

Improving Quality and Safety for Older Adults

Robust methods for improving quality and safety remain an elusive goal. There is no cookbook that can be followed that will produce consistent results in all settings. Quality improvement interventions depend on implementation and are frequently context-sensitive, meaning that their success depends on a host of local factors, such as leadership support and other factors both internal and external to the organization. The Consolidated Framework for Implementation Research lists five major domains important to an understanding of quality improvement interventions: intervention characteristics, the outer setting, the inner setting, characteristics of the individuals involved, and the process of implementation. Various constructs were identified for each major domain, and are listed in **Table 23-3**.

TABLE 23-3 ■ CONSOLIDATED FRAMEWORK FOR IMPLEMENTATION RESEARCH

Intervention characteristics

- Intervention source

- Evidence strength and quality
- Relative advantage
- Adaptability
- Trialability
- Complexity
- Design quality and packaging
- Cost

Outer setting
- Patient needs and resources
- Cosmopolitanism
- Peer pressure
- External policies and incentives

Inner setting
- Structural characteristics
- Networks and communications
- Culture
- Implementation climate

Characteristics of individuals
- Knowledge and beliefs about the intervention
- Self-efficacy
- Individual stage of change
- Individual identification with organization
- Other personal attributes

Process
- Planning
- Engaging
- Executing
- Reflecting and evaluating

Data from *Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. Implement Sci. 2009;4:50.*

When contemplating embarking on a quality improvement project, it can be helpful to consider reporting guidelines for quality improvement research. The Standards for Quality Improvement Reporting Excellence (SQUIRE) is one of the best known reporting guidelines. It is not a "how-to" manual for conducting quality improvement interventions, but does list factors that readers judge important in order to understand the results of an evaluation of a quality improvement intervention, and as such many of these factors should be considered during the planning stages of a quality improvement intervention. The SQUIRE guidelines are summarized in **Table 23-4**. An additional helpful set of "questions to be asked" before beginning a quality improvement intervention involving practice guidelines has recently been written. Those 10 questions are presented in **Table 23-5**.

TABLE 23-4 REVISED STANDARDS FOR QUALITY IMPROVEMENT REPORTING EXCELLENCE (SQUIRE 2.0)[a]

TEXT SECTION AND ITEM NAME	SECTION OR ITEM DESCRIPTION
Notes to authors	• The SQUIRE guidelines provide a framework for reporting new knowledge about how to improve healthcare • The SQUIRE guidelines are intended for reports that describe system level work to improve the quality, safety, and value of healthcare, and used methods to establish that observed outcomes were due to the

	intervention(s). • A range of approaches exists for improving healthcare. SQUIRE may be adapted for reporting any of these. • Authors should consider every SQUIRE item, but it may be inappropriate or unnecessary to include every SQUIRE element in a particular manuscript. • The SQUIRE Glossary contains definitions of many of the key words in SQUIRE. • The Explanation and Elaboration document provides specific examples of well-written SQUIRE items, and an in-depth explanation of each item. • Please cite SQUIRE when it is used to write a manuscript.
Title and Abstract	
1. Title	Indicate that the manuscript concerns an initiative to improve healthcare (broadly defined to include the quality, safety, effectiveness, patient-centeredness, timeliness, cost, efficiency, and equity of healthcare)
2. Abstract	a. Provide adequate information to aid in searching and indexing b. Summarize all key information from various sections of the text using the abstract format of the intended publication or a structured summary such as: background, local problem, methods, interventions, results, conclusions
Introduction	*Why did you start?*
3. Problem Description	Nature and significance of the local problem
4. Available knowledge	Summary of what is currently known about the problem, including relevant previous studies
5. Rationale	Informal or formal frameworks, models, concepts, and/or theories used to explain the problem, any reasons or assumptions that were used to develop the intervention(s), and reasons why the intervention(s) was expected to work
6. Specific aims	Purpose of the project and of this report
Methods	*What did you do?*
7. Context	Contextual elements considered important at the outset of introducing the intervention(s)
8. Intervention(s)	a. Description of the intervention(s) in sufficient detail that others could reproduce it b. Specifics of the team involved in the work
9. Study of the Intervention(s)	a. Approach chosen for assessing the impact of the intervention(s) b. Approach used to establish whether the observed outcomes were due to the intervention(s)
10. Measures	a. Measures chosen for studying processes and outcomes of the intervention(s), including rationale for choosing them, their operational definitions, and their validity and reliability b. Description of the approach to the ongoing assessment of contextual elements that contributed to the success, failure, efficiency, and cost c. Methods employed for assessing completeness and accuracy of data
11. Analysis	a. Qualitative and quantitative methods used to draw inferences from the data b. Methods for understanding variation within the data, including the effects of time as a variable
12. Ethical Considerations	Ethical aspects of implementing and studying the intervention(s) and how they were addressed, including, but not limited to, formal ethics review and potential conflict(s) of interest
Results	*What did you find?*
13. Results	a. Initial steps of the intervention(s) and their evolution over time (*e.g.*, time-

	line diagram, flow chart, or table), including modifications made to the intervention during the project b. Details of the process measures and outcome c. Contextual elements that interacted with the intervention(s) d. Observed associations between outcomes, interventions, and relevant contextual elements e. Unintended consequences such as unexpected benefits, problems, failures, or costs associated with the intervention(s). f. Details about missing data
Discussion	*What does it mean?*
14. Summary	a. Key findings, including relevance to the rationale and specific aims b. Particular strengths of the project
15. Interpretation	a. Nature of the association between the intervention(s) and the outcomes b. Comparison of results with findings from other publications c. Impact of the project on people and systems d. Reasons for any differences between observed and anticipated outcomes, including the influence of context e. Costs and strategic trade-offs, including opportunity costs
16. Limitations	a. Limits to the generalizability of the work b. Factors that might have limited internal validity such as confounding, bias, or imprecision in the design, methods, measurement, or analysis c. Efforts made to minimize and adjust for limitations
17. Conclusions	a. Usefulness of the work b. Sustainability c. Potential for spread to other contexts d. Implications for practice and for further study in the field e. Suggested next steps
Other Information	
18. Funding	Sources of funding that supported this work. Role, if any, of the funding organization in the design, implementation, interpretation, and reporting

[a]September 15, 2015.

Data from http://www.squire-statement.org/index.cfm?fuseaction=page.viewPage&pageID=471&nodeID=1. Accessed February 9, 2016.

TABLE 23-5 IMPLEMENTING GUIDELINES IN YOUR ORGANIZATION: WHAT QUESTIONS SHOULD YOU BE ASKING?

QUESTIONS	COMMENTS
1. What are the motivations for implementation?	Are you considering implementing a guideline because of external pressures (eg, pay-for-performance, accreditation), an internal problem (you became aware that patient care in your organization needs improvement), or some other reason?
2. What is the political climate surrounding implementation?	In your organization, who wants the guideline implemented and why? Is this something everyone already agrees should be implemented, or are just a few people leading the charge? Is it your leaders who want the guideline implemented, or a few staff who really care about the topic?
3. What is the culture of your workplace?	Are people generally compliant when something new comes down the pike? Or is it hard to get people to adapt to new situations? Reflect on the last time a change occurred within your organization. How did it go? What were the problems? And what was the ultimate outcome?
4. Do you have the resources to move forward?	If resources are not available, can they be obtained? If not is guideline implementation realistic?
5. Assuming that your answers to the first four questions above support moving forward with guideline implementation, have you	Who will be the targets for guideline implementation? In what order? Will the guideline be introduced all at once or in stages? Will a champion be appointed to facilitate the process? If so who will make the most effective

considered how will you introduce practice changes based on the guideline into your organization?	champion?
6. What are your aims with respect to guideline implementation?	Do you have specific goals identified based on your implementation plan?
7. How will you measure your guideline implementation progress?	Specific process and outcome measures related to the key aims of implementation should be identified.
8. Does the guideline tell you anything about how it should be implemented?	Does the guideline provide specifics about prioritizing and timing the implementation of key strategies?
9. Does a small test of guideline implementation work?	Small tests of change are generally essential in order to identify key potential barriers and facilitators to implementation.
10. If answers to questions 1–9 are supportive of guideline implementation, how will you roll out that initiative more broadly in your organization?	How will organizational leadership support the roll out? Has an implementation team been identified? Is there a clear timeline and availability of staff time and other resources for the roll out? How will process and outcome data be collected and analyzed on a larger scale?

Ganz DA. Implementing Guidelines in Your Organization: What Questions Should You Be Asking? http://www.guideline.gov/expert/expert-commentary.aspx?id=49423. Accessed February 3, 2016.

The CMS has invested major resources into improving the care of Medicare beneficiaries over the last two decades through Quality Improvement Organizations (QIOs). Each state has a designated QIO, which is an organization that has entered into a contract with the CMS to execute a specific scope of work that may include focused efforts on improving care in hospitals, SNFs, and home health (http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityImprovementOrgs/index.html?redirect=/QualityImprovementOrgs/). In addition, the Affordable Care Act has mandated that SNFs implement a Quality Assurance and Performance Improvement (QAPI) program. Key elements of QAPI are outlined in **Figure 23-2**. The CMS has made available tools and resources to assist SNFs in implementation of QAPI (http://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/QAPI/qapidefinition.html).



Five Elements

Element 1: Design and Scope
A QAPI program must be ongoing and comprehensive, dealing with the full range of services offered by the facility, including the full range of departments. When fully implemented, the QAPI program should address all systems of care and management practices, and should always include clinical care, quality of life, and resident choice. It aims for safety and high quality with all clinical interventions while emphasizing autonomy and choice in daily life for residents (or resident's agents). It utilizes the best available evidence to define and measure goals. Nursing homes will have in place a written QAPI plan adhering to these principles.

Element 2: Governance and Leadership
The governing body and/or administration of the nursing home develops a culture that involves leadership seeking input from facility staff, residents, and their families and/or representatives. The governing body assures adequate resources exist to conduct QAPI efforts. This includes designating one or more persons to be accountable for QAPI; developing leadership and facility-wide training on QAPI; and ensuring staff time, equipment, and technical training as needed. The Governing Body should foster a culture where QAPI is a priority by ensuring that policies are developed to sustain QAPI despite changes in personnel and turnover. Their responsibilities include, setting expectations around safety, quality, rights, choice, and respect by balancing safety with resident-centered rights and choice. The governing body ensures staff accountability, while creating an atmosphere where staff is comfortable identifying and reporting quality problems as well as opportunities for improvement.

Element 3: Feedback, Data Systems, and Monitoring
The facility puts systems in place to monitor care and services, drawing data from multiple sources. Feedback systems actively incorporate input from staff, residents, families, and others as appropriate. This element includes using Performance Indicators to monitor a wide range of care processes and outcomes, and reviewing findings against benchmarks and/or targets the facility has established for performance. It also includes tracking, investigating, and monitoring adverse events that must be investigated every time they occur, and action plans implemented to prevent recurrences.

Element 4: Performance Improvement Projects
A performance improvement project (PIP) is a concentrated effort on a particular problem in one area of the facility or facility wide; it involves gathering information systematically to clarify issues or problems, and intervening for improvements. The facility conducts PIPs to examine and improve care or services in areas that the facility identifies as needing attention. Areas that need attention will vary depending on the type of facility and the unique scope of services they provide.

Element 5: Systematic Analysis and Systemic Action
The facility uses a systematic approach to determine when in-depth analysis is needed to fully understand the problem, its causes, and implications of a change. The facility uses a thorough and highly organized/structured approach to determine whether and how identified problems may be caused or exacerbated by the way care and services are organized or delivered. Additionally, facilities will be expected to develop policies and procedures and demonstrate proficiency in the use of root cause analysis. Systemic actions look comprehensively across all involved systems to prevent future events and promote sustained improvement. This element includes a focus on continual learning and continuous improvement.

FIGURE 23-2. Key elements of CMS Quality Assurance and Performance Improvement Program. (From http://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/QAPI/qapidefinition.html.)

Looking to the future, we expect that there will be an increasing emphasis on the public reporting of outcome (as opposed to process) measures of quality, along with increasing use of patient experience measures. This will likely result in new ways of collecting data, and require improved measures of risk adjustment. We also expect that that the "entity" for which quality and safety are being measured and reported, and which in turn is responsible for initiating quality and safety improvement practices, will be more tightly linked groups of providers, as part of the trend toward larger, integrated care delivery organizations that care for a defined population of patients.

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Chapter 24

General Principles of Pharmacology and Appropriate Prescribing

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Learning Objectives

- Understand the epidemiology of drug therapy.
- Understand the importance of pharmacokinetics and pharmacodynamics to prescribing decisions.
- Describe practical approaches to prescribing medications to older persons including reviewing current drug therapies, discontinuing medications when no longer indicated, considering nonpharmacologic treatment options, and reducing the dose.
- Describe measures of drug prescribing quality.
- Understand the concept of the prescribing cascade.
- Understand the importance of underuse of potentially beneficial drug therapy.
- Understand the special considerations regarding drug therapy in the long-term care setting.
- Recognize the potential gaps in information about drug therapy in older adults.
- Describe policy issues related to drug therapy by older adults.

Key Clinical Points

1. **Prescribing for older people offers special challenges because they take more prescribed medications than younger people. Older individuals are often at risk for drug interactions and adverse events.**
2. **When prescribing medications to older adults, consider pharmacokinetic and pharmacodynamic changes that are observed with aging.**
3. **Criteria have been developed by experts internationally to assess the quality of medication use in older adults that can be applied in clinical practice.**
4. **Many different factors go into making the best prescribing decisions for an individual patient, and it is essential that the risks are balanced against the benefits of each medication. An important tension exists between avoiding inappropriate medications and underuse of potentially beneficial drugs.**
5. **Prescribing cascades are common and important to consider in older adults with multiple chronic diseases who are likely to be prescribed multiple drug therapies.**
6. **Practical steps can be taken to optimize prescribing for older adults that include reviewing current drug therapies, discontinuing potentially unnecessary drug therapies, and considering**

nonpharmacologic treatment approaches.

INTRODUCTION

Prescribing for older patients offers special challenges. Older people take about three times as many prescription medications as do younger people, mainly because of an increased prevalence of chronic medical conditions among the older population. Taking several drugs together substantially increases the risk of drug interactions and adverse events.

While a physician can usually do little to alter the characteristics of individual older patients to affect the kinetics or dynamics of drugs, the decision whether to prescribe any drug, the choice of drug, and the manner in which it is to be used (eg, dose and duration of therapy) are all factors that are under control of the prescriber. This chapter discusses ways to optimize prescribing of drug therapy for older adults.

EPIDEMIOLOGY OF DRUG THERAPY

Writing a prescription is the most frequently employed medical intervention. Yet, creating optimal drug regimens that meet the complex needs of older persons requires thought and careful planning. Multiple factors contribute to inappropriate drug prescribing, including lack of adequate training of providers in safe prescribing practice, and in prescribing for geriatric patients. Further, a lack of routine use of safe medication prescribing behaviors such as checking drug allergies, double checking drug doses, adjusting doses for renal impairment, checking for potential drug-drug interactions, and medication reconciliation also contribute to prescribing errors. Avoidable adverse drug events (ADEs) are the most serious consequences of inappropriate and unsafe drug prescribing. The possibility of an ADE should always be borne in mind when evaluating an older individual. A valuable maxim in geriatric medicine posits that when evaluating virtually any new symptom in an older patient, the possibility of an ADE should be considered in the differential diagnosis. Advanced age, frailty, cognitive decline, and increased drug utilization are all factors that contribute to an individual patient's risk for developing a drug-related problem. US data indicate that older adults in the community are up to three times more likely to have an ADE that requires evaluation in an outpatient setting or in an emergency department, and are seven times more likely to require a hospital admission. In the inpatient setting, older adults account for more than half of hospitalizations complicated by an ADE. In the nursing home setting, the incidence of ADEs approaches 10 per 100 resident-months, of which over half may be preventable. These estimates are probably conservative because preventable ADEs were strictly defined and it was assumed that, in many cases, the prescription of the offending drug was indicated and the ADE was therefore not preventable. One of the most compelling explanations for the increased risk for ADEs in older patients is that we lack methods to adequately assess the harms associated with the use of multiple medications by patients with multiple chronic conditions.

A national sample of noninstitutionalized adults in the United States provided information on the use of prescription and over-the-counter (OTC) medications in the community by older adults. This 2006 survey demonstrated that use of all medications (prescriptions, OTC drugs, vitamins/minerals, and herbals/supplements) (**Figure 24-1**), and the use of prescribed drug therapies increased dramatically with advancing age. The highest prevalence of medication use was among women aged 65 and older. Among these women, 57% took five or more medications and 19% took ten or more.

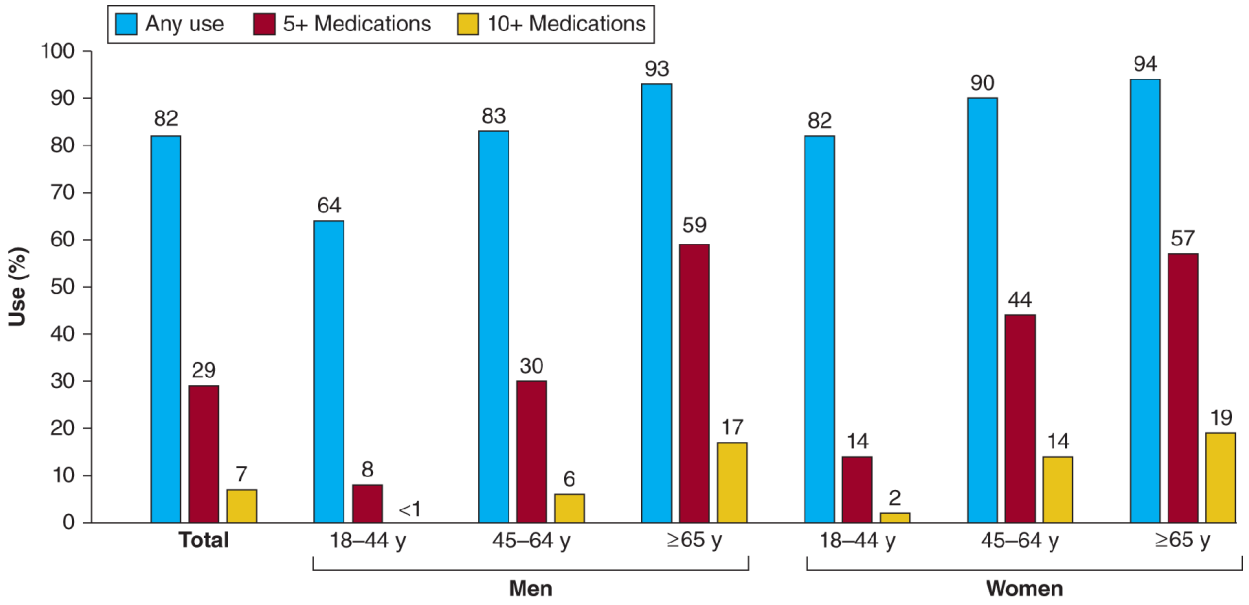


FIGURE 24-1. Use of medications during the preceding week, by sex and age. (Adapted from Slone Epidemiology Center. *Patterns of medication use in the United States: a report from the Slone Survey.* Boston, MA: Slone Epidemiology Center; 2006.)

Herbal medicines are frequently used by older adults, and physicians often do not question patients about such use. An estimated 22% of the US adult population takes an herbal medicine or supplement such as ginseng, ginkgo biloba extract, and glucosamine. In one survey, almost 75% of patients did not inform their physician that they were using unconventional treatments including herbal medicines. Herbal medicines may interact with prescribed drug therapies leading to adverse events, underscoring the importance of routinely questioning patients about their use of these therapies. Examples of herbal–drug therapy interactions include warfarin in combination with ginkgo biloba extract leading to an increased risk for bleeding and serotonin reuptake inhibitors in combination with St. John's wort leading to serotonin syndrome in older adults.

PHARMACOKINETICS AND PHARMACODYNAMICS

When prescribing medications to older adults, it is important to consider pharmacokinetic and pharmacodynamic changes observed with normal aging. Age-related pharmacologic changes combined with medical conditions that are more common in older adults can impact the pharmacokinetics of drug therapies. Understanding these changes can help to guide prescribing decisions.

Pharmacokinetics relates to the way the body handles a drug. Traditionally, pharmacokinetics involves consideration of drug absorption, distribution across body compartments, metabolism in the liver, and elimination by the kidneys. Drug absorption is largely unchanged with aging. However, changes in drug distribution, metabolism, and excretion can impact the clearance of a medication from the body in older adults. Age-related changes in body composition can affect the volume of distribution of a drug. With advancing age, older people have less lean body mass and greater fat stores relative to younger people. As such, drug therapies such as some benzodiazepines that are highly lipid-soluble have an increased volume of distribution and consequently prolonged clearance rates in older people relative to those who are younger. Much of the literature on age-related changes in drug metabolism has focused attention on reduced oxidative metabolism by cytochrome P450 (CYP) enzymes in the liver. In addition, elimination of many drug therapies occurs through renal clearance, and renal function often declines with aging (refer to Chapter 86, Changes in Kidney Function). Taken together, these age-related changes in pharmacokinetics would be expected to have substantial impact on the clearance of many medications commonly used in older adults. Conventional wisdom and prudent prescribing practice warrant that special care be taken in drug dosing for older patients, particularly in the case of highly lipid-soluble drugs, medications metabolized via reactions catalyzed by CYP enzymes, and renally excreted drugs.

In contrast to pharmacokinetics, pharmacodynamics relates to the effect that a drug has on the body. Aging is associated with enhanced sensitivity to a number of drug therapies. For example, older people may be more sensitive to the effects of benzodiazepines, opioids, and warfarin, exclusive of any age-related pharmacokinetic changes that might exist.

The science of geriatric pharmacology remains to be fully elucidated. A dogmatic approach to applying currently accepted principles of geriatric pharmacology in prescribing medications to older patients is probably inappropriate. For example, the risk for fall-related injuries in older patients with use of short–half-life benzodiazepines and so-called "Z-drugs" (eg, zolpidem) may actually be similar to that with use of long–half-life benzodiazepines. These observations are clearly at odds with what would be expected based on the pharmacologic changes that occur with aging. Schwartz has written that "clinical factors such as disease, functional status, concomitant medications, nutraceutical intake, and lifestyle may have greater effects and lead to greater variability in drug clearance and effects than based on pure aging."

Various strategies may assist in formulating the most appropriate and individualized drug dose for older patients. These approaches may include weight-based and renal-based dosing. Individualized dosing of renally cleared medications, particularly those with a narrow therapeutic index, is facilitated by the provision of estimates of glomerular filtration rates now routinely added to the results of laboratory panels. In addition, clinical decision support tools are commonly incorporated into electronic health records to assist in the choice of medication dose when ordering for patients with reduced renal function. Finally, while controversy remains concerning the clinical utility and practicality of applying pharmacogenetic data to the direct care of older patients (eg, to guide warfarin dosing), pharmacogenetic dosing holds both the promise and potential for enhancing the safety and effectiveness of geriatric pharmacotherapy in the future.

PHARMACOEPIDEMIOLOGY

Pharmacoepidemiology uses the science of clinical epidemiology to measure patterns of medication use and outcomes in large populations. Pharmacoepidemiology allows assessment of the safety and efficacy of medications in large populations, which are often more diverse than the participants in randomized trials, over long periods of time.

Advantages of Pharmacoepidemiologic Studies

The advantages of pharmacoepidemiology over randomized controlled trials include (1) detection of adverse events that are too rare or too delayed to be detected in randomized trials; (2) assessment of efficacy over longer periods in a broader population; (3) correlation of medication use with outcomes that may not have been assessed in randomized trials; (4) assessment of safety and efficacy of medications beyond the stringent monitoring of a randomized trial.

Pharmacoepidemiology is a particularly useful tool to assess medications in older adults. Older adults are often excluded from randomized trials, either on the basis of age alone, or because of comorbidities, co-medications, or functional impairment. Observational pharmacoepidemiologic studies can assess patterns of medication use, safety, and efficacy in frail individuals. It is particularly important to understand safety and efficacy over many years when deciding whether to continue or cease medications in older adults who have often been taking their medicines for decades. Many randomized trials only assess disease and mortality outcomes, and pharmacoepidemiologic studies can correlate medication exposure with functional and quality-of-life measures that may be more relevant to older adults. Pharmacoepidemiology assesses the effects of medications in the presence of medication management issues that occur in real clinical settings, for example, limited adherence and monitoring.

Limitations of Pharmacoepidemiologic Studies

Pharmacoepidemiologic studies are limited by confounding and bias. Interpretation of studies is limited by variable prescribing patterns, variable comorbidities, confounding by indication, severity and prognosis, and controlling for the time dependency of drug use. Studies that rely on large epidemiologic databases often contain very limited clinical information. There are several emerging approaches to manage confounders, including restricting study populations to more homogeneous groups, creating a propensity score to predict the probability of receiving a drug based on baseline covariates, and examining within-patient variability of drug exposure using crossover designs. Pharmacoepidemiology does much to inform prescribing for frail older adults.

PHARMACOECONOMICS

Pharmacoeconomics is the scientific subdiscipline of health economics that compares the value of one drug or drug therapy to another evaluating the cost, expressed in monetary terms, and effects, usually expressed in efficacy or

quality of life. Pharmacoeconomic data can be used to guide optimal health care resource allocation. In the United States, managed care funds consider cost-effectiveness when deciding on the availability of drug therapy. There are some concerns that the cost-effectiveness approach may be prejudicial to older adults because their survival time is less than younger patients. However, for most preventative interventions, such as the treatment of cardiovascular risk factors or osteoporosis the greater absolute risk of experiencing an outcome event such as stroke, myocardial infarction, or fracture indicates intervention in older adults is more cost-effective. This assumes a life expectancy at least as long as the time required to benefit. Thus consideration of cost-effectiveness can facilitate health care systems appropriately directing resources to the treatment of older adults.

MEASURING THE QUALITY OF DRUG PRESCRIBING IN OLDER PERSONS

Various criteria have been developed by experts internationally to assess the quality of medication use in older populations. One of the most widely employed approaches for the assessment of inappropriate prescribing are the Beers criteria. These criteria, initially developed in 1991 by a consensus panel of experts in geriatric medicine, geriatric psychiatry, and pharmacology, were updated and revised in 1997, 2003, 2012, and 2015. Use of drug therapies considered inappropriate according to the Beers criteria has been identified as an ongoing topic of widespread concern across all clinical settings.

The 2015 Beers criteria update was sponsored by the American Geriatrics Society (AGS) and involved a panel of 13 experts in geriatric care and pharmacology following an evidence-based approach. The 2015 update includes more than 40 potentially problematic medications or medication classes that were divided into five lists: two lists detail potentially inappropriate medications for most older adults or for those with specific conditions; a third list describes medications that should be used only with considerable caution; and two new additions to the 2015 update include a list of potentially clinically important drug-drug interactions, as well as a list of medications that should be avoided or dosed differently for people with impaired renal function.

A concern with using a limited list of “inappropriate” drug therapies like the Beers criteria to assess the quality and safety of drug prescribing to older patients relates to the extent that such a list captures the full spectrum of drug-related problems likely to befall older patients. For example, studies of older patients presenting to US emergency departments for ADEs, or of ADEs in older patients recently discharged from the hospital have suggested that the Beers criteria drugs capture only a very small fraction of the medications implicated in these events. The majority of these agents are not included among Beers criteria medications. Furthermore, only a minority of Beers criteria recommendations are based on high-quality evidence, attesting to the dearth of pharmacologic and drug safety and effectiveness research that directly focuses on the older population. A 2013 report issued by the US Department of Health and Human Services on the creation of a national action plan for ADEs prevention highlighted the need to explore strategies to improve medication prescribing more broadly. This report identified older adults as one of the most vulnerable groups for the development of ADEs. The action plan identified three classes of drug therapies that were associated with the highest risk for the development of ADEs. These were anticoagulants leading to bleeding, opioids leading to delirium and mental status changes, and insulin leading to hypoglycemia.

As implied above, very few drugs that cause difficulty for older adults are inherently bad. To address these concerns, a more comprehensive approach to evaluating the quality of pharmacologic care for older adults was developed by the Assessing Care of Vulnerable Elders (ACOVE) project. Knight and Avorn originally developed quality indicators for appropriate medication use. Updated in 2007, the ACOVE indicators include the need to document the indication for a new drug therapy, to educate patients on the benefits and risks associated with the use of a new therapy, the need to maintain current medication lists in patient medical records, the importance of documenting response to therapy, and the need for a periodic review of drug therapies. These ACOVE indicators and their rationale are summarized (**Table 24-1**).

TABLE 24-1 ASSESSING CARE OF VULNERABLE ELDERS (ACOVE) QUALITY INDICATORS[a]

INDICATOR TITLE	DESCRIPTION	RATIONALE
Medication list	An up-to-date medication list accessible to all health care providers that includes over-the-counter medications and herbal supplements.	Facilitates identification of potential drug-related causes of new symptoms, eliminates duplications, allows drug-drug interaction review, and streamlining of drug regimen to promote adherence.

Annual drug regimen review	An annual drug regimen review.	Provides an opportunity to discontinue unnecessary medications, or add necessary drugs.
Drug indication	All drugs prescribed should have a clearly defined indication.	Allows medications prescribed for unclear or transient indications to be discontinued.
Patient education	All vulnerable elders (or caregivers) should receive education about the use of any prescribed drugs.	Education may improve adherence and clinical outcomes, also can alert potential adverse effects.
Response to therapy	Response to therapy should be documented for all ongoing medical conditions.	Documenting response will help clarify whether a drug is meeting the therapeutic goal for which it was prescribed and provides a basis for continuation, modification, or discontinuation.

[a]Quality indicators for appropriate medication use in vulnerable elders.

Data from Shrank WH, Polinski JM, Avorn J. Quality indicators for medication use in vulnerable elders. J Amer Geriatr Soc. 2007 55:S373.

A different approach to identifying inappropriate drug therapy is the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP). The STOPP criteria were initially developed in 2008 using a Delphi consensus method with experts in geriatric medicine, clinical pharmacology, clinical pharmacy, geriatric psychiatry, and primary care. These criteria identify common instances of potentially inappropriate prescribing including drug-drug and drug-disease interactions, drugs that adversely affect those at risk for falls and duplicate drug class prescriptions. The criteria are organized by organ system, and the reason for each of the prescribing concerns is explained. The prevalence of older patients with at least one potentially inappropriate prescription identified using the STOPP criteria ranges from 21% to 39% in the primary care setting, from 26% to 77% in the hospital setting, and from 23% to 70% in nursing homes. Potentially inappropriate medications included in the STOPP criteria have been associated with avoidable ADEs in older people that contributed to acute care hospitalization. Version 2 of the STOPP criteria was published in 2014. The STOPP version 2 criteria list 80 evidence-based potentially inappropriate prescriptions for older adults and also categorize medications according to organ system. A list of the STOPP criteria is provided in an online supplement (http://ageing.oxfordjournals.org/content/early/2014/11/18/ageing.afu145/suppl/DC1) Medications with anticholinergic effects have drawn special attention in assessing problematic drug prescribing to older patients. Drugs with anticholinergic effects are commonly prescribed to patients with conditions ranging from depression to urinary incontinence to neuropathic pain and migraine headaches and are ubiquitous in over-the-counter cold remedies and sleep aids (eg, diphenhydramine). These therapies raise concerns for older patients because they are associated with serious adverse events including confusion, urinary retention, and constipation.

Anticholinergic drug therapies illustrate the importance of considering the cumulative burden of using different drugs with similar effects. The cumulative burden of these agents may more accurately reflect the potential risk for the development of adverse events. A series of scales have been identified to measure anticholinergic burden. One of these scales, the Anticholinergic Risk Scale, assigned points (from 1 [moderate] to 3 [very strong]) to commonly prescribed anticholinergic drug therapies based on the risk for developing anticholinergic adverse events. In a study of geriatric evaluation and management in the primary care setting, it was found that higher Anticholinergic Risk Scores were associated with an increased risk for anticholinergic-related adverse events including falls, confusion, dry mouth, and constipation.

Ultimately, many different factors go into making the best prescribing decisions for an individual patient. Appropriate prescribing needs to consider life stage, which goes well beyond simply knowing the patient's chronologic age. What remains essential is the need for ongoing assessment of the medication regimen in light of the individual's clinical status, goals of care, and the balancing of the risk and benefit of each medication.

A model for appropriate prescribing for patients late in life has been proposed. This model considers remaining life expectancy, goals of care, and the potential benefits of the drug therapy. One of the factors that the model considers is "time until benefit." Drug therapy used for prevention may have a time until benefit measured in years and therefore may not be always helpful to an individual with a limited life expectancy.

PRESCRIBING CASCADES

A particularly concerning aspect of suboptimal medication use in older adults relates to the occurrence of prescribing cascades. The prescribing cascade concept was created by Rochon and Gurwitz in 1997. A prescribing cascade begins

when an ADE is misinterpreted as a new medical condition. An additional drug therapy is prescribed, and the patient is placed at risk for the development of additional ADEs relating to this potentially unnecessary treatment (**Figure 24-2**). Prescribing cascades and other risks associated with drug therapy are particularly important for older adults with multiple chronic diseases who are likely to be prescribed multiple drug therapies. Selected examples of prescribing cascades are described below and summarized in **Table 24-2**.

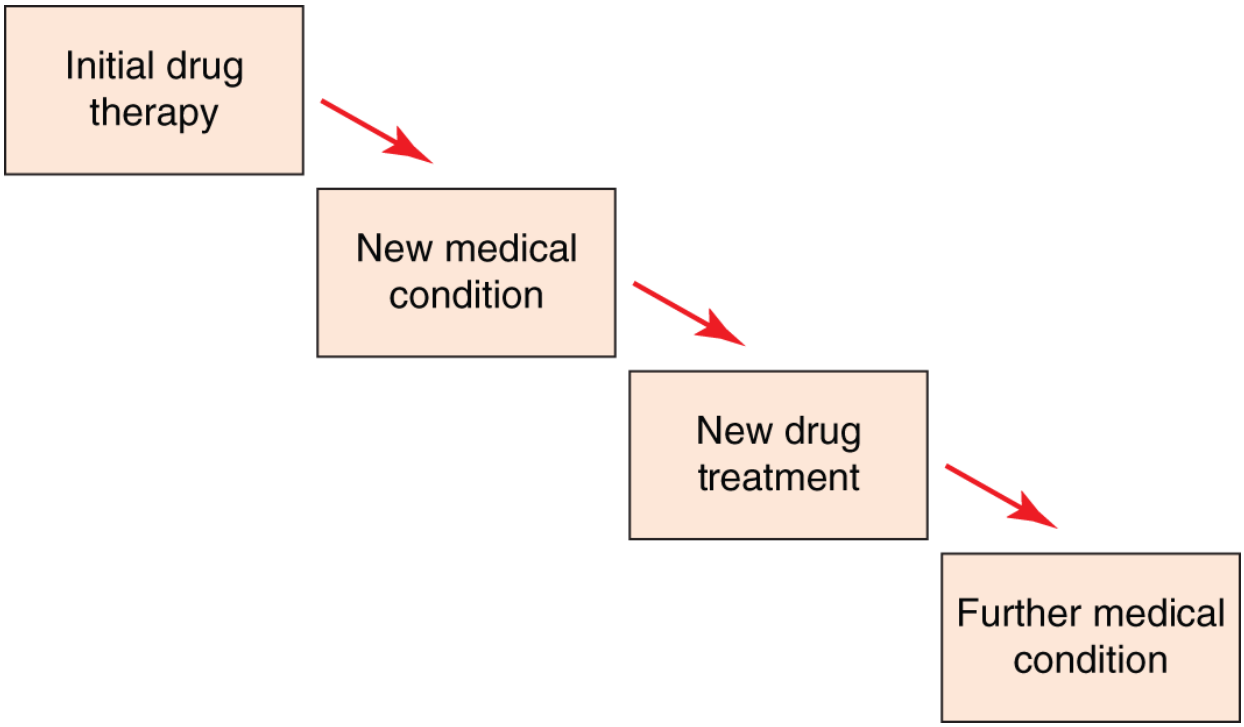


FIGURE 24-2. Prescribing cascade. (Adapted from Rochon PA, Gurwitz JH. Optimizing drug treatment for elderly people: the prescribing cascade. *BMJ*. 1997;315:1096–1099.)

TABLE 24-2 EXAMPLES OF PRESCRIBING CASCADES

INITIAL DRUG THERAPY	NEW MEDICAL CONDITION	NEW DRUG TREATMENT
Antipsychotic (typical and atypical)	Parkinsonism	Anti-Parkinson therapy
Metoclopramide	Parkinsonism	Anti-Parkinson therapy
Cholinesterase inhibitor	Urinary incontinence	Anticholinergic bladder therapy
Nonsteroidal anti-inflammatory drug (NSAID)	Gout	Antigout therapy

Drug-Induced Parkinsonism

Antidopaminergic-related adverse effects associated with antipsychotic agents have long been recognized, including the development of extrapyramidal signs and symptoms. This drug-related symptom may be potentially misdiagnosed as a new medical condition (ie, Parkinson disease).

The association between antipsychotic drug exposure and subsequent treatment of parkinsonism was identified among 3512 adults aged 65 to 99 who were enrolled in a Medicaid program and initiated on a drug therapy for the treatment of parkinsonian symptoms. Patients dispensed a typical antipsychotic therapy or clozapine in the 90 days prior to the initiation of anti-Parkinson therapy were more than five times more likely to begin anti-Parkinson therapy, relative to control patients who were not dispensed antipsychotic therapy. Furthermore, a dose-response relationship was demonstrated.

Antipsychotic therapy is widely used in older adults for the management of behavioral problems associated with dementia. One of the initial studies to explore the association between atypical antipsychotic drug therapy and the development of parkinsonism demonstrated that these newer “atypical” antipsychotics were also associated with parkinsonism and that this was in a dose-related fashion. Patients who are placed on antiparkinsonian therapy then

become vulnerable to the adverse events associated with this new therapy, including hypotension and delirium. A better approach is to discontinue or reduce the dose of the antipsychotic therapy. If an antipsychotic is deemed essential, it may be prudent to try to select a therapy with a more favorable adverse effect profile and to use this therapy at the lowest feasible dose.

Drug-induced parkinsonism has also been reported with other drug therapies, including metoclopramide. A case-control study of adults aged 65 and older in the New Jersey Medicaid Program demonstrated that metoclopramide users were three times more likely to begin drug treatment for Parkinson disease as compared with nonusers. Risk increased with increasing daily metoclopramide dose such that the odds ratio was 1.19 for up to 10 mg/day, 3.33 for 10 to 20 mg/day, and 5.25 for greater than 20 mg/day. Thus, drug-induced parkinsonism may lead to the initiation of anti-Parkinson drug therapy. Such drug-induced symptoms in an older person can be misinterpreted as indicating the presence of a new disease or be attributed to the aging process rather than to the drug therapy. This misinterpretation is particularly likely when the symptoms are indistinguishable from an illness, such as Parkinson disease that is seen in greater frequency in older persons.

Cholinesterase Inhibitors and Anticholinergic Therapy

Cholinesterase inhibitors (such as donepezil, rivastigmine, and galantamine) are often prescribed to manage the symptoms of Alzheimer disease and related dementias. Through their effects on the autonomic nervous system, cholinesterase inhibitors can sometimes precipitate urge urinary incontinence. However, new-onset or worsening urge incontinence is also commonly seen as part of the natural history of dementia. Thus, clinicians may misinterpret incontinence in patients with dementia as an unavoidable progression of their underlying disease, when it may in fact represent a potentially reversible drug-related adverse event. A population-based cohort study demonstrated that cholinesterase inhibitor use was associated with an increased risk for receiving anticholinergic medications to manage urinary incontinence, suggesting that the use of anticholinergic drugs in patients with dementia may sometimes represent an unrecognized ADE related to cholinesterase inhibitor use. In addition, the use of anticholinergic drugs by older adults with dementia may expose them to anticholinergic adverse effects (such as urinary retention and postural hypotension) and may also dilute the benefits of cholinesterase inhibitor treatment.

Many other prescribing cascade scenarios, such as the association between the use of hydrochlorothiazide therapy and the initiation of antigout therapy or the use of nonsteroidal anti-inflammatory drug (NSAID) therapy and hypertension, have been identified. Prescribing cascades only become apparent and preventable when health care providers carefully consider the relationship between the initiation of a new drug therapy, the adverse event profile of that therapy, and the development of a new symptom.

UNDERUSE OF POTENTIALLY BENEFICIAL THERAPY

Appropriate prescribing is also a highly dynamic process that changes with time, incorporating considerations of age-related physiologic changes (eg, changes in renal and hepatic function), disease-related factors, and shifts in the older individual's goals of care. An important tension also exists between avoiding inappropriate medications ("errors of commission") and the underuse of potentially beneficial drugs ("errors of omission"). As a result of these many influences, appropriate prescribing for older adults represents a complex and ever-shifting balancing act for clinicians.

Polypharmacy may be necessary and appropriate in some patients to permit the optimal management of their multiple chronic conditions. Underuse of beneficial therapy must be carefully balanced against inappropriate overprescribing ("errors of commission"). The tension between these two aspects of prescribing is complex; interestingly, overprescribing of inappropriate medications and underprescribing of beneficial medications are correlated, with both simultaneously present in more than 40% of older adults in some studies.

Conceptual Definition of Underuse

Underuse of medications is conceptually defined as the absence of initiation of an effective treatment in an individual with a condition for which there exists one or more medications with a favorable benefit-to-risk ratio. Frail older adults are often underrepresented in pivotal trials evaluating medications and the true benefit-to-risk ratio may be different from that observed in younger and healthier study participants. Thus, determinations of underuse require a careful assessment of whether randomized clinical trial results are truly generalizable to the older adult being cared for in real-world settings of care. Analyses focusing on older participants and postmarketing pharmacosurveillance studies

can provide a more complete picture of the likely benefits and risks of medications that may not be apparent at the time of initial marketing approval.

Operational Definition of Underuse

Attempts have been made to operationally define medication underuse in older adults. Analogous to the development of tools designed to define potentially inappropriate prescribing or "errors of commission." There are now tools available to assist with the operational definition of underuse of potentially beneficial medications. The Assessment of Underutilization (AOU) index is an implicit tool (ie, one that requires clinical judgment to apply) to help guide medication initiation. The AOU complements the Medication Appropriateness Index (MAI), which is an implicit tool to identify potentially inappropriate prescribing.

The START criteria represent an explicit tool to identify underuse of potentially beneficial medications. The START criteria include 34 evidence-based prescribing indications for older adults and also categorize medications according to organ system. The prevalence of potential prescription omissions, according to START criteria, was 23% among older adults in primary care, from 42% to 66% in hospitalized older adults, and from 42% to 44% among nursing care residents.

Assessing Underuse: Implications of Clinical Practice Guideline Recommendations

Different approaches to profiling underuse of potentially beneficial medications have been applied. A common approach to characterizing underprescribing is to assess the use of medications that clinical practice guidelines suggest should be prescribed to treat or prevent a condition in the absence of contraindications. This approach has been used in a number of studies to demonstrate underuse of specific drug therapies in the care of patients with heart failure, myocardial infarction, osteoporotic fractures, atrial fibrillation, and depression. Unfortunately, most clinical guidelines do not incorporate considerations such as life expectancy and time needed to derive clinical benefit as legitimate justifications to forego prescribing a "beneficial" medication to a patient. In addition, several studies have emphasized that caution should be exercised when applying disease-specific clinical practice guidelines to older adults with multiple chronic diseases.

Striking the Right Balance in Prescribing

Incorporating an individual's goals of care and preferences is critical to making optimal prescribing decisions relating to older patients. Holmes et al. have proposed a practical strategy whereby life expectancy, time to realization of treatment benefit, primary goals of care (eg, prevention, cure, or palliation), and validity of specific treatment targets (eg, cholesterol) are integrated to decide on appropriate treatments for older individuals with the aim of minimizing unwarranted polypharmacy. Information about estimating remaining life expectancy in older adults can inform decision making around prescribing a new medication, as can an understanding of the lag time until benefit is achieved for a specific medication under consideration. For example, in individuals with advanced dementia for whom there is a focus on quality of life as a primary goal, there may be opportunities to deprescribe medications that were previously considered essential (eg, lipid-lowering therapy with statins) to help reduce the overall pill burden, costs, and the potential for drug-drug interactions and ADEs.

SPECIAL CONSIDERATIONS REGARDING DRUG THERAPY IN THE LONG-TERM CARE SETTING

Long-term care residents include a disproportionate number of women, people of advanced age, and those with multiple medical problems, in particular dementia. Of all types of therapeutic interventions, medications are the most commonly used in the nursing home setting. Nearly half of all nursing home residents take nine or more different medications every day, placing this group at special risk for ADEs.

Antipsychotic Therapy in the Long-Term Care Setting

In long-term care facilities, excess use of antipsychotic therapy for the management of behavioral problems continues to be a focus of great concern. Atypical antipsychotic medications are among the drugs most frequently associated with adverse events in long-term care facilities. While recent data suggest that use of antipsychotic therapy has

declined in US nursing homes over recent years, nearly one in five long-stay nursing home residents continue to be prescribed antipsychotic medications. Despite a lack of strong evidence, among direct care staff in nursing homes, more than half believe that these medications work well to manage resident behaviors. Further, there is substantial variation in the use of antipsychotic therapy by geographic region and between nursing homes in the same region. A study of antipsychotic therapy use in 47,322 residents of 485 provincially regulated nursing homes found that antipsychotic prescribing rates were more than double in those with the highest rates compared to those with the lowest rates. Compared with individuals residing in nursing homes with the lowest mean antipsychotic prescribing rates, those residing in facilities with the highest rates were three times more likely to be dispensed an antipsychotic therapy irrespective of their potential clinical indication. There is accumulating evidence that any benefit from atypical antipsychotics for management of behavioral and psychological symptoms in Alzheimer type dementia may be offset by the increased risk for ADEs. There is also evidence that antipsychotic use is associated with an increased risk of death with both conventional and atypical antipsychotic drug therapy in older adults with dementia-related behavioral disorders. Health Canada and the US Food and Drug Administration have issued strong warnings about their use. Given these important safety concerns, the use of antipsychotic therapy should generally be reserved for situations where the benefit clearly outweighs the risk. Specifically, antipsychotic therapy is potentially indicated for situations where the behavioral problems pose a risk to the resident or others.

Risk of Adverse Drug Events in the Long-term Care Setting

The occurrence of ADEs that may have been prevented is among the most serious concerns regarding suboptimal medication use in the nursing home setting. Few studies have systematically examined the incidence of ADEs in the nursing home population. In a study conducted in two academic long-term care facilities in Ontario and Connecticut over a 9-month period, drug-related incidents were detected by computer-generated signals from a computerized physician order entry system, clinical pharmacist investigators, and periodic review of medical record. Incidents were classified by physician reviewers according to whether they represented an ADE, and if so, the severity (significant, serious, life-threatening, and fatal) and preventability of the event. During this study 815 ADEs were identified (9.8 ADEs per 100 resident-months). Of these, 42% were judged preventable. Of all ADEs, 4 (<1%) were fatal, 33 (4%) were life threatening, 188 (23%) were serious, and 590 (72%) were less serious.

In this study, residents using anticoagulants, atypical antipsychotic agents, diuretics, anti-infectives, and antiepileptics were at the greatest risk for ADE. Psychoactive drugs (ie, antipsychotics, antidepressants, and sedatives/hypnotics), cardiovascular and anticoagulants were the most commonly implicated drug categories associated with the occurrence of preventable ADEs (**Table 24-3**). Confusion, oversedation, delirium, and hemorrhagic events were the most commonly identified preventable ADEs (**Table 24-4**). Errors resulting in preventable ADEs occurred most often at the stages of ordering and monitoring. Among the prescribing errors, the most common were wrong dose, wrong drug choice, and known drug interaction. Dispensing and administration errors were less commonly identified. Independent risk factors for experiencing a preventable ADE included using medications in several drug categories, including antipsychotic agents, anticoagulants, diuretics, and antiepileptic. Extrapolating from the results of this research, 1.9 million ADEs per year may occur among the 1.6 million US nursing home residents and more than 40% maybe preventable. There are almost 86,000 fatal or life-threatening ADEs per year, of which 70% maybe preventable. Drug-related morbidity and mortality is one of the most important areas to target in efforts to both improve the quality of medical care for older persons and reduce the costs of health care for this population.

TABLE 24-3 FREQUENCY OF ADVERSE DRUG EVENTS AND POTENTIAL ADVERSE DRUG EVENTS IN LONG-TERM CARE FACILITIES BY DRUG CLASS[a]

DRUG CLASS	ADVERSE DRUG EVENTS NO. (%) (*N* = 815)	PREVENTABLE ADVERSE DRUG EVENTS NO. (%) (*N* = 318)	NONPREVENTABLE ADVERSE DRUG EVENTS NO. (%) (*N* = 497)
Atypical and typical antipsychotics	110 (11)	52 (16)	58 (12)
Antibiotics/anti-infectives	106 (13)	5 (2)	101 (20)
Antidepressants	77 (9)	41 (13)	36 (7)
Sedatives/hypnotics	61 (8)	43 (14)	18 (4)

Anticoagulants	167 (21)	65 (20)	102 (21)
Antiseizure	40 (5)	22 (7)	18 (4)
Cardiovascular	195 (24)	98 (31)	97 (20)
Hypoglycemics	49 (6)	26 (8)	23 (5)
Nonopioid analgesics	26 (3)	16 (5)	10 (2)
Opioids	51 (6)	26 (8)	25 (5)
Antiparkinsonians	11 (1)	4 (1)	7 (1)

[a]Drugs in more than one category were associated with some events. Frequencies in each column sum to greater than the total number cited.

Data from Gurwitz JH, Field TS, Judge J, et al. The incidence of adverse drug events in two large academic long-term care facilities. Am J Med. 2005;118:251.

TABLE 24-4 FREQUENCY OF ADVERSE DRUG EVENTS IN LONG-TERM CARE FACILITIES BY TYPE[a]

TYPE	ADVERSE DRUG EVENTS (*N* = 815)	PREVENTABLE (*N* = 338)
	NUMBER (%)	
Neuropsychiatric[b]	199 (24)	97 (29)
Hemorrhagic	159 (20)	53 (16)
Gastrointestinal	140 (17)	55 (16)
Electrolyte/fluid balance abnormality	80 (10)	40 (12)
Metabolic/endocrine	64 (8)	35 (10)
Dermatologic	36 (4)	4 (1)
Cardiovascular	36 (4)	15 (4)
Extrapyramidal symptoms/tardive dyskinesia	30 (4)	7 (2)
Fall without injury	21 (3)	11 (3)
Fall with injury	21 (3)	17 (5)
Infection	19 (2)	1 (> 1)
Syncope/dizziness	16 (2)	8 (2)
Anticholinergic[c]	9 (1)	3 (1)
Ataxia/difficulty with gait	9 (1)	5 (2)
Hematologic	8 (1)	3 (1)
Respiratory	6 (1)	4 (1)
Anorexia/weight loss	3 (> 1)	2 (> 1)
Functional decline[d]	3 (> 1)	2 (> 1)
Hepatic	1 (> 1)	1 (> 1)

[a]Adverse drug events could manifest as more than one type.

[b]Neuropsychiatric events include oversedation, confusion, hallucinations, and delirium.

[c]Anticholinergic effects include dry mouth, dry eyes, urinary retention, and constipation.

[d]Adverse drug event manifested only as decline in activities of daily living without any other more specific type of event. Other types of events may have been associated with functional decline.

Adapted from Gurwitz JH, Field TS, Judge J, et al. The incidence of adverse drug events in two large academic long-term care facilities. Am J Med. 2005;118:251.

Failures in the design of systems of care are considered the most important contributor to the occurrence of medical errors, as well as the injuries that result from some of those errors. Enhanced surveillance and reporting systems for ADEs occurring in the nursing home setting are required as are continued educational efforts relating to

the optimal use of drug therapies in the frail older patient population. However, as Leape et al. concluded in regard to the occurrence of serious medication errors in the hospital setting, "preventive efforts that focus solely on the individual provider or which rely on inspection alone have limited impact. Analysis and the correction of underlying systems' faults is much more likely to result in enduring changes and significant error reduction." Ordering and monitoring errors in the nursing home setting maybe particularly amenable to prevention strategies that use systems-based approaches. The benefits of such an approach to error reduction in the hospital setting that uses computerized order entry have been reported. For example, a computer-based decision aid reduced in-hospital inappropriate dosing of psychotropic medications for geriatric inpatients. Successes in the hospital setting pave the way for similar efforts in the nursing home setting. For instance, clinical decision support at the time of medication ordering has been shown to improve the quality of prescribing to long-term care facility residents with renal insufficiency.

DEFICIENCIES IN INFORMATION ABOUT DRUG THERAPY IN OLDER ADULTS

Selecting the right medication and the right dose to prescribe for an older person is difficult because so little evidence is available to guide choices. Decision making often has to draw on information obtained from the experience of patients very different from those encountered in clinical practice, where patients often have several medical conditions and are taking more than one drug. The findings of clinical trials of treatments for conditions commonly affecting older people cannot directly be extrapolated to that age group, as older persons, particularly frail persons and those with multiple illnesses, have often been excluded from participation in such studies. This poses challenges to the adoption of clinical practice guidelines developed to improve the quality of health care for many chronic conditions. A review of clinical practice guidelines for nine common chronic diseases promulgated by national and international medical organizations found that most clinical practice guidelines did not modify or discuss the applicability of their recommendations for older patients with multiple comorbidities. Most did not comment on burden, short- and long-term goals, and the quality of the underlying scientific evidence, nor give guidance for incorporating patient preferences into treatment plans. Boyd and colleagues have reported that if relevant guidelines were followed, a hypothetical 79-year-old patient with osteoporosis, osteoarthritis, type 2 diabetes mellitus, hypertension, and chronic obstructive pulmonary disease would be prescribed 12 medications. There are several ways in which the quality and availability of information about the use of drugs in older persons might be improved. These include enhancing the inclusion of older persons in drug trials, and using observational studies and systematic reviews to provide information to guide clinical decision making.

Inclusion of Older Persons in Clinical Trials

In 1989, the US Food and Drug Administration published "Guidelines for the Study of Drugs Likely to be Used in the Elderly." The guideline was intended to encourage routine and thorough evaluation in older populations of the effects of new drugs being proposed for federal approval so that physicians would have sufficient information to use such drugs properly in their older patients. The guidelines state "there is no good basis for the exclusion of patients on the basis of advanced age alone, or because of the presence of any concomitant illness or medication, unless there is a reason to believe that the concomitant illness or medication will endanger the patient or lead to confusion in interpreting the results of the study." In short, drug trials should include subjects that reflect the group that would eventually be prescribed the therapy. However this guideline has not been uniformly adopted.

A case in point is heart failure, which is overwhelmingly a disease of old age. More than 85% of patients hospitalized with heart failure are 65 years and older; nearly three-quarters of those individuals are 75 years and older. However, clinical trials assessing treatment modalities in patients with heart failure have frequently excluded older patients. More than 40% of Medicare beneficiaries surviving hospitalization for heart failure would have been excluded from the Studies of Left Ventricular Dysfunction Trial and the Metoprolol Controlled Release/Extended-Release Randomized Intervention Trial in Congestive Heart Failure simply on the basis of their age.

The underrepresentation of older individuals in clinical trials can be considered from a variety of perspectives. Older patients are often excluded from participation simply based on explicit (and arbitrary) age limits for convenience and study efficiency. Large numbers of older patients often need to be screened to enroll just one eligible study participant, with an adverse impact on costs and the ability to meet study timelines.

The participation of older individuals in clinical trials is also limited through exclusion criteria that strongly correlate with advancing patient age, including common medical conditions and commonly prescribed medications. Finally, even in the absence of explicit age limits or criteria that preclude eligibility based on clinical or functional

grounds, the older patient's participation in a clinical trial may never even be considered, relating to a confluence of factors, including bias, value judgments, and rationalization.

Age-based exclusions may also have important secondary effects on the participation of women in clinical trials. A number of studies have demonstrated a strong association between the average age of enrollees in a clinical trial and the participation of women, because women account for a substantially greater proportion of the older adult population than do men. Many of the ongoing concerns regarding the enrollment of women in cardiovascular clinical trials are intimately related to the exclusion of older participants.

The European Medicines Agency has begun to take steps to ensure that the needs of older people are taken into account in the development, approval, and use of medications. This will involve adapting regulatory frameworks to make certain that the use of newly approved medicines in older adults is supported by relevant data on the benefit-risk balance, and to improve the availability of information to patients and prescribers to support safer use of medications in older people.

POLICY ISSUES RELATED TO DRUG THERAPY IN OLDER ADULTS

Cost-Related Nonadherence

A prescription may be written but not filled, or filled and not taken regularly, because of financial considerations. The use of drug therapy has been shown to be directly related to coverage of drug costs. It is estimated that more than 40% of all Medicare enrollees in the United States had no coverage for outpatient drug expenditures prior to the implementation of the 2003 Medicare Modernization Act. In the United States, cost has been identified as an important reason that patients do not take medications that are prescribed by their health care provider. Specifically, among older adults prior to Medicare Part D, 13% of a national sample of 13,869 noninstitutionalized Medicare enrollees reported cost-related underuse of medications. Those in fair-to-poor health, with multiple comorbidities, and without coverage were most at risk.

Following the implementation of Medicare Part D, there were incremental improvements in medication affordability for older Americans. However, recent concerns have been raised that these trends, especially for Medicare beneficiaries with multiple chronic conditions, have plateaued or even reversed, indicating that high drug costs remain a persistent burden for this vulnerable population.

Limited Manufacturing of Low-Dose Formulations of Recommended Drug Therapy

Limited manufacturing of low-dose formulations of drug therapy may make it more difficult or expensive for patients to take their prescribed drug therapy. Low-dose therapy is often recommended for older adults but may not be manufactured or available from publically funded drug programs in the prescribed low dose. For example, there is considerable evidence supporting the efficacy and greater safety of low doses of thiazide diuretic therapy in the treatment of hypertension in the older patient population. The report from the panel members appointed to the Eighth Joint National Committee (JNC 8) suggests starting antihypertensive therapy at low doses. Low doses of thiazide diuretics often produce as large an antihypertensive effect as larger doses, with a reduced risk for metabolic abnormalities.

Medication Reconciliation

In the United States, The Joint Commission has required accredited facilities to implement a system of medication reconciliation to reduce medication errors at transitions of care. Medication reconciliation is defined as the process of identifying the most accurate list of all medications that the patient is taking, including name, dosage, frequency, and route, by comparing the medical record to an external list of medications obtained from a patient, hospital, or other provider (**Table 24-5**). Patients, and responsible physicians, nurses, and pharmacists should be involved in the medication reconciliation process. This reconciliation is done to avoid medication errors such as omissions, duplications, dosing errors, or drug interactions. Changes in medication (different dose, discontinued therapies, additional therapies), common during transitions between hospital and nursing home or institutional setting and home, are a frequent source of medication errors and confusion. ADEs attributed to medication changes occurred in 20% of patients on transfer from hospital to a nursing home, happening most commonly for patients on readmission to the nursing home. One study found that discharged patients understood the potential side effects of their medications less frequently than their attending physicians believed. One Canadian multisite study found that 25% of 325 older adults

experienced an ADE after discharge home from the hospital; half of these events were considered preventable. Medication reconciliation systems and processes have successfully reduced medication errors in many health care organizations. Pharmacy technicians at one hospital reduced potential ADEs by 80% within 3 months by obtaining medication histories of patients scheduled for surgery.

TABLE 24-5 FIVE STEPS OF MEDICATION RECONCILIATION

1. Develop a list of current medications.
2. Develop a list of medications to be prescribed.
3. Compare the medications on the two lists.
4. Make a clinical decision based on the comparison.
5. Communicate the new list to the patient and appropriate caregivers.

Data from JACHO website http://www.jointcommission.org/assets/1/18/SEA_35.pdf. Accessed February 1, 2016.

In the United States, policy efforts to promote the use of new health care information technology serve to encourage medication reconciliation as patients transition from one setting of care (eg, hospital, ambulatory primary care, ambulatory specialty care, long-term care, home health, rehabilitation) to another or from one provider of care to another. For example, the Health Information Technology for Economic and Clinical Health (HITECH) Act and Meaningful Use Criteria (Stage 1) require that health professionals who receive a patient from another setting of care or provider of care should perform medication reconciliation.

PRACTICAL APPROACH TO PRESCRIBING MEDICATIONS TO OLDER PERSONS

Review Current Drug Therapies

A periodic evaluation of the drug regimen that a patient is taking is an essential component of the medical care of an older person. Such a review may indicate the need for changes to prescribed drug therapy. These changes may include discontinuation of a therapy prescribed for an indication that no longer exists, substitution of a required therapy with a potentially safer agent, reduction in dosage of a drug that the patient still needs to take, or an increase in dose or even addition of a new medication (**Table 24-6**).

TABLE 24-6 PRACTICAL STEPS TO CONSIDER IN OPTIMIZING DRUG REGIMENS FOR OLDER ADULTS

Review current drug therapy.
Discontinue unnecessary therapy.
Consider adverse drug events as a potential cause for any new symptom.
Consider nonpharmacologic approaches.
Substitute with safer alternatives.
Reduce the dose.

Data from Rochon PA, Gurwitz JH. Drug therapy. Lancet. 1995;346:32.

Scott and colleagues have commented on the dangers of *therapeutic inertia*—whereby drugs continue to be prescribed in the absence of ongoing benefit, and *therapeutic momentum*—where more drugs are added in response to new but questionable indications, including unrecognized side effects arising from preexisting medications, potentially resulting in a prescribing cascade.

Randomized controlled trials examining the effect of medication reviews report mixed results. All studies have reported that medication review leads to recommendations for different types of changes, including elimination of drugs, increasing the number of drugs, therapeutic substitutions, or better dosing. However, few reported statistically significant changes in patient drug use and drug expenditures. Studies that involved direct contact between the consulting pharmacist and the patient appeared to be more effective than interventions aimed at recommending drug changes to the patient's physician. One intervention study found that patients were resistant to reducing medications to recommended levels, particularly psychoactive drugs.

To conduct a medication review, the physician should ask the patient to bring to the visit all the bottles of pills that they are using. For example, patients may not consider OTC products, ointments, vitamins, ophthalmic preparations, or herbal medicines to be drug therapies. Patients need to be specifically told to bring these therapies to the visit. In addition, patients should be instructed to keep a complete, accurate, and up-to-date medication list including OTC medications and herbal preparations. This list should be brought to every physician visit.

A patient-generated list is particularly important as patients are prescribed medications from several physicians and receive their medications from several pharmacies. Although there are an increasing number of effective medications for preventing or controlling a range of illnesses and for alleviating many symptoms, several studies show that adherence decreases, and adverse medication effects increase, with the complexity of the medication regimen. The goal should thus be the simplest regimen that controls the patient's symptoms and illnesses, and optimizes disease prevention. A medication grid, which displays each medication with dosage and frequency along with its indication, has been found effective at facilitating the reduction in medication complexity.

Discontinue Potentially Unnecessary Therapy

Physicians are often reluctant to stop medications, especially if they did not initiate the treatment and the patient seems to be tolerating the therapy. Sometimes, however, medications expose the patient only to the risks for an adverse event with limited or no therapeutic benefit. The use of chronic digoxin therapy among older adults with normal systolic function is one such example. When considering a change to a medication one approach described by Steinman and Hanlon is to match the patient's conditions to each of the medications. Through this process areas where there is a mismatch can be identified. For example, situations where a drug is used with no indication, conditions that may benefit from a therapy where a therapy is not currently being offered, and drugs that are being given for an appropriate indication but where there is room for improvement (eg, dose adjustment or substitution with a drug therapy with a better risk-to-benefit profile). Further, the match between the medical condition and the medications should be guided not only by clinical guidelines but also to the patient's goals of care.

Consider Nonpharmacologic Approaches

Physicians should limit prescribing of a new drug therapy to situations in which benefits clearly outweigh risks and to use drug therapy only after potentially safer alternatives have been attempted. For example, NSAIDs may be extremely useful in treating patients with rheumatoid arthritis. However, the use of this medication to manage pain in older adults with osteoarthritis may be inappropriate because safer options are available. Epidemiologic and clinical studies have characterized the adverse consequences of NSAID use in older persons, particularly the association between NSAID use and gastrointestinal bleeds and renal impairment. Thus, alternative approaches should be considered before NSAIDs are prescribed for indications such as osteoarthritis. Possible nonpharmacologic approaches, such as gentle exercise and weight reduction, may be beneficial alternatives to treatment with NSAIDs. When pharmacologic therapy is required, a drug therapy with a less adverse event profile, such as acetaminophen, should be used. However, if a clinician chooses to initiate acetaminophen at a higher dosage, the patient should be carefully counseled to avoid all other products that contain acetaminophen including OTC cold remedies and opioid analgesics that might be combined with acetaminophen.

Another example of clinical importance is the use of nonpharmacologic approaches to manage behavioral symptoms in dementia. Behavioral symptoms such as wandering and agitation are common clinical manifestations in dementia, and represent a major source of disability and caregiver distress. These symptoms frequently result in prescriptions for psychotropic medications such as antipsychotic drugs, but these drugs are on average only modestly effective and can provoke serious adverse effects. Thus, nonpharmacologic strategies are increasingly emphasized to manage behavioural symptoms in dementia, and are usually recommended as first-line treatments (refer to Chapter 66, Dementia Including Alzheimer's Disease, for discussion).

Hypertension is an example of a condition for which nonpharmacologic treatments may be beneficial with or without drug therapy. The benefit of dietary sodium reduction and weight loss in the treatment of hypertension in older adults was recently examined. Three months following the intervention, a withdrawal of hypertension therapy was attempted and patients were followed for the combined outcome measure (ie, occurrence of high blood pressure, treatment with an antihypertensive medication, or the occurrence of a cardiovascular event). Among 585 obese older adults, participants assigned to reduced sodium intake, weight loss alone, or to a reduced sodium intake and weight loss intervention were significantly more likely to remain free of an outcome relative to those participants assigned to usual care without a lifestyle intervention. This trial indicates restricting sodium intake and weight reduction are

beneficial nonpharmacologic therapies for hypertension management in older adults.

Reduce the Dose

Many ADEs are dose-related. A classic example of dose-related adverse events is the association between use of long elimination half-life hypnotic-anxiolytics, antipsychotics, and tricyclic antidepressants and the development of hip fracture. A dose-related association has been found for each class of drug. Many studies have illustrated dose-related ADEs. When prescribing drug therapies, it is important to use the minimal dose required to obtain clinical benefit.

Another clinically important example involves the intensity of diabetes treatment. The doses of oral hypoglycemic agents and insulin therapy should not result in too-tight glycemic control, as there is little evidence that tight glycemic control in older adults with type 2 diabetes is beneficial. Tight glycemic control has been consistently shown to produce higher rates of hypoglycemia in older adults. Realizing this point, the AGS has recommended in the Choosing Wisely campaign (an initiative of the American Board of Internal Medicine) that physicians should generally avoid using medications to achieve hemoglobin A_{1c} less than 7.5% in most older adults. The AGS suggests hemoglobin A_{1c} targets should reflect the individual older adult's treatment goals, health status, and remaining life expectancy. Additional information is provided in Chapter 110, Diabetes Mellitus.

SUMMARY

Optimizing drug therapy means achieving the balance between overprescribing of inappropriate therapy and underprescribing of beneficial therapy. Particular attention should be given to using all drug therapies only when required and at the minimum effective dose. Beneficial therapy should be prescribed when indicated. Financial pressures need to be recognized and strategies developed to make sure that older adults have access to drug therapies when needed. ADEs are common and system-level approaches need to be developed to minimize their impact.

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FURTHER READING

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Chapter 25

Complementary and Alternative Medicine

Seema Joshi, Joseph H. Flaherty

Learning Objectives

- Recognize current trends in the use of CAM therapies among older patients.
- Understand reasons for their use and guide patients appropriately.
- Develop an awareness of the commonly used modalities and their associated risks/benefits.

Key Clinical Points

1. **A large proportion of the US population is using CAM therapy, and the prevalence among adults may be as high as 44%.**
2. **Only a small proportion of adults using these modalities disclose this information to their clinicians.**
3. **Nonvitamin, nonmineral natural product use constitutes the most common CAM therapy.**
4. **Medical providers need to have a better understanding of CAM therapies to guide their patients appropriately.**

"Because the newer methods of treatment are good, it does not follow that the old ones were bad: for if our honorable and worshipful ancestors had not recovered from their ailments, you and I would not be here today."

—Confucius (551–478 BC)

BACKGROUND

Complementary and alternative medicine (CAM) and traditional medicine (TM) have existed for thousands of years in the East and seem to be a growing social phenomenon in the West. The general public has expressed an increased desire to embrace ancient philosophies and approaches to medical care. At the present time there is easy access to health care information from multiple sources along with changing individual expectations of health and the nature of health care systems. Worldwide, the population has continued to age with an associated accumulation of chronic diseases. In the face of increasing demands, conventional medicine has continued to advance in its capabilities, along with a continued evolution of technology. Despite all this, people continue to seek alternative approaches to maintain or improve their health. In the presence of multiple health care options, there have been a growing number of patients seeking CAM therapies with very few patients sharing this information with their physician for fear of criticism and humiliation. At the present time there is a paucity of evidence-based research in the field of CAM therapies, even though, during the last 15 years, there has been an increase in published literature. It is therefore important for medical providers to recognize the changing trend, the evidence that does exist, and the benefits and risks based on good research trials to guide their patients appropriately.

BRIEF HISTORY, DEFINITIONS, AND CLASSIFICATION OF CAM

In 1995, a panel of experts convened at the National Institutes of Health (NIH) to develop a definition of CAM. This was subsequently modified in 1997 by the Institute of Medicine Committee on the Use of Complementary and Alternative Medicine by the American Public: "CAM is a broad domain of resources that encompasses health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the dominant health system of a particular society or culture in a given historical period. CAM includes such resources perceived by their users as associated with positive health outcomes. Boundaries within CAM and between the CAM domain and the domain of the dominant system are not always sharp or fixed."

In 1998, the National Center for Complementary and Alternative Medicine (NCCAM) was created at the NIH. As of December 2014, the NCCAM was renamed as the National Center for Complementary and Integrative Health (NCCIH) to reflect that health care, especially if it is interdisciplinary, brings together complementary and conventional therapies (ie, integrative). The mission of the NCCIH was modified slightly: "to define, through rigorous scientific investigation, the usefulness and safety of complementary and *integrative health approaches* (instead of alternative medicine interventions) and their roles in improving health and health care."

One of the most widely used classification structures comes from the NCCAM. It includes the following categories:

1. Alternative medical systems: refers to an entire system of theory and practice that developed separately from conventional medicine. This includes traditional Chinese medicine, ayurvedic medicine, homeopathy, and naturopathy.
2. Mind-body interventions: include practices that are based on the human mind, but that have an effect on the human body and physical health, such as meditation, prayer, and mental healing.
3. Biologically based treatments: include specialized diets, herbal products, and other natural products such as minerals, hormones, and biologicals. Some well-known herbals/nonherbals include St. John's wort, *Ginkgo biloba*, and fish oil.
4. Manipulative and body-based methods: include therapies that involve movement or manipulation of the body such as massage, chiropractic, and osteopathic manipulation.
5. Energy therapies: include the manipulation and application of energy fields to the body. A number of therapies such as qi gong, Reiki, and therapeutic touch are included in this category.

Extent and Cost of CAM Therapies in the United States

Studies have shown that CAM use is widespread in the United States. This was first highlighted by a national survey done by Eisenberg and associates in the 1990s showing that 33.8% of Americans in 1990 and 42.1% of Americans in 1997 were using unconventional or CAM approaches. Two national surveys in 2002 and 2007 found that 36.0% and 38.3%, respectively, of US adults reported using CAM in the previous 12 months. The prevalence of use was highest among adults aged 50 to 59 with rates as high as 44%. Rates among older adults varied between 41% for those between 60 and 69 years and 32% for those greater than 70 years. These and other surveys have also pointed out that less than half of adults who used CAM in the past 12 months disclosed the CAM therapies to their physician.

The national survey results from the 1990s revealed that the annual number of outpatient visits to CAM providers exceeded the number of visits to all US primary care physicians, and the annual out-of-pocket expenditures for CAM were comparable to the annual out-of-pocket expenditures for hospitalization in the United States. The 2007 survey estimated the out-of-pocket expenditure for CAM to be around $34 billion. This figure represents approximately 1.5% of total health care expenditures and 11% of out-of pocket costs.

The 2012 survey also revealed regional differences in the use of complementary health approaches among adults in the United States. The use of practitioner-based chiropractic or osteopathic manipulation was nearly twice as high in the West North Central region as in the United States overall. Nonvitamin, nonmineral dietary supplement use was highest in the Mountain, Pacific, and West North Central regions, and yoga with deep breathing or meditation was approximately 40% higher in the Pacific and Mountain regions than in the United States overall.

Reasons for CAM Use

Studies on why people use CAM suggest several reasons. Some of these include the following:

1. Dissatisfaction with the health outcomes of orthodox medicine

2. Dissatisfaction with the medical encounter/doctor-patient relationship
3. Preference for the way alternative therapists treat their patients, including being caring, individualized attention, and ample time and information
4. Emergence of a new philosophy around nature and holism related to a postmodern value system
5. Heterogeneity of an individual's social network, resulting in exposure to a wider range of information and values
6. Alternative therapies fulfill a psychological need in the wake of the waning of organized religion, providing an alternative framework for making sense of illness, suffering, and misfortune
7. Prevent illness or for overall wellness
8. Reduce pain or treat painful conditions
9. Treat a specific health condition, or supplement conventional medicine

Commonly Used CAM Therapies

In 2012, nonvitamin, nonmineral dietary supplement use (17.9%) was the most common type of CAM used. This was followed by chiropractic and osteopathic manipulation (8.5%), yoga (8.4%), and massage (6.8%). Other complementary health approaches commonly used included meditation (4.1%) and special diets (3.0%). There has been a significant increase in use of several approaches to well-being such as deep breathing exercises, meditation, massage therapy, and yoga between 2002 and 2007. **Figure 25-1** shows the 10 most common therapies and **Figure 25-2** depicts some of the most commonly used natural products among adults. This chapter will review only some of the most commonly used CAM approaches.

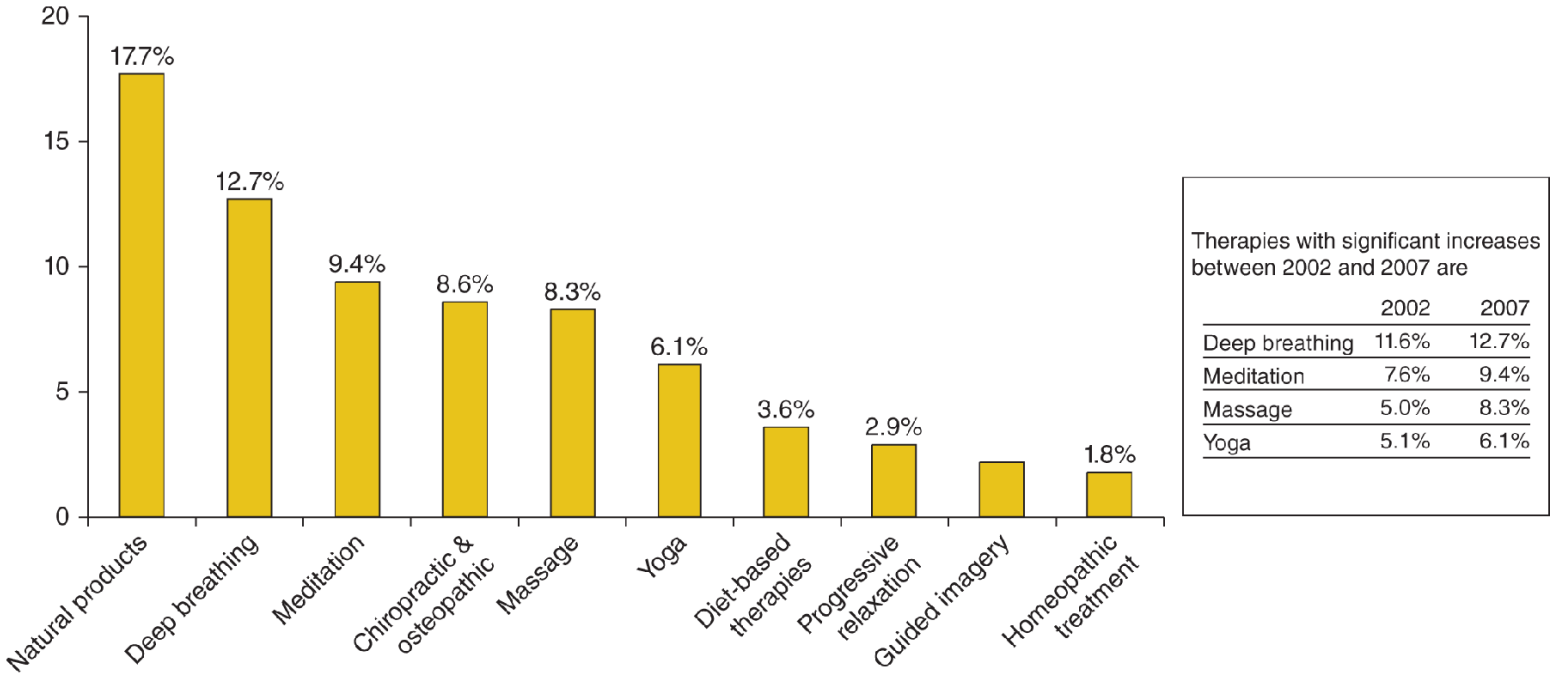


FIGURE 25-1. Ten most common CAM therapies among adults—2007. (Barnes PM, Bloom B, Nahin R. Complementary and alternative medicine use among adults and children: United States, 2007. *CDC Natl Health Stat.* 2008;12:1–23.)

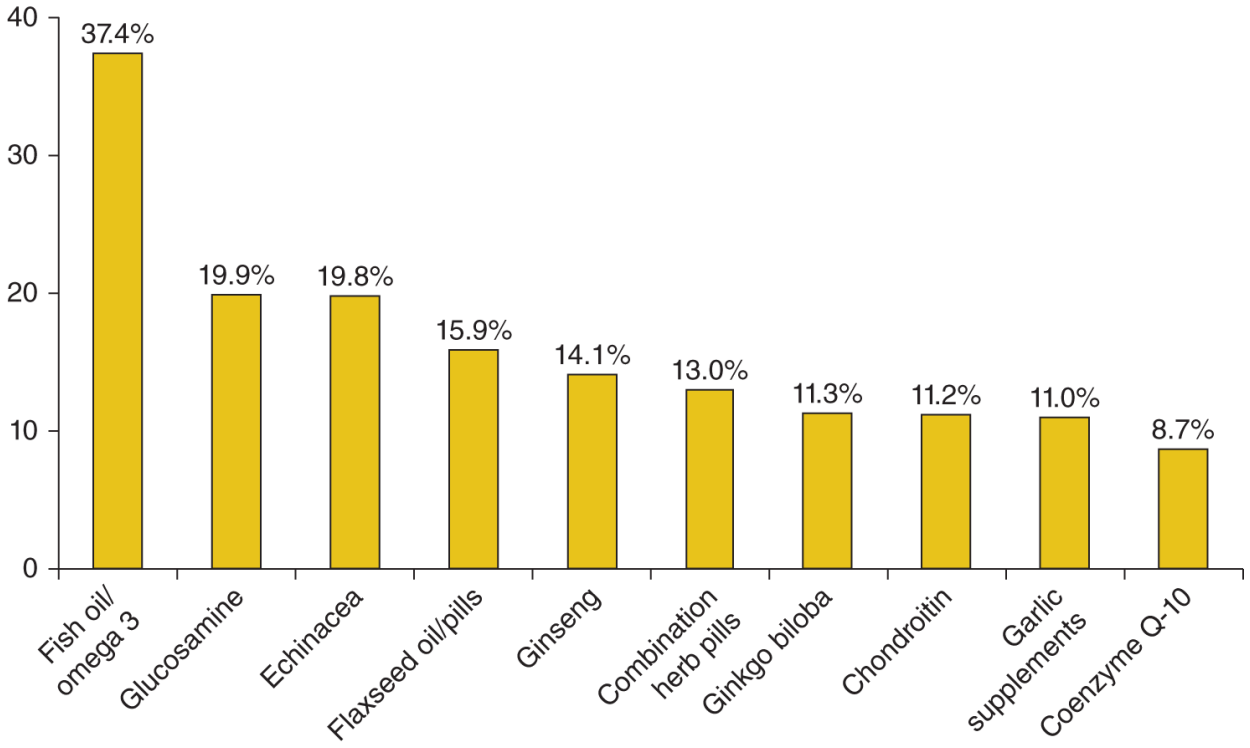


FIGURE 25-2. Ten most common natural products among adults—2007. Percentages among adults who used natural products in the last 30 days. (Barnes PM, Bloom B, Nahin R. Complementary and alternative medicine use among adults and children: United States, 2007. *CDC Natl Health Stat.* 2008; 12:1–23.)

Regulation of Dietary Supplements (Nonvitamin and Nonmineral Products) and Potential Risks

The Dietary Supplement and Health Education Act was passed by the Congress in 1994. As a result of this act, dietary supplements are not regulated as foods and are not subject to premarket safety evaluations. Manufacturers/distributors are not required to record, investigate, or forward to the Food and Drug Administration (FDA) any reports of injuries or illnesses that may be related to use of their products. It allows for product labeling claims as long as it does not diagnose, prevent, treat, or cure a specific disease. This raised concerns regarding the quality of products used, and the Institute of Medicine called upon the government for better quality control. In 2007, FDA announced that manufacturers of dietary supplements would need to evaluate their products for purity, strength, composition, and identity and report all serious adverse effects.

With increasing public use of dietary supplements, there is an increased risk of adverse interactions of supplements with each other, as well as prescription medications. Twenty-five percent of patients who take prescription medications also take at least one nonvitamin dietary supplement. Thus, clinicians need to be willing to facilitate discussions regarding use of CAM therapies and be aware of available resources such as the NCCIH.

Fish Oil/Omega-3 Fatty Acids

Observational studies have revealed low rates of coronary heart disease (CHD) death among the Inuit population of Greenland, despite a diet rich in fats. The low rates of death related to CHD in this population are attributed to omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) found in the fish and their impact on triglyceride levels, inflammation, platelet clotting, arrhythmias, and improvements in endothelial function.

There have been several observational studies and randomized trials examining the long-term effects of fish oil on the development and progression of atherosclerosis. These studies suggest that fish oil consumption may modestly reduce chronic progression of atherosclerosis. However, effect on the risk of coronary restenosis is not convincing. Fish and fish oil consumption in systematic reviews and meta-analyses have found significant reductions or strong trends toward reductions in CHD death (including risk of fatal myocardial infarction [MI] and sudden cardiac death) in populations with or without established CHD. Benefits of fish oil supplementation in patients with existing heart failure have been noted in some randomized trials. Patients with symptomatic heart failure already on recommended therapies have shown significant improvements in left ventricular ejection fraction with fish oil supplementation.

Although, observational evidence suggests that fish consumption may reduce the risk of ischemic stroke and atrial fibrillation, evidence from randomized trials is not convincing.

Common side effects of fish oil consumption include gastrointestinal disturbances such as nausea and fishy taste with eructation. Trials have not shown any clinically significant effect on bleeding risk in individuals taking aspirin/warfarin. If one chooses to take this supplement, the recommended dose according to the American Heart Association is 1 g/day of omega-3 fatty acids for those with CHD and 500 mg/day for those without CHD.

Glucosamine and Chondroitin

Glucosamine and chondroitin supplements are widely used in the treatment of osteoarthritis (OA). The benefits of treatment are uncertain and results of randomized trials have been controversial. The Cochrane Review is one of the most exhaustive meta-analyses of the effect of glucosamine on OA; this review included 20 randomized controlled trials (RCTs) involving 2570 patients. The mean age of participants was 60.7 years. The meta-analyses showed a 28% improvement in pain and 21% improvement in function from baseline. It also confirmed the safety of glucosamine with a side effect profile similar to that of placebo. In this review, efficacy of glucosamine was identified for trials that used a specific proprietary formulation.

A 2010 meta-analysis of 10 randomized trials involving 3803 patients concluded that compared with placebo, glucosamine, chondroitin, and their combination did not reduce joint pain or have an impact on narrowing of joint space. The age range of participants was between 58 and 66.

The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) was a multicenter trial involving 1583 patients who were randomly assigned to receive 1500 mg glucosamine (GH); 1200 mg chondroitin sulfate (CS); both GH and CS; 200 mg of celecoxib; or placebo for 24 weeks. The average age of participants was 57. The combination of GH and CS was not significantly more effective than placebo for pain relief or functional improvement in patients with OA of the knee in the pooled analysis. However, in a subgroup of patients with moderate-to-severe pain, 79% of patients in the GH and CS group had significantly reduced knee pain compared to 54.3% in the placebo group. Over a period of 2 years, no treatment achieved a clinically important difference in pain or function as compared with placebo.

Ginkgo biloba

Ginkgo has been used in traditional Chinese medicine for over 1000 years to treat a variety of illnesses. The supplement is an extract of the ginkgo leaf and its active constituents are flavone glycosides and terpenoids. Their antioxidant properties have been used for the treatment of many disorders including vascular problems, memory loss, dementia, and macular degeneration.

Current data on the efficacy of gingko for memory impairment and peripheral vascular disease are inconclusive. A meta-analysis of ginkgo by the Cochrane Collaboration was done to evaluate the efficacy of ginkgo for cognitive impairment or dementia. This review included 36 randomized, double-blind, placebo-controlled trials. The mean age of participants varied between 60.9 and 71.6. The analysis revealed significant improvements in cognition and activities of daily living at 12 but not 24 weeks. Also, clinical global improvement was observed at 24 but not 12 weeks.

The Ginkgo Evaluation of Memory (GEM) study, a randomized, double-blind, placebo-controlled clinical trial conducted in five academic medical centers in the United States between 2000 and 2008, followed 3069 adults ages 75 and older assigned to placebo of twice daily ginkgo supplements. The study did not show any benefits on dementia or mild cognitive impairment (MCI) with 6 years of ginkgo treatment. The study, however, did show a significant reduction in peripheral vascular disease events in the ginkgo arm versus the placebo arm.

Benefits of ginkgo supplements remain controversial; however, it is generally well tolerated but should be avoided or used with caution in patients receiving anticoagulants or antiplatelet agents.

Meditation

Meditation is a mind-body practice. There are many types of meditation, most of which originated in Eastern religious or spiritual traditions. These techniques have been used throughout the world for thousands of years. Meditation refers to a group of techniques, such as mantra meditation, relaxation response, mindfulness meditation, and Zen Buddhist meditation. Meditation may be practiced for many reasons, such as to increase calmness and physical relaxation, to improve psychological balance, to cope with illness, or to enhance overall health and well-being. The following elements are common to most practices:

- A quiet location

- A specific comfortable posture
- A focus of attention
- An open attitude

It is thought that some types of meditation might work by reducing activity in the sympathetic nervous system and increasing activity in the parasympathetic nervous system. A 2007 NCCAM-funded review of the scientific literature found some evidence suggesting that meditation is associated with potentially beneficial health effects. At the present time, overall evidence remains inconclusive.

Massage

Massage therapy dates back thousands of years and encompasses many different techniques. It generally involves varying degrees of pressure and manipulation to muscle and other soft tissue. This is done by therapists who, most often use their hands and fingers, but may use their forearms, elbows, or feet. Evidence suggests beneficial effects on pain and other symptoms associated with a number of different conditions such as back pain, depression, cancer, and HIV/AIDS. A 2008 Cochrane systematic review and 2011 NCCAM-funded clinical trial concluded that massage may be useful for chronic low back pain. Also, beneficial effects of massage therapy in pain associated with osteoarthritis of the knee were noted in a 2012 NCCAM-funded study. In another NCCAM-funded study, multiple 60-minute massages per week were helpful for people with chronic neck pain with improved pain and meaningful function.

Massage therapy appears to have few risks if it is used appropriately and provided by a trained massage professional. The effects however, are short term and therapy needs to be continued to sustain benefits.

Yoga

Yoga is a mind and body practice that typically combines physical postures, breathing techniques, and meditation or relaxation. Its origin traces back to ancient Indian philosophy. Yoga is the sixth most commonly used complementary health practice among adults in the United States, and its use has increased by 1% since 2002 based on the 2007 National Health Interview Survey (NHIS).

Benefits of yoga on chronic low back pain and function have been suggested by studies using carefully adapted set of yoga poses. Studies also suggest other health benefits such as reduction in blood pressure and heart rate, and possibly relieving anxiety and depression. A NCCAM-funded study involving 90 people with chronic low back pain found that participants who practiced Iyengar yoga (founded by B. K. S. Iyengar) had significantly less disability, pain, and depression after 6 months. The age range of participants was 23 to 66 years. In another study, also funded by NCCAM, researchers compared yoga with conventional stretching exercises or a self-care book in 228 adults with chronic low back pain. The mean age of participants was 48 years. The results showed that both yoga and stretching were more effective than a self-care book for improving function and reducing symptoms due to chronic low back pain.

These results were further complemented by a 2011 study of 313 adults with chronic or recurring low back pain suggested that 12 weekly yoga classes resulted in better function than usual medical care.

Overall, yoga seems to have beneficial effects on chronic low back pain and function and may improve quality of life. Yoga appears to be low impact and safe for most healthy people. It should be practiced appropriately under the guidance of a well-trained instructor.

Chiropractic Therapy

Chiropractic is a health care profession that focuses on the relationship between the body's structure (mainly the spine) and its functioning. It is based on the notion that the relationship between the body's structure and its function affects health. The term "chiropractic" combines the Greek words *cheir* (hand) and *praxis* (practice) to describe a treatment done by hand. Practitioners primarily perform adjustments to the spine or other parts of the body to correct alignment problems, alleviate pain, improve function, and support the body's natural ability to heal itself.

Chiropractic therapy (sometimes referred to as manual therapies) is one of the most commonly used CAM therapies for back pain. It may also be sought for other musculoskeletal conditions such as neck pain, shoulder pain, headaches, etc.

A review of evidence for manual therapies used for a range of conditions found that it may be effective for back pain, migraine, cervicogenic headaches, neck pain, upper- and lower-extremity joint conditions, and whiplash-associated disorders. However, it did not appear to benefit conditions such as asthma, hypertension, menstrual pain,

fibromyalgia, mid-back pain, premenstrual syndrome, sciatica, and temporomandibular joint disorders.

Chiropractic therapy generally appears to be safe. Some reported side effects include temporary headaches, tiredness, or discomfort in the parts of the body that were treated. There have been rare reports of serious complications such as stroke, cauda equina syndrome, and worsening of herniated discs, although cause and effect are unclear.

Acupuncture

Acupuncture is a component of Chinese medicine that involves stimulation of points on the body using a variety of techniques. The most commonly used and studied technique involves penetrating the skin with thin, solid, metallic needles that are manipulated by the hands or by electrical stimulation. The technique attempts to manipulate vital energy called "chi" that circulates in the body through 12 pathways called meridians. It is believed that disease occurs when the flow of chi in the body is disturbed or unbalanced.

Millions of Americans use acupuncture each year, often for chronic pain. At the present time there exists considerable controversy surrounding the benefits of acupuncture. Several mechanisms have been postulated to explain the effects of acupuncture. These include effects on cytokines, cortisol, oxytocin, immune modulation, autonomic regulation, and biomechanical and electromagnetic effects.

A NCCAM-funded study provides evidence supporting effectiveness of acupuncture in chronic pain. It also provides evidence that the effects of acupuncture on pain are significantly attributable to two components. The first is the patient's belief that treatment will be effective, the placebo- and context-related effects. The second is attributed to an acupuncture-specific component involving issues such as the locations of specific needling points or depth of needling.

Acupuncture seems to have beneficial effects in the following conditions: chronic pain, postoperative nausea and emesis, chemotherapy-induced nausea, dental pain, headache, hypertension, chronic obstructive pulmonary disease (COPD), and seasonal allergic rhinitis. Evidence for benefits in stroke, fibromyalgia, depression, and tobacco use disorder is limited. Acupuncture is generally safe, but can lead to the complications seen with any type of needle use.

CONCLUSION

A large proportion of the US population is using some form of CAM therapy, either alone or in combination with conventional therapy. Individuals are seeking providers that understand the interplay of mind, body, and spirit. It is therefore important for providers to explore and respond to this new dimension. It is also essential to respect patient concerns and facilitate communication related to the use of these therapies.

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Chapter 26

Team Care

Alice Bonner, Ellen Flaherty, Kathryn Hyer, Bradley Karlin, Terry Fulmer

Learning Objectives

- Identify differences between multidisciplinary, interdisciplinary, and transdisciplinary teams.
- Describe the roles of at least four different disciplines on care teams.
- List at least two positive outcomes from geriatric team care.

Key Clinical Points

1. **Team-based geriatric care is critical to the delivery of comprehensive, coordinated health care to older adults, their families, and caregivers.**
2. **Several evidence-based models for team-based care exist that may be useful for organizations wanting to develop training programs for geriatric team-based care.**
3. **Each discipline must clearly understand the unique role and function of other disciplines on the team.**

INTRODUCTION

Geriatric interprofessional team (IPT) care (also referred to as interdisciplinary team care) is essential to providing effective care for complicated older adults with multiple comorbidities. Research has demonstrated that IPT care is associated with enhanced functional and cognitive status, reduced depression and other psychological symptoms, and improved subjective well-being. Geriatric IPT care has also been shown to reduce hospital readmissions and outpatient service use. Specialized IPTs focusing on specific diseases such as congestive heart failure, stroke, myocardial infarction, or dementia have also demonstrated improved patient outcomes.

The current and projected health care workforce shortage, coupled with the aging of the population, dictate that care models be as efficient and effective as possible. Increasing numbers of frail, older adults with complex needs demand widespread adoption of geriatric IPTs. In this chapter, key components and benefits of geriatric IPT care are described along with the *patient-centered* IPT model, currently recognized as the standard of care.

BACKGROUND AND RECENT EVIDENCE FOR EFFECTIVENESS OF TEAM CARE

In the landmark report, *Crossing the Quality Chasm*, the Institute of Medicine (IOM) strongly urged that all health professionals receive interdisciplinary team training to ensure the delivery of patient-centered care. More recently, additional IOM reports specifically point to the need for interprofessional care for geriatric patients. For example, *Retooling for an Aging America* (2008) and *The Future of Nursing: Leading Change, Advancing Health* (2010), describe workforce requirements necessary for a health care system that will adequately meet the needs of older adults. Anticipating a shift toward population-based care, increasing the use of technology and bundled payment models such as accountable care organizations (ACOs), the reports include an emphasis on what has now become known as the

triple aim: better health, better care, and lower costs. The Joint Commission (TJC) has stated that shared decision making and an interprofessional health care team approach are essential to reduce medical errors and to provide improved patient safety in all health care organizations in America.

Reports from the Josiah Macy Jr. Foundation specifically point to the need for IPT care for geriatric patients. These reports emphasize the urgency of creating culture change around partnering with the patient to ensure a patient-centered and patient-directed care planning process that has been lacking in contemporary health care. Teams of the future will not succeed without this essential change of strategy. In 2014, The American Geriatrics Society (AGS) Partnership for Health in Aging Workgroup published a position statement on interdisciplinary team training in geriatrics. The workgroup cited the current body of evidence that interdisciplinary team training is an essential component of quality health care. The AGS position statement promotes the interdisciplinary care model for the following reasons:

1. Interdisciplinary care meets the complex needs of older adults with multiple, interacting comorbidities.
2. Interdisciplinary care improves health care processes and outcomes for geriatric syndromes.
3. Interdisciplinary care benefits the health care system as well as caregivers of older adults.
4. Interdisciplinary training and education effectively prepares providers to care for older adults.

The AGS statement targets not only professional associations but also credentialing and licensing bodies, as well as accreditation organizations and university administrators. The evidence has grown dramatically, yet training has not uniformly kept pace. According to the AGS statement all members of the team are expected to have the academic preparation to do the following:

- Understand their respective roles and responsibilities on the team.
- Establish common goals for the team.
- Agree on rules for conducting team meetings.
- Communicate well with other members of the team.
- Identify and resolve conflict.
- Share decision making and execute defined tasks when consensus is reached.
- Provide support for one another, including the development of leadership roles.
- Be flexible in response to changing circumstances.
- Participate in periodic team performance reviews to ensure that the team is functioning well and that its goals are being met.

Research indicates that training programs providing education in these essential areas are successful in enhancing the effectiveness of geriatric IPTs. The Geriatric Interdisciplinary Team Training Program (GITT) of the John A. Hartford Foundation developed a formal curriculum for team training, a curriculum that includes didactic materials and specific exercises to foster team development (http://hartfordign.org/education/gitt/). The GITT program has trained more than 1800 health care students and professionals across the country and developed training materials to encourage the development of effective geriatric teams. US academic institutions and organizations, including the Health Resources and Services Administration (HRSA)- sponsored Geriatric Education Centers, have sponsored additional Integrated Device Technology (IDT) training materials and websites.

In addition, the National Center for Interprofessional Practice and Education established in 2012 at the University of Minnesota is a public-private partnership that identifies ways to improve health, enhance patient care, and control costs through integrating interprofessional practice and education. By rigorously aligning and integrating the needs and interests of health professions' education with practice, the center aims to create a transformational "nexus" to incubate ideas, define the field, and guide program development (https://nexusipe.org/). See the Further Reading section for additional resources on team training.

RECENT STUDIES ON TEAM CARE

There is a small but growing body of evidence on the benefits of geriatric team care. Studies generally demonstrate that patient outcomes improve with implementation of an initial comprehensive geriatric assessment, conducted by multiple disciplines, in order to elicit and understand a patient's goals and establish a person-centered care plan.

Team management and internal performance also seem to drive outcomes. In a study of the 26 Program of All-Inclusive Care for the Elderly (PACE) sites, teams that ranked themselves as performing better had patients with better 3- and 12-month outcomes in activities of daily living (ADLs) performance and lower rates of urinary incontinence. It appears that the improved outcomes were related to coordination of services based on goals determined by the patient, the ability of team members to communicate well, and agreement from multiple providers on how to implement complex care and improve both short- and long-term patient outcomes and caregiver outcomes as well.

Studies focusing on patient satisfaction have demonstrated that the presence of a team champion and the involvement of physicians on the team are positively associated with greater perceived team effectiveness. Newer models of teams led by advanced practice registered nurses (APRNs), particularly in nursing homes, have also demonstrated improved outcomes and enhancements such as improved documentation of advance directives and advance care planning, and lower rates of preventable hospitalizations. Maintaining a balance among cultural values of participation, achievement, openness to innovation, and adherence to rules and accountability are also important aspects of team care. Another example of an initiative to promote and study team care is the RAND/Hartford Building Interdisciplinary Geriatric Health Care Research Centers Initiative. This program sought to establish centers that would not only focus on the development of new geriatric clinical and health services interventions, but also provide interdisciplinary education and training opportunities for junior and senior investigators. Outcomes included substantial funding for federal grants on aging, hundreds of publications, and career advancement for several faculty involved on the center teams. While research is sometimes considered a rather solitary pursuit (compared to clinical practice or teaching), there is evidence that team-based research centers may enhance productivity of investigators working on topics related to aging.

Finally, the fundamental concepts of team care and interprofessional team leadership have been widely implemented in the intensive care unit (ICU) setting, where many older adults receive care for a period of time. Programs such as Comprehensive Unit-based Safety Program (CUSP) establish teams, staffed by intensivists and nurses that also include pharmacists, social workers, family members, dieticians, therapists, and others. The focus is on preventing the next medical error or harm through implementation of a systematic program to develop a culture of safety and enhance collaboration among all geriatric and ICU team members.

POLICY CHANGES INCORPORATING THE IPT

The Patient Protection and Affordable Care Act (PPACA) promotes interprofessional care through a variety of mechanisms designed to impact access, cost-effectiveness, and quality in the care of frail older adults. Numerous demonstration projects to evaluate pay-for-performance or value-based purchasing programs linking interdisciplinary care across settings, particularly for at-risk, vulnerable populations, have been conducted through the Centers of Medicare and Medicaid Innovation (CMMI). In addition, certain state and federal programs that restrict payments to hospitals and other entities when adverse events or poor outcomes result from a lack of coordinated care have been implemented.

In some cases, state or federal regulations have been updated to reflect a shared accountability for coordination of care. No longer are hospitals, nursing homes, home health agencies and clinics permitted to point the finger at one another for failures in care coordination or poor outcomes. IPTs are required to work across disciplines not only within institutions, but also across and among health care settings and communities within states and regions. Despite these changes, reimbursement models that pay clinicians for team care have yet to be enacted. While progress has been made, there is a need to continue to move away from the traditional fee-for-service reimbursement model and evaluate bundled payment initiatives and others that recognize and include payment based on effective team care.

MODELS AND PRINCIPLES OF SUCCESSFUL TEAMWORK

Successful teamwork is paramount to the delivery of high-quality clinical care. This is especially true for teams caring for older adults who often present with complex and interrelated conditions. In a 2008 literature review, Xyrichis and Lowton found that team structures and processes influenced team performance. Teams with clear understandings of why they exist and how to accomplish tasks are more successful and more likely to have members who demonstrate respect. As team size increases, teams have a more difficult time creating a uniform culture and efficient meetings.

Members of teams caring for older adults bring complementary skills and perspectives that need to be woven

together to develop a comprehensive case formulation and to address what are often multiple biopsychosocial needs of older patients. For example, geriatric assessment is often shared among two or more providers who administer measures and other components of an assessment. Accordingly, geriatric health care teams are often *interdisciplinary*, rather than *multidisciplinary*, in nature. On multidisciplinary teams, team members apply professional skills and expertise from the perspective of their individual discipline. While multidisciplinary teams do allow for a broad range of knowledge and clinical expertise to contribute to the care of the patient, team members generally function in linear fashion and stay within their own "professional lanes."

On interdisciplinary teams, team members work in a more dynamic and interactive fashion. Members of interdisciplinary teams apply their individual perspectives and question one another to develop a richer and more holistic understanding of the patient. In addition, team members may contribute to the assessment and care processes that involve other team members and disciplines. In these ways, providers working on interdisciplinary teams often take one foot out of their professional lane, acting as an agent of a larger collective, focused on the patient's goals. Working on interdisciplinary teams can be stimulating and rewarding for many providers. By virtue of its more inclusive and interactive nature, the interdisciplinary team model can result in more effective care. At the same time, the interpersonal dynamics of an interdisciplinary team and the requirement to operate outside of the comfort of one's learned professional discipline can be challenging for health care professionals, particularly those with less experience working on teams.

A third type of health care team is the *transdisciplinary* team. Transdisciplinary teams extend integration and flexibility even farther than their interdisciplinary counterpart. On transdisciplinary teams, professional boundaries are even more permeable, and providers step farther outside of their traditional roles. The roles of team members on these teams are often characterized by greater "role release" (accepting that others outside one's professional discipline can engage in activities traditionally performed by those within that discipline) and "role expansion" (engaging in activities traditionally beyond one's professional discipline). Transdisciplinary teams are less common than interdisciplinary teams, which have become quite prominent and specifically recommended in many settings for the care of older adults.

Successful health care teams require effective communication, cohesiveness, role clarity, trust, and respect among team members. This is especially true for interdisciplinary and transdisciplinary teams. Without these, IPTs may lose their interactive and complementary identity; even worse, dominating or retreating behavior may develop among specific team members. The principles and processes of effective teams and key considerations for promoting successful engagement and functioning among team members are discussed below.

Team Dynamics and Process Issues

Team members possess extensive professional knowledge of their individual discipline but often have limited knowledge of other disciplines on the team. Beyond varied technical knowledge among team members, teams may be characterized by somewhat different values across professional disciplines. These differences are becoming less pronounced, with the evolution of IPTs in most health care settings and with many populations.

Professional disciplines vary significantly in how they characterize problems and their etiology. For instance, more medically oriented disciplines may focus on conducting diagnostic tests and explaining findings in biological terms, whereas the social sciences (eg, psychology, social work) may emphasize psychosocial issues and consequences. In addition to differences in understanding and formulating plans of care team members of different disciplines vary substantially in the nature of treatments they typically prescribe and in the length and frequency of patient visits. These differences in perspectives and approaches may lead to tensions among team members when roles and perspectives are unclear or poorly understood. However, on high-functioning and supportive teams, these different perspectives lead to a much deeper understanding of the patient and a more comprehensive and effective treatment plan.

As characterized by the National Center for Organizational Development of the Veterans Health Administration (www.va.gov/ncod), high-functioning teams excel in both function (effectiveness) and relationships (engagement). Effectiveness refers to the team's purpose and methods, role clarity, communication, awareness, and responsiveness (eg, how the team uses and shares information). Engagement is a function of the level of civility, respect, psychological safety, and cohesiveness of the team. There is a balance in the nature and function of relationships on the team. Limited attention to developing professional relationships may impede the development of trust and collaboration which can impair team function. However, excess focus on cohesion and collaboration may limit communication and prevent different opinions from being openly discussed.

While teams work toward a patient-centered outcome, individual team member competency remains essential. Teamwork requires discipline-specific clinical knowledge, skills, and communication processes that allow members to

be heard. Clinicians working in teams must have processes to communicate clearly, meet routinely, and understand their role in the care plan. Individual professional competency remains a key foundation for effective team care and optimal clinical outcomes.

Steps for Establishing High-Functioning Teams

The early development phase of health care teams is often marked by excitement and uncertainty. Implementing specific processes and norms can help to promote team effectiveness and engagement. **Table 26-1** provides a list of recommended tasks for new and developing teams and teams in the midst of transition.

TABLE 26-1 PRINCIPLES OF SUCCESSFUL TEAMWORK

1. Establish overall purpose and function of the team.
2. Determine team composition: which professions are needed, number of members, professional identities. Allow the problem and the population to define the composition of the team, not vice versa.
3. Determine the model of interprofessional teamwork (multidisciplinary vs interdisciplinary vs transdisciplinary).
4. Ensure clear understanding of the model by group members.
5. Learn about the norms and practices of other professions and promote understanding and respect for others' expertise.
6. Recognize the implications of specific language (idioms) by the professionals involved. Learn how to articulate information clearly to others.
7. Ensure the patient's health care goals will be shaped first and foremost by the patient, and also by different perspectives from various disciplines.
8. Establish team norms, rules, and commitment from team members. Create a mechanism for enforcing governance rules.
9. Promote ongoing evaluation of the effectiveness of the team.
10. Define acceptable behavior (willingness to work effectively with other professionals to develop a person-directed care plan; active participation, and respect for others' roles and opinions). Observe and value the participation of each member equally.
11. Identify and follow a decision process when roles overlap. Encourage and model open communication and collaboration. Resist setting rigid role boundaries.
12. Identify opportunities or requirements for team building meetings or retreats and team training.

An empirically informed framework for improving teamwork and communication among health care providers is TeamSTEPPS. Developed by the Department of Defense and the Agency for Healthcare Research and Quality, TeamSTEPPS includes training, feedback, ongoing coaching, and implementation support to improve team functioning. Adapted versions of TeamSTEPPS are now available for teams working in primary care and long-term care settings. Additional information about the program and training materials, including trainer manuals, multi-media resources, and evaluation tools are available at http://teamstepps.ahrq.gov. A preimplementation readiness assessment tool is also available to assess and help prepare teams and organizations interested in implementing TeamSTEPPS.

THE SUCCESSFUL TEAM MEETING

The team meeting is a critical component of the health care process. How well the team meeting is organized and executed significantly impacts the effectiveness and engagement of health care teams. Team meetings that are well-planned and organized increase team productivity, creativity, and cohesion, whereas team meetings that are poorly planned and executed decrease effectiveness, efficiency, and engagement and often cultivate negative attitudes toward teams. This, in turn, can lead to poor attendance and satisfaction among team members and limited improvement in health outcomes.

New teams should establish how often to meet and specify attendance requirements. The group should determine the time, place, and duration of meetings, as well as a system and roles for case presentations and care plan development. **Table 26-2** provides a summary of how to facilitate a team meeting.

TABLE 26-2 HOW TO FACILITATE A CARE PLAN TEAM MEETING

1. Review agenda and meeting objectives. Group reviews items/patients included, order of items, and time frames for completing agenda items. Add, reorder, or delete items as the group decides. Ensure that all team members agree with the agenda items (consent agenda).
2. Assign meeting leadership roles. Members may rotate the following roles but each meeting should include the following:

   Leader (calls meeting to order, has agenda, sets expectations)

   Timekeeper (keeps group on task)

   Recorder (keeps track of agreements about the care plan and modifications and is responsible for recording changes to care plan)
3. Bridge issues/topics from previous meeting: report follow-up from last meeting.
4. Consider these potential issues in order to create a high-functioning team:

   Acknowledge both verbal and nonverbal communication. Reward positive and address disruptive or negative attitudes and behaviors within the team.

   When conflict occurs, work to identify the underlying source of disagreement or misunderstanding and facilitate mutual listening and respect.

   Emphasize the importance of shared decision making.

   Suggest tools/techniques to enhance meeting flow, information gathering, decision making, and future planning.

   Facilitate problem solving through brainstorming and evaluation of potential solutions.

   Promote engagement (especially of less vocal team members) by asking questions of the team and making general process observations (eg, “I’ve noticed that we seem to have … . I wonder why that is?”)
5. Summarize action items from this meeting (recorder reports on discussion).
6. Increase team cohesion by regularly acknowledging positive actions of others and encourage others to do likewise. Promote recognition by one or more team members of specific, positive action (effort and/or outcome) or accomplishment of another team member or team as a whole since last meeting.
7. Set time/date for next meeting: Discuss objectives and agenda items for the next meeting; tasks each member will accomplish prior to the next meeting.
8. Ask each member to evaluate the meeting process and outcome. Evaluation can be verbal or written. What did the team do well that it should continue doing? What could the team do differently to improve the meeting and outcome/s?

MENTAL HEALTH CARE MODELS

Recent studies highlight the role that behavioral and psychological issues frequently play in the onset and maintenance of physical and chronic health conditions among older patients—and the high rates of unmet mental health need among older adults who infrequently utilize specialty mental health services. There is increasing interest and opportunity for mental health providers (eg, psychologist, psychiatrist, social worker, mental health nurse) to serve as integral members of geriatric IPTs. In addition to providing a range of mental health assessment and treatment services, mental health providers on care teams can help facilitate patients’ transition and adjustment to new living situations, as well as provide behavioral medicine interventions to manage pain, stress, disability, address sleep problems, facilitate weight loss, promote smoking cessation, and enhance self-care/self-management. Integrated mental health providers also apply their knowledge of psychology, systems, and group process to promote communication among care team members, patients, and their caregivers and to enhance the overall functioning of the team.

Mental health providers have been increasingly integrated into primary care teams, including in more than 100 primary care sites in the Department of Veterans Affairs (VA) health care system. Relatively robust literature in this area has shown integrated mental health care to be associated with increased clinical and functional outcomes, enhanced treatment acceptability, patient satisfaction, and cost-effectiveness. Two evidence-based models of integrated mental health care teams in primary care are care management and colocated/collaborative care. Increasingly, a blended model that combines the core components of the two approaches is being integrated into primary care settings.

In care management, a care manager—typically a registered nurse or social worker—engages in telephone

evaluation and triage of patients with potential mental health needs. For those with identified need, the care manager provides psychoeducation and follow-up by telephone to support implementation of the primary care provider's treatment plan, which generally consists of psychopharmacotherapy, as well as to support the person-centered plan. In some instances, the care manager may provide problem-focused counseling. The care manager closely tracks the patient's response and works with the primary care provider to make changes to the treatment plan if improvement is not realized. The systematic approach to assessment, treatment implementation and coordination, and maximizing treatment adherence is particularly valuable for older patients whose mental health symptoms (eg, slowing down, apathy, sleep changes, eating disturbances) are frequently attributed to aging or medical conditions.

Integrated Mental Health Care Models in Geriatric Care Contexts

An innovative model of integrated mental health care designed specifically for older, homebound patients that has been implemented in more than 130 sites in the VA health care system is the integration of mental health care into home-based primary care (HBPC). HBPC provides comprehensive, interdisciplinary, primary care services to older patients with complex and chronic disease in their home. A mental health provider (typically a psychologist) serves as a core member of the team and delivers a range of cognitive and psychological assessment and treatment services, as well as behavioral interventions for managing health-related issues. In addition, the mental health provider enhances team functioning and communication. An important focus is placed on systemically integrating mental health care into the processes of the overall team, rather than having the mental health provider function as a separate consultant.

A major issue that has presented significant challenges to many geriatric care teams is the management of unmet needs (often referred to as "challenging behaviors") commonly associated with dementia, such as agitation, aggression, vocalization, and care refusal. Increasingly, data have demonstrated the limited efficacy of antipsychotic medications and an increased risk of death associated with their use in individuals with dementia. This may appear to leave geriatric care providers with limited options.

Over the past few decades, multiple studies have demonstrated the effectiveness of behavioral, team-based approaches to preventing and ameliorating manifestations of distress in individuals with dementia. Promising approaches typically include behavior analysis in which the IPT works to identify intrapersonal, interpersonal, and/or environmental activators to and consequences of manifestations of distress and then develop individualized behavioral intervention plans based on this analysis. One such approach is STAR-VA, which has been implemented in more than 40 VA Community Living Centers (nursing homes) and has been shown to significantly reduce the frequency and severity of manifestations of distress, as well as reduce coexisting symptoms of anxiety and depression. STAR-VA owes its success to an individualized approach and highly interdisciplinary team care.

SKILLS OF DIFFERENT PROFESSIONALS ON TEAMS

IPTs are becoming increasingly more common in primary care, as practices organize "populations of patients" or "panels" shared by multiple team members (physician, nurse social worker, or pharmacist). An added incentive for this approach includes evidence that team-based care makes practices more efficient. According to the National Quality Forum, quality markers for these team-based practices include protocols for disease management based on evidence, access for all team members to electronic health records (EHRs), on-call systems to provide care during off-hours and on weekends, models where patients are encouraged to learn about their disease, the prognosis, and be partners in care, and routine team meetings where information is shared. When the care plan is driven by the patient's needs and values, care plan implementation is more likely to be successful. Consistent with other team models, primary care teams emphasize goals that are determined by the patient, focused on the patient's own definitions of health, well-being, and quality of life.

Much like the development of individual competencies for specific health professions, key competencies have also been identified for interprofessional teams. The American Geriatric Society's Partnership for Health in Aging (PHA), representing 10 health care disciplines and 28 professional organizations, developed a set of multidisciplinary competencies for working with older adults. The six essential domains for entry-level professionals working with older adults were identified as (1) health promotion and safety; (2) comprehensive evaluation and appropriate assessment; (3) care planning and coordination across the health care spectrum including end of life; (4) interdisciplinary care and team care; (5) caregiver support; and (6) knowledge of health care systems and benefits. Within the domain of interdisciplinary teams and teamwork two competencies are spelled out: (1) distinguish among, refer to, and/or consult with any of the multiple health care professionals who work with older adults, to achieve positive outcomes; and (2)

communicate and collaborate with older adults, their caregivers, health care professionals, and direct-care workers to incorporate discipline-specific information into overall team care planning and implementation.

An essential competency for teamwork is knowledge of other members' skills and capabilities. While more health professionals have exposure to other disciplines during training than in prior decades, few health care professionals learn the skills of all the disciplines likely to be part of an IPT. **Table 26-3** provides role descriptions for professionals and paraprofessionals who may be on a geriatric team.

TABLE 26-3 DESCRIPTIONS OF INDIVIDUAL PROFESSIONAL ROLES ON GERIATRIC INTERPROFESSIONAL TEAMS

DISCIPLINE	PRACTICE ROLES/SKILLS	WORK ENVIRONMENT	EDUCATION/TRAINING	LICENSURE/CREDENTIALS	HELPFUL LINKS
Medicine					
Physician	Diagnose illnesses and prescribe and administer treatment for people suffering from injury or disease. Physicians examine patients, obtain medical histories, and order, perform, and interpret diagnostic tests. There are two types of physicians: MD (Doctor of Medicine) and DO (Doctor of Osteopathic Medicine)	Physicians in primary care including those practicing: family medicine, internal medicine, pediatrics, obstetrics/gynecology, or surgery. May work in private offices, large group practices or clinics, or academic settings, often assisted by a staff of nurses and other administrative personnel.	4 y of undergraduate school, 4 y of medical school, and 3 to 8 y of internship and residency, depending on the specialty selected. There are combined undergraduate and medical school programs that last 6 y rather than the customary 8 y.	To be licensed, physicians must graduate from an accredited medical school, pass a licensing examination, and complete 1 to 7 y of graduate medical education.	http://www.ama-assn.org—American Medical Association http://www.nmanet.org/—National Medical Association http://www.bls.gov/oco/ocos074.htm—Occupational Outlook Handbook, 2014 Edition
Geriatrician	Physician with special training in the diagnosis, treatment, and prevention of disorders in older people; recognizes aging as a normal process and not a disease state.	Work in private offices or clinics, skilled nursing facilities or assisted living centers. Often assisted by nurses and other administrative personnel.	Complete a 1- to 3-y postgraduate fellowship training program in geriatric medicine or pass an exam Certificate of Additional Qualifications (CAQ) in geriatrics.	State licensure required for doctor of medicine degree; pass an exam CAQ in geriatrics. CE requirements.	http://www.americangeriatrics.org—The American Geriatrics Society
Physician Assistant (PA)	PAs practice medicine under the supervision of physicians. Provide diagnostic, therapeutic, and preventive health care services, they take medical histories, examine and treat patients, order and interpret laboratory tests and x-rays, make diagnoses, and treat injuries.	Work as members of the health care team. Most work in group practices or solo physician offices. Other setting include hospitals, rural clinics, community health centers, freestanding surgical facilities, nursing homes, school- or college-based facilities, industrial settings, and correctional systems.	Specially designed 2-y PA program located at medical colleges and universities. Must have bachelor's degree and over 4 y of health care experience before entering a PA program.	Pass the Physician Assistant National Certifying Examination open only to graduates of accredited PA education programs. To remain certified, PAs must complete 100 h of continuing medical education every 2 y. Every 6 y, they must pass a recertification exam.	http://www.aapa.org—American Academy of Physician Assistants Information Center http://www.nccpa.net—National Commission on Certification of Physician Assistants http://www.bls.gov/ooh/healthcare/physician-assistants.htm—Occupational Outlook Handbook, 2014 Edition

Advanced Practice Nursing					
Advanced Practice Nurses	Core competencies include expert coach, clinical consultant, research knowledge, clinical and professional leadership, collaboration, patient and nurse advocacy. Include certified registered nurse anesthetist (CRNA), nurse practitioners (NP), clinical nurse specialist (CNS), nurse midwife.	Independently or in collaboration with physicians	Graduate of a master's nursing or doctoral program and nationally certified	• Depends on state board of nursing • Registered nurse (RN) license and national certification	http://www.aacn.nche.edu/Publications/positions/cerreg.htm—American Association of Colleges of Nursing, Certification and Regulation of Advanced Practice Nurse
Nurse Practitioner	Over 192,000 nurse practitioners work with different populations. Almost two-thirds of all NPs are in primary care settings with about 3% focused on gerontology. NPs order and interpret diagnostic tests, diagnose and treat acute and chronic conditions, prescribe medications and other treatments. Emphasize health promotion and disease prevention.	Varied including clinics, hospitals, emergency rooms, urgent care sites, private physician or NP practices, nursing homes, schools, colleges, and public health departments			http://www.aanp.org/AANPCMS2/—American Academy of Nurse Practitioners http://www.aanp.org/images/documents/about-nps/npfacts
Clinical Nurse Specialist	Three spheres of practice include providing direct care to patients, working to improve nursing outcomes through consulting, and improving systems organization wide.	Clinicians defined by area of practice related to population (pediatrics, geriatrics, etc), setting (critical care, emergency center, etc), disease or medical subspecialty (diabetes, oncology, etc), type of care (rehabilitation, etc), type of problem (pain, wounds, etc)			www.nacns.org—National Association of Clinical Nurse Specialists
Doctor of Nursing Practice (DNP)	Advanced practice nurse with doctoral level training in systems and quality improvement, practice-based research.	Multiple settings—same as for advanced practice registered nurses (APRNs)			
PhD	Nurses or advanced practice nurses who are also trained to conduct research in academic and/or practice settings.	Multiple settings			
Nursing and Direct Care Workers					
Registered Nurse (RN)	RNs record patients' medical histories and symptoms, help perform diagnostic tests and analyze results, operate medical machinery, administer treatment and medications, assess patients, and help with patient follow-up and rehabilitation. They also teach patients and their families how to manage their health.	Most RNs work in health care facilities such as hospitals, skilled nursing facilities, or outpatient offices. Home health and public health nurses may travel to patients' homes, schools, community centers, and other sites.	There are three major educational paths to registered nursing—a 4-y bachelor's of science degree in nursing (BSN), a 2-y associate degree in nursing (ADN), or a 3-y diploma program. Diploma programs are largely being phased out.	Individuals must complete a national licensing examination in order to obtain a nursing license and are required to have 20 h of continuing education units (CEUs). Further training or education can qualify nurses to work in specialty areas, and may help improve advancement opportunities.	http://nursingworld.org—American Nurses Association http://www.ncsbn.org—National Council of State Boards of Nursing http://www.asrn.org—American Society of Registered Nurses http://www.bls.gov/ooh/healthcare/registered-nurses.htm—Occupational Outlook Handbook, 2014 Edition
Licensed Practical Nurse (LPN)/ Licensed Vocational Nurse	Care for people who are sick, injured, convalescent, or disabled under the direction of physicians and registered nurses. They measure and record vital signs, prepare and give injections, monitor catheters, dress wounds, collect samples for testing, and perform routine laboratory tests.	LPNs often work in nursing homes or outpatient office practices.	Most training programs, lasting about 1 y, are offered by vocational or technical schools or community or junior colleges. LPNs must be licensed to practice. Successful completion of a practical nurse program and passing an examination are required to become licensed.	The NCLEX-PN licensing exam is required in order to obtain licensure as an LPN. The NCLEX-PN is a computer-based exam and varies in length. The exam covers four major categories: safe and effective care environment, health promotion and maintenance, psychosocial integrity, and physiologic integrity.	http://www.ncsbn.org—National Council of State Boards of Nursing http://www.napnes.org—National Association for Practical Nurse Education and Service http://www.bls.gov/ooh/healthcare/licensed-practical-and-licensed-vocational-nurses.htm—Occupational Outlook Handbook, 2014 Edition

Certified Nursing Assistant (CNA)	Certified nursing assistants provide basic skilled care for patients in hospitals and residents of long-term care facilities, such as nursing homes.	Nursing assistants who work in nursing homes must be certified. They are frequently active providing personal care to frail or dependent individuals. Understanding cognitive impairment is important, as they often assist impaired patients with activities of daily living (ADLs). They often need to help lift or move patients.	Certified nursing assistants must complete a minimum 75-h federally mandated but state-approved education program in which they learn the basic principles of nursing care from a registered nurse. After completion of course most must complete supervised clinical work. Most CNAs have at least a high school diploma and receive a short period of on-the-job training.	After completing a minimum 75-h federally mandated but state-approved education program, nursing assistants take a competency exam that includes both theoretical and practical portions. Some states have additional hours of training and requirements such as continuing education and a criminal background check. In some states, nursing assistants can earn additional credentials, such as becoming a certified medication assistant (CMA).	http://www.bls.gov/ooh/healthcare/nursing-assistants.htm#tab-4 www.nahcacareforce.org—National Association of Health Care Assistants http://www.bls.gov/ooh/healthcare/nursing-assistants.htm#tab-1—Occupational Outlook Handbook, 2014 Edition
Home Health Aide	Home health aides help people who are disabled, chronically ill, or cognitively impaired in the community. In some states, home health aides may be able to give a client medication or check the client's vital signs under the direction of a nurse or other health care practitioner.	Home health aides held about 875,100 jobs in 2012. They generally work in the community visiting individual homes.	States vary in regulation of home health aides. Similar to CNAs, there may be background checks and minimum training requirements. Most aides have a high school diploma. Home health aides working in certified home health or hospice agencies must take minimum 75-h formal training and pass a standardized test.	Home health aides can be certified by providers approved for training or the National Association for Home Care & Hospice (NAHC). Although certification is not always required, employers may prefer to hire certified aides. Certification requires 75 h of training, observation and documentation of 17 skills demonstrating competency, and passing a written exam.	http://www.bls.gov/ooh/healthcare/home-health-aides.htm#tab-1—Occupational Handbook 2014 Edition
Personal Care Aides	Personal care aides help clients with self-care and everyday tasks, and provide companionship.	Personal care aides held about 1.2 million jobs in 2012. They work in a variety of settings, including patients' homes and larger care communities.	Most personal care aides are trained on the job. There are no formal education requirements for personal care aides, but most aides have a high school diploma.	A few states require aides to have specific training or certification. Background checks may also be required. There are no federal training requirements for personal care aides.	http://www.bls.gov/ooh/healthcare/personal-care-aides.htm—Occupational Handbook 2014 Edition
Psychiatric, Psychological, Social Work, & Spiritual Support					
Psychiatrist	Medical doctors who treat patients' mental, emotional, and behavioral symptoms. Care for physically or mentally ill, injured, disabled, or infirm individuals in hospitals, nursing care facilities, and mental health settings.		Medical school and residency specializing in psychiatry. Residency includes both general residency training and 2–3 y in area of specialization (eg, geriatrics, pediatrics).	State exam to practice medicine; Board of Psychiatry and Neurology offers exam for diplomate in psychiatry, though not required for psychiatric practice in Texas.	http://www.nahc.org—National Association for Home Care and Hospice http://www.vnaa.org—Visiting Nurse Associations of America
Psychologist	Study the human mind and human behavior. Research psychologists investigate the physical, cognitive, emotional, or social aspects of human behavior. Psychologists in health service fields provide mental health care in hospitals, clinics, schools, or private settings	Vary by subfield and place of employment. Some have private practices and others are employed in schools, hospitals, nursing homes, and other health care facilities.	A doctoral degree is required for independent practice as a psychologist and generally requires 5–7 y of graduate study, culminating in a dissertation based on original research.	Clinical and counseling psychologists usually need a doctorate in psychology, an approved internship, and 1–2 y of professional experience. In addition, all states require that applicants for licensure pass a national licensing examination.	http://www.apa.org—American Psychological Association http://www.abpp.org—American Board of Professional Psychology http://www.bls.gov/ooh/life-physical-and-social-science/psychologists.htm—Occupational Outlook Handbook, 2014 Edition

Geropsychologist	Geropsychology is recognized as a specific specialty by the American Psychological Association. Geropsychology is now a formal specialty for which board certification is available through the American Board of Professional Psychology (ABPP).	Geropsychologists work across a variety of geriatric and related settings, including in-home; outpatient geriatric clinics; primary care practitioner (PCP) offices; inpatient psychiatric units; general hospital wards; assisted living facilities; nursing homes.	Using ABPP criteria: Need to be licensed as a psychologist A. Education: (1) Evidence of two courses/seminars relevant to Geropsychology at the doctoral, internship, or postdoctoral levels (Geropsychology dissertation topic = 1 course) OR (2) At least 100 h of documented formal CE coursework relevant to Geropsychology (as deemed acceptable by ABGERO) over a period of no longer than 7 y B. Training: Formal training in Geropsychology: 1 y of formal, full-time supervised training in Geropsychology or its equivalent C. Experience: Self-identity as a Geropsychologist with at least 2 y of full-time post-licensure employment (or its part-time equivalent) as a psychologist, with at least 1 y devoted to professional services to older adults.	PhD in an APA-accredited program, and usually 1 y of work experience is necessary for licensure. ABPP credentials individual geropsychologists.	http://www.apa.org/ed/graduate/specialize/gero.aspx http://www.abpp.org/i4a/pages/index.cfm?pageid=3806
Social Worker (may also serve as care coordinator or case manager)	Assist patients with obtaining appropriate supportive resources in community that will improve quality of life. Provide counseling to individuals and families. Serves as an advocate for families by actively seeking benefits and services needed. Ensures appropriate referrals for suspected or actual abuse, neglect, or sexual assault.	Social workers or case managers may spend their time in an office or residential facility, but they also may travel locally to visit clients, meet with service providers, or attend meetings.	A bachelor's degree in social work (BSW) is the most common minimum requirement to qualify for a job as a social worker. A master's degree in social work (MSW) is typically required for positions in health settings and is required in most states for clinical work. (Care coordinators or case managers may have a degree in social work, nursing, gerontology, or other health fields.)	Clinical work requires a state license. Most states require 2 y (3000 h) of supervised clinical experience for licensure of clinical social workers. Fifteen h of continuing education are required per year. The National Association of Social Workers offers voluntary credentials. Social workers with a master's degree in social work may be eligible for the Academy of Certified Social Workers (ACSW), the Qualified Clinical Social Worker (QCSW), or the Diplomate in Clinical Social Work (DCSW) credential.	http://www.aswb.org—Association of Social Work Boards http://www.socialworkers.org—National Association of Social Workers http://www.bls.gov/ooh/community-and-social-service/social-workers.htm—Occupational Outlook Handbook, 2014 Edition
Medical Marriage and Family Therapist	Works with individuals and families with chronic or life-limiting illness. Using a biopsychosocial model, the therapist emphasizes education, family systems, and collaboration between therapist and health professionals to assist with complex problem solving.	Private practice, hospice agencies, hospitals, rehabilitation facilities, counseling centers, prison systems, and mental health organizations.	Master's or doctoral degree. Requires 500 family therapy contact hours under supervision. May work in hospital and government settings without licensure.	Optional licensure through 2+ y (2000 contact hours) of clinical supervision and completion of state licensing exam conducted by the Association of Marriage and Family Therapy Regulatory Boards (AMFTRB).	http://www.aamft.org—American Association of Marriage and Family Therapy http://www.amftrb.org/—Association of Marriage and Family Therapy Regulatory Boards http://www.bls.gov/ooh/community-and-social-service/mental-health-counselors-and-marriage-and-family-therapists.htm—Occupational Outlook Handbook, 2014 Edition

Chaplain	Provide pastoral visits with patients and family members at bedside. Offer spiritual support, counseling, and prayer with patients/families. Provide crisis interventions, eg, emergency room, last rites, arrange for leader in own faith.	Mainly present within hospital setting, including bedside, emergency room, intensive care unit (ICU), and waiting areas.	Master's degree in theology, plus a minimum of 1 y of clinical supervision. Can work in some settings without being fully certified	Certification is through the Chaplaincy Board of Certification credentials for this is BCC; however, credentials are not normally used. Most chaplains are ordained ministers, but not all. CEUs required are 50 h per year.	http://www.professionalchaplains.org—Association of Professional Chaplains
Psychiatric Technicians and Aides	Psychiatric technicians and aides care for people who have mental illness and developmental disabilities. Technicians typically provide therapeutic care. Aides help patients in their daily activities and ensure a safe, clean environment.	Psychiatric technicians and aides work in psychiatric hospitals, residential mental health facilities, and related health care settings.	Psychiatric technicians typically need postsecondary education with certificate, and aides need at least a high school diploma. Both technicians and aides receive on-the-job training. Programs in psychiatric or mental health technology are commonly offered by community colleges and technical schools.	In 2013, four states, Arkansas, California, Colorado, and Kansas, required licensure of psychiatric technicians. Although requirements vary, state licensure usually requires completion of an accredited education program and an exam. Psychiatric aides are not required to be licensed. The American Association of Psychiatric Technicians offers four levels of certification for psychiatric technicians.	http://www.psychtechs.org/—American Association of Psychiatric Technicians http://www.bls.gov/ooh/healthcare/psychiatric-technicians-and-aides.htm#tab-1—Occupational Outlook Handbook, 2014 Edition
Pharmacy					
Pharmacist	Distribute prescription drugs to individuals. Advise their patients, as well as physicians and other health practitioners, on the selection, dosages, interactions, and side effects of medications. Pharmacists monitor the health and progress of patients to ensure the safe and effective use of medication.	Most pharmacists work in a community setting, such as a retail drugstore, or in a health care facility, such as a hospital, nursing home, mental health institution, or neighborhood health clinic.	Clinical pharmacists must now receive a doctorate (PharmD). Annual CEUs required range from 12 to 15 h. Residency/advanced training for 1–2 y after obtaining a PharmD may be completed to become a clinical specialist.	Must graduate from a college of pharmacy that is accredited by the ACPE and pass a series of examinations. The North American Pharmacist Licensure Exam (NAPLEX), which tests pharmacy skills and knowledge, is required. Forty-four states and the District of Columbia also require the Multistate Pharmacy Jurisprudence Exam (MPJE), which tests pharmacy law.	http://www.nabp.net—National Association of Boards of Pharmacy http://www.aphanet.org—American Pharmacists Association http://www.ashp.org—American Society of Health-System Pharmacists http://www.ascp.org—American Society of Consultant Pharmacists http://www.bls.gov/ooh/healthcare/pharmacists.htm—Occupational Outlook Handbook, 2014 Edition
Pharmacy Technicians	Pharmacy technicians help licensed pharmacists dispense prescription medication to customers or health professionals.	Pharmacy technicians work in pharmacies, including those in grocery and drug stores and in hospitals.	Pharmacy technicians usually require a high school diploma or the equivalent. Pharmacy technicians typically learn through on-the-job training, or they may complete a postsecondary education program. Most states regulate pharmacy technicians.	Most states regulate pharmacy technicians. Consult states' board of pharmacy for specific regulations. Requirements for pharmacy technicians typically include high school diploma or GED; criminal background check; formal education or training program; exam; continuing education.	http://www.ashp.org/—American Society of Health System Pharmacist http://www.ptcb.org/—Pharmacy Technician Certification Board http://www.nhanow.com/home.aspx—National Health Career Association http://www.bls.gov/ooh/healthcare/pharmacy-technicians.htm#tab-1—Occupational Outlook Handbook, 2014 Edition

Dietary/Nutrition Services					
Dietitian	Provides nutrition therapy to include planning, implementing, and monitoring the nutrition of patients.	May work in office or health care settings.	BS degree in food and nutrition and internship experience are required to be eligible for RD exam; CEs are required (75 clock h every 5 y) to maintain registration; MS, PhD degrees available also.	RD is the credential for a registered dietitian in America. One must pass the national exam of the American Dietetic Association. Many states require licensure as well (LD, LDN). Same exam is required but processing of paperwork and fees are different and handled by each state.	http://www.cdrnet.org—The Commission on Dietetic Registration http://www.eatright.org—The American Dietetic Association http://www.bls.gov/ooh/healthcare/dietitians-and-nutritionists.htm—Occupational Outlook Handbook, 2014 Edition
Therapy					
Occupational Therapist	Help patients improve their ability to perform tasks in living and working environments. They work with individuals who suffer from a mentally, physically, developmentally, or emotionally disabling condition. Improve upper body function and ability to perform ADLs.	Practice in rehabilitation centers, home health care services, acute care settings, and skilled nursing facilities.	A master's degree or higher in occupational therapy is the minimum requirement for entry into the field with a minimum of 6 mo of field work; for occupational therapy (OT) assistant, an associate degree or OT assistant certificate is required with a minimum of 2 mo field work.	State exam required for the credential of occupational therapist registered (OTR). These exams are given at least 2 times a year. Twenty-four h of CEUs are required each biennium for relicensure.	http://www.aota.org—American Occupational Therapy Association http://www.bls.gov/ooh/healthcare/occupational-therapists.htm—Occupational Outlook Handbook, 2014 Edition
Occupational Therapy Assistants and Aides	Occupational therapy assistants and aides help patients develop, recover, and improve the skills needed for daily living and working. Occupational therapy assistants are directly involved in providing therapy to patients, while occupational therapy aides typically perform support activities. Both assistants and aides work under the direction of occupational therapists.	Occupational therapy assistants and aides work primarily in occupational therapists' offices, hospitals, and nursing care facilities.	Occupational therapy assistants typically need an associate's degree from an accredited program. Occupational therapy assistant programs are commonly found in community colleges and technical schools. In March 2013, there were 162 occupational therapy assistant programs accredited by the Accreditation Council for Occupational Therapy Education, a branch of the American Occupational Therapy Association.	Most states require occupational therapy assistants to be licensed or registered. Licensure typically requires the completion of an accredited occupational therapy assistant education program, completion of all fieldwork requirements, and passing the National Board for Certification in Occupational Therapy (NBCOT) exam. Some states have additional requirements.	http://www.aota.org/—American Occupational Therapy Association http://www.nbcot.org/—National Board for certification in Occupational Therapy http://www.bls.gov/ooh/healthcare/occupational-therapy-assistants-and-aides.htm#tab-1—Occupational Outlook Handbook, 2014 Edition
Physical Therapist	Provide services that improve or restore function and mobility, relieve pain, and prevent or limit permanent physical disabilities of patients suffering from injuries or disease. They restore, maintain, and promote overall fitness and health.	Practice in hospitals, clinics, skilled nursing facilities, and private offices that have specially equipped facilities. They also treat patients in hospital rooms, private homes, or schools.	Four-year college degree in physical therapy is required to be eligible for the state exam; master's and doctoral degrees in physical therapy are available; 30 CEUs every 2 y are required.	PT is the credential that is used by licensed physical therapists and PTA is the credential for licensed physical therapist assistant. To use either of these titles, one must pass a state exam. CEUs are required for both; titles and licenses must be renewed biannually.	http://www.fsbpt.org—Federation of State Boards of Physical Therapy http://www.apta.org—American Physical Therapy Association http://www.bls.gov/ooh/healthcare/physical-therapists.htm—Occupational Outlook Handbook, 2014 Edition

Physical Therapist Assistants and Aides	Physical therapist assistants (sometimes called PTAs) and physical therapist aides work under the direction and supervision of physical therapists. They help patients who are recovering from injuries and illnesses regain movement and manage pain.	Most physical therapist assistants and aides work in physical therapists' offices or in hospitals.	Most states require physical therapist assistants to have an associate's degree from an accredited physical therapist assistant program. In 2012 the Commission on Accreditation in Physical Therapy Education accredited 298 associate's degree programs for physical therapist assistants. Physical therapist aides usually have a high school diploma and get on-the-job training.	All states except Hawaii require physical therapist assistants to be licensed or certified. Licensure typically requires graduation from an accredited physical therapist assistant program and passing the National Physical Therapy Exam administered by the Federation of State Boards of Physical Therapy. Some states require that applicants pass additional state-administered exams, undergo a criminal record check, and be at least 18 y old. Physical therapist assistants also may need to take continuing education courses to keep their license. Check with your state board for specific licensing requirements.	http://www.capteonline.org/home.aspx—Commission on Accreditation in Physical Therapy Education https://www.fsbpt.org/—Federation of State Boards of Physical Therapy http://www.bls.gov/ooh/healthcare/physical-therapist-assistants-and-aides.htm#tab-1—Occupational Outlook Handbook, 2014 Edition
Speech Therapist	Assess, diagnose, and treat speech, language, or swallowing difficulties, which may include inability to clearly produce speech, rhythm and fluency problems like stuttering, voice disorders, problems understanding and producing language, cognitive communication impairments, such as attention, memory, and problem-solving disorders, swallowing difficulties.	Practice independently, in school systems, hospitals, rehabilitation hospitals, and skilled nursing facilities, or through home health visits.	Master's degree, supervised clinical experience. If certified, 30 maintenance hours every 3 y.	Most states require a passing score on national exam. Some states also require a Certificate of Clinical Competence in Speech-Language Pathology (CCC-SLP) offered by the American Speech-Language-Hearing Association.	http://www.asha.org/default.htm—American Speech-Language-Hearing Association http://www.bls.gov/ooh/healthcare/speech-language-pathologists.htm —Occupational Outlook Handbook, 2014 Edition
Recreational Therapist	A recreational therapist utilizes recreation involvement as a means to improve the physical, cognitive, emotional, social, and leisure needs of clients. They assist clients to develop skills, knowledge, and behaviors for daily living and effective community involvement.	Employed by health care agencies and work in hospitals or other health or residential facilities and adult day care programs. Some may work in homes and in the community.	Graduate of a baccalaureate degree program in recreational therapy accredited by a nationally recognized accreditation body or has documented equivalent in education, training, and experience.	Not all states require licensure to practice but following a formal internship, CTRs may take a nationally standardized certification exam administered by the NCRTC. Must be recertified every 5 y.	Recreation therapist may be assisted by a recreation therapy aide or assistant. http://www.caahep.org/Content.aspx?ID=61 https://www.nctrc.org/ https://www.atra-online.com/
Respiratory Therapist	Evaluate, recommend, and treat individuals with respiratory or cardiopulmonary disorders. Perform diagnostic tests and administer medications and interventions to improve oxygenation and ventilation. Are skilled in bilevel positive airway pressure (BiPAP) and ventilator start-up, management, and weaning. Insert and monitor arterial lines. Are skilled in attaining, maintaining, and managing the airway.	Hospitals, home health agencies, skilled nursing facilities, physician offices. Practicing under the direction of a physician.	Associate degree is minimal entry education. Both bachelor's and master's degrees available.	The National Board for Respiratory Care (NBRC) offers the certified respiratory therapist (CRT) credential to graduates from entry-level or advanced programs accredited by CAAHEP or the Committee on Accreditation for Respiratory Care (CoARC) who also pass an exam. The board also awards the registered respiratory therapist (RRT) to CRTs who have graduated from advanced programs and pass two separate examinations.	http://www.bls.gov/ooh/healthcare/respiratory-therapists.htm—Occupational Outlook Handbook, 2014 Edition http://www.nbrc.org/—National Board for Respiratory Care www.aarc.org/—American Association of respiratory care

Knowledge of Other Disciplines

As health plans and providers work to increase the "value" of health care teams, professionals are increasingly expected to work at "the top of their license" and to supervise paraprofessionals in many settings. Efficiency in these settings means performing tasks that only you are licensed to perform and learning to supervise others who can safely perform tasks within their license or role, often at a lower cost. States vary in their scope of practice regulations for

both professionals and paraprofessionals; thus we advise readers to consult state boards for specific practice regulations. **Table 26-3** provides a general overview; we urge readers to learn both the general skills of fellow team members as well as the specific skills each member brings by virtue of experience, interest, or additional training.

TEAM CONFLICT

Most health care teams will experience some conflict. This is not surprising, considering that members of IPTs differ in terms of personal and professional backgrounds, norms, values, beliefs, styles, and expectations.

Although frequently viewed as destructive or threatening, conflict can lead to enhanced decision making and growth among teams when addressed appropriately and proactively. Embracing conflict as inevitable and desirable, rather than harmful, is an important first step—and one of the most important ways to effectively manage conflict on health care teams. Accordingly, framing conflict as normative and valuable is an important part of establishing the norms and expectations of the team.

An important part of conflict management is how individuals interpret and react to disagreements among team members. If differences or actions of other team members are viewed in terms of alternative ideas and approaches among professional disciplines and part of group problem solving, reactions are likely to be quite different than if disagreements are taken personally. The former is sometimes referred to as "cognitive conflict," the latter as "affective conflict."

Failure to accept or openly address conflict can be detrimental to teams, can limit team growth, and negatively impact clinical decision making and quality of care. Teams that focus on maintaining a high level of agreement at all cost function less dynamically and creatively and, consequently, may fail to consider important information or treatment approaches. Similarly, failure to address conflict may lead to retreating behavior and impaired communication between team members. The degree to which teams accept and address conflict is often related to the developmental level, or maturity, of the team. As teams grow, roles become clearer and trust increases, teams often become more accepting of and sophisticated about managing conflict.

Finally, team leaders play a critical role in how well teams manage conflict. As leaders establish roles and set norms and expectations, they can help to create a culture of acceptance and understanding of the role of conflict in the team processes. In addition, effective team leaders model how to recognize and respond to conflict situations. Effective team leaders also work to maintain a safe and positive environment where openness and a collective orientation flourish and where the overarching mission of improving the well-being of patients remains the guiding force behind the team. **Table 26-4** provides some helpful tips on conflict resolution.

TABLE 26-4 COMMON APPROACHES TO NEGOTIATION AND CONFLICT RESOLUTION

1. Welcome conflict and use it as an opportunity for change. Address data, facts, assumptions, and conclusions.
2. Clarify the nature of the problem as seen by all parties, particularly the patient.
3. Try to identify areas of agreement. Focus on common interests, not individual perspectives.
4. Deal with one problem at a time, beginning with the less controversial issues.
5. Listen with understanding. Reflect and clarify when communicating.
6. Brainstorm.
7. Use objective criteria when possible.
8. Invent new person-centered solutions.
9. Evaluate and review the problem-solving process after implementing the plan.

ACCESS AND DISPARITIES

Achieving specific health outcomes of at-risk populations requires the combined skills of a wide range of professionals operating as a team. *Healthy People 2020* defines a *health disparity* as "a particular type of health difference that is closely linked with social, economic, and/or environmental disadvantage. Health disparities adversely affect groups of people who have systematically experienced greater obstacles to health based on their racial or ethnic group, religion, socioeconomic status, gender, age, mental health, cognitive, sensory, or physical disability; sexual orientation or

gender identity; geographic location, or other characteristics historically linked to discrimination or exclusion."

Several models of team care including federally qualified health centers (FQHCs), the patient-centered medical home (PCMH), and PACE have emerged as examples of programs focusing on team care that have demonstrated positive health outcomes for at-risk, vulnerable populations, including, but not limited to older adults.

FQHCs use team care to provide comprehensive primary and preventive care and social services to low-income medically underserved populations, including homeless, veterans, and public housing residents, regardless of their ability to pay. Approximately one-third of FQHCs report that older adults comprise up to 35% of their patient population.

PCMH is a care delivery model whereby patient treatment is coordinated through a consistent primary care team to ensure the patient receives the necessary care when and where they need it, in a manner they can understand. The objective is to have a centralized setting that facilitates partnerships between individual patients, and their personal health care team, and when appropriate, the patient's family. Care is facilitated by registries, information technology, health information exchange, and other means to assure that patients get appropriate care when and where they need and want it in a culturally and linguistically competent manner.

PACE began in San Francisco as an adult day care model. It has evolved into a program integrating Medicare and Medicaid financing with services for older adults or disabled people over 55 who are nursing home eligible in their state. The IPT is a central component of the PACE model. The focus of the team is on developing an individualized plan of care that includes but is not limited to all services covered by Medicare and Medicaid. The National PACE Association reports that more than 31,000 Americans were members of 105 PACE centers in 31 states in 2014. The PACE model is certified by the federal government with oversight and ongoing review of services while managed care organizations (MCOs) generally do not operate under the same stringent requirements.

Under the Affordable Care Act, almost half the states including large states such as Florida, California, and New York are now contracting with managed care companies and paying these companies a fixed monthly fee for all needed services. Both PACE and MCOs use team-based care to manage the care of complex older adults and are designed to reduce the costs of care by integrating Medicare and Medicaid. PACE programs provide centralized medical and social support services generally by providing transportation to an adult day care center a few days each week. For families caring for an older individual needing long-term care services, the PACE model provides caregivers a broad range of services focused on maintaining the person at home and avoiding transfer to a nursing home or other institutional setting.

EMPHASIZING CARE GOALS AND PERSON-CENTERED CARE PLANNING

A major role of the geriatric IPT is to coach the person (or in some cases, person and family) through the goal-setting process. The team should ask, "What are this person's goals for his/her own health and well-being, and how can we assist that individual in achieving those goals?" Whether the focus is on a short-term goal related to an episode of care (eg, returning home after hospitalization for a hip fracture) or a longer-term goal, such as coordinating complex home care or services to support family caregiving for an individual living with dementia, the IPT has a responsibility to elicit the individual person's own goals, hopes, and aspirations for his or her health and well-being. Tools and resources for teams to assist older adults in goal setting have been developed and are being integrated into EHRs and clinical care processes in many settings.

Person-Centered Care Planning

The process of care planning is the means of achieving consensus on how to best support the person, or person and family, to achieve his or her goals. If the older adult lacks decisional capacity or is unable to express him-/herself (eg, the person is on a ventilator), the family or legally responsible party may be asked to help the team determine what the person would choose for goals of care. Instruments such as the preferences for everyday living inventory (PELI) and others may be helpful to teams working with residents and families in long-term care.

A geriatric team developing care plans and treatment goals with older adults must be comfortable facilitating a person's wishes, not trying to influence what those goals should be. Team members communicate their own professional opinions, and all members need to respect the expertise that each professional brings to the group in order to optimize care planning.

The team must have a system for documenting the care plan, revising it as the clinical situation or patient's goals change, and indicating clearly who will be responsible for each care plan component. This documentation should be

completed before the end of the initial meeting and available to all team members, as well as to the patient and family in real time. In addition, there must be a system for communicating and continuing with next steps between care plan meetings. The wider use of EHRs has made care plans more dynamic and more practical, leading to a more useful tool to guide truly person-centered care.

SUMMARY

Effective geriatric care teams enhance management of complex syndromes experienced by older adults. Effective teams require team members with excellent clinical skills who are also trained in the structure and function of health care teams. This includes a focus on person-centered goals, rules to govern the team and team member behavior, plans to run meetings efficiently, clarity about the roles, responsibilities, and boundaries of each team member, team communication skills, and mechanisms for managing team conflict. Fulfilling these requirements can lead to care goals and plans that support the particular needs and desires of an individual older adult. The demographic imperative and limited workforce demand fresh approaches to team care, as well as new research upon which to build the science of efficient and effective geriatric team care.

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Chapter 27

Social Work

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Learning Objectives

- Understand the roles that social workers play in various health care settings, including direct service work, linkage roles, and support services.
- Identify key populations that social workers serve and some of the practice issues that arise with older adults in these groups.
- Determine health care settings where social workers practice and some of the issues that may arise for social workers in nursing homes, community mental health facilities, hospitals and health care facilities, hospice and palliative care, and home care.

Key Clinical Points

1. **Identify some of the practice issues that arise in older groups in key populations that face particular vulnerability because of oppression and/or poverty due to race, ethnicity, immigration status, sexual orientation, gender identity, or HIV/AIDS diagnosis.**
2. **Recognize some of the core issues that emerge when working with people who face abuse, neglect, mental health concerns, cognitive impairment, and substance or alcohol misuse.**

Social workers provide services to older patients across a continuum of care needs that range from supporting community living to providing palliative care services at the end of life. This occurs in many different health care arenas including institutional settings, such as acute care hospitals, chronic care settings, and nursing homes, as well as in patients' homes in the community. Social workers support and enhance the adaptive capacities of patients within their living environments and are knowledgeable about interviewing, assessment, and intervention in social problems faced by individuals, couples, families, and groups. Using negotiating skills, social workers also mediate conflicts and obtain resources for clients and their families. Knowledge of group process makes social workers effective in forming natural helping networks and serving as members of interdisciplinary teams. Their expertise in coordinating services within a single organization or across different agencies or settings helps to ensure appropriate and adequate care for older patients.

While 76% of social workers in health care settings work with older patients, not all social workers have specialized training in geriatrics. Proper care provided by gerontologically trained professionals including social workers can reduce the cost of care by 10% each year in hospitals, nursing homes, and patients' homes as well as improve psychosocial outcomes and reduce mortality.

This chapter describes the key roles for geriatric social workers, the practice issues they face, and the settings in which they work.

KEY ROLES FOR GERIATRIC SOCIAL WORKERS

The roles social workers play vary within health care settings (**Tables 27-1 and 27-2**). Social workers provide direct service to older adults and facilitate linkages between service workers and agencies.

TABLE 27-1 THE ROLES SOCIAL WORKERS PERFORM

ROLES	DESCRIPTION	EXAMPLES
Group worker	Social worker plans and conducts group activities for clients to help understand themselves better through a variety of methods; can be therapeutic, educational, social, or for support	Worker organizes a group for grandparents raising grandchildren to share information and provide support
Advocate	Social worker fights for, defends, and promotes patient's perspectives and rights	Social worker helps a patient destined for a nursing home receive home health care rather than be institutionalized
Case manager	Social worker assesses patient needs, connects patient to resources, and coordinates and oversees delivery and participation of services	The case manager coordinates the services. A patient might need rehabilitation therapy, psychotherapy, and home health care as well as transportation services
Educator	Social worker offers knowledge regarding health care information, processes, and procedures with patients and provides knowledge of patient with the team	In hospice, the social worker provides information regarding the dying process, pain management, stages of grief, and option for burial services
Discharge planner	Social worker prepares patient for next phases of departure from facility by designing a course of action	When patient leaves the hospital and goes home, the social worker may arrange transportation services, meal delivery, home care services, and assessment of home for safety
Therapist	Social worker engages clients in interpersonal interactions regarding client's behavior, feelings, attitudes, and perceptions	Social worker works with an older couple who is having marital problems resulting from stress of caregiving
Team member	Social worker collaborates with health professionals to provide efficient delivery of services	Social worker shares information with physicians and nurses and provides insight into the patient's cultural and personal life
Broker	Social worker connects patients to most relevant resources	Social work brokers help African-American elders overcome the racial and ethnic disparities they face in receiving health care, by building trust between the patient and health care professionals
Information and referral	Social worker has knowledge of community resources and offers connection to these agencies	Social worker has knowledge of respite care services and links caregiver of Alzheimer patient to the respite care agency
Mediator/arbitrator/advocate	Social worker facilitates conflict resolution	The social worker advocates for the older patient in a guardianship hearing

TABLE 27-2 THE SETTING WHERE SOCIAL WORKERS WORK AND THE ROLES THEY PERFORM

SETTINGS	ROLES
Home	Support patients' adjustment to health status, provide emotional support, address barriers in access to medical care (ie, transportation), provide education so that patient can make informed decisions, assess social support and referral to resources, and case management
Hospital	Assessment; discharge planning; prevention and treatment of mental and physical health; promotion of psychosocial health, advocacy in relation to aspects of human diversity; mediate between patients, families, and the health care team; group work; psychotherapy
Nursing home	Financial planning; psychosocial assessment and addressing emotional needs; care planning;

	mediation between residents, staff, and family; linking residents and families to resources
Assisted living facility	Negotiate placement and transition, support in navigating decision making and emotions regarding changes in autonomy, financial planning, and fostering communication
Senior center	Administration, program planning, case management, facilitate group and individual therapy, address life transitions, and organize advocacy groups
Department of Public Welfare	Case management, oversee and evaluate programs, community outreach, advocacy, development of services, income assistance, protective services, support parents raising grandchildren
Community mental health setting	Perform client assessments, conduct support groups, provide emergency and crisis services to older mental health clients and their families; referral to other resources in the community such as adult day care, respite services, and partial day treatment programs
Hospice	Liaison between care settings; case manager; address psychosocial needs of families and patients; support for adjustment to setting, treatment, illness, and death; educator, advocate, broker, and mediator between family members, patient, and medical professionals; team member; information and referral; group worker; and counselor
Adult day care/respite program	Assess clients' mental and physical abilities, plan and facilitate activities to maximize physical and cognitive functioning, facilitate support groups, provide information and support for Alzheimer and other disease processes, and referral to community resources
Primary care	Plan and implementation of safety and illness prevention programs, identify social factors that support prevention of illness and cause of disease, provide emotional and social support, facilitate support groups around a specific disease or mental illness, and provide education, information, and referral

Direct Service Provision

Social workers meet face to face with patients and consumer groups to provide services as caseworkers, marital or family therapists, and group workers or educators. Individual casework and counseling services help older adults who have mental health problems or need help with resolving issues in such areas as housing, finances, or interpersonal problems. Marital and family therapies include meeting with individual older adults, with partners, as well as with groups of older adults who are experiencing concerns related to their families. Such therapies could involve helping grandparents with resources and tools for raising grandchildren, aiding families in coping with an aging parent with dementia, or supporting older couples as they struggle with debilitating health problems that can create emotional and financial strain on the relationship. Group work services include support groups for older adults with a variety of health concerns, such as cancer, low vision, or early-stage dementia. Support groups have been particularly helpful to caregivers of patients with such diseases as Alzheimer. These groups run by social workers help caregivers better understand the disease process and provide information that helps them cope with problems of caregiving more effectively and thus improve the disease outcome. Groups also focus on self-help issues, where older adults learn to deal with such problems as alcoholism or smoking. Psychotherapy groups work to resolve such concerns as abuse (as victim or perpetrator), depression, and marital problems. Social workers also work directly with older adults and their families as educators and disseminators of information. For example, social workers provide educational sessions on caregiving, stress management, and various aspects of mental and physical health care.

Linkage Roles

Social workers link older adults to the services they need. This may be necessary because agencies fail to meet older persons' needs, because older adults lack knowledge of available resources or ability to access those resources, or because older adults and their families need help in overcoming fears and concerns they might have about using services. For example, family members struggling to provide home care to a mother with Alzheimer disease may be reluctant to participate in a support or educational group used by other family members in similar circumstances due to fear of revealing personal problems they and their mother face. Social workers can help overcome these fears by assisting family members in realizing that families coping with dementia face similar problems and have similar reactions to their circumstances. Social workers also work as case managers to help older adults receive services in a timely fashion. In general, case management involves screening, assessment, care planning, implementation, monitoring, and reassessment to evaluate ongoing service needs. Case management meets a variety of goals in

numerous settings. The social worker assesses problems and needs to determine eligibility for services and financial resources. The social worker also links older adults to the needed services. Family and friends may provide collateral information to help the social worker determine their capacity for support. Goals for a care plan are set by discussing older adults' perceptions of their needs. Social workers then identify interventions and resources designed to meet these goals. Subsequently, the social worker monitors the delivery of the services. When an older adult requires care over a longer period of time, a social worker will reevaluate needs and necessary interventions and resources. Ultimately, a social worker will conduct an outcome evaluation to determine if the patient's goals were achieved.

Social workers also work as mediators and advocate for their clients/patients. As mediators, social workers determine the issues behind a conflict. Social workers facilitate family discussion of issues identified by the family and older adults as important. For example, adult guardianship mediation can be used to discuss how the family can best help older adults preserve autonomy (or to maximize one's greatest level of independent functioning). When advocating for their clients, social workers often form partnerships with lawyers to aid victimized older adults who need legal redress. For example, social workers and lawyers can aid lesbian, gay, bisexual, and transgender (LGBT) older adults who face housing and service delivery discrimination in accessing benefits to which they are entitled.

PRACTICE ISSUES WITH POPULATIONS SERVED

Geriatric social workers strive to meet the basic human needs of all older adults, with a particular emphasis on those who are vulnerable due to oppression and poverty. With health care provided in a myriad of public and private settings, the social worker acts as a broker, a mediator, and an advocate for clients.

This section reviews key populations served by social workers and some of the practice issues that come into play with older adults in these groups.

Racial, Ethnic, and Cultural Diversity

Social workers are uniquely situated to respond to the needs of older adults across racial and ethnic groups because of their skills in training and cultural awareness in service delivery. Attention to cultural diversity includes sensitivity to differences in cultural history, language, values, religion, ethnicity, nationality, and regionality, as well as recognition of within-group variation. For example, social workers use cultural assessment strategies to understand clients' definition of a problem. During the assessment process, social workers working with culturally diverse groups evaluate attitudes toward health care and the clients' belief about the causes of illness and benefits of health care services. As social workers attempt to understand the clients' problems, they evaluate the language skills, educational level, and degree of acculturation of the older person. In addition, determining which family member has the authority to make care decision is important for the health care professional to know. For females, in some cultures, a male decides how care proceeds. In some Native American cultures, generational standing predominates in care decision making. The patient's use of language to label and categorize a problem, the availability and use of indigenous community resources, the decision making involved in problem intervention strategies, and the patient's cultural criteria for determining problem resolution are important issues for the social worker and other health care workers to consider in working effectively with older adults and their families.

While there are common themes that are relevant to people of color and other minority groups, each group has its own cultural history relevant to care. And this cultural history often contributes to health disparities that social workers must address. For example, racial and ethnic minorities have worse access to care than whites, and research suggests that this gap is not narrowing. Despite these collective findings, it is important to remember that racial, ethnic, and cultural groups are not homogenous. Individuals and families have their own themes, caregiving patterns, and stories of access to and discrimination in social service and health care delivery. Social workers identify barriers to seeking help, such as stigma, denial, and financial and access barriers resulting from service fragmentation and gaps in health care. For some older racial, ethnic, and cultural minorities, health problems are rooted in historic experiences of discrimination that prevent access to the social service system. Therefore, culturally specific interventions should consider the unique background and resources of the individual.

Initial contact with a patient requires understanding the individual's identity, including one's race, ethnicity, nationality, generational status, and religious background, for example. Nonverbal cues may be more meaningful than verbal expressions. These cues may provide information about knowledge or problems and ways of handling them. Knowing the client's sense of ethnic identity, attitudes toward formal services, and service preferences helps the social worker sort out cultural values and traditions and family beliefs and practices relevant to care.

Poverty

While government programs such as Social Security, Medicare, unemployment insurance, and welfare have reduced the extent of poverty in the older population, poverty remains a significant problem, resulting, in part, from the cumulative effects of lifelong discrimination, particularly for older adults of color, LGBT older adults, older adults above the age of 75, older adults residing in rural areas, and women. Underutilization of health and mental health services by older adults in poverty makes these groups a target for social work intervention. One significant barrier to meeting the needs of older adults in poverty is lack of knowledge about their problems and needs. Another barrier is that some older adults in poverty may lack resources, such as transportation, to access care. Gerontological social workers aim to understand and eradicate these barriers that impede the development and delivery of appropriate services. Social workers also connect older adults to formal and informal resources to aid impoverished older adults in rural communities, women, LGBT older adults, and racial/ethnic minorities.

Immigration and Refugee Status

Since the early twentieth century, rising numbers of older adults have arrived to the United States from Mexico, Cuba, and various countries in South America and Asia. Immigrants now account for one of every eight older persons in the United States. Over half of older immigrants have limited English proficiency. More than 40% of older adults with limited English proficiency speak Spanish. Older immigrants are also more likely to have lower incomes than nonimmigrants.

Older immigrants are more likely to live in households with extended family, children, and nonbiological family than are nonimmigrants. Families are often central to caregiving for aging relatives. However, demand for family caregiving often occurs in the context of limited coping resources, inadequate knowledge of services, misperceptions of eligibility requirements of government programs, and beliefs that children must provide caregiving. Unfortunately, multiple roles may result in greater caregiving strain and increased neglect and abuse of older family members.

Older immigrants also encounter cultural and linguistic barriers to service. Immigrants who migrate after age 60 face additional challenges, including little or no US work experience, limited ties to social institutions, and potential limited English proficiency. Despite these general statistics, however, older immigrants comprise a diverse population whose diversity is reflected in race and ethnicity, as well as age, length of residence in the United States, English language proficiency, and reasons for immigration. This diversity underscores the importance of culturally and linguistically appropriate services.

Social workers educate older adults and their families about available services and how to obtain transportation and financial resources to access these services. Through a culturally competent assessment, social workers can identify negative attitudes toward formal services, culturally specific definitions of illness and healing, and religiously acceptable perceptions of services for these families. Social workers can also connect older immigrants and their families to culturally and linguistically competent social services and providers.

Sexual Orientation and Gender Identity

LGBT older adults often comprise an invisible population that has special needs and social service barriers based on individual and collective experiences of discrimination. Many LGBT older adults came of age at a time when failure to conform to gender or sexual norms resulted in job termination, involuntary hospitalization, cessation of parental rights, and criminal punishment. A fear of discrimination among health providers prompts many older LGBT adults who were once open about their sexual orientation and/or gender identity to return to the “closet” when entering long-term care facilities. And, some LGBT older adults fail to disclose their sexual orientation and gender identity to health care providers who have treated them throughout their life. Fear of differential or discriminatory treatment also precludes LGBT older adults from seeking health care and social services at all, unless absolutely necessary. Discrimination and delays in accessing care leads to higher rates of disability, mental distress, excessive drinking, and poorer physical health outcomes for LGBT older adults. Intersections of various identities (eg, race, ethnicity, sexual orientation, and gender identity) can create even higher health risks for particular communities.

While the legal landscape for LGBT older adults is rapidly changing, many state and federal laws continue to limit access to services and rights for LGBT older adults. LGBT older adults and their children—who live in states that do not recognize marriage between same-sex couples—lack certain state and federal insurance, retirement, inheritance, and health benefits that can preclude access to social services. All hospitals and long-term care facilities that receive

Medicaid or Medicare funding must provide equal access to visitation rights to patients and visitors, regardless of sexual orientation, gender identity, or legally recognized relationship. Unfortunately, incidences of LGBT older adults who are denied visitation rights continue to surface.

Despite social, health care, and legal barriers for service delivery, many LGBT older adults have extensive support networks through partners and friends of similar age and rely on them for informal caregiving. Social workers can directly provide or connect LGBT clients to inclusive services and service providers and provide LGBT-friendly resources, such as physicians, living facilities, and attorneys to assist with health care documents.

HIV/AIDS

Many older people encounter HIV/AIDS either as patients with the disease or as caretakers for loved ones with HIV/AIDS. Approximately 50% of all Americans living with HIV are age 50 years or older. Many newly diagnosed people aged 50 and older are "late testers," meaning that they likely had HIV for years before their diagnosis and may face more immediate challenges than someone who is diagnosed early. LGBT older adults, and transgender people of color have particularly high rates of HIV/AIDS.

While HIV/AIDS greatly impacts individual health, it also leaves many people impoverished. Moreover, older adults with HIV/AIDS have higher rates of social isolation than younger adults, as they are more likely to live alone. Older adults with HIV/AIDS are also more reluctant to seek social service and mental health support. Because of the immense stigma still attached to HIV/AIDS, many older adults delay health care treatment and support services.

Social workers can help identify older adults with HIV and help improve access to services and social networks. Social workers can also offer educational information about HIV/AIDS and case management services that coordinate the raft of services that many patients with HIV/AIDS and their families need, such as caregiver respite services, home health care and hospice care, individual and group supportive counseling, and financial assistance.

Abuse and Neglect

The abuse or neglect of older adults often surfaces in a health care setting. Many types of mistreatment, such as physical abuse, sexual abuse, and neglect (including self-neglect), result in injury, pain, and physical and psychological impairment. Other types of abuse such as financial and identity theft are more difficult to detect. The assessment of mistreatment, which may require several contacts, involves an interview with the older adult to review the risk of abuse and cognitive ability and level of independent functioning of the older adult. While all states have mandatory or voluntary reporting laws, the older adult's willingness to receive help is voluntary. Social workers help assess the existence of elder abuse by providing education about the nature of abuse and prevention strategies. Social workers can be instrumental in helping older adults recognize the power imbalance in abusive relationships and devise strategies for protection. One of the biggest challenges that health professionals face consists of identifying and helping abused or neglected older adults who do not realize that they are victims of mistreatment.

Mental Illness

Centers for Disease Control and Prevention (CDC) reports estimate that nearly 20% of people 55 years or older experience some sort of mental health problem. The most common forms of mental health conditions include anxiety and depression. Older men have the highest suicide rate of any age group. Stigma toward mental illness leaves many older adults suffering in silence and fearful or ashamed to seek help. Language barriers and the lack of racial, ethnic, or culturally appropriate services also hinder older adults from seeking assistance. Social workers collaborate with a health care team to assess mental health issues and identify appropriate treatment and services. They can provide structured cognitive-behavioral, interpersonal, and problem-solving treatments that are effective mental health approaches, often in conjunction with prescribed medication. Pharmacologic interventions and psychosocial treatments are effective for older adults.

Cognitive Impairment

Social workers are involved with assessing older adults with dementia and their caregivers. Such an assessment considers the client's social and medical history, including a physical and mental status examination, an assessment of the individual's living environment, a functional ability assessment of both instrumental activities of daily living (IADLs) and activities of daily living (ADLs), social service needs and family dynamics, service and resource needs, and legal issues such as power of attorney and health care proxy, advance care planning, and end-of-life planning.

Social workers also play a variety of roles on the interdisciplinary team used when an older adult and his/her family experience dementia. In the early stages of dementia, social workers can support the older adult with dementia and provide cognitively stimulating programs. In some cases, the older adult is able to plan for his/her own future physical and financial needs, which the social worker can facilitate. Social workers also help family members struggling with the physical and emotional changes in their loved one as dementia progresses. As increasing numbers of older adults move in with family and rely on family members for informal caregiving, services and support for caregivers have grown. Social workers assist family members in navigating multiple caregiving responsibilities through therapy, resources, and support groups. Finally, social workers may function as case managers for individuals experiencing cognitive impairment.

Substance and Alcohol Misuse

Substance and alcohol misuse often remains unrecognized by health care professionals who sometimes mistake symptoms for other age-related problems such as depression and dementia. Risk factors for substance and alcohol misuse include social isolation, living alone, chronic pain, and a variety of losses such as retirement, widowhood, and mobility. Research suggests that a growing number of older adults misuse alcohol and other substances, including prescription medication and at a higher rate than previous generations. The National Survey on Drug Use and Health found that among individuals age 50 and older, over 12% were heavy drinkers, over 3% were binge drinkers, and nearly 2% used illicit drugs. Older men over the age of 65 had even higher rates of binge drinking at 14%. While misuse of individual substances or alcohol remains an important concern, another growing trend among older adults consists of mixing alcohol with psychoactive medications, which can have dangerous impacts for many older adults.

Social workers aid other health care professionals in assessing substance and alcohol misuse and providing the necessary treatment. Social workers also provide successful educational interventions with older adults who are unaware that they are consuming too much alcohol or misusing medications. Counseling can also aid the older person in changing behaviors and reducing stress that leads to overuse of alcohol and medications. Using motivational interviewing to help clients desire a change in their behavior has been effective with older people. Group and individual interventions using a cognitive-behavioral approach and self-help and psychoeducation groups approaches have also shown promise in addressing these problems. Additionally, social workers can provide couples and family interventions, which aid in reducing stress that may trigger overuse of alcohol and medications.

WHERE SOCIAL WORKERS PRACTICE

Medical social workers work in hospitals, nursing homes, mental health facilities, clinics, drug rehabilitation centers, and community health agencies. A medical social worker performs roles such as patient advocates and counselors, performing psychological assessments, referring patients and families to medical resources and providing patient and family assistance in obtaining financial and legal assistance. They provide education and support and link clients to resources.

Please review **Table 27-2** for a broader list of practice settings. Several of the central practice arenas are reviewed below.

Nursing Homes/Assisted Living Facilities

Social workers are employed in nursing homes of all sizes but when the size of the facility is 120 beds or larger, their employment is mandated under the Omnibus Budget Reconciliation Act of 1999. The number of older adults using nursing homes has declined during the last 20 years because of a reduction in disability among older adults as well as an increase in home health care and the expansion of assisted living facilities. Because these facilities are residences where people live, social workers have the responsibility of helping in all aspects of life, including the resident and their family, facility staff, and the overall institutional environment. Their assistance begins with the transition into the facility. Adjustment to a new living environment is faced by not only the older person but their family as well. The social worker provides direct services to residents and their families as part of an interdisciplinary team. They assess the psychosocial needs of the resident and aid in the development of a care plan under the government requirements of maintaining a minimum data set (MDS). The MDS is part of the US federally mandated process for clinical assessment of all residents in Medicare- or Medicaid-certified nursing homes. This process provides a comprehensive assessment of each resident's functional capabilities and helps nursing home staff (physicians, social workers, and nurses) identify

health problems and develop strategies to address them. Social workers also facilitate psychosocial well-being among residents and their families, linking the resident and family members to services inside and outside the facility, helping with discharge planning for the older adults who are discharged, and serving as advocates for appropriate care and treatment for all patients and their families. Because social workers are often the only staff members focused on the psychosocial needs of residents and their families, they are in the best position to identify and address mental health issues. Often they complete the cognitive, mood, behavioral, and psychosocial portion of the MDS and the resident assessment protocol and can readily identify the mental health needs of the residents.

Currently social workers in assisted living facilities serve in a less formalized capacity than those in nursing homes, hospitals, home care, and adult day programs due to lack of regulations that require social workers to be on the staff of these facilities. The role of social work will become an invaluable component of providing care as the complexities of medical issues grow in these facilities thus prompting the need for policies for regulation of the qualifications and availability of health care professions in these facilities.

Community Mental Health Facilities

Twenty percent of older adults experience mental health disorders, and almost 70% of them live in the community. Unfortunately, older persons are underrepresented in community mental health facilities, as mental health symptoms are sometimes mistaken for issues of aging by family, friends, and health professionals. When older adults seek treatment, they usually have more severe symptoms. Social workers are part of a team of mental health practitioners, which includes nurses, psychologists, and psychiatrists, work in these settings. Social workers do client assessments, conduct support groups, provide emergency and crisis services to older mental health clients and their families, and refer these people to other resources in the community such as adult day care, respite services, and partial day treatment programs. They often provide therapeutic interventions in the form of brief psychotherapy and behavior modification to individuals or groups and provide indirect services through community education and consultations in long-term care facilities. Social workers assist with supportive housing, daily living skills, transitional employment, and counseling needs.

Hospitals and Health Care Facilities

Social work practice with older adults in health care settings is focused on adaptation and coping with chronic illness, adjustment to disability and physical limitation, decisions about end of life, compliance with medical regimens, wellness, long-term care, and quality of life. Social workers also provide mental health services that address depression, substance abuse, management of long-term mental health issues, cognitive deficits, suicide prevention, and adjustment to changes in life by patients and families.

Medical social workers work in hospitals, nursing homes, mental health facilities, clinics, drug rehabilitation centers, and community health agencies. Medical social workers take on many roles such as patient advocates and counselors, performing psychological assessments, referring patients and families to medical resources and providing patient and family assistance in obtaining financial and legal assistance.

In hospital settings, social workers are members of an interdisciplinary team (consisting of physicians, nurses, social workers, and chaplains, among others), providing services to patients and families regarding assessments of a patient's cognitive, emotional, and behavioral status, as well as social support network. Social workers counsel patients and families, assisting them in adjustment to illness and providing crisis intervention and connection to community resources. Additionally, social workers identify interpersonal aspects of patients' lives that contribute to positive outcomes in relation to their chronic illnesses, such as addressing obstacles to medical compliance and environmental and financial obstacles, by acquiring information and accessing support resources for geriatric patients. Social workers advocate for the cultural, language, sexual orientation, ethnicity, religious, class, and other aspects of diversity by affirming and addressing these aspects of patients' lives. Social workers also advocate on behalf of patients with the health care team when patients face barriers to receiving care. For example, social workers can aid in the care of abused and neglected older adults by documenting and reporting instances of abuse and neglect and can testify in court with regard to these matters.

In acute care settings, where patient stays are very short, social workers focus on high-risk screening, brief counseling, bereavement services, discharge planning, collaboration, information, referral, follow-up, and emergency services on-call programs. Social workers are typically assigned to specific medical or psychiatric departments in hospitals. Patients are screened to determine whether they need social work services. Need for services is also conveyed to other health care professionals by having social workers attend team meetings and discharge planning

conferences, by referrals from nurses or physicians, or by requests from patients and families. A social worker's presence, when a diagnosis, death, or other unpleasant news is communicated, can ease shock and help individuals address the emotion loss and face forthcoming decisions. Additionally, the social worker can provide information regarding aspects of diseases, care options, and assistance in meeting the patient's needs.

Discharge planning is particularly important for older adults who are transitioning from the hospital to other facilities or their homes. Addressing older adults' needs during discharge is necessary, in order to allow the older adult the best possible scenario for recovery from illness. The social worker assesses caregiving needs, and availability of social supports, family support, and home and community environment, as well as financial supports when the patient leaves the hospital.

Hospice and Palliative Care

Hospice social workers practice in a variety of end-of-life settings, such as palliative care centers in hospitals, nursing homes, assisted living facilities, outpatient practices, residential hospice facilities, and in homes. Palliative care requires an interdisciplinary team, where the social worker is a crucial member providing psychosocial support and referral to resources, easing transitions between settings, and addressing issues of loss for patients and families.

Social workers help those who are approaching death and those living with chronic illness. Their work begins before patients enter into hospice or palliative care and continues with families and loved ones after end-of-life care ends. Social workers provide a variety of services to address the needs of patients, families, and caregivers in end-of-life care. Social workers in end-of-life care fulfill a variety of roles such as liaison, educator, mediator, advocate, broker, and counselor. As patients face debilitating illness in palliative care, social workers help with the transition between care facilities, assessing readiness for palliative care and beginning to address the emotional and psychological aspects of end of life. Social workers are pivotal in assessing and supporting patients, families, and caregivers in their psychological, spiritual, social, financial, and cultural needs at the end of life. Addressing loss in patients and families is essential, as individuals and families may have difficulty communicating and accepting their feelings regarding the losses they face. Identifying social support for patients and families is important, as they may reconcile their relationships with family and friends and find support in these relationships. Discord may arise when families are brought together at the end of life, and, therefore, social workers assist families to communicate and understand decisions that are made, emotions that are expressed, and relationships that are negotiated.

As an educator and mediator, the social worker provides information regarding the plan of care, the illness, and the process of dying; communicates with the heath care team; informs the patient of their rights; provides information regarding medical rights to accept or refuse medical interventions; and provides information regarding the grieving process for families and caregivers. Palliative and hospice social workers may lead support groups and provide in-service training to other professionals who are involved in the treatment process. They may also teach patients nonpharmaceutical techniques for managing pain. Palliative care and hospice care are related, but not quite the same. Some people transition from palliative care to hospice when they are in the final stages of an illness, but this is not the only pattern. Not all who receive palliative care are near death.

Social workers act as brokers for resources and services to address the needs of patients who are dying and their families, arrange services, facilitate communication among family members, provide services to fulfill last wishes, and provide assistance with funeral plan arrangements. As an advocate, the social worker supports and represents the patients' and families' needs, wishes, and desires to the health care team; recognizes the dying person as a social person during the end-of-life stages; and works toward fulfilling end-of-life wishes. As a counselor, a social worker addresses the psychological, emotional, and spiritual needs of the family in addressing losses and illness and reconciling relationships. Also, grief support to families, friends, and caregivers is provided after death through individual counseling sessions with family members, support groups, grief camps for children, and formal ceremonies and services for families who have lost loved ones. Social workers may act as navigators and care coordinators. They help patients and families understand their options, identify services they need, and fill out the necessary paperwork. They also help them fill out other important forms like advance directives.

Home Care

Home care is a term that encompasses a variety of services, including home health agencies, homemakers, home health aides and assistance, medical equipment and supplies, visiting nurses, caregiver respite, and other medical services that are provided in the home. One agency may provide one or several of these services to older adults.

Social workers in home care address a wide range of issues that are similar to and unique from other settings.

These fall into several areas including adaptation to illnesses and chronic conditions; decisions regarding end of life, dementia, and behavior management; caregiving; issues of abuse, neglect, and prescription drug misuse and handling theft; family discord; and connecting family members who live long distances from the older adult. In addition, financial management, addressing unsafe living conditions, connecting to resources to provide safe living quarters, social support, mental health, legal issues, and compliance to medical treatments are part of the social worker's job in home care for older people.

In order to address these diverse issues, home care social workers employ a case management approach, where interventions are crafted for individuals and their unique needs. Also considered in these situations are the families, caregivers, the environment, and the community resources that are available. Key aspects of these services include assessment, planning, management and coordination of resources, and advocacy. Social workers are equipped to communicate with older adults and assess their preferences, wishes, desires, emotional states, coping styles, needs, and cultural diversity issues involved in service delivery. When older adults continue living in their homes, social workers arrange and monitor services, such as meals on wheels or grocery deliveries. As caregivers are often involved, caregivers' burden is evaluated along with the need for respite services in case of illness or hospitalization. A holistic approach is employed, where psychological, spiritual, and cultural needs are met. For example, religious services can be arranged so that the older adult can continue practicing their faith.

Social workers provide a unique psychosocial perspective that allows for assessment and monitoring of older adults' ability to make decisions. Social workers can advocate on behalf of the older adult to the members of the home health team regarding termination of services and understand patients' perspectives and unique needs. Finally, social workers assist with discharge planning and transition from home to other medical providers when needed.

SUMMARY

Geriatric social workers are integral members in the health care team serving older patients. Their wide range of skill, as well as their knowledge of available services in a variety of settings, makes social workers valuable members of the team serving older patients.

The health care service delivery arena is changing as discussion evolves in the development of models of care that strive to contain the cost of care while dealing more effectively with treatment. The innovations focused on are the patient-centered medical home (PCMH), the accountable care organization (ACO), and the population health management system (PHMS), which combine new payment arrangements that reward for health outcomes achieved rather than paying a fee for each service rendered. Social workers are integral to these service delivery models.

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Chapter 28

Self-Management of Health Behavior

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Learning Objectives

- Understand the role of health care provider (HCP)–patient collaboration in promoting the self-management of health behavior in geriatric patients.
- Integrate the principles of self-management into daily clinical practice.
- Be able to collaborate with older adults in developing realistic and relevant health goals.

Key Clinical Points

1. **The traditional biomedical model of care follows a top-down format, where HCPs are expected to fix problems, and patients play a passive and compliant role. In contrast, collaborative self-management emphasises the patient-HCP partnership: the patient is an active agent with valuable knowledge, who is involved with (a) identifying the problem, (b) selecting an appropriate treatment regimen, (c) making detailed action plans, and (d) evaluating and providing feedback to the HCP on outcomes.**
2. **When working with patients, HCPs should keep in mind the five As advocated by the AMA: assess, advise, agree, assist, and arrange for action.**
3. **Older adults engage in self-management in response to a conscious health goal or to remove barriers in the path toward goals; health-related goals most often stem from concerns related to detection or prevention behavior; that is, older adults want to identify, alleviate, or avoid a specific physical or psychological symptom/condition.**
4. **The major factors driving self-management include setting a clear standard or goal, self-monitoring progress, feedback, self-evaluation, corrections, and enhancing self-efficacy beliefs.**
5. **Groups can be a powerful tool for teaching self-management skills to older adults. In bringing people together with a common problem and/or goal, group members actively collaborate with, learn from, and support one another. With time and practice, older adults develop the skills necessary for self-management. After these skills have been learned, HCPs need to actively transition members away from the group by slowly reducing group dependency.**

INTRODUCTION

Self-management is an essential factor for the long-term success of individuals who live with chronic disease and/or physical disability. Approximately 80% of older adults have at least one chronic disease, and the number of aging individuals in North America and throughout the world is growing rapidly. Despite provision of standard care by health care providers (HCPs), distressing statistics related to patient adherence suggest that something is amiss. Consider these few of many examples: only 40% of patients actually have the confidence to make recommended health behavior change; patients only recall about 50% of the information their physician communicates; and, of the 28% of individuals receiving physician advice to change physical activity, fewer than 40% received help related to specific

plans and fewer than 42% received follow-up support. The care and treatment of chronic conditions cannot progress unless there is a conscious effort to change HCP's training and, of equal importance, their practice.

Fortunately, these issues are increasingly being acknowledged in public health settings and by groups like the American Medical Association (AMA). A significant development is the recognition that self-management is a key pathway in improving health system performance. Put simply, patients should be treated as active agents in their health care. Self-management includes provider- and patient-driven behavior to address illness, treatment, and health maintenance; patients are the ones to ultimately decide when to initiate the process and to what extent they will adhere to recommended courses of action as prescribed by HCPs.

Self-management is as important to geriatric medicine as it is to other branches of health care. A guiding assumption of this chapter is that older adults' self-management of health behaviors is central to understanding the etiology, treatment, and downstream consequences of illness, chronic disease, and disability. Modern geriatric medicine should have as central focus the partnership between HCPs and patients. However, this direction will require HCPs to have a working knowledge of what motivates older adults to initiate health behaviors and the potential reasons for success or failure in self-management. As well, it necessitates that patients become informed and active self-managers.

The early sections of this chapter will define and provide a conceptual framework for self-management; later sections will review key studies in the area and offer HCPs guiding principles and suggestions for incorporating patient self-management into their practices. Applying this knowledge will enable geriatric HCPs to support their patients in a patient-center model of care so that patients attain improved health outcomes and quality of life.

Defining Self-Management

What is meant by self-management, and how does it differ from disease management or self-regulation? While perhaps tempting to use these terms interchangeably, Noreen Clark has argued that each refers to a distinct type of behavior. Thus, establishing clear definitions is an important first step in ensuring that HCPs understand how to integrate self-management in clinical practice.

Using Clark as a definitional guide, *self-care* involves actions taken by an older adult to promote or maintain a desired health status without the interaction or assistance of a HCP. Examples might include taking herbal supplements or participating in a walking group without receiving any specific advice or monitoring by HCPs.

Although self-care is important to older adults and their health, in this chapter we are specifically interested in health behaviors that either do or should directly involve HCPs. Clearly, older adults managing chronic disease and disability must frequently consult HCPs and adhere to the various therapies prescribed.

In health care settings, *adherence* refers to the collaborative relationship between patient and HCP. The patient is involved in decision making and carrying out care regimens. In contrast, *compliance* is an unquestioning and passive response by the patient; the relationship is one-way and top-down. Compared to compliance, adherence is significantly better in promoting persistence, and is particularly important when patients are managing a complex chronic disease. Adherence allows patients to develop a program that is realistic for their lifestyle and abilities.

Disease management refers to the broader context of care and treatment, and involves the HCP, the health care system, and the individual. For example, it includes providing patients with prescriptions, diagnostic testing, and support services. *Self-management* is a subset of disease management that involves the actions of the older adult, their family and caregivers, and their interactions/relationships with HCPs. Effective self-managers learn to use these human resources toward the goal of minimizing symptoms and optimizing function.

A key tool for self-management is *self-regulation*: the ability to derive strategies and alter behavior in order to reach a goal—in our discussion, the goal of successfully managing chronic disease. For example, a patient might use a blister pack to help manage their medication, or use a pedometer to monitor their daily physical activity. Though self-regulation is based in the individual, we contend that it should not be limited solely to patient-derived strategies (ie, the domain of self-care). Rather, the HCP must (a) provide opportunities to educate patients about the self-regulatory process, if they are to understand it, and (b) provide guided practice with self-regulation to effectively manage their health behavior.

While learning about and maintaining self-management of chronic disease requires a partnership between the patient/caregivers and the HCP, the partners' responsibilities may vary over time dependent on both disease developments and the patient's abilities. However, the ultimate goal should be for the patient to achieve as much independence as possible. These partnerships must strive to help older adults to acquire the self-regulatory skills essential to effective self-management of health behavior.

Health Behaviors Embodied in Self-Management

"Health behavior" refers to *actions that influence health*. As this encompasses a wide range of activities, it is useful to think of health behaviors as falling into four classes: health promotion, primary prevention, secondary prevention (screening), and tertiary prevention (treatment). Patients' motives and strategies to engage in each type of behavior differ. Further, the extent of adherence to each class can be influenced by both positive (taking action) and negative (avoiding action) responses. Self-management encompasses both responses. For example, one older adult might attempt to adopt and to maintain a therapeutic regimen of physical therapy for a frozen shoulder, yet another may decide not to go to the therapist to avoid the pain and discomfort of treatment. While avoidance/nonadherence by patients is rarely effective in managing symptoms, HCPs must recognize that self-management does not always involve what they may view as the "correct" response.

Health promotion is intended to maintain or to improve an older adult's current state of health; for example, healthy eating, regular exercise, engaging with the community, and meditation when used proactively to manage stress. Often, health promotion behaviors do not directly involve the HCP and are better conceptualized as a part of self-care than self-management. On the other hand, *primary prevention* is performed to reduce the risk of future health problems. Examples of primary prevention include wearing a seat belt, reducing saturated fat intake, and engaging in exercise to help prevent cardiovascular disease (**Table 28-1**). *Secondary prevention*, performed by the individual or the HCP, involves the use of screening tests to detect the presence of disease as early as possible, so that its progress can be stalled and its effects managed/reversed. This might include, for example, older women performing breast self-examinations or HCPs ordering mammograms. Finally, *tertiary prevention* occurs once a patient has received a diagnosis, and focuses on preventing further deterioration and maximizing quality of life. Examples of tertiary prevention include engaging in cardiac rehabilitation following myocardial infarction, monitoring blood glucose in type 2 diabetes, and taking nonsteroidal anti-inflammatory drugs (NSAIDs) to manage arthritis pain.

TABLE 28-1 EXAMPLES OF SELF-MANAGEMENT BEHAVIORS

HEALTH PROMOTION	PRIMARY PREVENTION	SECONDARY PREVENTION
Eating a healthy diet	Using sunscreen every day	Performing breast or testicular self-examination
Exercising regularly	Flossing and brushing teeth each day	Scheduling regular checkups with the dentist, optometrist, and physician
Meditating regularly to maintain psychological well-being	Getting an influenza shot	Checking blood pressure regularly
Maintaining a healthy social network	Wearing a seat belt every time you are in a car	Monitoring blood glucose levels in pre-diabetes
Volunteering in the community	Choosing restaurants that serve heart-healthy meals and offer senior-sized portions	Conducting a home safety inventory for potential tripping hazards

In geriatric medicine, HCPs must encourage and actively facilitate older adults' development and practice of self-management skills. They must also work to build adherence to desired detection, prevention, and promotion behaviors, and related self-confidence in these actions. Later in the chapter, we will discuss the research literature in self-management, which holds promise for successful collaborations between older adults and HCPs in achieving these goals.

A CONCEPTUAL FRAMEWORK FOR SELF-MANAGEMENT

Having defined self-management and discussed different types of health behavior, the next step is to ask the following questions: Why is self-management important? What motivates older adults to engage in self-managed health behavior? And, what causes success or failure in effective self-management? In answering these questions, we offer a conceptual framework that will serve two important roles. First, it will be used to examine evidence from research on self-management. What are the features of successful programs designed to promote self-management? What are important gaps in the knowledge? Second, it will provide HCPs with a template for examining current practices and/or

developing new practice initiatives that target older adults' self-management of health behavior.

Why Self-Management?

Today, chronic disease is responsible for about 70% of annual mortality, and costs governments billions in both direct and indirect expenditures. At the level of the individual, chronic disease can have a negative and substantial effect on well-being, such as limiting daily activities (eg, dressing, bathing, and mobility), increased pain and fatigue, and poor mental health.

Self-management plays a foundational role in chronic disease management for three main reasons. First, nearly all disease outcomes are mediated by the patient's own behavior. For example, adherence to medication, medical advice, and a healthy lifestyle are all determinants of health. Second, the nature of chronic disease means that patients might spend years—if not decades—living with a given condition. Though HCPs play a key role in educating, supporting, and guiding patients, contact between HPCs and their patients is limited. Self-management is required for patients to effectively manage their condition and their lives outside of the clinic. Finally, research consistently links empowerment to positive well-being. *Empowerment* refers to the process of granting autonomy, devolving power, and enabling people to gain control over their health. Though often discussed at the level of the community (eg, empowering minority groups), empowerment is also beneficial to individuals. For instance, individual (psychological) empowerment might manifest as a greater sense of control and self-worth.

What Motivates Self-Management?

Older adults engage in self-management *in response to a conscious health goal or to remove barriers in the path toward goals*. In geriatric medicine, health-related goals most often stem from concerns related to detection or prevention behavior; that is, older adults want to identify, alleviate, or avoid a specific physical or psychological symptom/condition.

If the symptom is new to them, then older adults' self-management behavior is frequently encouraged by a family member and begins with seeking a diagnosis. However, in many instances, patients seek follow-up treatment for chronic disease. Here, prevention and management of symptoms becomes the goal. A common example among older adults is the pain associated with osteoarthritis. Often patients perceive chronic pain as being beyond their control: they believe that the HCP has the sole remedy to *fix* their problem, and discount the role of self-management. In seeking help, they might expect to obtain new medication or an increased dose of their current medication. In short, patients create *a commonsense view of what the pain means and how to alleviate it*. Likewise, the physician may feel that pain from osteoarthritis is rooted in some underlying pathology (ie, that it is a biological problem), and immediately rule out collaborative self-management. Unfortunately, the HCP's actions may reinforce patients' theory about the cause of, and solution to, the pain. Such a decision discourages self-management and reinforces patients' notion that they have no role to play in treating their chronic condition. This example illustrates that both *patients' common sense understanding of their medical condition* and the *behavior of HCPs* contribute to the motivation to self-manage health behavior. Active partnerships between patients and their HCPs develop the motivation to take action and are essential in shaping patients' self-management behaviors.

Howard Leventhal and colleagues have been instrumental in promoting a *commonsense model of self-regulation* for health behavior and have conducted considerable research on what motivates people to seek treatment. Their model also has relevance to adherence/self-management over time. A critical feature is its *bottom-up*, as opposed to *top-down*, organization. The focus begins with an older adult's perceptual experiences (eg, feeling off-balance or weak) and physical symptoms (eg, pain and fatigue)—the raw sensory experience that something is wrong. Moods and emotions related to this raw sensory experience, as well as feelings of competence in being able to manage the problem, are also important in determining higher-order reasoning such as, "I'm in trouble and need help."

The commonsense model identifies five features of health events that motivate people to act: label/symptom, timeline, consequences, cause, and perceived control. The following scenario provides an explanation of how they operate.

> Fred has noticed that he seems to have weakness and some mild discomfort in his upper legs when getting out of the car or rising from a kneeling or sitting position—*perceptual experience/symptom*. Originally, he thought they might be the result of an overuse injury, the inevitable effects of aging, or a complication related to the tension he has been experiencing with his youngest son —*suspected cause*. However, the symptoms have persisted for 8 weeks, and he long ago resolved the conflict with his son —*timeline*. He has also noticed that friends of his age are not reporting this problem. He reasons that if aging were the cause, more

of his friends would have the same symptoms. The symptoms are very frustrating because they have all but stopped him from working around the house and seem progressively worse because now he has discomfort when rising from his chair after watching TV—*consequences*. Fred questions his suspected causes and worries that he may have nerve damage in his spine or a musculoskeletal disease—*loss of control*.

Fred's initial cause-and-effect explanations of his symptoms are consistent with his commonsense reasoning about the relationship between stress and illness and age and illness and may have delayed his seeking treatment. However, when their duration and their absence among his peers suggest that they are not a normal problem of aging or stress, he becomes motivated to seek treatment. Leventhal and his group have found that, in addition to these five factors, *fear is an important motive for action, but that without an action plan, fear does little to promote constructive behavior*. For Fred, an action plan might consist of *intending* to call his physician tomorrow morning after breakfast to make an appointment for the following week.

Of course, older adults' commonsense models are not created in a vacuum; they are influenced by the social system: factors at interpersonal, institutional, and cultural levels, and our understanding of self-management has to be considered from a systems-based perspective (**Figure 28-1**).

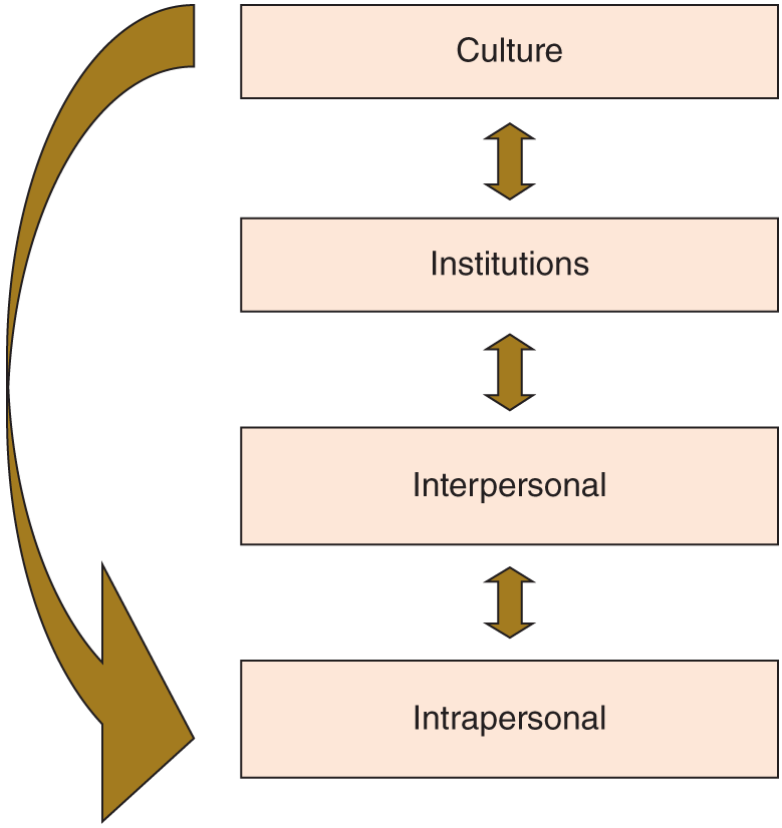


FIGURE 28-1. Multiple levels of influence that can affect older adults' self-management. Note that culture indirectly influences all levels in self-management, but can especially influence the individual (intrapersonal) due to prevailing ageist stereotypes.

Factors from multiple aspects of the system can both facilitate and inhibit older adults' actions. For example, a wife's insistence may result in her husband going for a prostate examination for potential detection of cancer (interpersonal influence). TV documentaries on the biology of aging may lead older adults to adopt a regimen of vitamin supplementation (institutional influence). Grown children may openly verbalize an emotional objection to their older adult parents seeking treatment for a symptom, convinced that doctors are just trying to collect money on procedures for benign aches and pains, in effect "ripping off" Medicare (cultural influence)! Other powerful cultural stereotypes in our society can discourage physical activity among older adults.

Symptoms do not always lead older adults to seek a solution, even when they are severe and persistent. In many instances, older adults self-manage their symptoms through avoidance. For example, a woman ignored rectal bleeding for more than a year until acute pain forced her to visit the emergency room, where colon cancer was diagnosed. She knew that something was seriously wrong long before this event, but she was afraid that, once she went for a diagnosis, she would be hospitalized, and that would be the end of life as she knew it. In other cases, avoidance can be triggered by older adults' beliefs about specific health behaviors. For example, older adults may have adopted

stereotypes that support their position that they are too old to be physically active or that losing weight is unhealthy for them.

Figure 28-2 provides a conceptual framework for understanding the complexities of self-management. We will elaborate on three features in the following sections: (a) facilitating factors; (b) inhibitory factors; and (c) knowledge, skills, strategies, and resources.

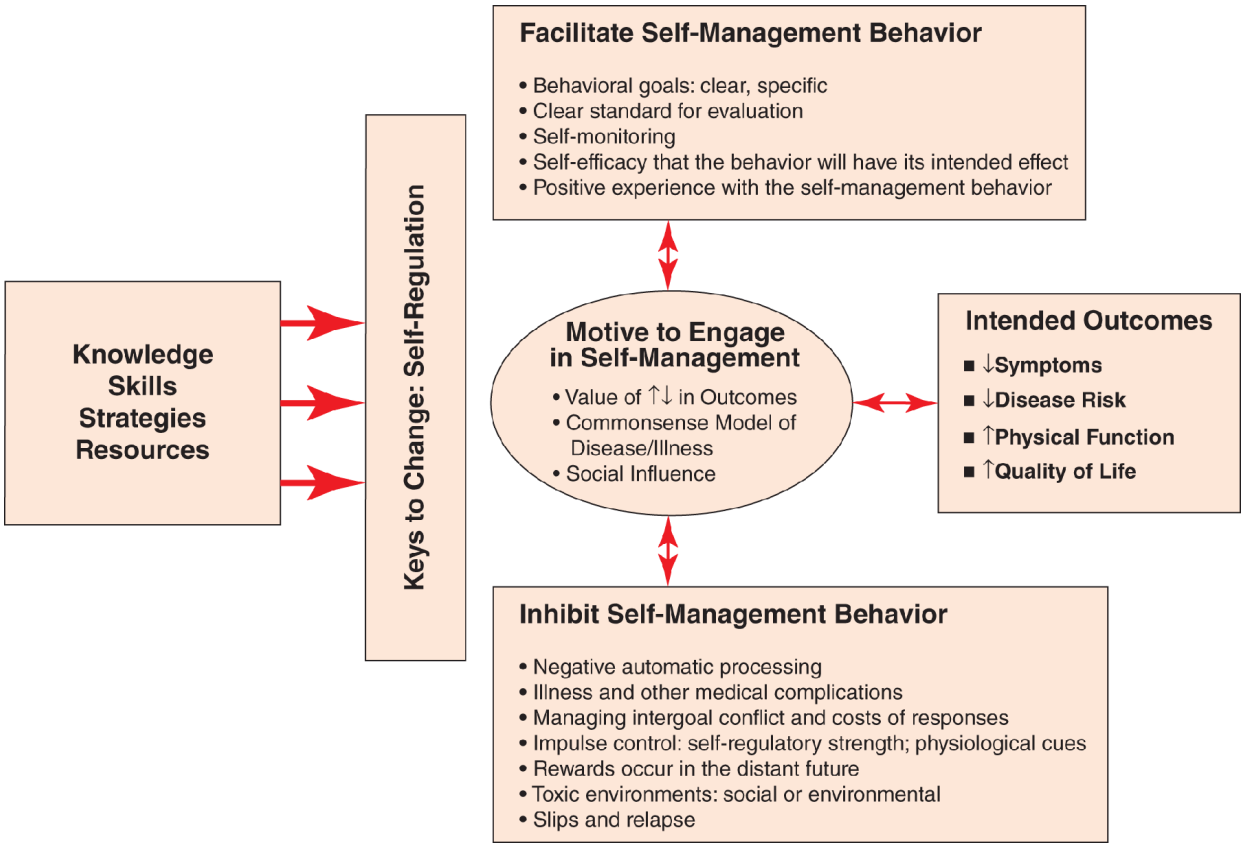


FIGURE 28-2. A blueprint for self-management.

Facilitating Factors in Self-Management

More than three decades of research in psychology has identified several factors that promote effective self-management of health behavior. Consider the following example.

Helen is an obese, physically compromised older adult. She is frustrated by several consequences of her poor health, including the fatigue she experiences when moving, the loss of some of her functional independence, and a recent confirmation by her HCP that she has type 2 diabetes. In collaboration with her physician, Helen decides to join a community-based program offered by a regional health alliance. The program treats physical disability and diabetes in older adults using a combination of caloric restriction and increased physical activity. When she first enters the program, the intervention team evaluates her diet and activity patterns, and based on these data, she and an interventionist together establish goals for modifying them over the next month. In addition, they discuss the importance of establishing weekly behavioral goals related to self-monitoring and evaluation of her progress. Together, they decide that Helen will time herself while walking four laps at the local YMCA track (approximately 400 m) each month and also record her fatigue on a simple 10-point scale (0 = no fatigue whatsoever and 10 = as tired as she has ever felt). Helen's progress and her confidence in being able to complete the prescription are checked weekly. Her goals are adjusted as necessary. On a monthly basis, Helen is asked to reflect on what she has done and to notice what effects, if any, the program is having on various aspects of her life (**Table 28-2**). As a result of this self-evaluation and a number of successes in pursuing the goals that she helped to set, Helen gained confidence in the skills necessary to make progress in changing her behavior. She could see the changes happening as she practiced these self-regulatory processes to manage her chronic health condition.

TABLE 28-2 ■ FACTORS THAT PROMOTE EFFECTIVE SELF-MANAGEMENT

SELF-REGULATORY	

SKILL	EXAMPLE
Establishing proximal and distal goals	Helen and her HCP discuss her current diet and activity patterns in order to develop realistic, challenging goals *together*. In addition to long-term goals, proximal (monthly and weekly) goals are also set.
Self-monitoring progress toward goal	Helen logs her diet and her exercise workouts each day. She also "tests" herself each month by walking around a track four times and seeing how much this tires her out.
Attaining feedback	Helen meets with her HCP weekly to discuss her log book. The HCP provides constructive feedback on how Helen is doing.
Self-evaluating progress toward goal	Helen looks back and reflects on her previous log entries to make note of any progress she is making toward her goals, and whether she is noticing any changes in other areas of her life. She notes that it takes less effort for her to walk around the track, and that she can now ride the bike 10 min longer than she could 2 wk ago. All of these changes are seen as progress toward her goal of increasing her physical activity level.
Making corrections to goal-directed behavior	Once Helen has developed confidence of physical activity, the HCP helps Helen think of other ways to reach her health goals. He suggests that Helen gradually increase her fruit and vegetable intake. Helen brainstorms practical ways to reach short-term goals, such as buying precut vegetables for snacks.
Raising self-efficacy beliefs	Helen is encouraged to celebrate the progress she has made and to take pride on her hard work. This increases Helen's confidence in her abilities to successfully change her health behaviors, regardless of barriers that she encountered along the way.

The above scenario and the description provided in **Table 28-2** illustrate how self-regulation generates effective self-management. The skills inherent in this process warrant repeating since they are part of the tools that both patients *and* HCPs must engage in and practice when self-managing health behavior. They include the following:

1. Setting clear, specific, and reasonably challenging goals for behavioral change—*setting a clear standard or goal*
2. Monitoring personal behavior and how it influences reaching goals and the rate of change—*self-monitoring progress*
3. Providing feedback and information on each health behavior goal that has been collaboratively established between the HCP and the older adult—*feedback*
4. Self-evaluating progress related to the goal—collecting the older adult's personal judgments and emotional reactions about their pursuit of goals and making or not making progress—*self-evaluation*
5. Correcting behavior as a result of feedback and self-evaluation, leading to more effective and persistent change in the direction of established goals—*corrections*
6. Encouraging belief in the ability to organize and to take action associated with the specific circumstances that they are trying to change in order to achieve specific goals and to persist in and increase behavioral change, despite the setbacks, difficulties, or rate of progress—*self-efficacy beliefs*

The *interaction of these multiple factors* influences the success that older adults will have with their health behavior change. However, their collaboration with HCPs influences the entire self-regulatory process: as partners, the HCP and patient can make informed judgments about expectations and outcomes. In the example above, consequences could include Helen's reduced calorie consumption, increased walking, and better control of blood glucose (outcomes strongly valued by the HCP), but also compliments from family, friends, and HCPs, and personal satisfaction with her accomplishments (outcomes strongly valued by the patient). Regular reflection on progress (feedback) and comments about how it has affected life (outcome information) by both parties characterize a normal self-evaluative process and influence her desire to adhere to the collaborative prescription for change. The HCP's comments about change in Helen's outlook and persistence, and Helen's surprise and pleasure in being able to stick with reduced caloric consumption over a month, jointly contribute to her self-efficacy (confidence) to adhere to their plan over the next month. This scenario follows recommended patient-centred collaborative practice outlined in the AMA's *Physician Resource Guide to Patient Self-Management Support* (accessible via http://selfmanagementalliance.org/). Its appendix provides physicians with simple tools that are helpful in encouraging patients and physicians to engage in steps toward patient self-management.

Inhibitory Factors in Self-Management

For some older adults, behavioral practices that reflect effective self-management of chronic disease are well learned and resistant to threats like competing behaviors and events. Many older adults consistently visit their physicians when they encounter novel physical symptoms, schedule screening examinations and vaccinations as recommended by HCPs, and take supplements and daily walks without fail. However, HCPs must often ask older adults dealing with chronic disease or disability to adopt new remedial or preventive behaviors, or to change dysfunctional patterns of behavior. Under such circumstances, a number of factors can inhibit effective self-management.

Operating on auto pilot

Clearly, a major threat to effective self-management is *operating automatically*. The self-regulation needed to adopt a new behavior or to change an old pattern requires conscious control of thought and action; the patient must have a goal in mind, and actively strive toward it. If an older adult behaves without thinking, opting for the routine path of dysfunctional behavior, hope for change is futile.

Why do older adults persist in seemingly mindless, automatic patterns? According to Walter Mischel's research, strong emotions—which are common in older adults—shut down their rational thinking and derail attempts at conscious behavior change. In our studies with older adults, these emotions have a variety of causes, including frustration with failed treatments, not wanting to be a burden to caregivers, and acute illness or injury that disrupts action plans. The important lesson from Mischel's research is that self-management planning cannot ignore these emotions.

An alternative explanation is that automatic behaviors may work to simplify day-to-day life. The problem, of course, is that some customary routines ("I always have a doughnut with my coffee") run counter to the strategies or prescriptions that HCPs hope to make a part of older adults' health self-management ("Avoid foods with a high glycemic index"). Well-established routines may be associated with positive outcomes, such as enjoyment or a sense of control or predictability. Replacing well-established behaviors with healthier options (ordering salad instead of fries) could be seen as undesirable or challenging (it doesn't taste as good; it costs more), or might go against social norms (being the only one to order salad) and cultural traditions (abnormal to eat raw vegetables). Finally, automatic behaviors may be attractive simply because they require less effort.

Overriding established routines takes both attention and perseverance; this may be especially difficult when the older adult is tired or is attempting to manage multiple behaviors simultaneously. In addition, decades of Eastern writings and recent research in Western psychology on *mindfulness* convincingly argue that North American society encourages automatic responding. Many find it difficult to pay attention to where they are headed and whether or not the direction of their path is consistent with what they value because it is foreign to them. During their younger and middle-aged lives, people are consumed with the demands of their occupational roles and with preparing their children to be "successful" in our fast-paced society. There is little time for self-awareness, and physical symptoms such as fatigue are viewed as barriers that need to be suppressed. This behavior pattern continues into old age.

Slips, relapses, and intergoal conflict

A second general threat to effective self-management is the occurrence of slips and relapses in behavior and intergoal conflict. The failure to remain true to personal goals is often distressing, and older adults are no exceptions to this experience. For this reason, slips and relapses often spark negative emotions that contribute to giving up on adopting or maintaining new self-regulatory behavior that can facilitate self-management. For example, Byrne, Cooper, and Fairburn conducted a qualitative study comparing obese women who were either successful or unsuccessful in maintaining weight loss after an initial intensive treatment. They found that relapse was related to (a) the failure to achieve weight goals and dissatisfaction with the weight achieved, (b) the tendency to evaluate self-worth in terms of weight and shape, (c) a lack of vigilant weight control, (d) a dichotomous (black-and-white) thinking style, and (e) the tendency to use eating to regulate mood. The theme that emerges is that relapse is often triggered by negative thoughts and feelings about self-management, which can arise from (a) unrealistic expectations about outcomes, (b) eliminating a behavior that is used to cope with life stress, or (c) having zero tolerance for slips.

We have also found that slips in self-management are often related to competing events—intergoal conflict. A common example for older adults is vacation or family gatherings, which compete for time and priority with preventive actions. In these situations, self-management takes a back seat and can even lead to negative thoughts, such as "I just don't have time for this program on vacation," or "I don't like the feeling of guilt that I am suddenly experiencing; something's got to give." Notice the black-and-white thinking style, where other goals and active self-management of health behavior are incongruent. However, with the development of appropriate self-regulatory skills, two goals need not be in conflict. HCPs should encourage patients to see goals as complementary rather than

competing. For example, an older adult could spend time with grandchildren by going on a walk or cooking a healthy meal *together*.

Barriers and toxic environments

Barriers are obstacles that make self-management difficult or impossible. According to Marcia Ory and her colleagues, barriers often evolve from negative stereotypes related to the six most common myths of aging (**Table 28-3**). These ageist stereotypes are reflected in the media and social and health care services. Expert witnesses who testified before the US Senate Special Committee on Aging reported that the media and marketing often depicts older adults as helpless, feeble, and ineffective. In the realm of health care, Ory and her colleagues found that doctors tend to provide less aggressive treatments to older patients, and that self-management programs typically target younger populations. Furthermore, behavioral and lifestyle interventions are believed to have only minimal impact on older adults, despite accumulating evidence to the contrary.

TABLE 28-3 POPULAR MYTHS OF AGING

	MYTH	REALITY
1	To be old is to be sick	Although chronic illnesses and disabilities do increase with age, the majority of older people are able to perform functions necessary for daily living and to manage independently until very advanced ages. The effects of population aging are mediated, in part, by declining disability rates.
2	You can't teach an old dog new tricks	People are capable of learning new things over the entire life course—including into old age. This relates to cognitive vitality as well as the adoption of new behaviors.
3	The horse is out of the barn	The benefits of adopting recommended lifestyle behaviors continue into the later years. It is never too late to gain benefit from highly recommended behaviors, such as increasing physical activity or quitting smoking.
4	The secret to successful aging is to choose your parents wisely	Genetic factors play a relatively small role in determining longevity and quality of life. Social and behavioral factors play a larger role in one's overall health status and functioning.
5	The lights may be on, but the voltage is low	The majority of older people with partners and without major health problems are sexually active, although the nature and frequency of their activities may change over time.
6	Older adults don't pull their own weight	The majority of older adults who do not work for pay are engaged in productive roles within their families (eg, assisting with child care) or the community at large (eg, volunteering or activism).

Poor physical and social environments, as well as lack of resources for effective self-management, can also interfere with health behavior. For example, unsafe neighbourhoods may discourage walking, and living in a food desert makes healthy eating difficult. Other barriers might be rooted in the more-immediate environment or the patient themselves: for example, their level of motivation, their commonsense understanding of their disease, or their home and family. Consider an older woman with hypertension, who has been advised to lower her sodium intake. When she attempts to change her cooking style, she receives negative feedback from her husband and promptly reverts to her old method. To remove this barrier, it may be necessary for the HCP to educate the patient's husband on hypertension and/or advise the patient on cooking strategies (eg, gradually reduce sodium levels). It is important to note that identifying and reducing the effect of barriers by arming the patient with adjustment strategies is an ongoing process, and some trial-and-error may be necessary before a successful solution is found.

Costs and the problems of distant benefits

Psychological research from multiple theoretical perspectives illustrates that the anticipated costs of behavior weigh heavily on the decision to seek or to persist with a treatment. For example, research has shown that the fear of a medical procedure, without a plan to deal with the fear, is a significant barrier to treatment. Not surprisingly, in our own work on lifestyle behavior, we find that negatively interpreted physical symptoms during activity are barriers to older adults' continued involvement with exercise programs.

Another common challenge for older adults is what researchers have described as *temporal discounting* or the

delay of gratification necessary to reach some outcomes. Willingness to persist with treatment for weeks and sometimes months before any major outcome is realized may wane. Many older adults may be faced with delayed gratification both in achieving desired distant outcomes and in the heavy, daily costs of treatment (eg, fatigue, following a complex medication and supplement schedule). No wonder patients may perceive self-management as complex and stressful, which may lead to avoidance or nonadherence.

Knowledge, Skills, and Strategies

The final component of our conceptual blueprint for self-management addresses the knowledge, skills, and strategies that inform self-regulation and, in turn, promote effective forms of self-management. Patients' knowledge about illness, chronic disease, and disability is important from at least two perspectives. First, patients must know about the origin and course of the disease itself. For example, it has been well documented that adults are better at managing diabetes when they understand the importance of self-monitoring their blood glucose level and have specific action plans to implement when values are below or above the target. As such, it is essential for HCPs to explain disease in a way that corresponds with patients' background (eg, ethnicity, education) and current cognitive abilities rather than the HCP's view of the management of the disease. Second, consistent with Leventhal's commonsense model of illness and disease, older adults' personal views of their health conditions must be explored and expanded. As we saw in **Figure 28-1**, important areas that these personal views can include are (1) symptoms, (2) perceived causes, (3) anticipated consequences, (4) degree of perceived control over the process and course of the disease, and (5) the timeline for disease progression and achieving symptom management.

Skills and strategies refer to intervention methods that have been proven effective in promoting the self-regulation of positive and negative factors toward health behavior change. As we review selected examples from the literature, we will identify elements that are consistent markers of success and indicate how the methods fit into the blueprint.

LESSONS FROM THE LITERATURE ON SELF-MANAGEMENT

The following section will showcase examples of self-management research and programs, which illustrate their potential for encouraging positive health behavior. Although some of the research does not directly involve physicians as the HCP, these programs work best when physicians understand and support their goals and know about their evidence-based effectiveness.

Selected Research by Investigators From Stanford University

Some of the most visible and rigorously studied programs of comprehensive self-management have come from Stanford University's Patient Education Research Center. For example, Kate Lorig has published widely on the Arthritis Self-Management Program (ASMP) that has since evolved into a generic Chronic Disease Self-Management Program (CDSMP). ASMP and CDSMP are led by individuals with chronic health conditions who receive 20 hours of training based on detailed manuals for group facilitation. ASMP is disease-specific, emphasizing the management of arthritic pain. It is delivered in 2-hour group sessions (10–15 individuals) that meet once a week for 6 weeks. Major topics include pain and stress management, exercise, problem solving, communication skills, especially for physician/patient interactions, nutrition, medications, and nontraditional treatments.

CDSMP is designed to treat people who have a range of chronic diseases and is delivered in 2.5-hour sessions every week for 7 weeks. Topics include managing physical symptoms and negative emotions, exercise, problem solving and decision making, communication skills, nutrition, medication use, and the use of community resources. In both programs, leaders function as facilitators, rather than lecturers, actively engaging participants to develop personal goals and specific action plans for each week. Regular feedback is a crucial component, and the objective is to enhance patients' confidence in their ability to acquire specific behaviors or skills in each area of content.

Despite the limited time allotted to address such a broad range of complex health behaviors, data from randomized clinical trials of both ASMP and CDSMP have been encouraging. **Figure 28-3** summarizes 12 years of research on ASMP as reported by Lorig. Note that the 6-week ASMP interventions lead to enduring positive changes in self-efficacy, as well as reductions in level of pain and frequency of physician visits.

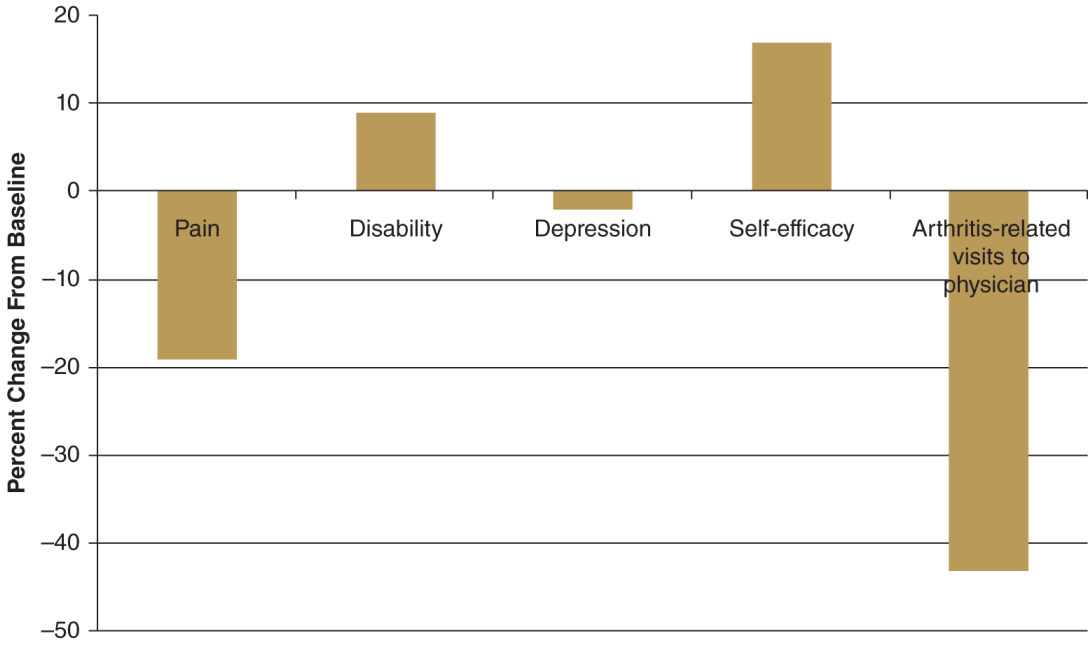


FIGURE 28-3. Twelve years of research on the Arthritis Self-Management Program. (Data from Lorig K, Holman H. Arthritis self-management studies: A twelve-year review. *Health Educ Q.* 1993;20:17.)

In a 6-month randomized trial of CDSMP, intervention patients experienced statistically significant increases in weekly minutes of exercise, frequency of cognitive symptom management, improved communication with physicians, and enhanced self-reported health as compared to control patients. Other improvements favoring intervention patients were lower levels of health distress, fatigue, disability, and fewer limitations in social/role activities. They also had fewer hospitalizations and days in the hospital. However, they did not differ from controls in their pain or physical discomfort, shortness of breath, or psychological well-being.

While self-efficacy beliefs appear to play an important role in the apparent success of ASMP and CDSMP, establishing proximal, weekly goals and providing feedback on goal attainment are also important. These latter steps help to create short-term incentives and to guide behavior in the desired direction. The mastery experienced in reaching these goals is a source of information that reinforced self-efficacy, the confidence to continue with these successful actions. Moreover, to sustain efforts in the face of inevitable barriers and to assist with problem solving, the interventions encourage participants to enlist support from HCPs, peer groups, and significant others.

The same self-regulation principles that facilitate self-management can be found in other types of interventions that employ an individual, as opposed to a group, format yet are designed to reach large segments of the population. One example of this approach is the case management system for health care originally developed by DeBusk and his colleagues at Stanford University to modify and to reduce coronary risk factors. The program is run by nurses who receive 80 hours of special training by multidisciplinary experts to deliver interventions for smoking cessation, exercise training, and dietary-drug therapy for hyperlipidemia. Scheduled interventions during a 1-year period include (1) questionnaires that patients complete and then mail to the nurse case manager; (2) computerized progress reports mailed to patients, based on those questionnaires; (3) 14 nurse-initiated phone contacts; (4) four one-on-one patient visits to the nurse case manager; and (5) eight patient visits to the blood chemistry laboratory. **Figure 28-4** illustrates the interdependence of physician, case manager (implementer), and patient using phone contacts and the computerized system to facilitate self-management. Note that the computerized system serves a dual role, one for data management and another in providing knowledge and information on self-regulatory skills that are essential to health behavior change.

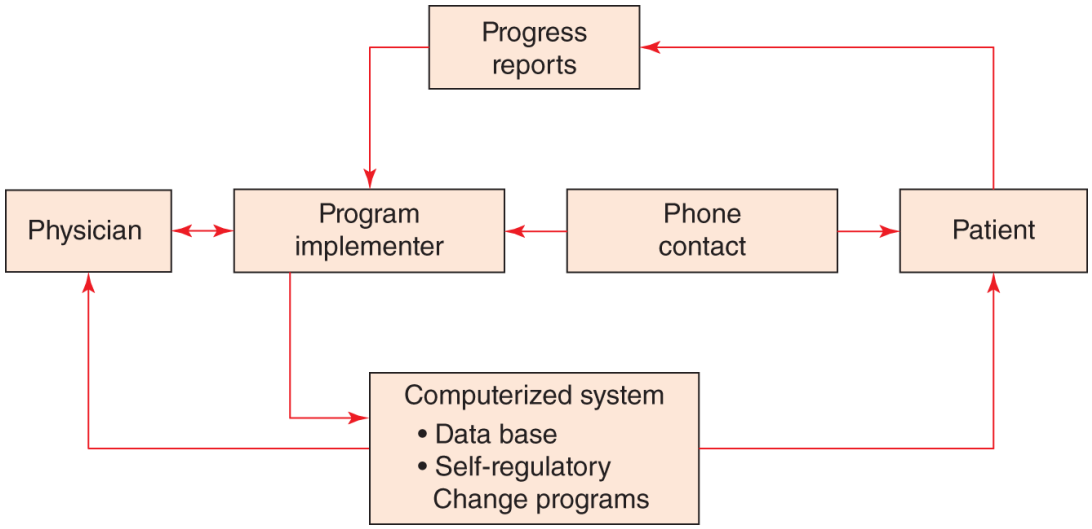


FIGURE 28-4. Case management model for coronary risk modification. (Data from DeBusk RF, Miller NH, Superko HR, et al. A case-management system for coronary risk factor modification after acute myocardial infarction. *Ann Intern Med.* 1994;120:721.)

The initial study using this system was conducted on adults with a mean age of 57 who were hospitalized for acute myocardial infarction. Patients were randomized to this treatment or usual care and then followed for 1 year. At the 1-year assessment visit, biochemically determined rates of smoking cessation were significantly higher in the case-managed group (CMG—70%) than in the usual care control group (UC—53%), and on a treadmill test performed at 6 months, patients in CMG had higher cardiovascular fitness. At 1 year, lipid-lowering drugs had been prescribed to approximately 80% of patients in CMG but only 21% in UC. While corresponding differences in plasma cholesterol favored those in CMG, patients in both groups experienced decreasing levels of dietary cholesterol and fat from baseline to the 1-year assessment.

Haskell and his colleagues at Stanford conducted a related study of risk-reduction in middle-aged to older adults who had coronary atherosclerosis. Their study was a randomized trial with two groups: UC and intensive risk management (IRM). Their trial design did not include a computerized management system but did have an objective measure of disease progression and 4 years of follow-up. Patients were provided with short- and long-term goals and an individualized action plan for risk reduction. Progress was tracked, and short-term goals were adjusted using telephone and mail contacts as well as face-to-face clinic visits every 2 to 3 months across the 4 years of the study. The staff included experts in the content areas of interest, such as nutrition, exercise, smoking, and lipid management.

After 4 years of treatment, patients who were randomly assigned to UC showed little or no change in study outcomes. By comparison, those in IRM showed dramatic changes in their health, improving their cholesterol profile, lowering saturated fats, losing weight, increasing their physical activity, and improving the functional capacity of their cardiovascular system (**Figure 28-5**). This shift in health behavior was reflected in significant reductions in cumulative cardiac deaths at the 4-year assessment visit (**Figure 28-6**). As in the case management study by DeBusk, at some point during the course of this study, 93% of those in the IRM condition were placed on drugs for lipid management, compared to only 30% in the UC condition. Since patients in both studies improved in areas unrelated to blood lipids, not all of the observed effects could be attributed to the introduction of lipid-lowering drugs into treatment. The superiority of results for the intervention groups in both studies hold the positive implication that drug therapy can be enhanced by being embedded in a program that establishes clear goals for therapy and provides more frequent evaluation of patients' health status.

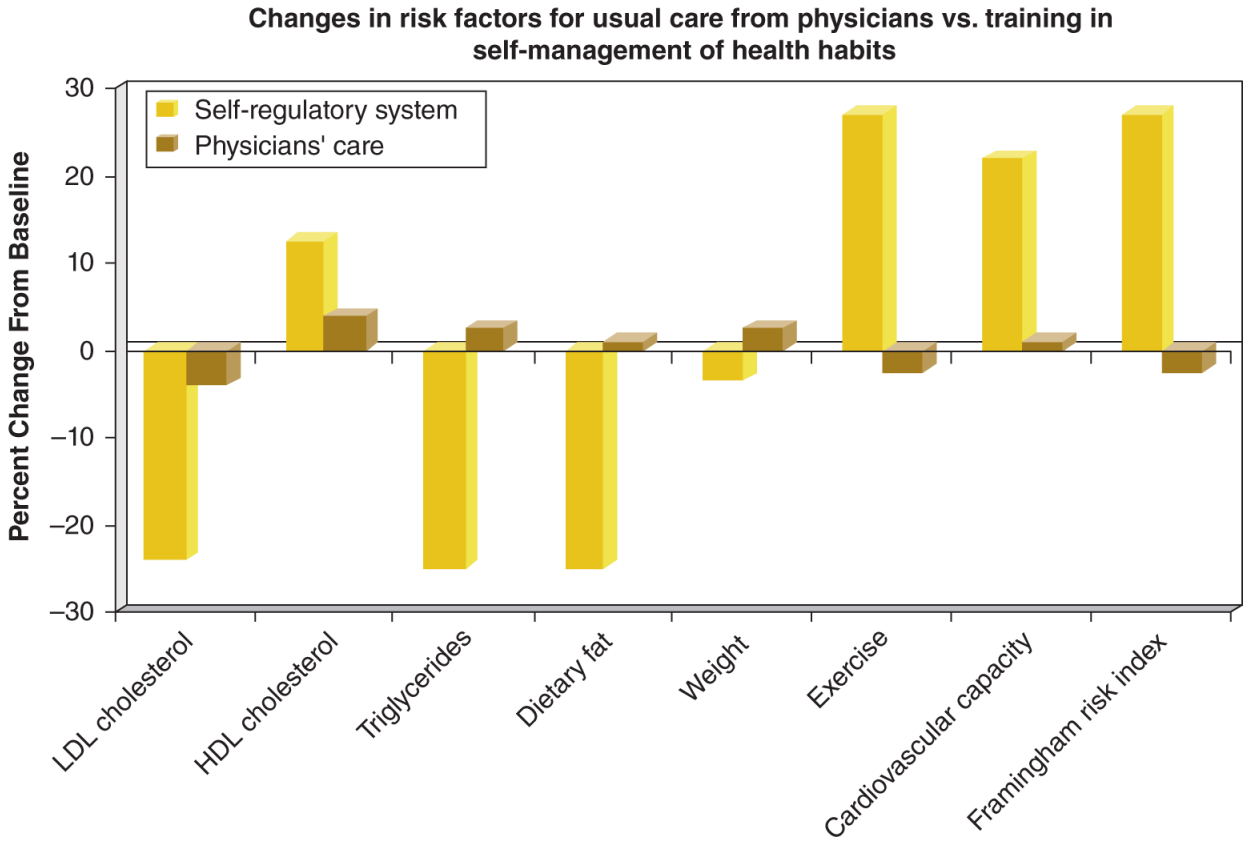


FIGURE 28-5. A comparison of a self-regulatory system for self-management with usual care. (Data from Haskell WL, Alderman EL, Fair JM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). *Circulation*. 1994;89:975.)

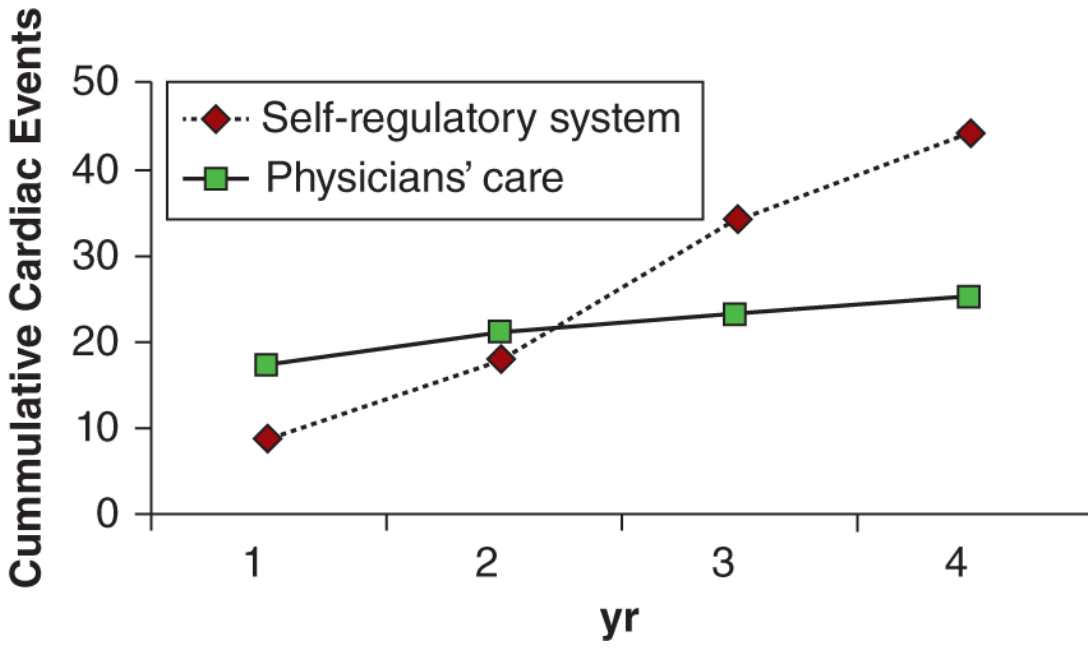


FIGURE 28-6. Four-year cumulative cardiac events with a self-regulatory intervention as compared to usual care. (Data from Haskell WL, Alderman EL, Fair JM, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease: the Stanford Coronary Risk Intervention Project (SCRIP). *Circulation*. 1994;89:975.)

One other study that deserves mention is a workplace project described by Bandura. Although it was not conducted on older adults, it underscores the potential value of social support in self-management. The goal of this project was to lower cholesterol in workers by reducing foods high in saturated fats. A nutritionist supervised the self-management system that was conceptually similar to the previously described programs conducted at Stanford. At the 3-month

assessment, plasma cholesterol between those assigned to an experimental group dropped about 10 mg/dL as compared to a control group; however, this difference increased to approximately 17 mg/dL when spouses participated in the program (**Figure 28-7**). Whereas the effects of the intervention appear to have been compromised somewhat by the inclusion of individuals who had relatively low plasma cholesterol (ie, thus were less susceptible to change) at the onset of the program (**Figure 28-7**), they also suggest that self-managing lipids is particularly beneficial to those who need it most—those with more severe disease or disability.

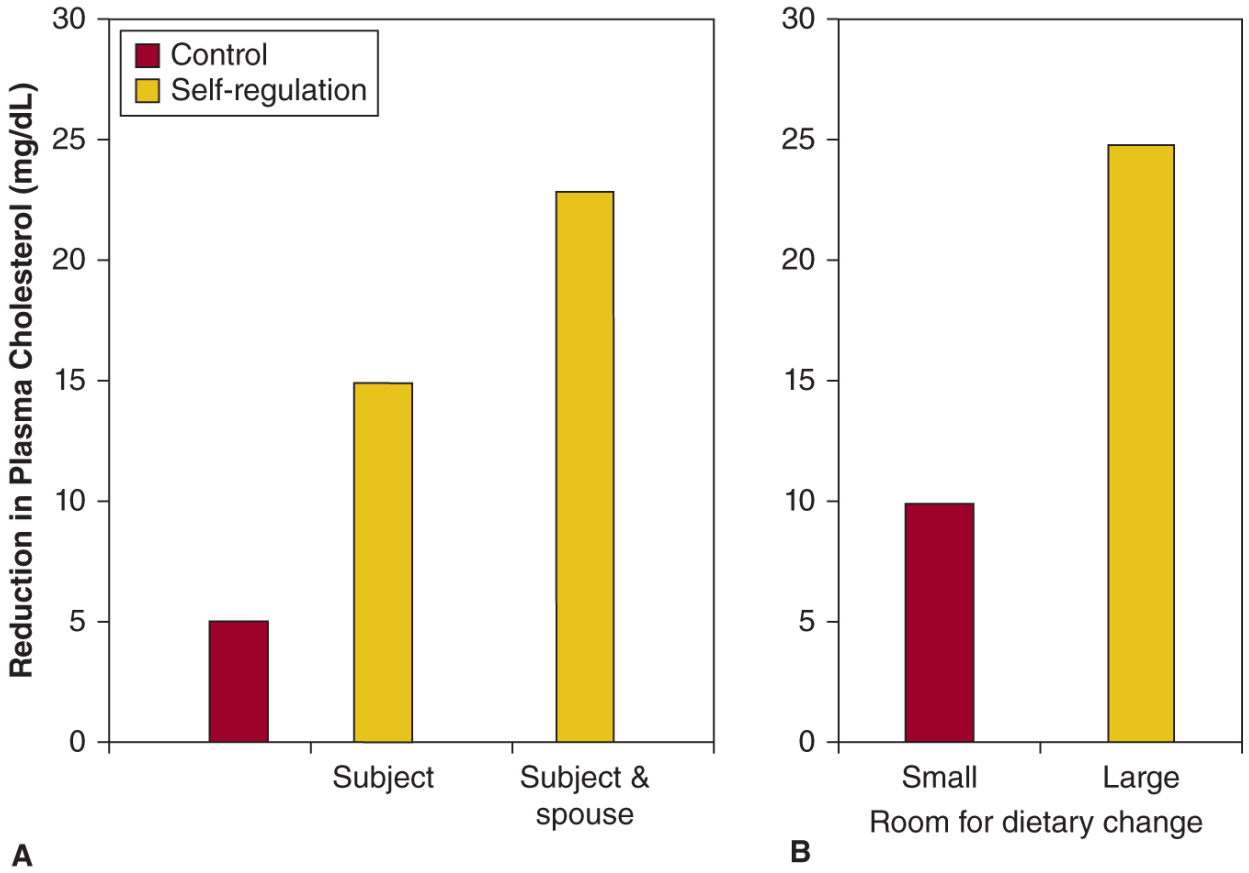


FIGURE 28-7. The effects of spouse support and the law of initial values on plasma cholesterol. (Reproduced with permission from Bandura A. Health promotion by social cognitive means. *Health Educ Behav.* 2004;31:143.)

The research at Stanford is exceptional in combining *sound social cognitive theory* with *creative translational models*. Kate Lorig's use of group-based interventions conducted by lay health leaders and Robert DeBusk's use of a computerized system to deliver a program of self-management exemplify creative approaches. These research teams have also been conscious of what Bandura calls *social diffusion*, or the promotion and adaptation of efficacious programs to diverse cultural contexts. Bandura highlights these three components of translational research on self-management as essential to society-wide health promotion.

Individual Versus Group-Based Interventions

The work at Stanford indicates the benefits of incorporating groups into programs to instill self-management of health behavior for older adults when appropriate and possible. In our research, in three different randomized controlled trials (RCTs), we have compared the effects of group-mediated cognitive-behavioral self-management (GMCB) among (a) apparently healthy but inactive older adults (b) older patients who qualified for cardiac rehabilitation with a standard model, and (c) frail, overweight older adults at cardiovascular risk. In each of these RCTs, the treatments involved either usual care center–based exercise (ie, appropriate for older adults), standard center–based rehabilitation exercise (ie, cardiac rehabilitation), or comparison to an education group, interventions involved center-based exercise therapy. In the usual or standard therapy, patients met two to three times a week for exercise only. For the exercise plus counseling GMCB treatment, patients met less often for center-based exercise to promote home-based exercise, but when they did exercise at the center, they also met afterward in small counseling groups, designed to provide the knowledge, motivation, self-regulatory skills, and resources to be more physically active and to reduce self-perceived

mobility disability (**Table 28-4**). Toward the end of the intensive phase months of treatment, the group facilitator focuses the participant on the participants' role as dominant in their successful progress. As participants self-manage much of their own activity during that period, the facilitator gradually diminishes their role and contact until older adults are managing completely independently. The results of the studies show that after standard and GMCB groups had been heavily involved in their respective treatment plans, older adults who had been more compromised at entry into each study achieved greater reductions in self-perceived mobility disability in the GMCB condition than those who had been randomly assigned to usual or standard exercise therapies (see **Figure 28-8**). In addition, at the end of reduced follow-up or no contact periods, those in the GMCB treatment group sustained their greater improvements compared to the comparison groups (ie, improved MET capacity, a measure of cardiovascular fitness), physical activity, and confidence to perform a timed walk test than those in standard treatment.

TABLE 28-4 GROUP MOTIVATED SELF-REGULATORY SKILLS TAUGHT IN GMCB INTERVENTIONS

WEEK IN PROGRAM	SELF-REGULATORY GOAL	EXAMPLE ACTIVITY
Week 1	Promote and develop group identity	Participants create and adopt a group name.
Week 2	Learn how to self-monitor effort, symptoms, and behavior	Participants are taught how to log physical activity and assess the perceived effort of an activity.
Week 3	Set individual and group goals	Participants are taught how to set specific, realistic, yet challenging goals for themselves and the group as a whole.
Week 4	Planning how to exercise independently	Participants are paired with a buddy and asked to brainstorm solutions to barriers that they may encounter when attempting to exercise.
Weeks 5 & 6	Foster social support for individual and group goals	Each participant presents their individual goal to the group, and indicates how it will help the group achieve the group goal. Group members offer feedback on the goal and how to best achieve it.
Week 7	Encourage self-reinforcement and self-evaluation	Participants are taught how to use self-reinforcement to achieve future goals.
Week 8	Increasing exercise independence	Participants work in pairs to design individualized exercise plans for the next week.
Week 9	Recognition of environmental cues	Participants are asked to brainstorm what cues they can use to facilitate home-based activity (benefit of broader recognition through group involvement than by any one individual).
Week 10	Develop coping strategies	Participants report their past week's successes and failures. Group members are encouraged to suggest ways in which others can improve or avoid barriers.
Week 11	Learn how to prevent and deal with relapses	The group identifies signs of relapse and develops strategies for overcoming relapse.
Week 12	Increasing self-efficacy	Participants are reminded of their successes and improvements. They develop specific goals for their first week of totally independent home-based activity, and a general plan for their first month.

Note: All weekly plans were integrated such that goals were continually assessed and revised. In preparing for self-management, from week 8 to 12 participants continued to plan and try their programs when away from the center. In summary, participants practiced for transition and gradually weaned themselves from the group toward independent exercise.

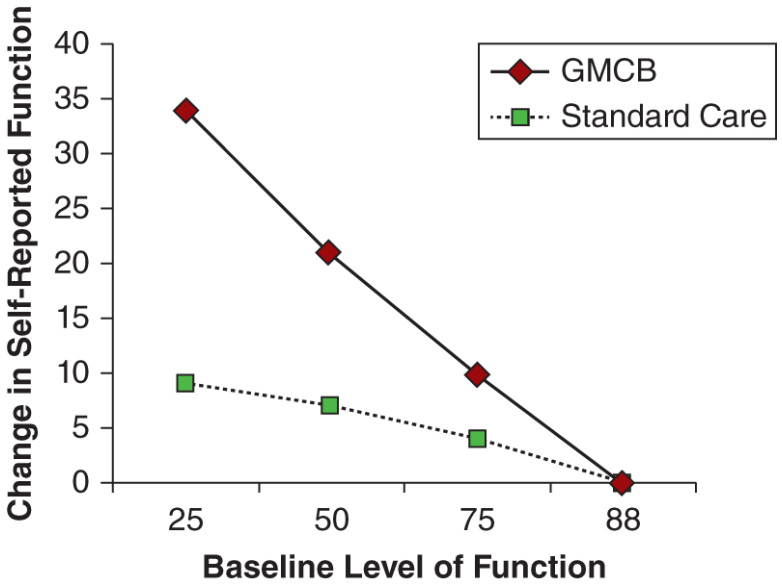


FIGURE 28-8. Three-month changes in self-reported physical function in traditional versus a group-mediated cognitive-behavioral intervention. (Adapted with permission from Rejeski WJ, Foy CG, Brawley LR, et al. Older adults in cardiac rehabilitation: a new strategy for enhancing physical function. *Med Sci Sports Exerc*. 2002;34:1705–1713.)

These successful examples show that groups are useful in developing participant self-regulatory skills. The group is developed to foster an active, collaborative learning of rehabilitation and self-regulation not only between HCP and patient but also between patient group members. Over the course of the group intervention, patients are encouraged, to integrate the skills they learn and, with mutual input, to test and to evaluate their successes and failures in using these skills in their home-based activity. Belonging to a group whose members' goal is active involvement and collective change is a powerful agent that creates the impetus for, and, eventually, the practice of, effective self-management. Results from cancer research have shown that it is not group contact per se but how the group is leveraged that promotes effective self-regulation.

How can group potential for health care improvements be maximized? As Yalom noted in his classic text on the use of groups for psychological therapy, group cohesiveness must be developed. In the preceding example on cardiac rehabilitation, we used classic formative techniques to optimize the dynamics of these small groups (n = 7–10 members). Older adults suffering from cardiovascular disease or other chronic diseases have a common motivation for uniting in a group. This disease is theirs, and they have elected this approach to treatment. Older adults best suited to groups are receptive to the concept of therapy and (a) discussing their disease, (b) learning from other members, (c) developing group goals, and (d) interacting with other members in practicing self-regulatory skills. Within this receptive context, group goal-setting and social support can emerge. HCPs can assist in enhancing these properties during the limited life of the group. For example, a group norm of strong attendance is essential. Occasional absences must be expected; however, general sporadic attendance makes a group difficult, if not impossible, to manage. This failure is more likely when patients are passively carrying out their therapy, group mission and identity are not emphasized, and the partnership between HCP and patient members is minimal.

This kind of therapeutic group must also aim for its members' eventual departure so that they can become more independent in their self-management. This is why, for the GMCB treatments in all three studies, there was practice of independent activity outside the center while participants were still in the intensive training phase. It is also why contact with the facilitator was gradually reduced in that phase, then continued to be reduced in the transition of participants to full self-management. Later in the follow-up a few additional "booster" training and education sessions were used to aid/sustain self-management and encourage adherence to their program. The group or alumni group can be the magnet that draws former members back for "reinoculation" sessions to assist in long-term maintenance of self-management behavior.

Although the group can be used to foster self-management and the learning of self-regulatory skills, practitioners should be mindful of caveats. First, as Bandura and others have noted, groups can create dependency, and older adults may quickly revert to their old ways when their group terminates. However, this phenomenon is far more probable when groups are used as a passive form of delivery, and the HCP makes no systematic attempt to coalesce a unique agent of change. Cancer research suggests that if groups have no specific purpose other than to allow patients to meet with their peers, then the effects on self-management are nil. However, when transition from the group to independent

self-management is planned, as was the case in the group-mediated cognitive-behavioral counseling research previously described, dependency is first reduced, then eliminated.

Heterogeneity in Symptoms and Health States

Self-management programs frequently target chronic diseases, such as diabetes, asthma, chronic obstructive pulmonary disease (COPD), or arthritis that require managing medications and lifestyle in response to specific symptoms. In such instances, the outcomes of effective self-management are often clear and reinforcing to patients. They realize that their active involvement in disease management makes a difference. They experience increased confidence in managing their symptoms, and enhanced perceptions of personal control become a central part of their commonsense model of the disease process.

Unfortunately, this success does not come to everyone with a chronic disease. For example, if the disease or symptom becomes worse and/or they experience a considerable loss in function, older adults may perceive a loss of control that understandably inhibits the motivation for active self-management. Ample research has shown that when doubt surrounding the effectiveness of behavior is strong, the impetus either to expend effort on action plans or to pursue goals for change is weak.

Before we discuss possible solutions to such challenges, it is useful to recognize that goals exist in a hierarchy. In the current context, a common goal for older adults is “to maintain a healthy state.” However, its pursuit is not necessarily conscious and active until it is threatened by either the loss of function or the emergence of physical symptoms. Once this occurs, then older adults are inclined to institute “do goals,” such as taking medication to relieve symptoms or participating in physical therapy to improve their balance. Because such “do goals” are more specific than the global goal of a healthy state, their achievement requires an action plan or a sequence of steps to follow. If medication is prescribed, it may involve going to the medicine cabinet at a specific time of day, opening the bottle, and taking the medication as well as monitoring medication use and impact over time. In the case of physical therapy, it involves making appointments, scheduling transportation to the appointment, clarifying the physiotherapist’s teaching of exercises for balance improvement, trying the exercises at home at a specific time of day, and monitoring the impact of the regimen on personal balance control.

With a better understanding of goal hierarchy, we can propose ways to help older adults whose motivation to engage in self-management has been depleted. Scheier and Carver have emphasized that Western culture frowns on giving up on goals, yet they argue that in some contexts, *goal disengagement* is an important coping process. Aging inevitably presents some insoluble problems. Our physical systems deteriorate, yielding predictable declines in mental and physical functioning. From a self-management perspective, detaching from an unrealistic goal allows the HCP and patient to recalibrate less ambitious goals that still point the patient in the same persistent direction, while enhancing their sense of partnership. For example, a physical activity goal of 150 min/week may be trimmed to 80 min/week. Experts believe that following this principle of partial disengagement—moving from an unrealistic to a more realistic and achievable goal without totally abandoning a particular behavioral domain—is essential because *it keeps the person engaged with life* and may well delay the onset of further health problems.

Unfortunately, some circumstances may dictate total elimination of activities that provide older adults with a purpose for living. We have seen many older, chronically diseased individuals who eventually have to give up valued activities due to a variety of impairments in the later stages of functional decline. In these instances, some older adults disengage and cope effectively by redirecting their energies into other domains, such as spirituality. In effect, they redefine or reprioritize their higher-order goals to accommodate their limited health state. Others fail to cope: they cling to old concepts, are unwilling to let go, and create enormous suffering for themselves and their families. Indeed, contemporary research suggests that failing to disengage from past goals that are no longer feasible creates intense regret among older adults and predisposes them to depression and physical symptoms like constipation and skin disease. HCPs may be terribly frustrated in attempting to pursue a partnership on a treatment path that is unacceptable to the patient.

Mindfulness-based interventions may be particularly beneficial in this realm of self-management for older adults, and they are being offered more and more as part of either hospital outpatient or community outreach programs. They teach centering skills, designed around breathing, assist with learning how to relate differently to activities of the mind, and they foster insights designed to promote acceptance of life experiences that are not subject to personal control. Although further discussion of this topic is beyond the scope of this chapter, interested readers may consult the Further Reading section by Baer (2006).

Complexity of Evaluating Research on Self-Management: An Illustration

To date, several hundred studies have been conducted in the area of self-management, but the set of adequately designed experiments is smaller. A recent paper in the *Annals of Internal Medicine* tackled the onerous challenge of providing a statistically based review of 53 randomized trials of chronic disease management programs for older adults. It concluded that programs targeting diabetes and hypertension produced clinically important benefits, but to determine which elements of the interventions were actually responsible for the observed effects was impossible. Although this paper did not find a beneficial effect of self-management in patients with osteoarthritis, a more focused literature review suggests that its effect on their *pain and function* is statistically significant but small in magnitude.

The results of self-management programs that target objective measures of physical disability among older adults with multiple chronic diseases are more encouraging. Several critical reviews have shown that strength training and walking programs produce robust improvements in physical functioning and small-to-moderate clinical effects on various functional tasks, such as rising from a chair, climbing stairs, and walking 400 m. For example, in a pilot study of adults 70+ years who had compromised function at baseline, we demonstrated a clinically significant change in scores on the Short Physical Performance Battery (SPPB), a well-validated measure of physical functioning that includes very basic tests of balance, strength, and mobility disability (**Figure 28-9**). In fact, results of the full-scale multicenter trial on this population reported in *JAMA* in 2014 demonstrated that a multicomponent physical activity program, anchored with walking, was effective in lowering the incidence of major mobility disability across a period of 42 months as compared to a health education control group. Other studies demonstrate that training older adults for balance has noticeable effects on preventing falls.

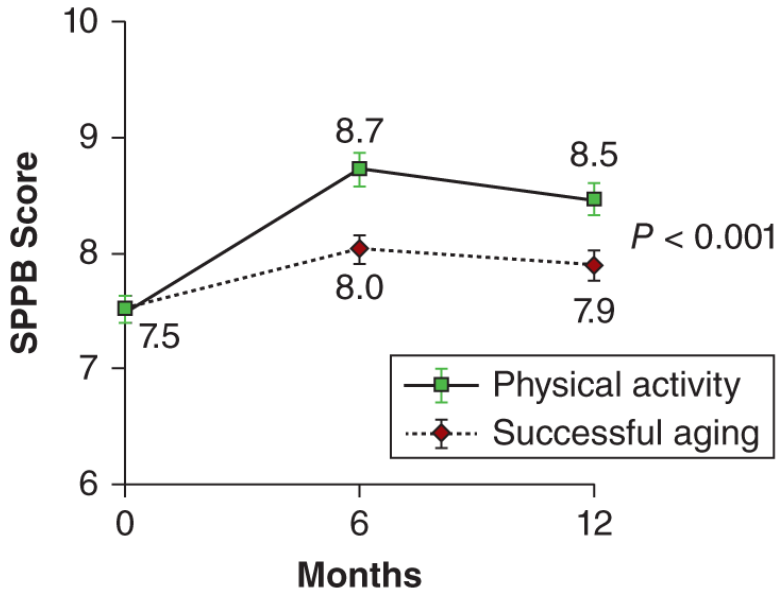


FIGURE 28-9. Comparison of a physical activity intervention with a successful aging intervention on SPPB scores. Means estimated from repeated-measures analysis of covariance adjusted for gender, field center, and baseline values. (Pahor M, Blair SN, Espeland M, et al. Effects of a physical activity intervention on measures of physical performance: results of the lifestyle interventions and independence for elders pilot (LIFE-P) study. *J Gerontol A Biol Sci Med Sci*. 2006;61A:1157.)

Thus, research findings on the topic of self-management vary considerably. Why do they differ so widely both within and between diseases? What conclusions can we draw for clinical practice?

First of all, the value of attributing clinical meaning to the strength of effects that are statistically averaged across studies, even after grouping them according to specific characteristics, such as tailored treatment or group versus individual treatment, is questionable. Among the many reasons for this concern, three stand out: (a) varying lengths and intensities of the interventions, from 6 weeks to 42 months; (b) targeting multiple outcomes; and (c) including patients with a broad range of disease severity. These variable elements preclude making many useful clinical generalizations. For example, we know from our extensive research in weight management that the intensity and duration of treatment are critical factors in the success of behavior change. Also, when studies target multiple outcomes, individual behaviors are rarely given the attention that is required for behavior change to occur The clinical effectiveness of self-management on osteoarthritis pain is much greater in intensive studies of pain management, such as those of Frank Keefe, a leader in this area, than in short-term community programs that target multiple outcomes, such as the arthritis

self-management program. While both programs have benefits, comparing them is not clinically appropriate because they are inherently different.

As for disease severity, both the chronic disease and disability literatures reflect good evidence that people with mild disease have less room for improvement in function than those with more severe disease or disability. Of course, for most health conditions, there comes a point where severity offers little room for hope, but this sad state represents only a minority of the older adult population. Reviews that include studies without controlling for the severity of patients' conditions are obviously misleading. Severely ill or disabled individuals require different treatments that may not be classified as self-management.

Perhaps more important for geriatric HCPs is the clinical utility of the information presented both in this section dedicated to research and the previous section on a conceptual blueprint for change. How does the geriatrician use the information we have presented? Can specific principles and suggestions be proposed to optimize self-management in geriatric medicine?

PRINCIPLES AND SUGGESTIONS FOR INTEGRATING SELF-MANAGEMENT INTO GERIATRIC MEDICINE

Self-management is good medicine. If the huge benefits of these few habits were put into a pill, it would be declared a scientific milestone in the field of medicine.

Albert Bandura

Partnerships in Self-Management: A Description and Conceptual Rationale

A central position of this chapter is the importance of establishing partnerships between patients and HCPs. An inherent quality of any effective self-management program is that the patient is an active partner in treatment. This position is supported by the American Medical Association. Their suggestions are clearly outlined in their *Physician Resource Guide*, an excellent resource for physicians who have any chronic disease patients as part of their practice, specifically older adults. What is actually meant by the term *partnership*? How does traditional care differ from collaborative care? How do these two approaches influence the approach a HCP should take to patient education?

Traditional Versus Collaborative Patient Care

Bodenheimer and his colleagues have offered an excellent description of traditional and collaborative care paradigms in chronic disease management. **Table 28-5** identifies their six key questions about patient care, together with examples based on each of these paradigms. In a traditional medical model, patients take a passive role; while HCPs identify the problem, provide solutions, and expect patients to comply with recommendations and prescriptions. Under this system, noncompliance is viewed as a dysfunctional patient problem. In contrast, when partnerships are established in collaborative care, patients are allowed to define their problems; the patient and HCP share responsibility for the creation of treatment plans; HCPs facilitate and guide treatment; and noncompliance is viewed as a shared problem to be solved. Indeed, in some instances (most obviously involving side effects from pharmacologic therapy) noncompliance may be a wise and rational step, indicating that treatment plans should be modified or expanded.

TABLE 28-5 SIX KEY QUESTIONS

	TRADITIONAL CARE	COLLABORATIVE CARE
What is the relationship between patient and health professionals?	Professionals are the experts who tell patients what to do. Patients are passive.	Professionals are experts about the disease and patients are experts about their lives.
Who is the problem solver? Who is responsible for outcomes?	The professional.	The patient and professional share responsibility for solving problems and for outcomes.
What is the goal?	Compliance with instructions. Noncompliance is a personal deficit of	The patient and the professional make informed choices and realistic goals. Lack of goal

	the patient.	achievement is a problem to be solved by modifying strategies.
How is behavior changed?	External motivation.	Internal motivation. Through partnerships and HCP encouragement, patients gain understanding and confidence for self-management.
How are problems identified?	By the professional, eg, changing unhealthy behaviors.	By the patient, eg, pain or inability to function; and by the professional
How are problems solved?	Professionals solve problems for patients.	Professionals teach problem-solving skills and help patients in solving problems.

In suggesting that patients be allowed to help to define and solve their problems, we do not mean that they should supplant HCPs as diagnosticians, surgeons, occupational therapists, pharmacists, etc. Likewise, collaboration may not be a viable or realistic option in certain circumstances: for instance, during an emergency procedure or when interpreting test results. However, these circumstances represent only a small portion of total HCP/patient interactions. In regular, day-to-day practice, the patient can be involved in many aspects of chronic disease management.

Listening forms the foundation of collaborative care. HCPs must listen carefully to what patients are saying about their health status and treatment. Consider the example of an older patient in cardiac rehabilitation: While the HCP was primarily focused on his heart health, the patient's main concern was his impotence. After considerable dialogue, close examination of his medications, and consultation with his cardiologist, his beta-blocker was changed. Within a very brief time, his erections improved, and his entire attitude toward treatment changed. He was now emotionally able and willing to consider how he could prevent further disease. In fact, what motivated him to exercise, take lipid-lowering medication, and watch his diet was the realization that the vessels that served the penis were also subject to atherosclerosis. The benefit of listening to the patient's concerns and then collaborating on a solution provided huge gains in adherence to the traditional goals of cardiac rehabilitation. This process also contributed to his understanding of the system-wide impact of both disease and adherence on the rehabilitation prescription.

Part of this process includes the tell-back collaborative inquiry where patients describe their understanding of their conditions and treatment, followed by the physician supplying additional information as needed, again followed by the physician inquiring about the patients' understanding/feelings about the added information. The mutual sharing of information increases understanding. Traditional and collaborative medical care leads to entirely different sets of goals and strategies for patient education. According to Bodenheimer and colleagues, the traditional model is delivered by HCPs and reinforces patients' need to follow "what the doctor orders." By contrast, in a partnership model, education is synonymous with the concept of self-management (**Table 28-6**). Geriatric HCPs are part of a larger network of services, professionals, and advocates that promote the health of older adults. Thus, an important goal of geriatric medicine is to teach patients to leverage resources in their communities and within the health care system. Using such resources enables older adults to reach effective solutions for their current problems—and possibly compress future disability and morbidity into the last few months or years of life. This perspective is at the heart of what the Healthy Aging Research Network concluded in 2006:

TABLE 28-6 ■ CONTRASTS BETWEEN TRADITIONAL AND COLLABORATIVE MEDICINE

	TRADITIONAL PATIENT EDUCATION	SELF-MANAGEMENT EDUCATION
What is taught?	Information and technical skills about the disease.	Skills on how to overcome problems.
How are problems formulated?	Problems reflect inadequate control of the disease.	The patient identifies problems he/she experiences. These may or may not be directly related to the disease.
Relation of education to the disease	Education is disease-specific and focuses on disease information and technical skills.	Education provides problem-solving skills that are relevant to self-management and reducing the consequences of chronic conditions in general.
What is the theory underlying the education?	Disease-specific knowledge creates behavior change, which in turn produces better clinical outcomes.	Greater patient confidence (self-efficacy) in their capacity to make life-improving changes yields better clinical outcomes.

What is the goal?	Improved disease management via compliance with the prescribed therapeutic regimen.	Improved clinical outcomes via increased self-efficacy for adherence behaviors.
Who is the educator?	A health professional.	A health professional, peer leader, or other patients, often in group settings.

> Healthy aging is most easily achieved when physical environments and communities are safe and support the adoption and maintenance of attitudes and behavior known to promote health and well-being and by the effective use of health services and community programs to prevent or minimize the impact of acute and chronic disease on function.

The Conceptual Importance of Partnerships in Health Care

Partnerships have immense significance to the development and maintenance of effective self-management and health in older adults for several reasons. First, older adults' commonsense models play a key role in determining health behaviors. For example, consider research by Halm and colleagues on minority, inner-city adults with chronic asthma. More than half of patients believed that they *only* had asthma when they were experiencing acute symptoms; these individuals were less likely to take corticosteroids and use peak flow meters. In the absence of a partnership between patients and their HCPs, these—and other—commonsense beliefs risk going unnoticed.

Second, the importance of partnerships is also supported by epidemiologic studies indicating that physician advice can strongly enhance older adults' desire and confidence in their ability to perform specific health behaviors. Third, many older adults choose not to discuss health-related self-care with physicians because they are unsure whether they will approve of what they are doing. Thus, geriatricians are often unaware of whether or not their patients are in counseling, dieting, exercising, or receiving other forms of health-related treatment. A lack of awareness about other treatments may severely compromise the process of disease self-management.

When HCPs engage their older patients as partners in a health care plan, discussions are more likely to be open and mutually enlightening. Finally, through partnerships, HCPs are in a good position to teach patients effective self-regulation of health behavior. Communication and buy-in occur when goals are clearly specified and action plans are articulated, monitored, and evaluated on a regular basis to enhance patients' motivation and confidence in various treatment regimens.

How do HCPs best promote self-management in the context of their own practices? Are particular target behaviors of interest? The following section describes several fundamental principles that can—and should—be common to chronic disease self-management efforts. In addition, HCPs may wish to consider connecting their patients to inpatient and/or outpatient self-management programs, such as the Arthritis Self-Management Program. In situations where programs aren't available or accessible, an online or telehealth version may be a potential favorable alternative.

How to Develop a Self-Management Partnership

HCPs can use the contrast noted between traditional and collaborative styles of interaction (see **Table 28-5**) as a guide to set concrete goals for themselves to establish a consistent model of care with patients and then to formulate plans of action in conducting their practice. If these steps sound familiar, it is because they are identical to those we suggested earlier for patients.

Because HCP/patient interaction is a two-way street, HCPs should also examine their own behavior to ensure that they are contributing to, rather than detracting from, the partnership to promote self-management. The same factors that limit the patient's contribution to self-management also pose challenges for HCPs trying to stick to their own plans of action to contribute to the partnership's achievement of goals. For example, consider HCPs' automatic behavior when meeting with patients. Faced with years of training and experience, HCPs are well-practiced in what questions to ask and what responses are indicative of trouble. Defaulting to autopilot may be an efficient way to "get the job done," but is not necessarily the same as patient-centered care. As with older adults attempting to break habits, HCPs must become aware of their behaviors and critically assess whether they are *listening* to patients or simply *responding* to them. Small, purposeful changes, such as warmly greeting the patient *prior to* turning to your computer/charts, can have a powerful, positive effect on the relationship as a whole. By definition, partnerships require cooperation between two or more people. An extremely important facet of promoting partnerships in geriatric medicine is enlisting patients' support and educating them about the skills and commitment required of *both* parties. Clearly, a major challenge for HCPs is that, in the traditional biomedical model, patients are relatively passive, *expecting physicians, nurses, and other HCPs to fix their problems*. While health care remains a problem-solving enterprise, the

partnership model must (a) identify problems collaboratively; (b) specify options and choose a treatment together; (c) make detailed action plans; and (d) clarify for patients the steps for evaluation, including feedback to the HCP. Communication between HCPs and patients should reinforce the patients' active role in health care, underscoring diverse behaviors that include adhering to medication regimens, monitoring symptoms, or altering lifestyle behaviors.

Fostering Collaboration

Meichenbaum and Turk's classic text, *Facilitating Treatment Adherence: A Practitioner's Guidebook*, offers HCPs the following practical advice to facilitate collaboration in self-management:

1. Ascertain the patient's preference for each aspect of the treatment regimen.
2. Assess the patient's previous experience with self-management.
3. Ensure that the patient has the requisite skills and resources for implementation.
4. Introduce change gradually over the course of several visits, so as to learn together how the patient is doing.
5. Break complex tasks that require more demanding adherence into actions that can be handled sequentially.
6. Begin the collaboration with a step that can be readily accomplished to foster immediate patient control and direction.
7. Enlist support of family or other strong allies.
8. As the patient assumes an increasing level of self-management, gradually reduce the HCP's role in order to foster greater patient responsibility.

All of these suggestions imply frequent, ongoing contact with patients—a necessary aspect of managing chronic disease. Physicians and nurses must carefully plan how they use contact time with patients to most efficiently build the collaboration. HCPs could benefit from following the many practical, evidence-based guidelines suggested for a variety of patients to foster treatment adherence. We also suggest the HCP follow the five As (ie, assess, advise, agree, assist, arrange) that the AMA advocates for use in the visits to the physician's office to develop the self-management process over time. These practical suggestions characterize a physician tip sheet for self-management support and can be learned by all members of a health care team that are in the physicians' offices and extend to their health care network.

With the exception of smoking, physicians are not aggressive in giving patients advice about lifestyles, despite the profound effect that changes in lifestyle behaviors have in accruing, preventing, and treating chronic disease and disability. For adults aged 65+ who report on their physician's guidance, only 31.3% are told to get more exercise; 41.5% are given advice to eat more fruits and vegetables; 38.2% are instructed to reduce their dietary fat; 25.5% are told to reduce stress; and 82.8% of current tobacco users are advised to stop smoking. Keep in mind that these eye-opening statistics only concern one of the most prevalent forms of physician behavior—providing advice—not teaching or actively changing patient behavior. The number of older adults who are assisted in self-managing lifestyle behaviors is disappointingly low.

Implementing a Framework for Effective Self-Management

Self-management is heavily influenced by older adults' commonsense models of health-related problems and treatment options. When they are unclear about the meaning of their symptoms and conditions, they may experience anxiety and/or avoid important self-management behavior. Incorrectly interpreting a symptom as "nothing to worry about—it's old age" can lead patients to be passive, and they may fail to take action that could prevent downstream morbidity. On the other hand, overreacting to the single occurrence of a symptom may result in overcompensation; for example, resting, when the correct reaction should be increased physical activity. Clarifying and *documenting* the *type, intensity, frequency, and duration of symptoms* that older adults are experiencing should be a priority of any practice. These data should be updated on follow-up contact calls or at scheduled visits.

Any diagnosis should also be accompanied by information about both the disease/health state *and* the patients' role in managing the health event. Simply asking older adults whether or not they understand the problem they are encountering, and promptly moving on if they say they do, is unadvisable for two reasons. First, they may be embarrassed to admit that they don't understand common disease states, such as hypertension or diabetes. Second, even if patients think they understand a specific diagnosis, components of their commonsense models may well be in error (see **Figure 28-1**) and detract from adherence to recommended and agreed-upon action. HCPs discussing self-

management with older adults in relation to these diagnoses can underscore the importance of their partnership, using it as a platform for mutual understanding (a) to set concrete goals in specific areas, (b) to establish action plans, and (c) to discuss the importance and means of providing feedback about these action plans (see **Table 28-2**). For these latter three steps, we refer the reader to an easy-to-use tool: the Ultra-Brief Personal Action Plan, outlined in the appendix of the AMA's *Physician Resource Guide*. This tip sheet outlines five straightforward elements that address the specifics of planning and provide a good beginning for the patient and HCP to work together. The plan also uses patient self-efficacy to complete the action plan as an initial marker of whether the plan should be modified and it engages the patient in ways to adjust the plan so they have joint ownership of it, thereby encouraging the likelihood of greater adherence.

Once the HCP is assured that patients are getting the idea of self-management and are actively participating in it, HCPs should be able to link their older patients to resources in either their own network or the community that might be valuable in managing their health states. For example, someone who is obese and has elevated glucose should be referred for weight loss. Referrals should be proactive when possible; that is, if patients are receptive, HCPs should arrange the initial contact with resource personnel. They must also be aware of whether or not patients have the economic means, time, and transportation required to take advantage of the proposed resources. Taking time to match and plan greatly increases the likelihood that older adults will follow up on recommendations. Once enrolled, HCPs must monitor patients' progress with outpatient programs if they really are to function as active partners in self-management.

Targets for Self-Management: General Practices

HCPs must specify behavioral targets and have concrete goals for self-management that patients can understand and accomplish. For example, a number of *screening behaviors* should be a part of every geriatric practice. These include colon screens, breast examinations, skin cancer screening, prostate examinations, bone mineral density, and physical disability. Without having specific action plans in place to ensure participation in these screenings, adherence rates will suffer. Here are some suggestions, based on the framework we proposed earlier:

1. Underscore the threat of electing not to be screened.
2. Educate the patient on what the screening involves, such as details of the procedure, whether it is/isn't painful, and any potential side effects. Combined with Step 1, aim to *highlight why screening is important (eg, early detection)*, while *reducing fear* of the screening procedure itself.
3. Schedule visits for patients, as opposed to simply suggesting that screening be completed.
4. Systematically monitor screening tests for each patient and be certain that feedback is provided immediately.
5. Schedule follow-up visits immediately when test scores are abnormal.
6. Display rates of participation in screening tests by patients in your practice in highly visible areas. Set goals of 100% participation.

With older adults, take time to evaluate and to advise on lifestyle health behaviors, such as (a) caloric consumption, (b) healthy eating practices, (c) smoking behavior, (d) level of physical activity, and (e) depression/anxiety. An efficient way to do this is asking patients to complete a basic lifestyle self-report questionnaire prior to their appointment (eg, while in the waiting room). If electronic, results, scored by computer, can provide a clearer picture for both partners, and build the foundation for ongoing interaction that effective self-management requires.

How HCPs summarize and communicate patients' health status can have powerful repercussions on self-management. Simply telling the patient, "You seem to be doing fine," might be well intended, but it lacks clarity and may be deceiving. For example, when older adults have two comorbidities, they are at risk for future decline in functional independence. If they consider this risk normative, and the HCP says they "seem to be doing fine," they may not try to do anything to improve their condition; in fact, they may conclude that they are overreacting. Feedback and guidance must be specific for individuals to understand their health status. General, nonspecific feedback can unintentionally reinforce *a counterproductive commonsense model* of older adults' health status.

Targets for Self-Management: Assessing and Acting on Physical Disability

Because the loss of mobility is such a catastrophic health event for older adults, we feel strongly that every office visit should include a brief assessment of physical function with specific recommendations promoting active lifestyles. Such

programs have preventive value not only for mobility loss but in managing multiple health problems. According to data from the Centers for Disease Control and Prevention (CDC), physicians ask 56.6% of 65- to 79-year-old adults about their level of physical activity, but only ask 38.9% of those age 80 or older—an apparent age bias. Even more disappointing is the fact that physicians only give 12.6% of adults aged 65+ assistance in structuring an exercise program; when assistance is given, no information is provided on how to successfully self-manage it, and systematic follow-up is very poor. Physicians report that they do not counsel patients because they lack practical tools, time, reimbursement, and confidence that counseling will trigger behavior change essential to the self-management process.

Fortunately, there are some simple tools for assessing physical capacities of older adults. One is the SPPB, developed by Dr. Jack Guralnik and his colleagues at the National Institute of Aging. It takes about 10 minutes to complete, can be easily conducted by a nurse or trained volunteer, and only involves three tasks: walking 4 m (13 ft), completing a simple chair-sitting exercise, and performing two very brief static balance tests. As shown in **Table 28-7**, scores on each test range from 0 to 4—total scores range from 0 to 12—with a higher score indicating better function. This test has been shown to predict both morbidity and rates of nursing home admissions.

TABLE 28-7 THE SHORT PHYSICAL PERFORMANCE BATTERY (SPPB)

COMPONENT	SCORE	TASK
Balance tests	0—unable to hold for 10 s 1—held for 10 s	Side-by-side stand—participant stands with feet side by side and attempts to hold for 10 s without moving feet.
	0—unable to hold for 10 s 1—held for 10 s	Semi-tandem stand—participant stands with one side of heel touching the big toe of the other foot and attempts to hold for 10 s without moving feet.
	0—held for < 3 s 1—held for 3–9 s 2—held for 10 s	Tandem stand—participant stands with one heel directly in front of toes of other foot and attempts to hold for 10 s without moving feet.
Gait speed test	Range of 0–4, where: 0—unable to do the walk 4—took < 4.82 s	Participant walks 4 m at their usual pace while a HCP times them with stopwatch.
Chair stand test	If the patient cannot complete the task, end the test here. If they can do it, move to repeated chair stand test.	Participant folds arms across chest while sitting in a chair, and then attempts to stand up without use of arms.
Repeated chair stand test	Range of 0–4, where: 0—cannot perform 5 in a row *or* took longer than 60 s 4—performed 5 in < 11.19 s	Participant folds arms across chest while sitting in a chair and attempts to stand up and sit back down as quickly as possible.
SPPB Score:	**Range: between 0 and 12.**	

Our own research has found that SPPB test results have a motivational effect on older adults. Given this specific feedback, they are more responsive to receiving and seeking information about remedial physical activity to enhance their basic performance. Fortunately, an increasing number of community-based programs offer physical activity for seniors. Also, physical therapy referrals are valuable for patients who have severe deficits in balance or lower-leg strength. Physical therapy generally helps to improve function in older adults who have physical limitations. Improvement is sustained through supportive resources in the community when older adults subsequently participate in structured physical activity programs. Note that the SPPB was not designed to assess functioning in more-fit individuals; other tests are more appropriate for them. Also, whereas clinicians often argue that they have neither the time, space, nor staff to administer performance-based tests of function such as the SPBB, we have developed an innovative, computer-animated, self-report test of mobility that can be completed on an iPad is just 3 to 5 minutes—the mobility assessment tool-short form (MAT-sf;). It has excellent clinical utility as demonstrated by several recent publications.

Following from the feedback given through the SPPB or the MAT-sf, a companion suggestion, is to have older adults engage in a highly specific action plan, that they are willing to do themselves and that they are reasonably

confident they can carry out by a certain date. Once again we refer the reader to The Ultra-Brief Personal Action Planning Tool from the AMA's *Physician Resource Guide*. It is useful and provides opportunity for the HCP to interact with the older adult. Together, they develop a simple and specific action plan that is achievable and enhances the self-management mastery so necessary for older adults to gain confidence with self-management. The tool builds on the plan by (1) assessing the older adult's confidence in carrying it out; (2) adapting the plan by problem solving and using other strategies and supports to increase the person's confidence in execution; and (3) arranging a follow-up HCP visit so both patient and HCP can evaluate plan progress.

This section on implementation should make clear that optimal self-management can only be attained if ***both partners adhere*** to its collaborative practices. This means that the person with chronic conditions must be engaged in and adherent to self-management behaviors *and* providers must be engaged in and adherent to the practice of helping this person increase their self-management capacity. As a closing guide, we offer additional practical suggestions on how to maintain adherence from the classic textbook by Meichenbaum and Turk.

1. *Anticipate nonadherence:* There are variety of reasons for nonadherence; some of which neither the HCP nor the patient can control. Do not treat it as a sign of failure on your part or typecast older adults who struggle with self-management as nonadherers. Either response is destructive to the process of mutual problem solving.
2. *Consider self-management from the patient's perspective and establish a collaborative relationship:* Carefully study the inhibitory factors discussed earlier in this chapter. Understanding them can lead to a renewed appreciation of the challenges that patients face and result in renegotiating more realistic self-management goals. Meichenbaum and Turk remind us that "*An acceptable regimen that is carried out appropriately is better than an ideal one that is ignored*".
3. *Be patient-oriented:* HCPs should gain knowledge of their patients' commonsense understanding of their disease or functional problem and the proposed treatment. Listen carefully to what patients say and to what they do ***not*** say. For example, are patients really not listening when they say nothing? Perhaps they are embarrassed about their lack of understanding. In addition to clear instruction from the HCP, patients should articulate their understanding of what the HCP said.
4. *Customize treatment*: When an older adult has a chronic problem, a reasonable question is whether standard treatment really exists. As part of self-management, the HCP must be prepared to work with the patient to adjust and to modify standard protocols. Needs vary from person to person. Frail people, the cognitively impaired, or those with language or educational barriers may need additional supports within the health care system to encourage/facilitate their self-management. Self-management cannot be a one-size-fits-all goal.
5. *Use family or significant other support:* Because other people can facilitate or hinder older adults' self-management, family and/or significant others must be included in the health care partnership. They should understand the chronic disease, the nature of the treatment, and the goals of self-management. The obvious benefit is their support for the approach being taken without eliminating or blocking the older adults' role in the self-management process. Assess what these "providers" are doing to help the older adult be more engaged in their self-management.
6. *Provide accessibility and continuity of care:* If patients find difficulty gaining access to HCPs, if your staff do not show the same interest and care as you, and if you do not draw on other HCPs and community programs that could assist in treatment (eg, psychosocial specialists for depression, exercise rehabilitation specialists for older adults), self-management has a greater risk of failure. Developing an integrated, highly communicative group of HCPs is essential for effective self-management. Older adults are likely to need acute care as well as community care. They move in and out of different parts of the system. Keeping track of these movements provides opportunity for continuity of care as well as an informed health care team and informed older adults.
7. *Repeat everything, and don't give up:* Intervention research in a variety of areas suggests that for chronic problems, patients must be "reinoculated." Long-term maintenance requires repeating education and behavioral practice about treatment regimens and modifying the self-management approach to counter declines or lapses in adherence.

Building on the suggestions of points 5 to 7 specifically, progressive HCPs whose practice serves a geriatric population with its higher incidence of chronic disease may improve their practices. They can assess their resources and evaluate their available support for chronic disease self-management. Once again we refer the reader to the AMA's *Physician Resource Guide*. The appendix for this guide includes a tool that is useful for assessment of primary care resources and supports for chronic disease self-management. The tool suggests two categories of assessment: patient

support and organizational support. Guidance is provided on how to score HCPs' primary care resources to determine adequacy as well as identify areas for improvement. The tool is designed to be used for immediate feedback and also for comparison to ensure quality is sustained and identified need for improvement of areas is addressed.

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Chapter 29

Rehabilitation

Cynthia J. Brown, Diane Clark

Learning Objectives

- Name and describe the conceptual models used as the framework for rehabilitation.
- Explain the advantages and disadvantages of each site of care for rehabilitation.
- List providers who are commonly members of the interprofessional rehabilitation team.
- Identify common rehabilitation interventions, in addition to exercise.
- Name at least two types of adaptive aids and how they are used.

Key Clinical Points

1. **In addition to the history and physical examination, an evaluation should include assessments of cognition, motivation, depression, social support, and financial resources, as these factors can have a significant impact on rehabilitation outcomes.**
2. **It is important for the provider to understand the range of available rehabilitation settings, both inpatient and community based, and the advantages and disadvantages of each setting.**
3. **An interdisciplinary team is often required to meet the complex rehabilitation needs of older patients and while team members have defined roles and functions, there is considerable overlap in the services provided.**
4. **Exercise is the cornerstone of physical rehabilitation, with each prescribed exercise being related to achievement of a goal and ultimately to an improvement in function.**
5. **Adaptive aids include devices that allow persons with physical limitations to participate in activities, such as basic and instrumental activities of daily living, with greater ease and/or less pain. Categories of adaptive aids include mobility aids to assist people to move around within their home and community, bathroom aids to assist with bathing and toileting, and self-care aids that assist with dressing, personal hygiene, cooking, and other activities.**

DEFINING REHABILITATION

The purpose of rehabilitation is to restore some or all of a person's physical and mental capabilities that have been lost as a result of disease, injury, or illness and to help achieve the highest possible level of function, independence, and quality of life. The techniques and modalities used to achieve these goals are numerous and typically do not differ for younger versus older persons. However, rehabilitation outcomes and approaches are frequently different for the older adult. For example, most young adults experience a single acute event that results in disability. Older adults are more likely to have multiple comorbid conditions that, over time, result in disability. Even if the older persons have acute events, like a hip fracture or a stroke, their underlying comorbid conditions may impact on the outcomes of rehabilitation. Older patients may also have subclinical physical or cognitive comorbidities, which become evident when challenged by a new disability. For example, mild cognitive impairment may be first recognized during rehabilitation after a hip fracture, when the patient has difficulty learning how to use a new assistive device.

Goals of rehabilitation for older adults usually focus on recovery of self-care ability and mobility, while for younger persons reentering the workforce or returning to school may be the goal. In general, recovery for older adults requires a longer period of time to achieve, and functional outcomes are usually worse when compared with younger adults. It is important to discuss rehabilitation goals with all patients and focus therapy toward achieving those goals. For example, older persons may have been avid golfers or fishermen, and return to this activity may be important for their quality of life. Rehabilitation efforts and goals of care may also be impacted by a person's values and beliefs about exercise and social roles. For example, if a patient has never cooked and does not believe that this is an important task to learn, taking the patient to the kitchen to learn how to prepare a meal may be viewed as a useless task. Participation by the patient and family in the development of the goals of rehabilitation is critical to achieve a successful outcome.

Disability is common in older persons and can have a significant impact on function and quality of life. In order to better understand the process of disablement, a variety of theoretical models have been explored and are presented below.

History of the Disability Framework

In an attempt to provide a framework for the discussion of the consequences of disease and injury, Nagi developed the first disablement model in the 1960s (**Figure 29-1**). The model uses four related yet distinct phenomena considered by Nagi to be the basis of rehabilitation and include active pathology, impairment, functional limitation, and disability. Active pathology was described as a disruption in the normal cellular function and the body's efforts to regain a normal state. Impairment, which usually results from active pathology, referred to an abnormality or loss at the tissue or organ level. Functional limitation described restrictions at the individual level, while disability described a physical or mental limitation in a social context. Nagi's view of disability was a product of the interaction between individuals and their environment. Importantly, individuals could have similar functional impairments that result in different patterns of disability, depending on the environment in which they function.

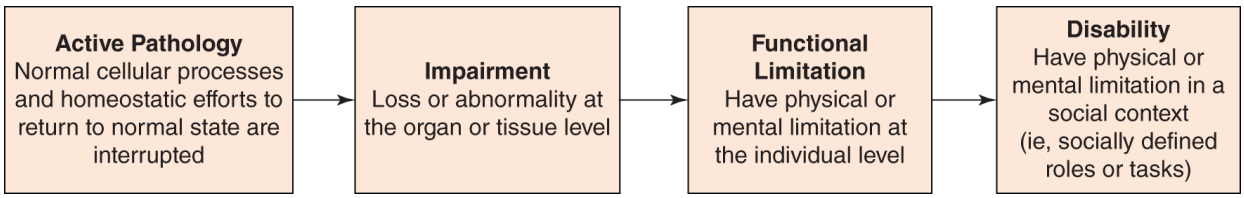


FIGURE 29-1. Schematic of the Nagi disablement model with definitions. The first disablement model was described by Nagi in the early 1960s. The initial disablement model focused on a linear progression to disability and has been replaced over time with new models such as the International Classification of Functioning, Disability, and Health (ICF). Importantly, the Nagi model was the first attempt to describe the process of disability. (Jette AM. Toward a common language for function, disability, and health. *Phys Ther*. 2006;86[5]:726.)

In 1980, the World Health Organization's (WHO) *International Classification of Impairments, Disabilities, and Handicaps* (ICIDH) was developed in Europe. Like Nagi's disablement model, the ICIDH characterized three distinct concepts related to disease and health conditions: impairments, disabilities, and handicaps. While the ICIDH was developed to classify function and disability, it failed to receive endorsement by the World Health Assembly. A major criticism of these early disablement models was that these presented the response to disease or illness as a static process with a linear progression through the disablement process. It was recognized that the interaction between disease and disability is more complex, particularly for older persons. Recognition of this complexity led to significant dialogue within the rehabilitation community and to a major revision of the ICIDH.

In 2001, the WHO released the *International Classification of Functioning, Disability, and Health* (ICF) (**Figure 29-2**), which attempted to incorporate, from a biological, personal, and social perspective, a biopsychosocial view of health. The ICF characterizes decreases in function as the consequence of a dynamic interaction between various health conditions and contextual factors. Health conditions are described as diseases, disorders, injuries, or aging. Contextual factors are divided into two categories: environmental factors and personal factors. Environmental factors include the physical, social, and attitudinal environment in which people live. These might include individual environment like furniture placement in the home or societal environment like policies regarding access to buildings. Personal factors are characteristics of the individual, which are not part of the health condition or illness. These might include gender, fitness, or coping styles. Listed across the center of the model are the three domains of human function: body functions and structures, activities, and participation. Body functions and structures are the physiologic

functions and the anatomic parts of the body. The execution of a task or action by a person is an activity, while participation is the application to a real-life activity. For each of these three domains of human function, there are several levels on which the function can be experienced. These include functioning at the level of the body or body parts and the level of the whole person and the whole person in their environment. Disability is defined as any decline at any of these levels.

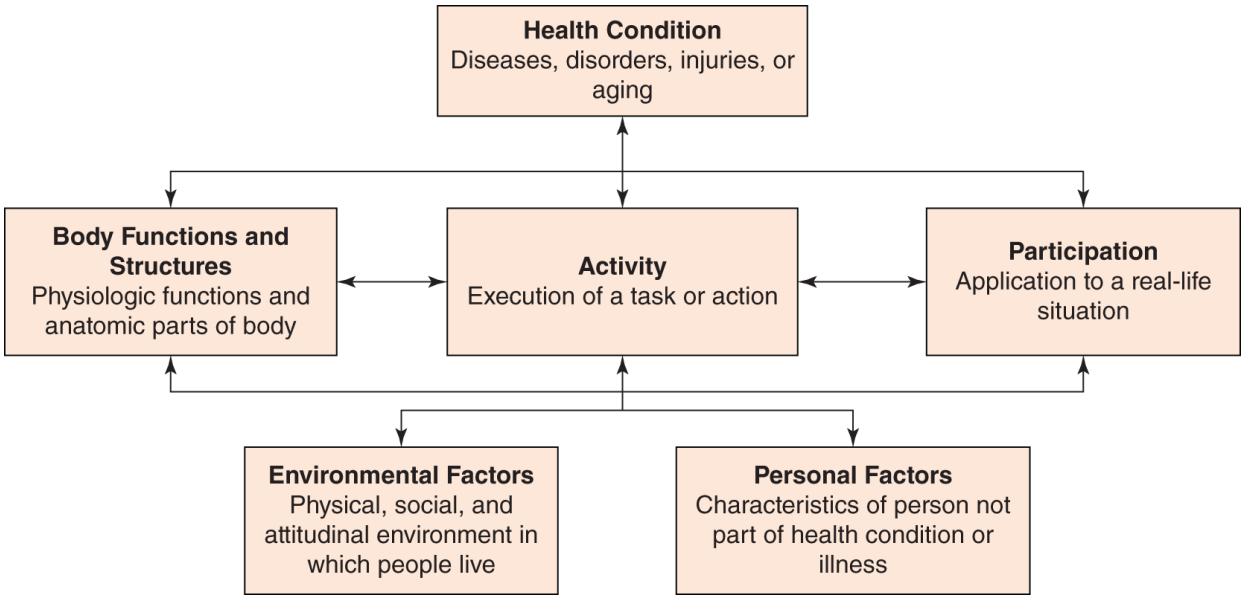


FIGURE 29-2. International Classification of Functioning, Disability, and Health (ICF). The latest version of the ICF focuses on the interaction between various factors and the impact these factors have on health and functioning. Prior models focused on disability and portrayed the path to disability as a linear process. This model attempts to incorporate, from a biological, personal, and social perspective, a biopsychosocial view of health. (Reprinted with permission of the World Health Organization. *Towards a Common Language for Functioning, Disability and Health: ICF*. Geneva, Switzerland; 2002.)

Using the ICF model, we could describe an older woman who has a history of osteoarthritis of the knees and hypertension who presents to rehabilitation after a hip fracture. She lives alone in a second-floor apartment and has a daughter who lives at a distance 6 hours away. The patient has a large circle of friends and regularly attends social gatherings at the local senior center. **Figure 29-3** demonstrates how this patient's problems might be placed in the ICF model, with the goal of generating hypotheses about the best treatment options. Important issues include not only improving the patient's strength and walking ability but also addressing where she will live after discharge and how to keep her active in her community. Understanding the relationships between the different components and addressing them is the key to a successful rehabilitation.

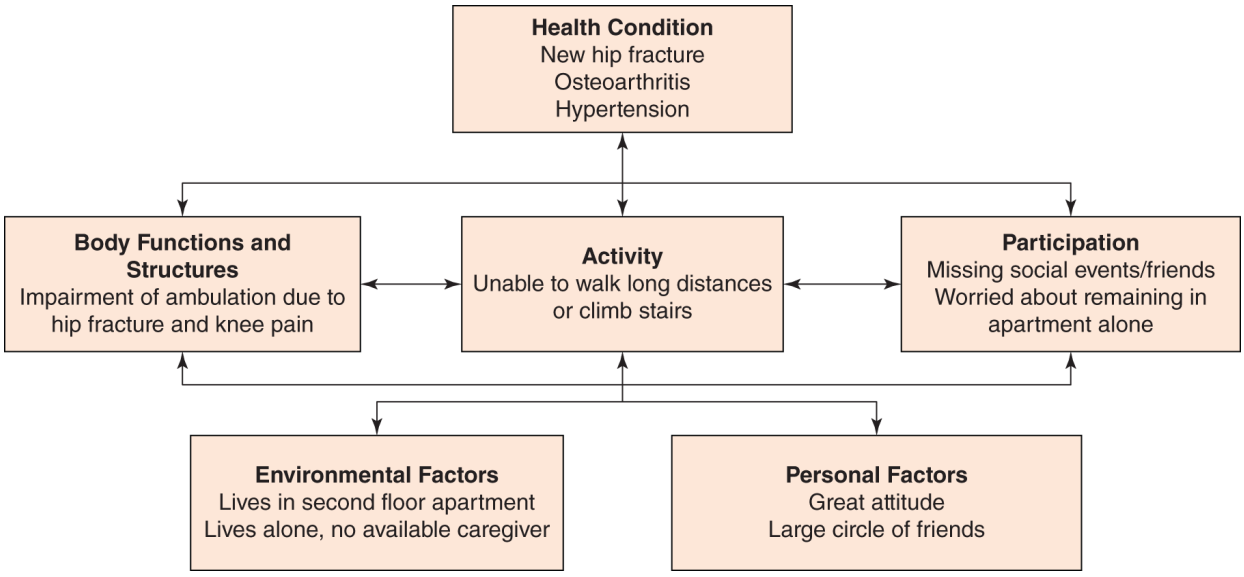


FIGURE 29-3. Using the ICF model to describe patient function. This figure demonstrates how a patient's problems might be placed in the ICF model with the goal of generating hypotheses about the best treatment options. In the case of this patient with osteoarthritis and new hip fracture, the ICF model illustrates how addressing where the patient will live after discharge and how to keep the patient active in the community are as important as improving the patient's strength and walking ability. Understanding the relationships between the different components and addressing them is the key to successful rehabilitation. (Authors' own work using WHO ICF model.)

It is believed by many that the ICF framework has the potential to provide a standard disablement language, which could facilitate dialogue across disciplines. The ICF model attempts to reflect the interactions between different components of health and avoids the linear view of previous models. This framework also looks beyond disease and mortality to focus on how people live with their disabling conditions.

EVALUATION

Goals of Evaluation

An important goal of evaluation is to identify the cause of the disability for which rehabilitation is required. While there is frequently a final common pathway for many disabling conditions, the cause may impact on treatment and outcomes. For example, a person's walking difficulty could be caused by osteoarthritis of the knee or a meniscal tear. For the patient with osteoarthritis, an exercise program focused on strengthening the musculature around the knee has been demonstrated to decrease pain and improve the ability to walk. For the patient with a meniscal tear, surgical intervention may be a better option. Evaluation prior to rehabilitation is also important to identify comorbidities that may directly or indirectly affect rehabilitation outcomes. While the older person may have osteoarthritis causing limited walking ability, they may also have poor cardiac or pulmonary function that further limit walking ability. Another goal of evaluation is to determine the best site for rehabilitation to occur. Several settings are available, including an inpatient rehabilitation facility, a subacute nursing home, or a home. The appropriate setting is usually determined through evaluation of the disability and comorbid conditions that may affect rehabilitation. The next section outlines the evaluation process and focuses on creation of an individual treatment plan that addresses the patient's unique disabling conditions.

Function-Oriented History and Physical Examination

During the initial evaluation, the history and physical examination can help characterize the disabling conditions and lead the clinician toward the most effective types of treatment. Determining if the functional decline occurred suddenly or has taken a more slowly progressive course may be very helpful in determining the cause of the disability. Symptoms associated with a given activity may also help narrow the cause to a specific organ system. For example, while the impairment may be difficulty in walking, the limitation could be caused by shortness of breath or pain with weight bearing. Differentiating the causal pathway, in this case cardiopulmonary versus musculoskeletal, helps to refine the work-up required and assists the provider in targeting the appropriate therapy. Functional status and residence prior to the illness or injury may also help guide expectations of rehabilitation.

Table 29-1 lists several brief screening maneuvers, which can be done in the physician's office when evaluating a patient for disability. These assessment tools can be used to quickly assess baseline functional status as well as monitor progress during rehabilitation. If these screening tests are positive, additional testing should be performed, as the screening tests are often not as accurate as more detailed maneuvers. A variety of standardized measures are available to further test function during basic and instrumental activities of daily living (IADLs).

TABLE 29-1 PHYSICAL PERFORMANCE TESTS USED TO ASSESS FUNCTION

SCREENING ACTIVITY	ATTRIBUTE ADDRESSED	FUNCTIONAL IMPLICATION
Put a heavy book on an overhead shelf	Upper extremity strength and range of motion	Ability to perform housework
Grasp a piece of paper and resist its removal	Pinch strength	Grooming and feeding self
Write a sentence	Fine motor coordination	Feeding self
Timed rise to standing five times[a]	Lower extremity strength	Ambulation and stair climbing
[a]		

Gait speed	Dynamic balance, predicts falls, and morbidity and mortality	Ambulation and general function with ADLs
Standing balance[a]; feet side by side, semitandem and tandem	Static balance	Balance with progressively smaller base of support
Life space assessment[b]	Mobility within the home and community in the 4 weeks prior to assessment	Addresses factors in addition to physical function that might impair mobility
Rhomberg; standing with eyes closed and assess sway or loss of balance	Proprioception	Ability to balance without visual input

Authors' own work summarizing physical performance measures from [a]Studenski SA, Perera S, Wallace D, et al. Physical performance measures in the clinical setting. J Am Geriatr Soc. 2003;51(3):314; [b]Peel C, Sawyer-Baker P, Roth DL, et al. Assessing mobility in older adults: the UAB Study of Aging Life-Space Assessment. Phys Ther. 2005;85:1008–1019.

For example, lifting a heavy book overhead tests shoulder range of motion and strength. If a person is unable to achieve this task, additional range of motion and muscle testing should be done to isolate the cause of the difficulty.

Many of the screening tests listed have normative values and have been well validated for the geriatric population. The short physical performance battery includes three of the screening tests gait speed, timed chair stands and static balance with worse scores being associated with falls, nursing home placement, and mortality. The University of Alabama at Birmingham (UAB) Study of Aging Life-Space Assessment is a validated instrument that measures a person's mobility in the home and community during the month preceding the assessment. Importantly, the Study of Aging Life-Space Assessment goes beyond measuring the individual's ability to perform specific tasks by assessing the person's actual pattern of mobility, which may help identify factors other than physical impairment, such as emotional or socioeconomic factors, which might be limiting mobility.

In addition to the history and physical examination, an evaluation should include assessments of cognition, motivation, depression, social support, and financial resources, as these factors can have a significant impact on rehabilitation outcomes. A variety of validated assessment tools can be used to screen for cognition and depression, such as the Mini Mental State Examination (MMSE) and the Geriatric Depression Scale, respectively. Assessment of current methods utilized by the patient for coping with disability, including use of assistive devices, level of assistance needed, and any limitation of activities, should also be explored.

Determining Rehabilitation Potential

Many factors influence the choice of who would benefit from rehabilitation and the success of those rehabilitation efforts. Assessment for rehabilitation potential needs to be done when the acute medical illness has resolved. A patient with a hip fracture and concurrent delirium may do poorly on initial assessment but, once the delirium clears, may progress nicely with rehabilitation. At times, the medical condition will need to be treated concurrently with rehabilitation efforts. After a prolonged intensive care unit (ICU) stay, a patient may have significant orthostatic hypotension, which will resolve as they regain the upright position during rehabilitation. **Table 29-2** lists a variety of acute medical illnesses that might delay referral to rehabilitation until these are resolved.

TABLE 29-2 FACTORS FOR WHICH REHABILITATION MAY NEED TO BE DELAYED UNTIL RESOLVED

FACTOR OF INTEREST	REASON FOR POSSIBLE DELAY IN REHABILITATION
Delirium or altered level of consciousness	Unable to cooperate or learn
Hemodynamic instability	May make it unsafe to carry out certain types of exercise
Occult fracture and bony metastasis	Weightbearing or resistance exercise could worsen fracture or cause fracture
Acute infections (eg, bladder infection and pneumonia)	May cause confusion, fatigue, and/or hypotension
Acute skin or joint infection	May cause fatigue, pain, and/or muscle splinting
Acute inflammatory disease (eg, certain rheumatologic and neuromuscular conditions)	Resistive exercises may impair recovery
Acute orthopedic conditions	Joint instability may preclude use of certain exercises, and functional goals

	may be limited

Adapted from Hoenig H, Cutson T. Geriatric rehabilitation. In: Hazzard WR, Blass JP, Halter JB, Ouslander JG, Tinetti ME, eds. Principles of Geriatric Medicine and Gerontology. 5th ed. New York, NY: McGraw-Hill; 2003.

Other determinants of rehabilitation benefit include motivation, cognition, and prior functional status. Comorbid illness may have a significant effect on rehabilitation efforts and may even cause a change in rehabilitation approaches. For example, a patient with chronic obstructive pulmonary disease (COPD) on home oxygen who falls and fractures a hip may not be able to tolerate more than 5 minutes of therapy at one time. The rehabilitation approach might be changed to include frequent walks of short duration by therapy and nursing, as opposed to an hour-long therapy session twice a day. **Table 29-3** lists a variety of factors that might influence either the use of rehabilitation or the goals of the rehabilitation. In some cases, like terminal illness with a short life expectancy, the goals of care may need to be addressed with the patient and family, and palliative care may be a more appropriate option. For other factors, like lack of motivation, well-defined patient-centered goals that are easily measured may help overcome this potential obstacle.

TABLE 29-3 FACTORS THAT MAY INFLUENCE THE SUCCESS OF REHABILITATION INTERVENTIONS

Cognitive impairment	Goals may be more limited. Take advantage of skills patient already has, use interventions that do not require carryover.
Disability has been present for many years	Goals may be more limited and directed to compensatory strategies or treatment of deconditioning.
Motivation is limited	Goals need to be well defined and reached in measurable steps.
Patient had prior rehabilitation for the same problem	Rehabilitation may be limited unless new functional decline has occurred.
Terminal illness	Intervention is directed toward reducing caregiver burden and patient discomfort.
Severity of disability	Extremely mild disability may not require intervention. Extremely severe disability may have very limited potential for benefit.
Social and cultural circumstances	Absence of a caregiver, financial limitations, and cultural beliefs may preclude use of certain techniques or technologies.
Malnutrition	Unable to build muscle; rehabilitative interventions may be limited unless nutritional status is improved.

Adapted from Hoenig H, Cutson T. Geriatric rehabilitation. In: Hazzard WR, Blass JP, Halter JB, Ouslander JG, Tinetti ME, eds. Principles of Geriatric Medicine and Gerontology. 5th ed. New York, NY: McGraw-Hill; 2003.

After careful evaluation, including a function-oriented history and physical examination, assessment of factors that may impact on rehabilitation outcomes, and the development of goals with the team, including the patient and the family, we are ready for the final step prior to initiation of rehabilitation, choosing the site for rehabilitation. Determining the optimal setting in which rehabilitation should occur is based on many of the factors previously evaluated, as well as patient preference.

COMPONENTS OF REHABILITATION

The Organization of Rehabilitation

Settings for care A variety of settings are available, both inpatient and community based, in which to receive rehabilitation services. It is important for the provider to understand the range of available settings and the advantages and disadvantages of each setting. While the provider may be responsible for helping match the patient to the optimal setting, insurance and cost also play a role. Rehabilitation services are available through Medicare Part A on a time-limited basis. Patients must demonstrate that they are making progress with rehabilitation goals in order to qualify for services.

Inpatient rehabilitation is offered in rehabilitation centers and Medicare-skilled nursing facilities. In order to qualify as a Medicare-certified inpatient rehabilitation hospital, a certain percentage of all admitted patients must have

at least one of 13 conditions, which include diagnoses like stroke, burns, and neurologic disorders. Patients must be managed by an interdisciplinary team of skilled nurses and therapists, be seen daily by a physician, and require 24-hour rehabilitation nursing care. Rehabilitation is intensive with patients receiving a minimum of 3 hours of therapy daily. As the rehabilitation center offers 24-hour-a-day medical care, patients in need of close medical supervision during therapy can receive it. However, the patient must be able to tolerate the intensity of therapy provided, which may be difficult for the older patient.

Like the rehabilitation center, Medicare-approved skilled nursing facilities must provide 24-hour nursing care. While physicians must be available 24 hours a day, they supervise care and can visit the patients less frequently. Interdisciplinary care may not occur, although therapy services, dietary, pharmacy, and social services are available. There are no requirements for intensity or duration of therapy sessions, or any required case mix. This setting allows for a slower rehabilitation pace, which may be necessary for some older patients with multiple comorbid diseases. The availability of 24-hour nursing care is also a benefit for persons who are unable to care for themselves or who do not have caregivers at home.

Home health benefits for rehabilitation, including part-time nursing and therapy services, are also available through Medicare to patients who are defined as "homebound." This includes patients for whom leaving the home is difficult or who require help of another person to get out of the home. A physician must order Medicare home health services, certify a patient's eligibility for the benefit, and a face-to-face encounter must occur within the 90 days prior to the start of home health care, or within the 30 days after the start of care. These services must be recertified every 60 days. While the intensity of the rehabilitation is less and the nursing services are part time, many patients prefer rehabilitating in their own home. If the patient has the necessary support system, this can be an excellent option.

While a number of studies have examined the effect of the rehabilitation setting on outcomes, the results remain unclear. For patients with hip fracture, the setting of care does not appear to have an impact on outcomes. After a stroke, patients who are treated in inpatient rehabilitation hospitals or special stroke units are more likely to be discharged to home and with improved function. Ultimately, factors such as patient prognosis, level of medical and nursing care needed, and intensity of therapy the patient can tolerate will help determine the optimal setting for rehabilitation.

Rehabilitation Providers

An interdisciplinary team is often required to meet the complex rehabilitation needs of older patients. While team members have defined roles and functions, there is considerable overlap in the services provided. For example, while the physical therapist may focus on transfer and gait training, the occupational therapist may also encourage practice of transfers while performing self-care skills. In addition, there are different levels of education and licensure required for different providers. **Table 29-4** outlines the types of rehabilitation providers and their usual methods of evaluation and treatment.

TABLE 29-4 REHABILITATION PROVIDERS AND TYPICAL METHODS USED FOR EVALUATION AND TREATMENT

PROVIDER	PRIMARY METHODS OF EVALUATION AND TREATMENT
Physical therapist	• Assessment of motor control and impairments such as joint range of motion, muscle strength, and balance • Assessment of gait and mobility • Provision of appropriate assistive devices • Exercise training to increase range of motion, strength, endurance, balance, coordination, and gait • Treatment with physical modalities (heat, cold, ultrasound, and electrical stimulation), soft tissue and manual therapy techniques
Occupational therapist	• Evaluate self-care skills and other activities of daily living • Home assessment • Self-care skills training; recommendations and training in use of assistive technology • Fabrication of splints
Speech therapist	• Assessment of all aspects of communication

	• Assessment of swallowing disorders • Treatment of communication deficits • Recommendations for alterations of diet and positioning to treat dysphagia
Nurse	• Evaluation of self-care skills • Evaluation of family and home care factors • Self-care training • Patient and family education • Liaison with community
Social worker	• Evaluation of family and home care factors • Assessment of psychosocial factors • Counseling
Dietician	• Assess nutritional status • Alter diet to maximize nutrition
Recreation therapist	• Assess leisure skills and interests • Involve patients in recreational activities to maintain social roles
Prosthetist orthotist	• Makes and fits prosthetic limbs • Makes a variety of orthotics including braces, ankle-foot orthoses, splints, and shoe inserts • Assesses fit of orthotics

Revised and updated by authors. Twersky J, Hoenig H. Rehabilitation. In: Salerno J, ed. Geriatric Review Syllabus: A Core Curriculum in Geriatric Medicine. New York, NY: American Geriatrics Society; 1999:84.

Key members of this interdisciplinary team are the patient and the family. An important component of chronic disease management is patient self-management, and patients must be active participants in the decision-making process. The team is responsible for establishing goals, in collaboration with the patient and the family, and developing a treatment plan to achieve those goals. In addition to teaching the patient, a key component of rehabilitation is training the caregiver or family. Specifically, caregivers must be taught how to assist with exercise programs, ambulation, and activities of daily living (ADLs). The caregiver may need to know how to use adaptive equipment or even how to transfer the patient safely, if the patient is not independent with this task. Communication among all team members, including the patient and their family, is critical for success.

Process of Care: Rehabilitation Interventions

A variety of interventions are available to treat physical impairments and disability. The selection of intervention strategy is determined by the results of the assessment. All interventions should either directly or indirectly lead to an improvement in activity and/or participation. Major categories of interventions include (1) exercise/physical activity; (2) modalities including thermal agents and electrotherapy; (3) adaptive aids such as walkers, canes, and devices to improve ADLs; and (4) orthotics (splints and braces) and prosthetics (artificial limbs).

Exercise/physical activity

General Principles of Exercise Exercise is the cornerstone of physical rehabilitation. Each exercise prescribed for a patient should be related to achievement of a goal, and all goals should lead to improvement in function. For example, a common exercise for patients is elbow and shoulder flexion. Typical goals related to these exercises are feeding one's self, dressing one's self, or reaching overhead to retrieve an item from a shelf. The expected functional outcome for each exercise should be shared with the patient and his/her family. The involvement of the patient and the family is important to maximize adherence.

In setting goals for exercise programs, it is important to consider any pathology that is present. If there is irreversible damage to the neuromuscular system, then the potential for improvement in muscle function is limited. Amyotrophic lateral sclerosis is an example of a pathology in which improvement in muscle function is limited. However, in most cases, decline in muscle strength results from a combination of pathology and deconditioning occurring secondary to inactivity. The deconditioning component is reversible, and therefore some improvement in

muscle strength is possible.

A common question often asked is whether exercise is safe for older adults. The number of adverse events reported as a result of exercise in adults is relatively low, with adverse events being more common with vigorous exertion and in persons with atherosclerotic heart disease. To facilitate a safe response, close monitoring before exercise, during exercise, immediately after exercise, and 24 hours after exercise is important. In addition, prior to the initiation of an exercise program, it is important for medical conditions such as congestive heart failure and diabetes to be stable and under optimal medical management. Exercise should be supervised initially to assure appropriate changes in heart rate and blood pressure. There is an expectation that minor muscle soreness will occur with most types of exercise, and patients should be counseled to expect some discomfort. Some patients with osteoarthritis may actually experience a decrease in joint discomfort with exercise. Because increased activity typically has a positive effect on insulin resistance, patients with diabetes may experience a need for less medication to control blood glucose levels.

For exercise to cause a change in physical function, the body must be stressed greater than the usual stress of everyday life. Therefore, it is important that patients are challenged in their exercise programs. For example, when a patient achieves a specific goal, such as walking 30 m at 0.5 m/s, the goal needs to be increased to a greater distance and/or speed. In comparison to younger adults, older adults need a longer recovery time both during an exercise session (between bouts) and between sessions. Improvement may also take longer for older versus younger adults, which should be considered when setting time frames for the achievement of goals.

There are many classification systems for types of exercise. In the following discussion, we will describe exercise types based on the anticipated outcome, including exercise to increase muscle strength, aerobic capacity, balance, flexibility, and motor control.

Exercise to Increase Muscle Strength A typical exercise program to increase muscle strength involves movements performed against resistance. The resistance can be weights, rubber tubing or bands, or the person's own body weight. To achieve optimal results, the resistance should be 60% to 80% of the person's maximal lifting ability. For the majority of older adults who are starting an exercise program, it is wise to begin at a lower level (~ 40%–50% of maximal capacity) until the person has mastered the movement patterns.

Sarcopenia refers to the age-related decline in muscle strength, which naturally occurs as we age. At approximately 50 years, individuals begin to experience a decline in muscle strength. This decline in muscle strength typically does not interfere with function until persons are 70 years or older. The cause of the decrease in muscle function is thought to be multifactorial and may include changes in muscle metabolism, endocrine alterations, decreased physical activity, and nutritional factors. One of the most effective treatments is high-intensity resistance exercise training.

Adequate muscle strength is essential to both balance and gait. A positive correlation has been shown between lower extremity muscle strength and gait speed, demonstrating that persons with higher levels of muscle strength walk faster. Balance is determined both by sensory input and motor output. Even if sensory input is appropriate and the person senses they are falling, without adequate muscle strength, the individual will fall.

Bone density can be positively affected by exercises designed to increase muscle strength. Prior to initiating a program to increase muscle strength, it is important to know the individual's bone status, or the extent and location of osteoporosis and/or osteopenia. In persons with osteoporosis, the amount of resistance may need to be modified to avoid overstressing bones and causing a fracture.

Exercise to Increase Aerobic Capacity Exercise programs designed to increase aerobic capacity involve continuous activity (such as walking, cycling, and stair stepping), usually performed for at least 20 minutes at an intensity that is 50% to 80% of one's maximal oxygen consumption. Older adults who are beginning a program may need to start with 5 to 10 minutes of continuous activity at a lower intensity. In fact, several sessions of shorter duration (ie, 10 minutes) per day have shown similar benefits as one session of 30 minutes. To achieve benefits, endurance training needs to be performed three to five times per week. For older persons in rehabilitation programs who have physical limitations, the specific activities may need to be modified. For example, cycling may not be possible for a person who has significant hemiparesis after a stroke. Adaptations, such as securing the person's foot to the pedal, may allow the individual to exercise. Moving to another venue, such as a therapeutic pool, may be another option.

A benefit of aerobic capacity training is an increase in maximal oxygen consumption, which is defined as the amount of oxygen consumed while performing the maximal workload that one can perform for 2 to 3 minutes. Improving the maximal amount of work that a person can perform is not necessarily a direct benefit because daily activities are performed at submaximal, rather than maximal, levels of exertion. However, with an increase in maximal oxygen consumption, a given amount of submaximal work is performed at a lower percent of maximal oxygen consumption. Consequently, as a result of aerobic capacity training, submaximal work expressed as a percentage of

maximal oxygen consumption is lower. From a functional perspective, activities such as dressing, bathing, and performing housework can be performed with less fatigue and for longer time periods.

Aerobic exercise has positive benefits for persons with hypertension, hypercholesterolemia, and obesity. Regular aerobic exercise has been shown to decrease resting blood pressure, resulting in either a decrease in the amount of or a need for medications. Although aerobic exercise often does not decrease total cholesterol, many studies have shown positive benefits for high-density lipoprotein cholesterol and triglyceride levels. For both treatment and prevention of obesity, aerobic exercise is a key component of a successful program.

Aerobic exercise also has benefits for cardiovascular and pulmonary diseases. For persons with angina, participation in a regular endurance exercise program produces an increase in the "anginal threshold," allowing persons to exercise at higher levels prior to the onset of angina. Persons with chronic pulmonary disease typically experience less breathlessness with activities, as a result of a regular exercise program. One of the most effective treatments for claudication is walking to the onset of pain, which ultimately produces an increase in the distance walked prior to the onset of claudication.

Exercise to Improve Balance Balance, defined as the ability to remain upright as the body's center of gravity shifts relative to the base of support, declines as people age. The somatosensory, visual, and vestibular systems contribute to our ability to maintain balance. Balance is an essential component to walking because walking involves a continuous shift of the body's center of gravity relative to the base of support.

Balance exercises are important for persons who have fallen or who are at high risk of falls. Exercises are prescribed that are appropriate for the individual's current level of function. For example, low-level exercises may involve standing and shifting one's center of gravity. As the person progresses, he/she may practice standing on one extremity or walking on a balance beam. Exercises performed with eyes closed force the use of the vestibular and somatosensory systems. Exercises performed on altered surfaces, such as foam or carpet, force the use of the visual and vestibular systems. For persons with a specific abnormality of the vestibular system, such as benign positional vertigo, there are specific exercises that often are helpful.

Flexibility Exercises The goal of flexibility exercises is to increase range of motion of a body part by increasing muscle length and/or joint motion. The most effective and safe approach is a prolonged, low-intensity stretch of the muscle/joint with limited motion. Having a sufficient amount of motion is important for many functional activities. For example, going up and down stairs using a reciprocal gait pattern requires at least 90 degrees of knee flexion. Reaching overhead requires 120 to 150 degrees of shoulder flexion and abduction. In addition, sufficient range of motion at the hip and ankle is important for maintaining standing balance. Excessive range of motion, however, decreases stability and can lead to pain, decreased mobility, and falls.

Parkinson disease is an example of a common condition in older adults in which flexibility exercises are important. Persons with Parkinson disease assume a flexed posture, resulting in loss of cervical and thoracic extension. Prescribing exercises early in the course of the disease may prevent the severity of the postural abnormalities. Maintaining spinal extension is important to prevent compromise of respiratory capacity, and to minimize gait and balance disorders.

Task-Oriented Exercises to Improve Motor Control Older persons may lose their ability to perform tasks because of abnormal tone (spasticity) and/or muscle weakness. Task-oriented exercises are used to improve coordination and motor performance. Constraint-induced movement therapy (CIMT) is one method used to improve motor function. With constraint-induced movement therapy, the stronger, less affected extremity is "constrained" using a cast or mitt. The person is forced to use the affected extremity and practice tasks needed for daily living. This method typically involves participation in therapy for 4 to 6 hours per day. The approach is based on learning theory and assumes plasticity of the central nervous system with reforming of neural connections after injury. A Cochrane review reported greater improvements in upper extremity motor function in persons poststroke with constraint-induced movement therapy compared to conventional treatment. These differences were not significant at 6 months.

A second method used to improve walking performance and balance is treadmill training with partial body support. A harness is connected to an overhead system, which is mounted on a treadmill. By providing partial weight support in combination with a speed-controlled treadmill, patients can perform a greater amount of task-specific practice compared to traditional methods of gait training. A recent Cochrane review of treadmill training with and without body weight support after stroke concluded that persons who are able to walk appear to benefit the most from this intervention. Potential benefits include an increase in walking speed and walking endurance.

Designing Exercise Prescriptions Exercise should be prescribed in an individualized manner similar to prescriptions for medications. The components of an exercise prescription include mode (type of activity), frequency (number of times per day or week), intensity (level of exertion), and duration (length of time of each individual session). Sufficient research is not available to determine the ideal exercise prescription for older adults with the variety of comorbidities that are typically present. However, for some types of exercise, such as moderate- to high-intensity strength training, there is evidence that exercising every other day or every third day is optimal because of the need for recovery time. Because specific guidelines for persons with pathology are not available, pre- and postexercise monitoring is essential. Vital signs and blood glucose levels (if diabetes is present) need to be checked prior to and after exercise. Persons who are beginning an exercise program or increasing their current exercise level need to be asked how they are feeling 24 hours after exercise. Severe muscle soreness and general body fatigue are signs that the exercise stress was excessive.

Physical modalities Physical modalities that are often used with older adults include heat and cold agents, aquatic or pool therapy, electrotherapy, and phototherapy (monochromatic infrared energy—MIRE). For most of these agents, there is limited evidence of effectiveness as a sole intervention. However, when used in combination with other therapies, especially exercise therapy, these modalities can enhance the effectiveness of the overall intervention. The most common indication for use of physical modalities is pain management. Because older adults may have reduced mental status, or impaired circulation and sensation, using modalities in older adults requires caution. Educating patients and their families on the rationale for use of modalities is essential, especially if these are to be used in the home environment.

Thermal Agents (Including Aquatic Therapy) Thermal agents include superficial and deep heating modalities and cryotherapy. Physiologic effects of heat include increased blood flow and edema, increased extensibility of connective tissue structures, and decreased pain. Superficial modalities primarily increase the temperature of the skin and underlying subcutaneous tissue and include hot packs, heating pads, and paraffin. Superficial heat is beneficial for persons with osteoarthritis, rheumatoid arthritis, and conditions resulting in cervical and low-back pain. The most popular deep heating modality is ultrasound, a form of acoustic energy, which when absorbed by tissues is converted into heat. Ultrasound is often used for tissue contractures, tendonitis, and pain resulting from musculoskeletal disorders. Ultrasound should not be administered close to the brain, eyes, reproductive organs, pacemakers, or arthroplasties.

Cryotherapy includes cold packs, ice massage, cold water immersion, and vapocoolant sprays. Physiologic effects of cold include cutaneous vasoconstriction, decreased nerve conduction velocity, decreased spasticity, and increased joint stiffness. Cold therapy provides short-term analgesia and often allows patients to move when movement otherwise would be too painful. Cold therapy should be avoided in persons with arterial insufficiency, impaired sensation, cold hypersensitivity, and Raynaud disease.

Aquatic or pool therapy is an alternative to physical modalities and/or exercise on land. A therapeutic pool provides a combination of heat and buoyancy for support of upright activities. Patients with muscle weakness and pain often can walk and exercise in a therapeutic pool when movement on land is limited. Because total body heating produces significant vasodilation, patients with cardiac insufficiency may experience chest pain. All patients need to be careful exiting the pool because of the possibility of postural hypotension. Persons with heat intolerance, such as those with multiple sclerosis, may require a “cool” pool with temperatures below 90 degrees Fahrenheit.

Electrotherapy Electrotherapy can be used as an intervention for pain management, muscle activation, wound healing, and urinary incontinence. Transcutaneous electrical nerve stimulation (TENS), a popular treatment for pain, involves placing electrodes over peripheral nerves, nerve roots, or painful areas. The mechanism of action is unclear but probably involves the release of endogenous endorphins in the cerebrospinal fluid, which block pain by binding to opiate receptors. Adverse effects of TENS are minor and typically involve skin irritation secondary to sensitivity to the electrodes or gel. Contraindications to the use of TENS include persons with impaired sensation and/or cognition and persons with either a pacemaker or an implanted cardiac defibrillator. Systematic reviews have shown TENS to be effective when provided at an appropriate intensity for postoperative pain, osteoarthritis, and painful diabetic neuropathy.

Neuromuscular stimulation is used to activate muscles addressing treatment goals in persons after stroke, spinal injury, or knee surgery. For persons poststroke, electrical stimulation can be used to enhance functional movement patterns, such as contraction of the anterior tibialis muscle to prevent foot drop during the swing phase of gait or contraction of the quadriceps at heel strike during gait. After knee surgery or injury, persons often “forget” how to

contract the quadriceps muscle as a result of pain and/or joint effusion. Neuromuscular simulation can be used to "retrain" the quadriceps muscle counteracting atrophy that occurs with immobilization.

An important difference between normal muscle contraction and electrically induced muscle contraction is the order of recruitment of motor units. With normal muscle contraction, the smaller fatigue-resistant motor units are recruited first, followed by larger, fatigable motor units. With electrical stimulation, the larger-diameter fatigable fibers are recruited first. The consequence is that fatigue occurs fairly quickly with neuromuscular stimulation. Providing adequate rest periods and limiting the duration and frequency of contractions are strategies to lessen fatigue.

Electrotherapy used for wound healing involves application of electric current either directly to a wound or to the skin surrounding the wound. Electrical stimulation is approved for Medicare coverage for the treatment of stasis, arterial pressure, and diabetic ulcers that have not responded to conventional therapy. Animal and human studies have shown that electrical stimulation increases both DNA and collagen synthesis; directs epithelial, fibroblast, and endothelial cell migration into wound sites; inhibits the growth of some wound pathogens; and increases the strength of scar tissue. The effectiveness of electrical stimulation is demonstrated in randomized controlled trials, with the strongest evidence being demonstrated in the treatment of pressure ulcers.

Phototherapy (MIRE) Devices that deliver MIRE were approved by the Food and Drug Administration (FDA) in 1994 to increase circulation and decrease pain. This treatment involves placing pads over the lower leg and foot. The pads contain diodes that emit light energy in the near-infrared spectrum (890-nm wave length). The typical treatment protocol involves 30-minute treatments, three times a week, for a total of 12 treatments. The infrared photo energy is thought to release nitric oxide from hemoglobin. Nitric oxide relaxes smooth muscle cells, dilating blood vessels and improving circulation. MIRE has been used for the treatment of peripheral neuropathy, with the goal to improve sensation and decrease neuropathic pain. Research studies are conflicting; however, the majority of them have shown that MIRE was no more effective than placebo in improving sensation.

Adaptive aids Adaptive aids include devices that allow persons with physical limitations to participate in activities, such as basic and instrumental activities of daily living, with greater ease and/or less pain. Categories of adaptive aids include mobility aids to assist people to move around within their home and community, bathroom aids to assist with bathing and toileting, and self-care aids that assist with dressing, personal hygiene, cooking, and other activities. It is not unusual for older persons to have devices that they do not need, often as a gift from a friend or relative. The opposite also occurs when older persons need devices that are not prescribed. The devices described below need to be prescribed by a professional, and the patient or family or caregiver needs to be instructed in their use. Devices that are used incorrectly can lead to falls and other adverse events. It can be helpful for the professional (typically a physical or occupational therapist) to make a home visit to assess whether the prescribed adaptive devices can be used safely in the patient's home.

Mobility Aids Canes are the most popular mobility aid for older adults because they are lightweight and easy to use when space is limited. Canes are used to decrease weight bearing (and pain) in an extremity with an arthritic joint and to improve balance by increasing the base of support. When adjusted to the proper height, the handle of the cane is at the level of the wrist when the arm is fully extended. Canes should be used in the hand on the side opposite of the involved extremity. Many people will incorrectly use the cane in the hand on the side of the involved extremity. The cane then acts as a brace for the involved extremity, producing an abnormal gait pattern and limiting range of motion of both the hip and the knee of the involved side. To achieve a normal gait pattern, patients are instructed to hold the cane in the hand opposite the involved extremity and advance the cane and the involved extremity simultaneously. Patients then swing through with the uninvolved extremity while bearing weight on the cane and, to a lesser degree, the involved extremity. For stairs, patients are taught to go "up with the good and down with the bad." To ascend the stairs the uninvolved extremity is advanced up the stairs first, while the involved extremity and the cane remain on the lower step. To descend the stairs, the involved extremity and the cane are lowered first and then the uninvolved extremity descends to the same step. For persons with decreased sensation in the lower extremities, a cane can also provide proprioceptive input to the brain by transmitting information from intact proprioceptors in the hand.

Two major types of canes are straight canes and quad canes. Straight canes are usually made of aluminum or wood, with a variety of handles available. Quad canes are aluminum canes with a four-legged base. One advantage of a quad cane is that the cane does not fall if the person releases the handle. A disadvantage of some quad canes is that the base is too large to place on stairs, making stair climbing difficult.

Crutches are usually not used with older adults because a higher level of coordination and skill is required. The two major types of crutches are axillary and forearm crutches. If axillary crutches are used incorrectly, shoulder injury

and/or axillary nerve damage can occur. Forearm crutches are more functional because a cuff secures the crutch on the patient's arm allowing use of the hand to manipulate objects. Crutches are usually used to provide bilateral support. However, a single crutch can be used instead of a cane if additional unilateral support is needed.

A walker usually is prescribed when a cane does not provide sufficient support. Walkers provide bilateral support and are easier to use than crutches. Walkers should be adjusted so that the user maintains an erect posture and is not required to lean forward to reach the walker. There are several types of walkers that vary in stability and function. The standard four-point or "pick-up" walker requires that the person pick it up with each step, requiring arm strength and endurance, and producing a slow walking speed. With a two-wheeled rolling walker, the person can use a more normal gait pattern and speed. Having two rather than three or four wheels provides more stability. A four-wheeled walker, called a "rollator," has hand brakes so that it can be locked when the user is standing up and sitting down. This type also has a platform seat for resting, and a basket for carrying objects. The rollator requires greater skill because of the use of the hand brakes. It is preferred for outdoor use because the wheels are larger and move easier over sidewalks and slightly rough terrain. A final option is the Merry Walker, which provides the maximal amount of support. This type of walker includes front, side, and back bars, and a seat for resting. Merry Walkers are larger and more difficult to manipulate in homes. They are often used in institutional settings for persons with severe balance and coordination deficits.

A wheelchair should be prescribed for a person who can no longer walk safely or when walking endurance is low. The wheelchair allows the person to continue to do activities such as shopping that require extended periods of standing and walking. Quality of life is maintained and social isolation is avoided. Two main types of wheelchairs are manual and power chairs. There are many options available for customizing a chair for individual needs. In considering the optimal chair, both stability and mobility need to be considered. For example, a back height that is too high makes propelling the chair independently difficult thus impairing mobility, whereas a back height that is too low may not provide adequate trunk support. There are a variety of manual wheelchairs available with many different features. The width of the seat can range from narrow to wide to accommodate larger persons. Removable arm rests and foot rests are available and make transfers easier and safer. Fixed foot rests are not recommended because they can contribute to falls. Consultation with the occupational therapist or physical therapist is recommended, as the therapist would know best how to order appropriate parts to maximize function.

Manual wheelchairs are lighter in weight than power chairs and are fairly easy to fold and load into a car for travel. Power chairs and scooters provide enhanced mobility outdoors and in the community. Most power chairs are difficult to maneuver in homes. In addition, a car carrier is needed for travel.

Prescribing a wheelchair for use is an important decision, and the advantages and disadvantages for each patient need to be considered. For patients who are able to walk, having a wheelchair may discourage walking, leading to decreased muscle strength and endurance and increasing the probability of falling. However, not prescribing a wheelchair as walking ability declines can negatively affect quality of life. Patients and families need to be counseled on appropriate use of a wheelchair based on their unique needs.

Table 29-5 illustrates some of the commonly prescribed types of canes, walkers, and power chairs and describes some of the benefits and drawbacks of using the different mobility aids as well as clinical situations in which the device might be useful.

TABLE 29-5 KEY FEATURES AND CLINICAL SITUATIONS WHERE AMBULATORY DEVICES MIGHT BE BENEFICIAL

AMBULATORY DEVICE	SUPPORT PROVIDED	DEVICE BENEFITS	DEVICE DRAWBACKS	CLINICAL SITUATIONS WHERE DEVICE MIGHT BE BENEFICIAL
Straight cane	Unilateral	Assists with balance and proprioception Reduced weight bearing on opposite side	May not provide enough support Doesn't stand up on its own, making it difficult to carry objects and open doors	Osteoarthritis of knee or hip Peripheral neuropathy
Quad or 4-point cane	Unilateral	More stable than straight cane Allows greater weight bearing on device	Heavier than single- point cane Increased base of support may increase risk of tripping over device	Stroke with hemiparesis

Standard "pick-up" walker	Bilateral	Very stable and allows non-weight-bearing movement	Must be lifted and advanced requiring strength and coordination Gait pattern and turns not smooth due to lack of wheels	Hip fracture where non-weight-bearing needed Unilateral amputation, prior to prosthesis
Two-wheeled rolling walker	Bilateral	Easier to advance than standard walker Allows smoother, faster gait pattern than standard walker	Less stable than standard walker Turns less smooth than rollator due to fixed wheels	Deconditioning Parkinson disease
Rollator or 4-wheeled walker	Bilateral	Allows for smoother, faster gait than standard walker Turns easily due to front rotating wheels Good for outside walking because of large wheels Has seat for resting	Less stable than standard or rolling walker Requires increased coordination due to brakes More expensive than rolling or standard walkers	Cardiopulmonary disease Peripheral neuropathy with balance difficulty
Manual wheelchair	Full body	Often used by caregivers and in nursing homes for ease of patient mobility	Requires use of arms and some cardiopulmonary endurance or someone to push the chair	Nonambulatory patients with cognitive impairment Low-level spinal cord injury patients with good endurance
Power wheelchair	Full body	Allows community mobility for those with limited ambulatory ability Controls do not require intact UEs	Need cognitive ability to operate safely May need home modifications	Neurologic diseases (eg, high-level spinal cord injury, MS, ALS) Multiple limb amputations
Scooter	Full body	Similar benefits to power wheelchair, but may be more acceptable to patient than power wheelchair	Need to be able to operate controls with UEs	Significant cardiopulmonary disease

ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; UEs upper extremities,

Data from Brummel-Smith K, Dangiolo M. Assistive technologies in the home. Clin Geriatr Med. 2009;25(1):61-77 and Brown CJ, Peel C. Rehabilitation of the Older Adult. In: Halter JB, Hazzard WR, Ouslander JG, et al (eds). Hazzard's Textbook of Geriatric Medicine and Gerontology, 6th ed. New York, NY: McGraw-Hill Inc; 2009.

Bathroom and Self-Care Aids For many older adults with physical disabilities, the bathroom is a challenging and unsafe place. Devices are available for use in a typical home bathroom to make activities easier and safer. Grab bars located close to the toilet and shower or tub should be considered for all older adults. Many older adults have difficulty rising from a regular toilet seat because of the low height. A raised toilet seat can be secured to a regular toilet. For persons who need more assistance, bedside commode chairs are available. Some bedside commode chairs have wheels, and can be rolled over a regular toilet. Tub benches are available for individuals who have difficulty getting out of a regular tub, and shower chairs are available for persons who cannot stand independently to take a shower.

Devices are also available to assist patients with ADLs. Occupational therapists can assist with identifying the most appropriate adaptive aids. Some examples for dressing include aids to assist with manipulating buttons, securing pants, and putting on/off shoes and socks. For eating, enlarged handles on utensils and modified plates are available. Having an appropriate aid often results in independence in performing a task versus needing to ask for assistance.

Electronic Devices (Environmental Control Units/Augmentative Communication Aids) Devices are available that use more sophisticated technologies to allow patients a greater degree of independence and enhanced communication. Environmental control units typically are used for patients with severe disabilities to allow turning on/off lights and controlling other electronic devices. Whatever voluntary motion is available is used to control the unit, usually through a joystick, mouth stick, or eye motion. Devices used to enhance communication include communication boards, voice amplifiers, and telephone adaptations. For strategies to enhance communication, consultation with a speech and language pathologist is recommended.

Orthotics and prosthetics Orthotics and prosthetics are external devices used to enhance function. Orthoses typically are used to either restrict or assist motion and are named according to the joints or body parts that are affected. For example, ankle-foot orthoses (AFO) include the foot and ankle, and knee-ankle-foot orthoses extend from the thigh to the foot.

The most commonly used orthoses for older adults are foot orthoses and ankle-foot orthoses. Foot orthoses include shoe inserts and other devices placed inside the shoe. Inserts can be used to relieve pain or to protect insensitive feet. Examples of commonly used foot orthoses include heel spur cushions, scaphoid pads to correct flattening of the arches, and metatarsal pads to transfer weight from the metatarsal heads to the metatarsal shafts. AFOs are used for patients with either weakness or paresis of dorsiflexors to prevent foot drop during gait. These orthoses can be made of plastic or metal. Plastic orthoses can be interchanged between shoes but do not provide as much support as metal orthoses. Appropriate use of foot and ankle orthoses can improve function by providing a safe, more comfortable gait.

For individuals with diabetes and severe diabetic foot disease, Medicare will cover one pair of therapeutic shoes and inserts or shoe modifications each year. Physicians must provide a pedorthist or podiatrist with certification that the person has diabetes.

Many older adults require prostheses because of amputation resulting from vascular disease. In prescribing prostheses for older adults, important considerations include ease of donning and doffing, stability during activities, and overall function. In persons with severe dementia or advanced cardiopulmonary disease, wearing a prosthesis may not be practical. Persons who are not independent in basic ADLs skills, such as transferring and dressing, typically are not good candidates for prosthetic use. To achieve the optimal outcome, the patient should be involved in a preprosthetic training program to improve strength and endurance. The physician should work closely with the physical therapist and prosthetist to assure that the prosthesis is evaluated for correct fit and that the patient receives training on use of the prosthesis.

SPECIFIC CONDITIONS TREATED WITH REHABILITATION

Pulmonary Rehabilitation

Patients with chronic respiratory diseases frequently experience disability owing to decreased exercise tolerance and symptoms like dyspnea and anxiety. The established benefits of pulmonary rehabilitation include improved exercise capacity, a decreased sensation of dyspnea, and overall improvement in quality of life. The cornerstone of most pulmonary rehabilitation programs is exercise, although other components may include education and behavioral modifications like energy-conservation techniques. As with other rehabilitation programs, pulmonary rehabilitation can occur in inpatient, outpatient, and home settings with equal success. Exercise programs are individually tailored to meet the patients' needs, and patients are usually encouraged to exercise three times a week or more to a level where they experience moderate dyspnea. Training regimens vary, depending on the goal of the rehabilitation. For example, many patients with COPD experience dyspnea with upper body activity, like bathing or grooming. An exercise program that targets strengthening of the arms with elastic bands or light weights helps decrease the dyspnea and work effort required for these tasks. Treadmill or track training will improve walking endurance but not strength, so a variety of training exercises are usually utilized.

A recent Cochrane review concluded that pulmonary rehabilitation showed both statistical and clinical improvements in dyspnea and disease-specific quality-of-life-measures. Supervised programs offered greater benefit than unsupervised ones, and patients with severe disease appeared to benefit the most when compared to those with mild-to-moderate COPD. However, many questions still remain about what components are essential and how to best assess outcomes after rehabilitation.

Cardiac Rehabilitation

Cardiac rehabilitation (CR) is increasingly recognized as an important component of an interdisciplinary treatment strategy for patients with a history of myocardial infarction (MI) and stable angina and patients after coronary artery bypass graft (CABG) surgery. Many of the benefits of CR occur through the exercise component of these programs. Exercise training has been found to decrease coagulability, increase fibrinolysis, improve endothelial function by moderating inflammation, and improve endothelium-dependent vasodilation. These beneficial effects can be demonstrated by the reduction in C-reactive protein seen with exercise and the improvement in hyperemic myocardial flow after CR. Disability or functional decline is often associated with a variety of cardiac conditions, and participation

in CR can improve fitness and reduce the signs and symptoms of exercise intolerance. This can lead to improved functional independence. In addition to exercise training, CR provides a structured environment for risk factor management through patient monitoring plus support of compliance and adherence. However, despite evidence of the beneficial effects, CR remains underutilized, with a 15% to 25% participation rate among eligible patients.

In low-risk individuals with heart failure and after MI or stenting, exercise-based CR has been found to be safe with no increase in short-term mortality and effective with demonstrated reductions in risk of hospital admission and improvements in patient's health-related quality of life compared with control. Studies have also demonstrated equal effectiveness of home-based and center-based programs in improving outcomes of exercise-based CR. In a study of more than 600,000 Medicare patients hospitalized for acute coronary syndrome, percutaneous coronary intervention, or CABG, the 12% who participated in cardiac rehabilitation had a lower rate of mortality compared to nonparticipants (2.25% vs 5.3%). This benefit was sustained at 5 years with a mortality rate of 16.3% for participants versus 24.6% for nonparticipants. In addition, there was a dose-response relationship with participants who attended 25 or more sessions having a 20% lower 5-year mortality rate compared to those who attended fewer than 25 sessions.

For patients with congestive heart failure, randomized clinical trials conducted during the last decade have demonstrated that CR can improve exercise tolerance, quality of life, and disease-related symptoms, without adversely affecting left ventricular function. While there is no consensus regarding the optimal exercise program, guidelines support the use of regular aerobic and/or strengthening exercises. Exercise training induces peripheral and central adaptations, including improvement in vasodilation among active muscle, decreased sympathetic nervous system activation, and increases in peak cardiac output, heart rate, and stroke volume. These adaptations lead to a reduction in the commonly observed exercise intolerance because of fatigue and dyspnea. Using peak oxygen consumption (VO_2) to measure exercise capacity, improvements have ranged from 15% to 30%. Other common symptoms associated with heart failure such as shortness of breath, ability to perform ADLs, anxiety, depression, and general well-being have all been improved with CR. The magnitude of improvement has ranged from 15% to 50% for each of these variables, and improvements in quality of life can be seen as early as 2 months after initiation of the exercise program. In addition to improvements in symptoms and quality of life, reduction in mortality has also been demonstrated. Increased sympathetic nervous system activity and higher plasma and tissue cytokine concentrations are associated with worsening disease and poorer prognosis in patients with heart failure. Exercise training causes a downregulation of these systems, with a resultant 28% reduction in total mortality and hospitalization and a 29% reduction in death rate. Prior to initiation of an exercise program, patients must be clinically stable with controlled fluid status for at least 3 to 4 weeks.

The literature demonstrates a beneficial effect of CR for a variety of cardiac diagnoses, including acute MI, congestive heart failure, and after CABG surgery. Exercise training positively affects both the basic pathophysiology of coronary artery disease and the underlying disease process. This, in turn, minimizes the impact of disability, improves quality of life, and reduces mortality. Referral to CR increases the likelihood of participation and long-term compliance, which can have significant beneficial effects for the patient.

Peripheral Arterial Disease

Lower extremity peripheral artery disease is common in older persons, with a prevalence of 16% to 34% in patients older than 65 years. Studies have demonstrated that the optimal exercise rehabilitation program for improving the distance walked prior to the onset of claudication uses intermittent walking to the onset of pain. The increased distance achieved occurs through improvements in cardiopulmonary function, peripheral circulation, and walking economy. Improvements require an exercise program of at least 6 months duration to be effective. Treadmill walking has been shown to be more effective than strength training in achieving these results.

Amputation

In the United States, approximately 27,000 new major lower extremity amputations among those who are 65 years or older are performed each year. Peripheral vascular disease and diabetes mellitus account for more than 90% of these amputations. The estimated 5-year survival after amputation is 30% to 55%, with the incidence of ipsilateral revision as high as 50% and contralateral amputation in the subsequent 2 years as high as 20%.

During the initial postoperative period, goals include relieving pain, preventing medical complications, and preventing mobility problems, particularly muscle atrophy and contractures. Between 60% and 80% of persons undergoing a lower extremity amputation experience phantom limb pain. Approximately 10% of those who experience phantom pain rate the pain as severe enough to be disabling. Conflicting evidence exists regarding the success of

adequate pain control preoperative or perioperatively on the incidence of phantom pain. However, there is little controversy regarding the importance of adequate pain control for persons undergoing amputation.

Common medical problems after amputation include poor wound healing, skin breakdown, and falls. Early mobilization with or without a prosthesis is critical for recovery of function. Older persons who already have decreased lean muscle mass are at risk of additional muscle atrophy. Joint contractures occur when patients spend significant periods of time sitting in a chair or a wheelchair and can have a negative impact on their ability to ambulate with prosthesis. Initially after amputation, older persons are instructed in the basics of self-care and mobility and then discharged to home. Rehabilitation occurs later after healing of the amputation site and can occur in a rehabilitation facility, in the home, or as an outpatient.

For the older adult, comorbid conditions and premorbid functional status impact the success of the surgery and subsequent rehabilitation. Prior to surgery, the older person should be medically stable, with special attention being paid to cardiopulmonary status. Level of amputation should also be considered. The energy expenditure required for a transtibial amputee is much less than for a transfemoral amputee and may predict a person's ability to regain ambulatory ability. However, while preserving the knee joint may be beneficial, preoperative evaluation should carefully assess the risk and benefit of knee preservation to avoid surgical revisions and longer lengths of stay in the hospital.

Prosthesis use can decrease energy expenditure with transfers and ambulation and should at least be considered, irrespective of age. While firm criteria for prosthetic prescription do not exist, Medicare has developed a guide for selection of prosthetic knee and ankle components. Indications for prosthesis are based on the likelihood that a person will reach or maintain a defined functional state within a reasonable time and that the person is motivated to ambulate. For example, an individual with the potential to be ambulatory at a household level may qualify for a lower performance prosthetic knee than someone with the potential to be active in the community and/or pursue athletic activities.

Considerations in determining the potential functional status of someone after an amputation may include prior ability to walk, medical status as it relates to the person's ability to meet the physiologic demands associated with prosthetic use and ability to learn new skills. These measures would certainly be useful when developing goals for the patient after amputation. A variety of lower limb prosthetic devices are available. To date, studies have not included a large enough sample of older persons to determine the optimal socket or foot design for this population. This determination should be made with the input of the patient, physician, prosthetist, therapists, and insurance company.

Stroke Rehabilitation

Rehabilitation after stroke can begin as early as 24 to 48 hours poststroke once the patient is medically stable and focuses on return to previous mobility and self-care activities as well as the prevention of medical complications like pressure ulcers or deep vein thrombosis, and minimization of spasticity. Provision of emotional support to the patient and family is essential. There appears to be a statistically significant and clinically important benefit from organized inpatient interdisciplinary rehabilitation in the postacute period. In several randomized controlled trials, either organized inpatient interdisciplinary rehabilitation or stroke unit care demonstrated improved outcomes, including reduced odds of death. Guidelines for the management of stroke were developed by Veterans Affairs and the Department of Defense and rate the quality of available evidence. The guidelines present algorithms for initial assessment as well as management after rehabilitation referral (http://www.healthquality.va.gov/guidelines/Rehab/stroke/).

Techniques used during stroke rehabilitation vary and are tailored to the needs and deficits of an individual patient. Strengthening, facilitation techniques that progress movement and task-oriented approaches, like constraint-induced therapy, are common. The goal of therapy, no matter the approach, is improvement of function and quality of life.

After a stroke, patients may have a variety of impairments in addition to muscle weakness. Dysphagia places patients at risk of aspiration and can be silent in up to one-third of patients with dysphagia. Communication disorders including aphasia also occur in one-third of patients, with prognosis being worse for patients of advanced age, or with delayed treatment. During the first month after a stroke, the incidence of bladder incontinence is 50% to 70%, although it returns to levels seen in the general population by 6 months. Treatment can include timed voiding schedules and monitoring of postvoid residuals. Hemiplegic shoulder pain is also a common occurrence, affecting 34% to 84% of patients poststroke. Major risk factors include advanced age and changes in muscle tone, which occur after the stroke. Treatment involves proper positioning to avoid joint subluxation and early range-of-motion exercises to prevent contractures and spasticity. There is some evidence that electric stimulation can improve hemiplegic shoulder pain for

up to 6 months after treatment. Depression is another frequent complication after stroke, one that can have a significant negative effect on rehabilitation. Incidence ranges from 15% to 70% depending on the study, and several antidepressant medications have been associated with improvement. An organized, interdisciplinary team approach helps to address these common sequelae after stroke.

Parkinsonism

Physical manifestations of parkinsonism include muscular rigidity, tremor, bradykinesia, postural instability, and gait disturbances. Muscle rigidity and bradykinesia are often manifested by difficulty initiating movement, which causes patients to have significant difficulty performing even simple ADLs. Owing to postural instability and gait disturbances, patients with parkinsonism are more likely to experience falls and are at risk of injury owing to slow reaction speed.

At this time, there are no guidelines or generally accepted rehabilitation techniques for persons with Parkinson disease. Traditionally, therapy has focused on improving posture, range of motion, exercise capacity, and gait. There is evidence that exercise programs including resistive and flexibility exercises can improve physical function. A recent review demonstrated improvements in gait speed, balance and freezing episodes with exercise. Another commonly used technique is an external cueing strategy where auditory pacing, use of a walking stick, or visual cues can help improve gait and decrease episodes of freezing for some patients. Because of the success of rhythmic cueing, studies are being done to explore the use of treadmill training as a method to improve the gait pattern of patients with parkinsonism. Results from a systematic review are promising, with improvements in gait speed, stride length, and walking distance being seen. The “Training Big” program is being used increasingly frequently to improve motor performance through the use of repetitive high-amplitude movements. Originally used to amplify voice, studies are reporting significant improvements in gait speed and other functional measures. The long-term benefits of all the exercise interventions are still unknown.

Osteoarthritis and Total Joint Replacement

Osteoarthritis is the leading cause of impaired mobility in older persons because of the associated joint pain, muscle weakness, and atrophy. In persons with osteoarthritis of the knee, the severity of the knee pain is directly correlated with the degree of muscle weakness. Several randomized trials have demonstrated the efficacy of strengthening exercises to lessen pain and improve function. Weight loss combined with strengthening exercises was shown to be more effective than weight loss alone for improving function and reducing pain. If pain occurs with an exercise, that exercise should be avoided, and monitoring by a physical therapist during the initial rehabilitation period is reasonable. Osteoarthritis of the hip is less amenable to exercise, probably because improving strength in the ball and socket hip joint does not provide the same support as strengthening the hinged knee joint. Efforts to relieve pain will help the person with arthritis maintain physical activity levels and minimize the effects of deconditioning and muscle weakness.

Total joint arthroplasty is the most common elective surgical procedure done in the United States. The primary indications for arthroplasty are mobility limitation and progressive pain, despite conservative treatments like exercise and use of mobility aids. After total joint replacement, the principal goal is to attain the highest level of functional independence possible. Rehabilitation after a total hip replacement focuses on strengthening exercises and gait training. Precautions to reduce the risk of hip dislocation may be required during the initial months of post hip replacement. For example, in the early stages of recovery from the traditional posterolateral approach, patients may need to avoid crossing their legs, flexing their hips more than 90 degrees and rolling their legs in and out to decrease the risk of hip dislocation. Raised toilet seats are also recommended to prevent excessive hip flexion during the first few months after surgery. After total knee replacement, rehabilitation is focused on pain control, reduction of swelling, improving range of motion, and strengthening the muscles around the knee. Recovery from total knee replacement requires the patient work hard to attain and maintain range of motion during the first few months after surgery, which is distinct from hip replacement surgery.

Falls

A multicomponent strategy has been demonstrated in a series of randomized controlled trials to be highly effective in reducing falls in all older persons. These successful interventions have included strength and balance training as important components. In one meta-analysis, exercise programs alone have been demonstrated to reduce the risk of falling. To date there is insufficient evidence to determine whether interventions focused on modifying environmental

home hazards reduce injuries.

Hip Fracture

Hip fractures are common, with approximately 95% being caused by falls. Excess mortality of 12% to 20% has been documented after hip fracture and as much as 80% of those who survive fail to regain their prior level of function. One year after hip fracture, one-third of the patients who had been independent with walking were no longer independent.

The initial rehabilitation efforts are focused on early mobilization to prevent complications of bed rest, like deconditioning and deep vein thrombosis. Post repair, decreased weight bearing on the fractured limb is standard and patients are taught to walk with an appropriate assistive device. The amount of weight that can be placed on the repaired limb depends on fracture stability. If possible, patients should be allowed to bear weight as tolerated as opposed to “touch-down” weight bearing, which is often difficult for older patients to achieve. There is mounting evidence that exercise following hip fracture is beneficial with higher-intensity/duration programs showing more promising outcomes, although the optimal exercise program to maximize function after hip fracture has not been determined.

Sarcopenia and Deconditioning

While there is considerable variation in the loss of muscle mass with aging, cross-sectional studies indicate that strength declines at a rate of 12% to 15% per decade after the fifth decade. This age-related loss of muscle strength and mass is termed sarcopenia. Sarcopenia leads to losses of muscle strength, power, and endurance, which are all critical to daily function. The decline in power output, or the ability to contract a muscle quickly, may also be related to an increased risk of falls, as well as difficulty with functional tasks.

A variety of factors appear to impact on the loss of strength, in addition to age. Reduction in anabolic hormones and local growth factors may also contribute to the observed decline. There appear to be gender differences in response to the same exercise program, with older women showing a blunted response to muscle fiber hypertrophy when compared to older men. The most effective resistance programs for older women occur twice a week, suggesting that older women required longer recuperation periods between bouts of resistance exercise. It has been suggested that, in addition to these factors, the frequently observed decline in physical activity may be a significant mediator in the recognized strength and muscle mass loss.

This decline in physical activity, or deconditioning, is often associated with acute illness or chronic disease. Patients with osteoarthritis may limit activity because of pain. As a result, they lose muscle mass and strength, making daily activities more difficult to accomplish. Over time, the patient will tend to perform fewer activities, as they continue to lose strength and endurance. Bed rest during acute care hospitalization can also lead to loss of strength and muscle mass, even after only a few days. The adverse outcomes associated with this low level of activity include functional decline and increased nursing home placement, even after controlling for severity of illness and comorbidities. Early mobilization has been demonstrated to improve functional outcomes for a variety of patients, including those with a hip fracture or pneumonia.

While no consensus exists regarding the optimal training program, numerous studies have demonstrated resistance exercises to be very beneficial in the treatment of sarcopenia and deconditioning. Increased muscle mass and strength occur with loading the muscle at 60% to 80% of one-repetition maximum (1RM), two to three times a week. Some researchers also recommend that at least once a week low-intensity, high-velocity resistance training should be done to address the loss of power that occurs with sarcopenia.

Improvement in muscle strength and power through endurance exercise can reduce the difficulty older adults may experience in performing daily functional activities and may promote spontaneous additional physical activity. While sarcopenia owing to aging may not be reversible, other components of the observed decline in physical activity can be ameliorated with exercise.

Pain

For older persons, pain is common and frequently associated with adverse consequences such as depression, anxiety, and impaired ability to walk. In the community-dwelling older adults, 60% to 75% experience persistent pain, and, in the nursing home, rates range from 45% to 80%. Having persistent pain may worsen the level of physical activity achieved, and the associated deconditioning can contribute to further pain and disability.

Many of the physical modalities, such as thermal agents (heat or cold) and electrotherapy, can be beneficial in relieving pain. There is evidence that participation in an exercise program can improve pain and function. The prescribed exercise program needs to be individualized for the patient and focused on improving range of motion, strength, and endurance. For additional information on pain management, the American Geriatrics Society has guidelines on the pharmacologic management of persistent pain in older persons (http://www.americangeriatrics.org/files/documents/2009_Guideline.pdf).

PHYSICAL ACTIVITY AND EXERCISE POSTREHABILITATION

Many people complete rehabilitative episodes of care with persistent impairments and loss of function. These individuals are at higher risk for the development of secondary and tertiary complications due to lack of physical activity and exercise. Facilitating the transition of individuals with disability from rehabilitation to community-based physical activity and exercise programs is one strategy that is proving to be successful in increasing activity. Physicians and other professionals should be aware of the importance of promoting healthy lifestyles in individuals postrehabilitation.

CONCLUSION

Because disability is common among older persons, rehabilitation is an important component of geriatric health care. Defining the cause or causes of disability will allow the rehabilitation team to provide treatment in the optimal setting for the individual patient. Much remains unknown about the most effective rehabilitation techniques for patients with multiple comorbidities; however, available literature supports the continued use of rehabilitation to improve function, independence, and quality of life for older persons.

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Chapter 30

Legal Issues

Marshall B. Kapp

Learning Objectives

- Appreciate the general legal environment within which physicians function when providing medical care to older patients.
- Understand the elements of a medical malpractice claim brought against a health care provider.
- Engage in the process of shared decision making and informed consent with older patients in a legally appropriate manner.
- Advise patients and families about available tools to facilitate advance health care planning.
- Apply in clinical practice the legal requirements for confidentiality of patient information and permissible exceptions to those requirements.

Key Clinical Points

1. **Maintain and apply in clinical practice an acceptable level of knowledge and skill for your specialty (ie, keep up with your field).**
2. **Engage in the process of informed and voluntary shared decision making with your patients or their decision-making surrogates.**
3. **Discuss the topic of advance health care planning in a timely and supportive manner with patients, ascertaining the patient's relevant values and treatment preferences in various contingencies.**
4. **Respect and safeguard the confidentiality of patients' medical information, but understand the circumstances under which it is legally permissible or even mandatory to reveal what would otherwise be confidential information.**

INTRODUCTION

The law regulates human relationships, both prospectively and retrospectively, in a wide variety of ways. To a large extent, the legal implications of medical practice are generic, in the sense that these apply to patients of all ages. Rules developed to deal with the care of younger adults apply with full force to older persons, whose rights do not diminish just because of advanced chronological age. However, a patient's advanced years may sometimes raise issues demanding particular attention by the involved participants in the professional/patient relationship. This chapter concentrates on several selected aspects in which the law influences the delivery of geriatric services through its impact on the recognition and enforcement of the respective rights and responsibilities of the parties, within the specific dynamics of an older patient/health care provider relationship.

OVERVIEW OF HEALTH CARE REGULATION

The US Constitution establishes a federal system of government, under which health care delivery and other matters are regulated at the national (federal), state, and local levels. Under separation of powers principles, such regulation takes the form of constitutional (federal, state, and local) provisions, statutes enacted by elected legislatures, rules or regulations promulgated by executive branch administrative agencies like health or social service departments on the basis of authority conferred on the agency by the legislature via a statute, and common law doctrines created by the courts as a matter of public policy and prior case precedent. These various forms of regulation may impose specific or general duties on parties, may authorize but not require parties to act in specific ways, or may prohibit parties from engaging in particular conduct. Health care regulation may be directed at individual health professionals or at health care facilities, agencies, institutions, and other organizations.

Regulation of Health Professionals

One primary mechanism for regulating individual health professionals to assure adequate qualifications and acceptable conduct is licensure, which entails the requirement that an individual satisfy—on both an initial and a continuing basis—certain enumerated standards to be permitted to practice a particular profession. Professional licensure ordinarily occurs at the state level through statutes (such as state Medical Practice Acts or Nursing Practice Acts) and regulations promulgated by a state's licensing body (such as the Medical Board or Nursing Board) to implement the Practice Act. Licensure statutes and regulations limit certain activities to licensed professionals; engaging in those activities without prior state approval (in other words, practicing medicine or nursing without a valid license) subjects the wrongdoer to potential civil fines and even criminal sanctions.

Many statutory and regulatory requirements or prohibitions imposed on health professionals occur as conditions attached to payment for professional services under government insurance programs, especially Medicare and Medicaid. Professionals who treat patients covered by these government programs must satisfy the positive (eg, "Thou shalt" maintain adequate patient records) or negative (eg, "Thou shalt not" engage in self-referral) "strings" placed on the payment of public dollars to receive compensation for services rendered.

Another significant manner of health professional regulation under the civil law is tort liability in private lawsuits claiming malpractice; this form of regulation is discussed below. Particularly egregious, intentional misbehavior (such as patient abuse or billing fraud) may subject a health professional to criminal law punishments.

Regulation of Health Care Facilities and Agencies

Besides regulating individual health professionals, government additionally regulates provider facilities and agencies through licensure requirements, conditions attached to the receipt of compensation under public insurance programs including Medicare and Medicaid, criminal prohibitions on specific behaviors such as the filing of false claims, and civil liability for malpractice claims brought by or on behalf of individual patients. For example, Congress enacted the Nursing Home Quality Reform Act, codified at Title 42 US Code §#1395i-3(a)-(h), as part of the Omnibus Budget Reconciliation Act (OBRA) of 1987, Public Law No. 100-203. This act, which has been amended several times subsequently, contains many of the recommendations proposed in a 1986 Institute of Medicine report that Congress had directed the Department of Health and Human Services to commission. OBRA 1987 amended the Social Security Act, Titles 18 (Medicare) and 19 (Medicaid), to require substantial upgrading in nursing home quality and enforcement. To implement this legislation, Department of Health and Human Services published a series of regulations, which have been codified at Title 42 Code of Federal Regulations Part 483. Violation of these regulations subjects nursing homes to a range of sanctions, up to decertification from participation in the Medicare and Medicaid programs.

STANDARDS OF CARE AND PROFESSIONAL LIABILITY IN GERIATRICS

Overview of Malpractice Liability

In a private civil lawsuit predicated on a theory of professional negligence, the plaintiff is required to establish four distinct elements by a preponderance of the evidence (a more likely than not standard) (**Table 30-1**). First, the patient/plaintiff has the burden of proving that the professional/provider defendant owed the patient an obligation defined by the appropriate standard of care. The existence of this duty ordinarily is established by showing that there existed, within the relevant time frame, a professional relationship between the patient and provider; that is, the plaintiff was a patient of the provider for diagnostic and/or therapeutic purposes.

TABLE 30-1 ELEMENTS OF A PROFESSIONAL NEGLIGENCE CLAIM

1. Duty owed by professional/provider to the patient
2. Breach or violation of duty
3. Damage or injury to the patient
4. Causal (both general and proximate) link between the professional/provider breach of duty and the injury suffered by the patient

Second, the plaintiff must present sufficient evidence that the professional/provider breached or violated the appropriate standard of care within the professional relationship. The professional/provider does not guarantee particular results, let alone perfection. By the same token, however, it is not enough for professionals/providers to "do their best" if their conduct does not rise to the applicable level of care, even when the errors or omissions were unintentional (ie, negligent). How the law determines the applicable level of professional care is discussed in the following section.

The third element that a medical malpractice plaintiff is required to prove is the occurrence of some financially compensable injury or damage. Besides special or economic (pecuniary) damages that include such quantifiable items as lost income and past and future health care–related costs, plaintiffs may be awarded general or noneconomic (nonpecuniary) damages for such difficult to quantify things as pain and suffering, mental anguish, grief, and other emotional complaints. In recent years, juries have become much more willing to award substantial noneconomic damages to older patients claiming medical negligence. In very rare circumstances, punitive or exemplary damages may be awarded over and above compensatory damages, where the defendant's conduct has been not merely negligent, but actually reckless or malicious. For example, a jury might award punitive damages when it finds that a patient has developed serious pressure ulcers because of a hospital's or nursing home's demonstrated ongoing pattern of neglect.

The final component of proof in a professional malpractice lawsuit is the element of causation. To succeed, a plaintiff must persuade the jury, to a reasonable (not absolute) degree of medical certainty, that his or her injuries were the result of the defendant's negligence. A plaintiff must prove not only that the defendant's negligence was a "substantial factor" in bringing about the injury or that "but for" (*sine qua non*) the defendant's negligence the injury would not have happened, but further that there were no intervening, superceding (ie, not reasonably foreseeable) forces that acted to break the chain of proximate or direct causation between the defendant's negligence and the patient's injury. For example, a physician might negligently fail to diagnose cancer in an older patient in a timely manner and the patient, on learning that cancer is at such stage that it cannot be treated effectively, commits suicide. Assuming the availability of effective treatment if the cancer had been properly diagnosed in a timely manner, representatives of the deceased patient may argue that "but for" the physician's negligence the death would not have taken place; however, the physician would respond that the patient's act of committing suicide was an intervening, superceding (ie, not reasonably foreseeable) factor that disrupted the chain of proximate causation between the physician's negligence and the patient's injury.

Developing and Disseminating Standards of Care

Legal standards of care have been established mainly by the courts as a matter of common law on an incremental, case-by-case basis. State statutes, such as those containing professional licensure requirements, also help to define the required standards of care.

Under the traditional formulation, a professional who is accused of negligent acts or omissions in a medical malpractice claim is usually held to a standard requiring the professional to have and exercise that level of knowledge and skill ordinarily possessed and exercised by competent, reasonable professional peers (determined on a national rather than a local basis) in similar circumstances. Put differently, under long-standing tort principles of negligence, professionals have been judged legally according to the prevalent practice or custom of peer professionals in clinical circumstances like the situation that confronted the particular defendant in the case immediately before the court.

However, there is a significant current trend in many states to deviate from the traditional customary professional standard of care in favor of imposing more objective, external standards of "reasonableness" against which the professional's behavior is to be evaluated by the jury. An objective, evidence-based standard of reasonableness may exceed (ie, require more knowledge and sophistication than) the prevailing customary practice within the professional community at the time in handling a specific clinical challenge presented by a patient. Thus, the state of the art in a

particular area of care, required under a reasonableness standard, frequently may not be synonymous with and reflected in the current customary practice within the practitioner community. Courts adopting a reasonableness standard often recite the famous maxim of Judge Learned Hand: "Courts must in the end say what is required; there are precautions so imperative that even their universal disregard will not excuse their omission."

When a reasonableness standard is imposed on malpractice defendants, expert witnesses may be allowed to testify, and thereby educate the lay jurors, regarding the appropriate professional conduct under the circumstances. To establish what conduct would have been reasonable, the parties may also introduce other kinds of evidence to supplement the testimony provided by the expert witnesses (**Table 30-2**). Additional forms of evidence introduced for this purpose may include professional codes of ethics, medical journal literature, textbooks (learned treatises), the *Physician's Desk Reference* (PDR) and pharmaceutical package inserts (PPIs) pertaining to the correct use and dosage of prescription drugs, pertinent statutes or regulations, voluntary accreditation standards such as those of the Joint Commission, and, of increasing importance, pertinent clinical practice guidelines or parameters.

TABLE 30-2 ■ PROOF OF THE STANDARD OF REASONABLE CARE UNDER THE CIRCUMSTANCES

1. Expert testimony about appropriate care
2. Professional codes of ethics
3. Medical journal literature
4. Textbooks (learned treatises)
5. *Physician's Desk Reference* (PDR) and pharmaceutical package inserts (PPIs)
6. Relevant statutes or regulations
7. Voluntary accreditation standards
8. Clinical practice guidelines or parameters

Leaders in health care delivery and financing acknowledge (although frequently not in public) that a good deal of routine medical practice has long been predicated more on habit and inertia than on solid empirical evidence establishing clinical efficacy. Out of a concern about both wasteful resource usage and the quality of patient care, in the last several decades professional organizations and specialty societies including the American Geriatrics Society and the American Medical Directors Association, governmental agencies led by the federal Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI) established by the Affordable Care Act (ACA), and individual institutions and agencies in the United States and elsewhere have engaged in a concerted movement to develop, collect, and disseminate to practicing clinicians a variety of evidence-based clinical practice guidelines or parameters to educate practitioners about whether a particular diagnostic or therapeutic intervention actually has been demonstrated to produce desired health benefits for patients. The Institute of Medicine has defined clinical practice guidelines as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."

In a related vein, the American Board of Internal Medicine Foundation and Consumer Reports have partnered in a Choosing Wisely initiative designed to encourage and enable patients and physicians to share in making decisions about medical care that is supported by available evidence, not duplicative of other tests or procedures already received, and necessary for that particular patient. Numerous medical specialty organizations have joined in this initiative, identifying common practices in their respective specialties for which physicians and patients ought to ask questions about the value obtained from routine use.

The legal ramifications of clinical practice guidelines or parameters continue to evolve. Nevertheless, there is a growing tendency for the courts to admit into evidence, on behalf of either side to a malpractice dispute (ie, for either inculpatory or exculpatory purposes), properly validated, scientifically supported contemporary practice parameters on the issue of the standard of care to be applied under any particular set of circumstances. This development already has consequences, in that surveys show that plaintiffs' attorneys consider health professionals' compliance with or deviation from relevant practice parameters in making decisions about whether to initiate malpractice litigation at all and how to conduct settlement negotiations for claims that are pursued.

INFORMED CONSENT

Basics of Informed Consent

The informed consent doctrine originates with the ethical principle of autonomy or self-determination, especially regarding the physical integrity and dignity of one's own body. A health professional/provider may be held civilly liable, usually under a negligence theory but in rare cases under a battery or intentional tort theory, for subjecting a person to any diagnostic, therapeutic, or research-related intervention without that person's effective consent to the intervention. In their legal formulation, the substantive parts of the informed consent rule have evolved over time as a function of state common (judge-made) law. Moreover, the majority of states have, by now, enacted statutes and regulations spelling out a jurisdiction's specific details regarding informed consent, for clinical care generally and/or within particular settings such as nursing homes or public mental institutions.

For a patient's decision about whether to accept or reject a suggested medical intervention to be considered legally valid, three separate but interrelated elements must be present (**Table 30-3**).

TABLE 30-3 ELEMENTS OF LEGALLY VALID MEDICAL DECISION MAKING

1. Voluntary
2. Informed
   a. Diagnosis or nature of the problem
   b. Expected benefits
   c. Risks
   d. Alternatives, including complementary and alternative interventions
   e. Risks and benefits of refusal
   f. Cost implications
   g. Level of uncertainty
3. Competent/capable decision maker

First, the patient's participation in the decision-making process and the final decision(s) regarding intervention must be voluntary, as opposed to being unduly dictated by force, fraud, duress, or any other actual or perceived ulterior form of constraint or coercion. Second, the patient's agreement or disagreement with recommended interventions must be properly informed. The professional is obligated to disclose sufficient information about the proposed intervention to empower the patient to make a knowledgeable, intelligent consent or refusal. The third essential element of legally effective medical decision making is adequate capacity on the part of the patient to cognitively and emotionally understand and manipulate pertinent information about personal care.

In terms of the informed component of the informed consent doctrine, there are two competing standards for determining how much information about a proposed medical intervention must be shared with the patient in advance. The medical custom or reasonable professional standard requires the disclosure of such information that an objective reasonable, prudent professional would disclose under similar circumstances. By comparison, the materiality or patient orientation standard compels the sharing of information that might make a difference (ie, might be material) in the decision-making process of a reasonable, average patient in similar circumstances. The different states are approximately evenly split between these two competing standards of information disclosure.

Under either the materiality or the reasonable professional standard, the basic components of information disclosure implicated by the professional's fiduciary or trust obligations to the patient include the following items: diagnosis or nature of the patient's medical problem; nature and purposes (the expected benefits) of the proposed interventions; reasonably foreseeable risks associated with the intervention, specifically, the likelihood of a risk materializing and the severity or gravity if it does occur; reasonable alternative interventions and their anticipated risks and benefits; and the reasonably foreseeable risks and benefits of not undergoing the proposed intervention. Other informational items that a health professional should seriously consider disclosing to the patient are complementary and alternative medicine alternatives, which are increasingly popular with older individuals; cost ramifications to the patient of proposed alternatives; professional-specific information pertinent to the particular intervention (for instance, the professional's own track record with the particular intervention or any financial incentives the professional has regarding the patient's course of care); and the level of uncertainty within the medical community concerning the particular intervention.

Informed consent to a medical intervention may be implied or expressed. There are many situations in which a

patient's permission to proceed with a medical intervention does not need to be put into words but, instead, may be implied from the context. This happens when, through demonstrative actions, the patient indicates a wish (or at least willingness) to undergo a specific intervention by voluntarily submitting to it in a manner that the health professional can reasonably rely on to conclude that the intervention has been authorized. Implied consent is appropriate for most routine, noninvasive, nonrisky kinds of medical interventions such as taking a patient's blood pressure or listening to the heart. Implied consent is not an exception to the general informed consent requirement, but just a different (created by behavior instead of words) form of permission.

Express consent (put into spoken or written words), by contrast, is more appropriate when the proposed medical intervention is intrusive and/or significantly more risky than ordinary, everyday life. With a small number of exceptions created by particular state statutes for designated kinds of interventions (such as testing for the HIV virus), express consent in the form of spoken rather than written patient words is quite legally adequate, as long as the consent is voluntarily and competently given on the basis of sufficient information being disclosed. However, for particularly intrusive or risky interventions, the professional/provider should consider documenting the patient's decision to consent or refuse by asking the patient to sign a separate written form, in addition to the professional making a progress note in the patient's medical record. Also, voluntary accreditation standards with which the provider complies, such as those of the Joint Commission, may require the use of separate written consent forms for particular sorts of medical interventions.

Decisional Capacity Issues

Sometimes, a patient is not mentally and/or emotionally capable of assimilating pertinent information and engaging in a rational, voluntary decision-making process about the proposed and alternative medical interventions. Some older persons with dementia, depression, or other age-related mental disorders are so impaired that they fall into this category. When the patient personally lacks adequate decisional capacity, the health professional is not at all relieved of the duty to obtain informed consent but, instead, must work with someone else who is willing to act as a surrogate on the patient's behalf.

Assessing decisional capacity in older persons entails a functional inquiry. Among the basic questions to be posed are the following (**Table 30-4**): (1) Can the person make and communicate in an understandable form any decisions at all? (2) Is the person able to offer reasons for the choices made, indicating some degree of reflection and consideration? (3) Are the reasons given based on logical reasoning proceeding from factually accurate suppositions? (4) Can the patient appreciate the ramifications (ie, the likely risks and benefits) of the options outlined and the choices expressed, and the reality that these ramifications apply to that patient? (5) Does the individual, in fact, comprehend the practical implications of his or her choices?

TABLE 30-4 ■ COMPONENTS OF FUNCTIONAL ASSESSMENT OF DECISIONAL CAPACITY

1. Ability to communicate decisions
2. Ability to give reasons for decisions
3. Reasons given are logical and factually accurate
4. Appreciation of ramifications
5. Comprehension of ramifications

A patient's present cognitive and emotional capacity should be evaluated on a decision-specific, rather than a global or all-or-nothing, basis. A patient may be capable of making some kinds of decisions, but not others; partial or limited capacity is quite possible even when total capacity is not. Moreover, capacity may fluctuate within a specific patient according to variables such as time of day, day of the week, physical location, acute and transient physical problems, other persons available to support or coerce the patient's choice, and medication reactions. Older individuals may be especially vulnerable to fluctuations in capacity induced by these factors. Some of these factors may be susceptible to manipulation by caregivers (eg, through changes in the timing of drug administration) so that discussions with the patient (rather than or in addition to the surrogate) about the care plan can take place under the most lucid circumstances possible.

Advance Health Care Planning as Prospective Decision Making

There are several legal mechanisms available to maximize a patient's medical autonomy. An older person (although these planning tools are available to any decisionally capable adult) may, while still competent, execute certain legal instruments to take steps to anticipate and prepare for eventual incapacity by voluntarily delegating or directing the exercise of future medical decision-making power. Although oral advance medical directives, theoretically, are completely legally valid, patients should be encouraged to execute written versions to maximize the likelihood that the directive will be ultimately respected by family members and health professionals. Organizational providers are required by the federal Patient Self-Determination Act to initiate discussions with competent patients about the availability of advance medical directive opportunities.

The durable power of attorney (DPOA) consists of a written document in which an individual (the principal) appoints an agent, or attorney-in-fact, to make various kinds of decisions for the principal. Each state has enacted one or more statutes that explicitly authorize the use of a DPOA for health care to empower an agent (including a nonfamily member) to make medical choices on a patient's behalf, should the patient later lose decision-making capacity. A DPOA may be immediate in nature, meaning that it comes into effect as soon as the agent is named. In a springing DPOA, on the other hand, the legal authority transfers (springs) from the patient to the agent only on the occurrence of some specified future event, like a declaration of the principal's incapacity by a designated number of examining physicians. The patient should be informed by attending health professionals when they have decided to act as though decision-making authority has sprung to the designated agent, so that the patient can utter a protest, if desired, to the agent's exercise of power.

The DPOA is a proxy directive, and hence distinguishable from a living will, which is an instruction-type directive. In an instruction directive, a presently competent patient documents his or her wishes regarding future medical treatment (eg, "no extraordinary measures" or "keep me alive forever no matter what pain or expense") rather than naming an agent to make future treatment decisions in the case of eventual incapacity. The two kinds of legal devices are not mutually exclusive; indeed, patients may be encouraged to execute them in tandem because the living will can help an agent named under a DPOA to exercise the patient's substituted judgment (defined below) more accurately.

When a patient is decisionally incapable but has not previously executed an instruction or proxy directive, in a majority of states health professionals may rely on legislation empowering family members and enumerated other persons to make medical decisions for incapacitated persons. In states with such family consent statutes, the approved procedure usually consists of documenting unanimous agreement among the attending physician, specified relatives or others (listed in a stated order of preference), and sometimes consultant physicians as well.

When there is no valid proxy or instruction directive, family consent statute, or judicial precedent in one's jurisdiction authorizing the family to act as patient surrogate, or in those relatively uncommon situations in which family members strongly and irreconcilably disagree about the best course of care for their decisionally incapacitated loved one, judicial creation of a guardianship or conservatorship (nomenclature varies by jurisdiction) may be advisable to transfer decision-making power formally and definitively from an incapacitated patient to a single, specific surrogate. However, the official legal process (ordinarily entailing significant financial, time consumption, and emotional costs) should not be initiated unless and until less formal approaches, such as mediation or consultation with an Institutional Ethics Committee (IEC) or ethics consultation service, have been exhausted in an effort to reach a sufficient level of agreement among all the interested stakeholders. In a guardianship/conservatorship case, professionals who have evaluated and/or treated the alleged incompetent person usually are called on to provide evidence to the court in the form of a written affidavit and/or live sworn testimony. Many jurisdictions have public or volunteer guardianship programs that operate to provide surrogate decision makers for individuals with substantially impaired cognitive and/or emotional capacity who have no suitable family members or other private parties to be appointed guardians for them.

In the past, a surrogate has been expected to make decisions consistent with the guardian's view, as a trust agent, of the patient's best interests. The more modern trend, however, is toward enforcement of a substituted judgment standard of proxy decision making, whenever it is realistically feasible. Under this latter approach, the surrogate is obligated to make those decisions that the patient would make, according to the patient's own preferences and values to the extent these can be accurately ascertained, if the patient were presently able to make and express his or her own competent decisions.

The latest innovation in advance health care planning is the Physician Orders for Life-Sustaining Treatment (POLST) Paradigm. (The precise title for this concept may vary among different jurisdictions.) A POLST is a mechanism to convert a patient's treatment wishes into the tangible form of a written physician's order. Because health care professionals are accustomed to carrying out medical orders, there is evidence that when treatment instructions are

expressed in the form of a POLST they are substantially more likely to be honored and implemented in practice than are wishes expressed only in the form of a patient's prior expression or a surrogate's current representation of the patient's inferred preferences. Unlike an advance directive, a POLST is appropriate only for a patient who is so seriously ill that a physician exercising sound judgment would not be surprised if that patient died within the next year. Individual states are presently at different points concerning the degree of POLST penetration in medical practice. Some states have enacted statutes and/or regulations specifically authorizing POLST, while other states are in earlier stages of legal recognition, although in no state are there any laws that would prohibit either physicians from writing a POLST today for an appropriate patient or emergency medical services (EMS) or other health care professionals from following a POLST.

CONFIDENTIALITY

In the course of providing care, health professionals routinely are exposed to very private information about patients and their families. Professionals owe patients a fiduciary responsibility to hold in confidence all sensitive patient information entrusted to them as a consequence of the professional/patient relationship. This ethical obligation, predicated on the patient's important interest in protecting personal privacy and avoiding the social stigma and potential discrimination that breach of one's medical privacy might entail, is enforceable legally under both state and federal law.

State Law

Every state, both within its various state professional practice acts and in separate statutes pertaining to particular health care delivery settings, has legislatively enacted provisions pertaining to the confidentiality duties of health care professionals, institutions, and agencies. Often, state agencies have published accompanying regulations to implement these statutes. Moreover, a strong common law health care confidentiality doctrine has been forged by state court decisions rendered over time. Violation of state common law or the relevant statutory or regulatory requirements regarding the confidentiality of patient information may subject erring health professionals/providers to civil damage suits, brought by or on behalf of the patient whose privacy was improperly infringed; additionally, violation of state Practice Act provisions may subject the violator to administrative sanctions by the state, including license suspension or even revocation.

However, numerous exceptions to the general confidentiality rule have been recognized, either by the courts as part of the common law or embedded in state legislation or regulation (**Table 30-5**). The most prominent exception occurs when a patient, expressly or impliedly, voluntarily and knowingly waives, or gives up, the right to assert the confidentiality of particular information. These waivers take place daily to make information available to third-party payers (for instance, Medicare claims processors and private health insurers), quality of care auditors (such as Joint Commission surveyors), and other public and private entities like health care surrogates authorized to make medical decisions on behalf of a decisionally incapacitated patient. Also, because the modern delivery of health care most often is a team endeavor, each patient implicitly gives permission for the sharing of certain otherwise private pieces of information among the members of the treatment team. Internal information sharing of this nature is essential to optimal care, especially for accomplishing coordination and continuity of long-term care for older patients with disabilities. Indeed, failures in communication among the multiple providers involved in the care of a patient needing such coordination and continuity may form the basis for negligence liability claims when harm results.

TABLE 30-5 EXCEPTIONS TO THE DUTY OF CONFIDENTIALITY

1. Patient permission (waiver)
2. Danger to others
3. Mandatory or permissive reporting statutes
4. Legal process (court order)
5. "Treatment, payment, and health care operations" (HIPAA)

Second, the usual confidentiality duty may be outweighed in situations of jeopardy to innocent, at-risk third parties, such as happens when a patient with serious sensory or cognitive impairments insists on continuing to drive an

automobile or maintaining loaded firearms in the home for protection against intruders. Particular details regarding methods for the health professional to discharge the responsibility to report a credible threat of harm to public health or law enforcement authorities vary on the basis of state statutory and case law.

Third, the patient's reasonable expectation of privacy must give way when the health professional is mandated by state statute to report to enumerated public health or law enforcement authorities (eg, Adult Protective Services [APS]) the professional's reasonable suspicion that certain conditions or activities have occurred or are occurring. Such reportable conditions or activities may include elder mistreatment or neglect (in many states including cases of self-neglect within that definition), domestic violence, infectious diseases, births, and deaths. Some states that have declined to mandate the reporting of particular situations to public authorities nonetheless encourage voluntary reporting; a few states have pursued this approach regarding cases of suspected elder abuse or neglect. Those states supply an incentive for voluntary reporting by expressly providing legal immunity against any form of civil or administrative liability for covered persons making good faith reports to public authorities. Mandatory and voluntary reporting statutes embody the state's exercise of either its inherent police power to protect and promote the general health, safety, welfare, and morals of the community or its *parens patriae* power to step up and safeguard individuals (such as persons with serious cognitive or emotional disabilities) who are not capable of protecting themselves. Further, a health professional may be compelled to reveal otherwise confidential information about particular patients by the force of legal process, namely, by a judge's issuance of a court order requiring such release. This is a possibility in any civil or criminal lawsuit involving a factual dispute about a patient's physical or mental condition. A court order (as opposed to a subpoena or subpoena *duces tecum*, which is issued simply as an administrative, nondiscretionary matter by the court clerk rather than by a judge) requiring one to produce personally identifiable patient information may overrule the state's provider/patient testimonial privilege statute that ordinarily would prohibit the provider from testifying in a legal proceeding regarding private patient information. Every state testimonial privilege statute provides for judicially compelled testimony on the part of the health professional when, for example, the patient has placed his or her own health condition and medical treatment in issue in a lawsuit. This could occur when, for instance, the individual challenges the allegations propounded by others about one's mental impairments made in a guardianship/conservatorship petition.

Federal Law

Particular health care settings There are a variety of federal statutes and regulations imposing on health professionals/providers particular confidentiality obligations when care is provided within specific types of health care settings, including federal penal institutions, veterans affairs facilities, military institutions, federal community health centers, and facilities specializing in the treatment of persons having drug and alcohol addiction. Violation of these laws may result in substantial civil fines. Statutes and regulations setting the conditions for receipt of Medicare and Medicaid payments contain confidentiality provisions, set within general patients' rights standards, applicable specifically to nursing homes and home health agencies. Noncompliance with those provisions could trigger a range of regulatory sanctions, at the extreme including decertification of the facility or agency from participation in federal health care financing programs.

Health insurance portability and accountability act Federal regulations codified at Title 45, US Code of Federal Regulations Parts 160 and 164 implement the Health Insurance Portability and Accountability Act (HIPAA) of 1996 (Public Law No. 104-191, title XI, Part C). These regulations, published in the form of a Privacy Rule and a Security Rule, impose on covered health care entities (defined as any health providers who transmit any patient-related information electronically) an extensive set of requirements regarding the handling of personally identifiable medical information contained in patient records. These regulations impose severe criminal and civil sanctions for unauthorized disclosures of personal health information. Substantively, HIPAA and its implementing regulations in essence codify preexisting state statutory and common law protections for patients, with the addition of provisions making it clear that patients now have the right to access the information contained in their own medical records. (Previously, state law had varied or was unclear regarding the issue of patient access to records.) HIPAA contains provisions authorizing covered entities to transmit personal health information to certain others for purposes of "treatment, payment, and health care operations" such as quality assurance or marketing. These and other exceptions explicitly contained in HIPAA basically track the preexisting state statutory and common law exceptions discussed in the previous section.

SUMMARY

Individual health care professionals and organizational providers serving older patients inevitably and continuously interact with laws and the legal system. This chapter has outlined a handful of the arenas in which this interaction is likely to occur. For advice in particular circumstances, especially pertaining to relevant state law, specialized legal consultation should be sought from knowledgeable attorneys in private practice, counsel and/or risk managers employed or retained by the health provider, the professional's or provider's liability insurance carrier, or an Institutional Ethics Committee.

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Chapter 31

Perioperative Evaluation and Management

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Learning Objectives

- Understand perioperative concerns that are unique to older adults.
- Identify strategies to optimize postoperative management in older adults, including pain control, prevention of delirium, and anticoagulation use.

Key Clinical Points

1. **Age alone is not a reliable predictor of operative risk and should not be the sole criteria for deciding who should and who should not have surgery. However, advanced age is associated with a higher prevalence of chronic diseases, which are strong predictors of operative risk.**
2. **The basic preoperative assessment should include a review of physical function, cognitive ability, competency, availability of social support, and symptoms of depression.**
3. **Current data suggest that many "routine" preoperative screening tests are ordered because of preoperative "protocol" or for medicolegal concerns, rather than medical necessity. The need for many such tests can often be eliminated with thorough history and physical examination.**

THE OLDER SURGICAL PATIENT

The anticipated rapid increase in the aging population will challenge the surgical and medical communities with an expanding group of patients who will require surgical interventions, often major, much later in life. Among the most frequently performed surgical procedures in this age group are hip and knee replacements, cataract extractions, coronary artery bypass grafting, colorectal resections, and cholecystectomies. In coming years, health care systems will struggle not only with the need to provide surgical care that prolongs life but also promotes the greatest level of functional independence for older patients, without an excessive risk of complications.

When factors influencing postoperative complications are examined, chronological age remains an independent risk for adverse surgical outcomes. Advancing age is a marker for significant medical comorbidities that can complicate surgical procedures. The age-associated reduction in the capacity to adapt to physiologic stress, a progression in functional frailty, and the number of comorbid illnesses are better predictors than age alone for tolerating the rigors of surgery poorly. In addition to increasing overall operative risk, these factors also prolong recovery times, contributing to postoperative functional declines, and increase the need for rehabilitation, nursing, and home care support after surgery. Therefore, a comprehensive review of each patient's medical, social, cognitive, and functional status is essential. Whenever possible, the preoperative clinical assessment should include a discussion with the primary care provider. The primary care provider typically has the greatest experience with the patient and is often able to provide

useful insights, such as history of developing delirium during hospitalizations, which prove useful in guiding the older adult through surgery. Lack of communication between the surgical and the medical providers leads to a failure to incorporate important clinical issues and patient concerns with subsequent impact on perioperative care of the older patient. Formal "comanagement" approaches have become increasingly common, involving both medical and surgical specialists in the perioperative period and appear to improve overall quality of care, including decreased length of stay. The critical nature of the transition between inpatient and outpatient and subacute care has been recognized as an important area for quality improvement.

Because the medical and surgical managements of older patients often overlap, a comprehensive review of the medical and surgical goals and any ethical implications should be routinely completed. The primary goal of surgery is to maximize the lifespan and functional status of patients in a manner that preserves dignity, self-esteem, and independent function; limits suffering and pain; and occasionally palliates adverse clinical symptoms. To accomplish these goals, an ongoing dialogue between medical and surgical providers is essential.

HOW AGE INCREASES SURGICAL RISK

The effect of age on risk of surgery is reviewed in Chapter 33 "Surgical Outcomes." An effort to identify reversible factors associated with perioperative morbidity in geriatric surgical patients is critical to improving surgical outcomes (**Table 31-1**). In patients older than 80 years, the most prevalent operative risk factors are a history of coronary artery disease (CAD), impaired pulmonary function, and prior neurologic events.

TABLE 31-1 PHYSIOLOGIC CHANGES OF AGING AND EFFECTS ON PERIOPERATIVE CARE

SYSTEM	CHANGE	SIGNIFICANCE
General	↓ Skeletal muscle mass ↓ Thermoregulation	Altered volume of distribution Potential drug toxicity Greater frailty ↓ Functional recovery
Skin	↓ Reepithelialization ↓ Dermal blood vessels	↓ Rate of wound healing
Cardiac	↑ Vascular stiffness ↑ Ventricular stiffness Conduction system degeneration Valvular degeneration ↓ Maximal heart rate Cardiopulmonary deconditioning ↑ Prevalence of coronary artery disease	↑ Blood pressure and ventricular vascular load Hypertension Ventricular hypertrophy ↑ Sensitivity to volume shifts ↓ Heart rate response ↑ Risk of high-grade arteriovenous blocks ↑ Risk of myocardial ischemia
Pulmonary	↓ Elastic recoil ↑ Chest wall stiffness ↑ V/Q mismatch ↓ Airway protections	↑ Potential for respiratory failure, (eg, sedative drugs) ↑ Risk of aspiration and infections
Renal	↓ Number of nephrons ↓ Decreased sodium and water excretion Prostatic hypertrophy	↓ Half-life of drugs cleared by the kidney ↑ Risk for fluid overload ↑ Urinary retention and infection risk
Immune	↓ Immune function	↑ Risk of infections
Hepatic	↓ Blood flow ↓ Microsomal oxidation	↑ Half-life for drugs cleared by the liver
Endocrine	Insulin resistance Impaired insulin secretion	Hyperglycemia

One example of how age increases operative risk is the age-associated changes in cardiac physiology. Primarily as a result of a loss of vascular compliance, the left ventricle demonstrates an increase in stiffness, impaired diastolic relaxation, and an increase in filling pressures. These changes subsequently make the ventricle less tolerant of shifts in intravascular volume. An acute increase in volume (eg, from intravenous fluids administered during surgery) leads to a further increase in left ventricular filling pressures and could result in pulmonary congestion as a consequence of the age-related increase in diastolic stiffness. Conversely, an acute loss of intravascular volume, such as the third spacing of fluid or intraoperative blood loss, reduces preload to the stiffened ventricle and could produce a marked reduction in systolic blood pressure. CAD, a common comorbidity, also increases risk; adding the intraoperative burden of myocardial ischemia to the already impaired diastolic relaxation leads to a further worsening of ventricular filling pressures and increases the risk of pulmonary edema.

Alterations in renal and hepatic metabolism place the older patient at a greater risk of perioperative drug toxicities. Previously unrecognized cognitive impairment may cause an older person to decline substantially with the stress of surgery. Such a decline may present atypically, such as the development of an acute confusional episode or frank delirium. Adverse changes in cognitive function will often prolong a hospital stay and worsen clinical outcomes. Significant age- and disease-related reductions in skeletal muscle mass (sarcopenia) decrease the capacity of the older patient to make a functional recovery, possibly resulting in a discharge to a subacute or long-term care facility.

The older patient may be unable to adequately communicate concerns or clinical history to a health care provider. Therefore, maximizing the communication and exchange of data between the surgical team and the medical providers can help ensure the best possible outcome for the older patient. Clinical programs that foster close communication among surgeons and consulting internists or geriatricians have demonstrated improved surgical outcomes and greater functional recoveries. Teamwork and communication between the various services are critical to promoting the best possible understanding of the patient's clinical situation, helping to mitigate surgical risk.

In summary, because normal aging does not account for the bulk of operative risk, the clinician's task is to identify underlying illnesses in older patients and assess their impact on perioperative risk.

SPECIFIC CONSIDERATIONS IN OLDER ADULTS

Cardiac Complications

CAD and heart failure (HF) are highly prevalent in older populations and remain the primary cause of death for the older patient. An estimated 25% to 30% of all perioperative deaths are attributed to cardiac causes. Because older adults are more likely to have significant CAD and HF, patients should be carefully screened for signs and symptoms of occult or overt disease. The left ventricular ejection fraction (LVEF) is an independent risk factor for major adverse cardiac events (MACE) with an increased risk of death when the LVEF falls below 40%. The risk of MACE is also higher among patients with HF with preserved LVEF than those without HF. Two-thirds of older adults with HF have normal left ventricular systolic function, and as previously noted the age-associated increases in vascular and left ventricular stiffness result in a greater sensitivity to volume shifts. Age-related declines in the electrical conduction system place the older patient at a greater risk of drug-induced bradycardia or high-grade atrioventricular blocks. A history of prior myocardial infarction or a low LVEF is associated with a greater risk of ventricular tachycardia. Older age (> 65 years) is also an independent risk factor for perioperative stroke and a history of stroke is a predictor of perioperative MACE.

Pulmonary Complications

Postoperative pulmonary complications are another important cause of postoperative morbidity and mortality. Besides patient-related risk factors such as cigarette smoking and history of chronic lung disease, advanced age is an important predictor of adverse postoperative pulmonary complications. With increasing age, the respiratory system demonstrates several changes in function, which may include a loss of pulmonary elastic recoil, decreased diffusion capacity, and reduced cough and gag reflexes, as a consequence of either neurologic injury or respiratory muscle weakness. Postoperatively, it is common for older patients to experience atelectasis or aspiration. An estimated 14% of older patients will have a major pulmonary perioperative complication (atelectasis, pneumonia, respiratory failure, exacerbation of chronic lung disease, bronchospasm, pleural effusion, pneumothorax, and airway obstruction), particularly after an abdominal or a cardiothoracic procedure. Postoperative pneumonia in older patients is associated with a 15% to 20% mortality rate. A detailed pulmonary and occupational exposure history prior to surgery can help

predict impaired respiratory function. Because neurologic events that may impair airway protection are occasionally subtle, obtaining a history of swallowing difficulties or prior aspiration may prompt postoperative interventions aimed at reducing aspiration risk.

Renal Complications

Renal function is reduced as a result of glomerular and tubular senescence. The progressive sclerosis of glomeruli that occurs with increasing age is hastened by comorbid conditions like hypertension, diabetes mellitus, and CAD. In the older patient, the serum creatinine often does not fully reflect the reduction in renal function. The age-associated reduction in skeletal muscle reduces creatinine production, so a reduced creatinine clearance is not always as apparent, even in the setting of diminished filtration. Baseline renal insufficiency results in greater risk for volume and pH disturbances in the perioperative period. Older adults are more susceptible to preoperative dehydration, intraoperative fluid shifts, hypotension and hypovolemia, factors associated with the development of acute tubular necrosis, the most frequent cause of postoperative renal dysfunction. Certain medications and use of contrast dye can also contribute to renal toxicity. Also, alterations in renal (and hepatic) metabolism place the older patient at a greater risk of perioperative drug toxicities.

Infectious Complications

Postoperative infectious complications represent a major source of morbidity and mortality for older adults. In addition, the development of a surgical site infection or other health care–acquired infection can substantially increase length of stay and associated health care costs. The extended use of indwelling devices, prolonged ventilation, and length of stay are important risk factors for postoperative infections. Infections associated with devices and prosthetic material can present unique treatment challenges. The treatment of significant infections often requires extended courses of parenteral and/or oral antimicrobial therapy, which can raise issues related to safety and tolerability of antimicrobial agents, including nephrotoxicity. Prolonged need for antimicrobials can also increase the risk of *Clostridium difficile* infection. Prevention strategies are evolving and include targeted preoperative decolonization for *Staphylococcus aureus*.

Functional Capacity

Functional impairment is an index of the severity of many chronic diseases, and its severity predicts operative risk to some degree. For example, poor performance on a bicycle ergometer is a better predictor than the Goldman criteria of surgical outcomes and postoperative pulmonary complications. Sarcopenia (severe depletion of skeletal muscle mass) is also an independent predictor of postoperative morbidity and mortality among older adults undergoing emergency surgery. The metabolic demands of surgery and the physical immobility associated with recovery may promote further declines in strength and function. Not infrequently, a previously independent older adult can become so frail postoperatively that rehabilitative care is needed. Promoting clinical services that increase physical activity and rehabilitation during the surgical recovery process may improve the level of functional independence, shorten recovery times, and prevent readmissions. Postoperatively, the “transitional” care plan must be seamless. Some patients also benefit from referral to a formal cardiac or pulmonary rehabilitation program.

Emergency Surgeries

While emergency surgeries are associated with a higher overall death rate in all age groups, this finding is most apparent among older patients who have the highest mortality rates as a consequence of a greater number of complications. The causes for the increased risk are multifactorial. The identical surgical disease in the older adult may present later in its course, and diagnosis can be delayed because of an atypical presentation. Also, the older patient may undergo surgery later due to efforts to “optimize” comorbidities prior to surgery. In the older patient, a delay in a needed nonemergent surgery may have a greater risk if the delay could result in an emergent procedure. Therefore, clinicians should be aware that if the time needed to optimize the patient for surgery is extended, an anticipated elective procedure could become a higher-risk emergent procedure.

Other Concerns

A neurologic event, such as a stroke, may increase the risk of aspiration by impairing the ability to swallow, to move food through the esophagus, and to control respiratory secretions. Advancing age is also associated with a decrease in

esophageal peristaltic wave amplitude, reduced tone of the lower esophageal sphincter, a greater incidence of hiatal hernias, delayed gastric emptying, and increased gastroesophageal reflux, all of which are factors that may increase the perioperative aspiration risk. Impaired glucose regulation and risk for stress hyperglycemia are common in this age group and may increase infection risks. Thus, careful monitoring to control blood sugars perioperatively may have important benefits. Pressure ulcers are another important postoperative complication (see Chapter 52 "Pressure Ulcers"). Age-related changes in mobility and sensation can contribute to breakdown of skin integrity. Aggressive preventative measures including frequent assessment and pressure unloading are essential aspects of postoperative management.

Taking the time to thoroughly discuss what is involved with a particular surgery with older patients and their families can help promote a clearer understanding of risk and benefits and reduce false expectations. Incorporating regular patient and family conferences can be helpful. In such discussions, it is often apparent that an older patient has a different outlook and acceptance of a specific level of care. Shorter-term goals, such as the quality, not quantity, of life may be most important. Additionally, the overall tolerance of surgery may be different than that of a younger person. The understanding that a longer time to recover may be necessary is often best communicated in this forum. It is also important to inform the patient and family that an intermediate-care program may be needed, such as a subacute care center, a rehabilitation unit, as well as the extended use of home care services.

Period of Risk

Anesthesia is generally considered a safe procedure in older patients, with a progressive decline in complication rates being observed in recent years (see Chapter 32 "Anesthesia"). Preoperative risk factors are a better predictor of 7-day mortality than is the duration of anesthesia or the experience of the anesthesiologist. Once the preoperative risk factors are controlled for, the type of anesthesia (eg, spinal vs general) fails to predict outcomes. The greatest period of risk for complications remains the time immediately after surgery, with half of adverse events occurring within 3 weeks of surgery.

PREOPERATIVE MANAGEMENT

General Principles

As is the case with all patients scheduled to undergo surgery, the goal of the preoperative evaluation in older adults is to assess current health status and optimize medical conditions that impact perioperative outcomes. After an initial assessment, additional testing to grade the severity of medical comorbidities may be indicated to further refine the individual patient's risk of perioperative complications. Providers should engage the patient and family members in an informed discussion weighing the risks, benefits, and alternatives to the proposed procedure by inviting questions, and incorporating their beliefs and preferences into the perioperative management plan.

History and Physical

The accurate assessment of risk begins with a detailed review of the clinical history and physical examination. Underlying decline in cognitive function is an essential aspect of the risk assessment of the older patient and may reduce the validity of reported signs and symptoms. A discussion with family members should be sought if clinical data are unclear, cognitive impairment is profound, or the responses are misleading.

The basic assessment should include a review of physical function, cognitive ability, competency, availability of social support, and symptoms of depression. Cognitive impairment places the patient at an increased risk of perioperative delirium and an extended hospital course. Older patients should be screened for impairments using the Mini-Mental State Examination (MMSE) or similar standardized screening instrument. An older patient with little family or social support who undergoes surgery is likely to have a protracted recovery period. Therefore, a preoperative evaluation by a social worker with experience in geriatric medicine is helpful in structuring a supportive network of resources to facilitate the recovery process. Subacute nursing care facilities may play a particularly helpful role in advancing the frail older patient through the recovery process and back to independence. Many institutions have active geriatrics consult services, which can provide detailed guidance on discharge planning issues.

The physical examination can be altered by age and disease. For example, a systolic ejection murmur suggesting aortic stenosis may represent aortic valve sclerosis rather than a hemodynamically significant valvular stenosis. Additionally, markers of severe aortic stenosis, a diminished S2, or a delay in the carotid upstroke may be less

apparent in older patients. When the examination is uncertain, echocardiography and Doppler studies are warranted to establish an accurate cardiac diagnosis, particularly if the murmur is late peaking or radiating to the carotids. Because of various physical and social limitations, reliable access to a primary care may be an issue for some older adults, and thus, previously undiagnosed medical conditions, such as Parkinson disease, major depression, or symptomatic hypothyroidism, may be exposed during the preoperative assessment.

Medications

The preoperative examination is an ideal time to review medication lists and to readdress the overall benefit of each drug for the patient. Aspirin, clopidogrel, nonsteroidals, and other antiplatelet drugs increase the risk of perioperative bleeding and, if not essential, should be held for a recommended 5 to 7 days. Drugs with anticholinergic properties, such as diphenhydramine or meclizine, can increase the risk of perioperative delirium and should be held or discontinued. Chronic benzodiazepine use is common and often underrecognized. These drugs should be tapered, when possible, to reduce the risk of withdrawal symptoms. Holding diuretics for 24 hours prior to surgery should be considered if these are not needed to treat excessive volume or symptoms of pulmonary congestion in patients with HF.

Patients on antiepileptic, cardiovascular, and antihypertensive medications typically should take their medications on the morning of surgery. Abrupt discontinuation of β-blockers and clonidine is associated with significant cardiovascular complications. Patients using these medications can be managed with intravenous metoprolol, or transdermal clonidine patches if unable to resume oral intake postoperatively. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are commonly held on the morning of surgery to avoid the known risk of hypotension upon induction of anesthesia. Oral hypoglycemics are generally held the night prior to surgery, to reduce the risk of perioperative hypoglycemia. Patients who require insulin typically receive 50% to 80% of their usual dose of basal insulin on the morning of surgery. Rapid-acting or mealtime insulin is held on the day of surgery as patients are NPO. Postoperative glucose levels above 250 mg/dL can be safely managed with short-acting subcutaneous insulin while intravenous infusions of insulin is preferred if hemodynamic instability is present (a cause of variable absorption of subcutaneous insulin). Although acute adrenal crisis is an uncommon condition, it is reasonable to administer perioperative stress dose steroids for patients with adrenal suppression from chronic steroid exposure. A typical regimen consists of 25 to 50 mg of intravenous hydrocortisone every 8 hours depending on the magnitude of the procedure, and tapering over 2 to 3 days as permitted based on the postoperative course. For patients who develop postoperative adrenal insufficiency, replacement of both glucocorticoids and mineralocorticoids is necessary. Medications for seizure disorders, Parkinson disease, and agents for myasthenia gravis should be continued throughout the perioperative period to minimize the risk of worsening neurologic symptoms.

Preoperative Laboratory Testing

A variety of laboratory and specialty tests are often performed during the preoperative evaluation. However, current data suggest that many “routine” preoperative screening tests are ordered because of preoperative “protocol” or for medicolegal concerns, rather than medical necessity. It is estimated that two-thirds of laboratory tests that are ordered preoperatively are unnecessary, especially prior to low-risk procedures. In addition, the risk of false-positive results increases when testing for conditions that have a low prevalence, prompting further testing while contributing to surgical delays, health care cost, and patient anxiety. The need for many such tests can often be eliminated with thorough history and physical examination.

Chest radiographs (CXR) and electrocardiograms (ECG) are also ordered frequently during the preoperative evaluation. Again, data suggest that the “routine” use of either test is not indicated for all patients. Although ECG abnormalities are more common among older adults, the findings mostly confirm what is previously known, and also, most abnormalities do not change management. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines support preoperative ECG screening for all patients with known cardiac, vascular, or cerebrovascular disease, except for those undergoing low-risk surgeries. Routine ECG screening is also not recommended for asymptomatic older patients undergoing low-risk surgery. A preoperative CXR is not necessary for patients solely for the reasons of advanced age, stable chronic obstructive pulmonary disease (COPD), smoking history, and stable cardiac disease in the absence of active or unexpected clinical findings.

Preoperative Cardiac Evaluation for Noncardiac Surgery

As 25% to 30% of perioperative deaths are attributed to cardiac causes, much of preoperative risk assessment is focused on predicting these cardiac complications. The older patient has a high prevalence of CAD, which is often subtle or even silent until the stress of surgery. The current ACC/AHA guidelines offer a rapidly applied algorithm, which help guide appropriate preoperative testing and management (**Figure 31-1**). The coronary artery revascularization prophylaxis trial used a randomized design to compare preoperative revascularization (either percutaneous coronary intervention or coronary artery bypass grafting) versus medical therapy in patients with significant but stable coronary disease undergoing major vascular surgery. The results suggest that preoperative revascularization does not significantly alter long-term outcomes in terms of mortality as well as cardiac events. Based on these findings, a strategy of revascularization before elective vascular surgery in patients with stable cardiac symptoms is generally not recommended.

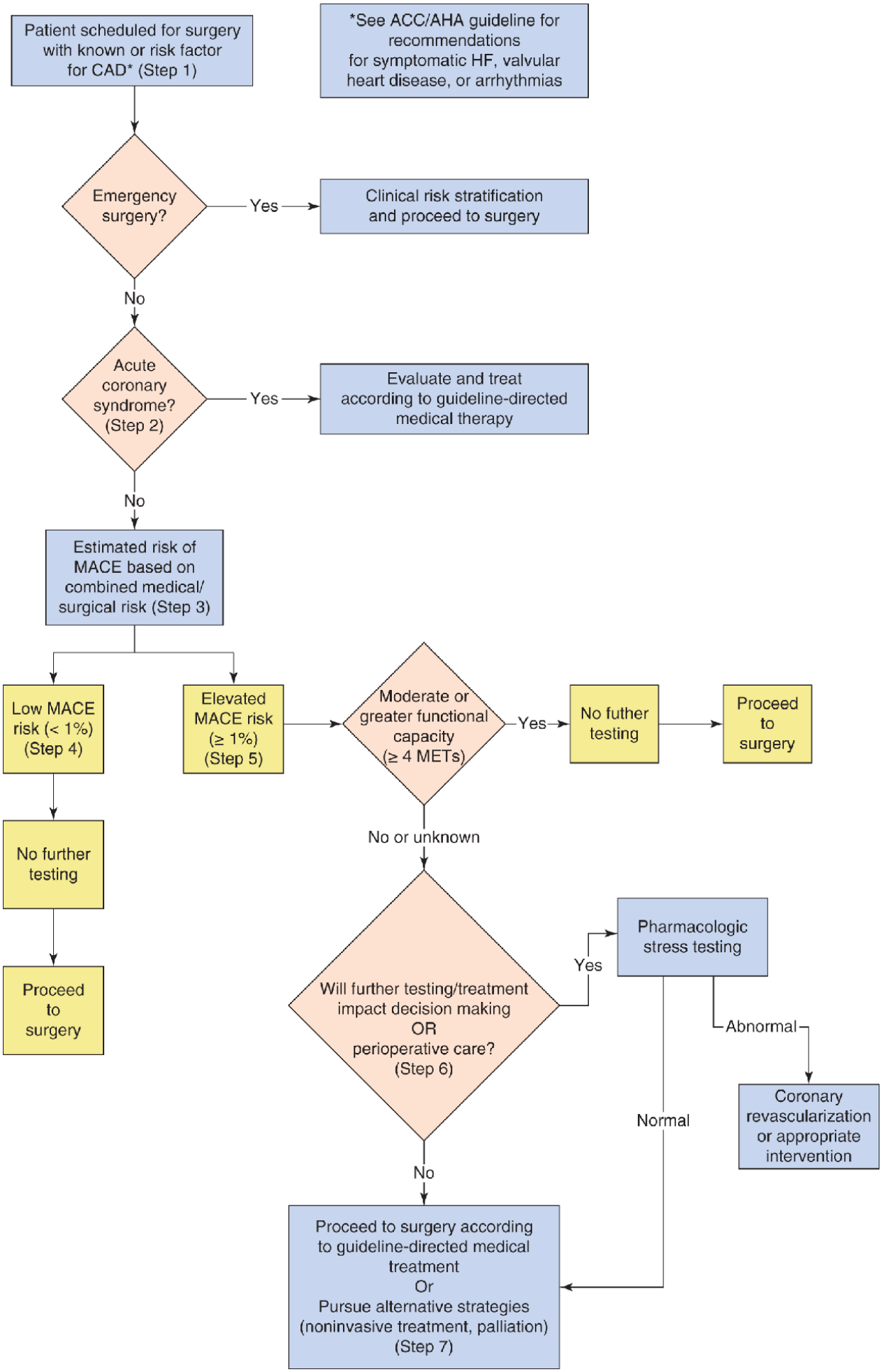

Patient scheduled for surgery with known or risk factor for CAD* (Step 1)
*See ACC/AHA guideline for recommendations for symptomatic HF, valvular heart disease, or arrhythmias
Emergency surgery?
Yes
Clinical risk stratification and proceed to surgery
No
Acute coronary syndrome? (Step 2)
Yes
Evaluate and treat according to guideline-directed medical therapy
No
Estimated risk of MACE based on combined medical/ surgical risk (Step 3)
Low MACE risk (< 1%) (Step 4)
Elevated MACE risk (≥ 1%) (Step 5)
Moderate or greater functional capacity (≥ 4 METs)
Yes
No futher testing
Proceed to surgery
No or unknown
No further testing
Proceed to surgery
Will further testing/treatment impact decision making OR perioperative care? (Step 6)
Yes
Pharmacologic stress testing
Abnormal
Coronary revascularization or appropriate intervention
Normal
No
Proceed to surgery according to guideline-directed medical treatment Or Pursue alternative strategies (noninvasive treatment, palliation) (Step 7)

FIGURE 31-1. Stepwise approach to preoperative cardiac risk assessment. (Adapted with permission from Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;64(22):e77–e137.)

An in-depth review of the preoperative assessment prior to noncardiac surgery is beyond the scope of this chapter. However, the reader is encouraged to review current guidelines. The aggressiveness of the evaluation should be determined by the patient's clinical symptoms. On occasion, medical concerns may require the cancellation of surgery. In general, surgeries can be categorized based on the following recommended time frames. Emergency surgery is defined as one in which life or limb is threatened if not operated upon, typically within 6 hours, leaving little to no time for a formal preoperative evaluation. An urgent procedure may offer a few more hours for evaluation prior to the operating room (6–24 hours). Surgeries where a delay of more than 1 to 6 weeks for a preoperative evaluation and management changes could negatively impact surgical outcomes are classified as "time-sensitive." Several oncologic procedures fall within this category. Lastly, elective procedures are those that have the potential to be delayed for several months or a year without a significant impact on surgical outcome. Elective procedures offer the best opportunity for preoperative medical optimization.

The initial history, physical examination, and baseline ECG are helpful in identifying potentially serious cardiac disease such as a prior myocardial infarction, angina, HF, conduction abnormalities, or arrhythmias. It is essential to define the severity of cardiac disease, its stability, and any prior treatments before surgery. A procedure is classified as low risk when the rate of associated MACE is less than 1%. Examples of low-risk surgeries are cataract surgery, endoscopic procedures, and most dermatologic surgeries. All other surgeries (MACE rate > 1%) are categorized as elevated-risk procedures. Vascular procedures or prolonged thoracic, abdominal, and head and neck surgeries are considered to be at even higher risk. One benefit of the ACC/AHA guidelines is the use of a simple flowchart to define surgical risk and provide management guidance in a stepwise process (see **Figure 31-1**). Seven key questions help to direct the decision process down the flowchart and are briefly reviewed.

- *Step 1. Determine urgency of surgery:* If a patient has an immediate need for surgery, with a poor likelihood of survival without it, then it is best to provide medical management as needed and permit the surgery without delay.
- *Step 2. Determine the presence of acute cardiac decompensation:* For procedures that are nonemergent, does the patient have active symptoms or signs of decompensated cardiac disease such as acute coronary syndrome? If yes, then guideline-directed medical treatment for the underlying cardiac condition is recommended.
- *Step 3. Estimate perioperative risk of MACE on the basis of the medical/surgical factors:* The ACC/AHA guidelines offer two objective cardiac risk stratification tools to estimate perioperative risk. The revised cardiac risk index (RCRI) score includes six independent risk factors to calculate a patient's risk of MACE that includes history of ischemic heart disease, heart failure, insulin-treated diabetes, chronic kidney disease with serum creatinine greater than 2 mg/dL, stroke/transient ischemic attack (TIA), and high-risk surgery (defined as intrathoracic, intra-abdominal, or suprainguinal vascular surgery) (**Table 31-2**). According to this widely used tool, patients with zero or one risk factors would have a low risk of MACE (< 1%), whereas those with two or more risk factors would be at elevated MACE risk (> 1%). Another option endorsed by the ACC/AHA is a risk-prediction calculator developed using data from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database. This online risk-prediction tool uses adjusted odds ratios for various risk factors and different surgical sites, thus providing a more detailed procedure-specific risk assessment.
- *Step 4. Patients with low MACE risk:* Most patients whose medical/surgical risk of MACE is estimated at less than 1% can proceed to surgery without further testing.
- *Step 5. Patients with elevated MACE risk:* For patients in whom the medical/surgical risk of MACE is greater than 1%, the need for further assessment is dependent on their functional capacity. This is best assessed in metabolic equivalents of task (MET) and is helpful in predicting risk (**Table 31-3**). The risk of perioperative cardiac and long-term complications is higher in patients unable to perform four METs of work during daily activities. Patients able to perform activities greater than four METs without symptoms are considered to have acceptable risk and can proceed to surgery without further testing.
- *Steps 6 and 7. Patients with elevated MACE risk and low/unknown functional status:* Noninvasive cardiac stress testing may be appropriate for individuals with limited or unknown functional capacity (< four METS) if the result of such testing is likely to either inform decision making or change perioperative care (see **Table 31-3**). An informed discussion between the medical and surgical teams and the patient regarding the possibility of further testing and willingness to undergo coronary revascularization is necessary prior to arriving at this decision.

Otherwise, the patient may choose to proceed to surgery, albeit at an elevated risk, or pursue noninvasive treatment or palliation.

TABLE 31-2 REVISED CARDIAC RISK INDEX

NUMBER OF RISK FACTORS[a]	MACE, %
0	0.4–0.5
1	0.9–1.3
2	4–7
≥ 3	9–11

[a]Assign one point for each of the following: history of ischemic heart disease; history of heart failure; history of stroke or TIA; diabetes requiring treatment with insulin; chronic kidney disease (serum creatinine level > 2 mg/dL); high-risk surgery.

MACE, major adverse cardiac events.

Data from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10):1043.

TABLE 31-3 ESTIMATED ENERGY REQUIREMENTS

1 MET	Activities of daily living, self-care	4–7 METs	Climb a flight of stairs or walk a hill
	Eat, dress, toilet		Walk, level ground at 4 mph/h
	Walk indoors		Run a short distance
1–4 METs	Walk 1–2 blocks on level ground (2–3 mph)		Do heavy work, scrubbing floors, moving furniture
	Do light work around the house such as dusting or washing dishes		Moderate exercise: golf (no cart), bowling, dancing, doubles tennis, throwing a ball
		> 10 METs	Strenuous sports: swimming, singles tennis, soccer

MET, metabolic equivalent of task.

Other Cardiovascular Concerns

Hypertension Whenever feasible, severe hypertension should be controlled before surgery. Continuation of preoperative antihypertensive medications throughout the perioperative period is critical, particularly if that agent is a β-blocker or clonidine.

Valvular disease Indications for the evaluation and treatment of valvular heart disease are similar to those in the nonoperative setting. Symptomatic mitral or aortic stenosis is associated with significant perioperative risk. Selected patients may be candidates for percutaneous valvotomy or valve surgery preoperatively. Symptomatic aortic or mitral regurgitant disease is typically of less risk during surgery when managed with intensive medical therapy and monitoring. The patient with both severe valvular regurgitation and reduced left ventricular function is best managed with the assistance of a consultant cardiologist.

Perioperative β-blockers Initiating β-blockers in the perioperative period is controversial as the published data have been inconsistent. This has made it difficult to provide strong recommendations for their use perioperatively. It is clear, however, that β-blockers should be continued for patients who are already taking them. Furthermore, starting β-blocker therapy should be considered perioperatively for patients at high risk of coronary events who are scheduled for elevated-risk noncardiac surgery, provided contraindications do not exist. It is clear that large doses of these agents should not be started on the day of surgery due to an increased risk of stroke and overall mortality. Caution is also advised as β-blockers increase the risk for hypotension and bradycardia, side effects that can be particularly dangerous in older patients. If initiated, β-blocker therapy should be prescribed several days to weeks prior to surgery at a starting dose with subsequent gradual dose adjustments to achieve a resting heart rate of 55 to 65 beats/min while avoiding hypotension. When prescribed, β-blocker therapy should be continued throughout the perioperative period and up to 30

days postoperatively.

Preoperative Pulmonary Evaluation

Estimating the risk of perioperative pulmonary complications is challenging for several reasons including differences in case definitions, surgical context, and variability in outcome measurement among studies. Additionally, many of the clinical risk predictors are not readily modifiable. Thus, the biggest utility of such an evaluation is to allow high-risk patients make an informed choice between surgical and nonsurgical treatment options. Patient-related factors that increase the risk of pulmonary complications include advanced age, presence of chronic lung disease such as COPD, American Society of Anesthesiologists class, functional dependence, impaired sensorium, frailty, and cigarette smoking. Procedure-related factors include emergency surgery, thoracic and upper abdominal procedures, prolonged operation (> 3 hours), and type of anesthesia and anesthetic agent. It is important to note that the procedure-related risk factors present a much higher risk for postoperative pulmonary complications than patient-related risk factors. Pulmonary function tests (PFTs) have not been shown to be predictive and are not routinely recommended prior to surgery. However, PFTs may be valuable in evaluating patients with unexplained dyspnea or determining the status of patients with undiagnosed pulmonary disorders.

High-risk patients should have an introduction to the proper use of incentive spirometry prior to surgery, to help reduce the risk of pulmonary atelectasis and associated complications. Aggressive efforts to promote smoking cessation prior to surgery should also be encouraged. Obstructive and reactive airway disease should be optimally controlled with metered-dose inhaler–based therapies prior to surgery. Besides the use of lung expansion techniques, promoting early mobility and providing adequate postoperative analgesia may decrease the risk of perioperative pulmonary complications.

Other Preventive Measures

The waiting period before an elective procedure can be used to promote activities that may enhance the recovery from surgery. Evidence suggests that patients who receive exercise training twice a week, education, nurse-initiated telephone calls, and an offer to participate in postoperative cardiac rehabilitation require fewer days in the hospital, less time in the intensive care unit, and greater improvements in measures of quality of life. Many surgeons recommend preoperative physical conditioning by encouraging patients to walk daily for 2 to 3 weeks prior to an elective surgery. This is generally coupled with early ambulation postoperatively.

Deep venous thrombosis (DVT) is a vexing concern in the postoperative patient. Pulmonary emboli remain one of the leading causes of postoperative deaths of older patients. Procedures commonly performed in the older person, such as hip or knee replacement and urologic or gynecologic procedures, place the older patient at a high risk for this complication. For most surgeries, subcutaneous low-dose unfractionated heparin or low-molecular-weight heparin (LMWH) should be started immediately after surgery and be continued until the time of discharge. Use of external pneumatic compression devices is another means to prevent postoperative DVT.

Do-Not-Resuscitate Orders

The need for surgery in patients with do-not-resuscitate (DNR) orders or concerns of medical futility may be an issue in some older patients. Unfortunately, many older adults still do not have discussions with their health care providers prior to a hospitalization concerning code status, even though this is often mandated. The Patient Self-Determination Act requires that hospitals and other health care facilities inform patients of their right to appoint a proxy or surrogate decision maker to act on their wishes regarding life-sustaining care should they become incompetent. Focused efforts by nurses, clinicians, and consultants to enhance communication can increase the use of advance directives. Debate exists about honoring these orders in the operating suite when a patient requests a DNR status and still must undergo surgery (eg, percutaneous feeding tube). Surgery may hasten a death as the result of an unanticipated complication. Most of the immediate operative causes for a cardiac arrest are more treatable than the causes of an arrest in other clinical settings, such as the nursing home, because these may include correctable conditions such as oversedation, arrhythmias, hypotension, pulmonary edema, or bleeding. It is common to suspend a DNR order during the procedure and for 24 to 48 hours afterward. If a complication occurs, the patient is treated and the family or those with decision-making responsibilities are consulted. An evaluation of survivability is made and a decision to suspend or continue the interventions is discussed. This process is less clear when there is a concern that the surgical procedure is potentially medically futile (ie, when a procedure would have only marginal benefit). Ongoing discussion in this clinical scenario

is essential.

POSTOPERATIVE MANAGEMENT

Postoperative management includes the appropriate use of medications for pain, increasing mobilization, proper use of urinary catheters, the treatment and prevention of delirium, and anticoagulation use.

Pain Control

Pain is often undertreated in older patients because of the concern of using potent analgesics in older patients and a misconception that pain sensations are diminished in such patients. Postoperative patients should be regularly asked about the severity of their discomfort using analog scales, and analgesics should be given according to anticipated needs rather than "as needed." Simply scheduling pain medications is another useful approach. Comments on the management of persistent pain, medication dosing, and metabolism, as well as associated toxicities, are well summarized by the American Geriatrics Society's comprehensive review of this topic.

Early Mobilization

Prolonged bed rest can adversely affect the older patient. Changes noted with prolonged immobility include a decrease in cardiac output and aerobic capacity, baroreceptor desensitization and orthostatic hypotension, skeletal muscle deconditioning, bone loss, hypercalcemia, joint contractures, constipation, incontinence, pressure sores, sensory deprivation, an increased risk for DVT, atelectasis, hypoxemia, and pneumonia. Early mobilization from bed is vital, helping to reduce the risk for complications. If the recovery process prevents full mobilization, then a physical therapy referral for range-of-motion exercises and the maintenance of an upright posture (chair) may reduce the frequency and severity of these complications.

Catheters

Postoperative urinary drainage is often managed by an indwelling catheter but this predisposes to urinary tract infection and associated complications. Catheter use should be short, with a goal of prompt removal by the morning after surgery. If there is a concern for urinary retention or bladder distension, then intermittent catheterization should be considered. The use of a urinary catheter beyond 48 hours should be avoided, except when retention cannot be managed by other means. Patients requiring longer-term use of a urinary catheter should not be given prophylactic antimicrobials.

Postoperative Delirium

An acute confusional state occurs in 10% to 15% of older patients undergoing general surgery, 30% of cardiac surgery patients, and, in one study, up to 50% of hip fracture repairs. Delirium is also a marker for worse functional recovery, and older patients with in-hospital delirium are at risk of significant long-term reduction in cognitive function (see Chapter 47).

Delirium is often subtle and can easily be missed. Clinical factors key to the diagnosis are a rapid onset, a disturbed level of consciousness, decreased attention and environmental awareness, memory deficits, disorientation, perceptual disturbances, and evidence of a condition that contributes to its development. A history of dementia as well as prior delirium, advanced age, and a prior decline in cognitive function are risk factors for perioperative delirium. As a rule, delirium fluctuates and may not be evident during all visits. Nursing staff and family members are often the most reliable source for the serial assessments of an at-risk patient.

Delirium often compromises postoperative care and extends length of stay. Behaviors can often be controlled with environmental measures, such as a bedside sitter, increased visitations by family, frequent orientation, minimizing abrupt relocations, and permitting patients to return to a more normal day-night cycle. If medically appropriate, the use of a sleep protocol is often helpful. Symptomatic control of agitation to prevent harm is occasionally needed. Unfortunately, no single drug has an accomplished record. High-potency antipsychotics such as risperidone, haloperidol, olanzapine, and quetiapine should be cautiously titrated to improve symptoms. Lower-potency drugs such as chlorpromazine and thioridazine should be avoided because of their associated anticholinergic and arrhythmogenic effects. If delirium is secondary to alcohol withdrawal, short-acting benzodiazepines can be used with close monitoring

for excessive sedation. Formal delirium prevention protocols can be helpful, especially in the intensive care unit setting.

Other Complications

Postoperative surveillance for myocardial ischemia, infarction, arrhythmias, and DVT should ideally lead to a reduction in mortality. Postoperative myocardial ischemia is the strongest predictor of cardiac morbidity. Anginal pain may be masked by narcotics or may be difficult to verbalize during recovery. Postoperative ST-segment changes on ECG are indicative of myocardial ischemia and are an independent predictor of events. Such changes are associated with a worse long-term survival. The optimal surveillance strategy for the diagnosis of postoperative ischemia or infarction has not been defined. In patients without documented CAD, surveillance should be restricted to patients who develop signs or symptoms of cardiovascular dysfunction. Cardiac troponin measurements should be part of the diagnostic plan for myocardial infarction detection, but additional research is needed to correlate outcomes to the magnitude of an isolated cardiac troponin elevation. As a rule, postoperative myocardial infarctions have a similar pathology to infarction occurring in a nonsurgical patient, the spontaneous thrombosis of the coronary artery. Therefore, when this complication occurs, appropriate medical management as well as an aggressive attempt at opening the infarct-related artery should be considered in the appropriate postoperative patient.

Postoperative arrhythmias are often caused by correctable noncardiac problems such as infection, hypotension, metabolic abnormalities (hypokalemia and hypomagnesemia), and hypoxia. Ventricular arrhythmias (frequent ventricular ectopic beats or nonsustained ventricular tachycardia) may occur in more than one-third of high-risk patients. Prophylactic use of antiarrhythmics other than β-blockers is not recommended. Sustained ventricular tachycardia with or without hemodynamic complications requires consultation with a cardiologist. Postoperative atrial fibrillation is common. Approximately 25% of older patients develop this rhythm. Age and the type of surgery are strong predictors for the development of atrial fibrillation. The prophylactic use of a β-blocker and amiodarone has shown some benefit by reducing the frequency of this rhythm, but is not routinely recommended.

Hemoglobin levels often fall after major surgery. Transfusions should be reserved for patients with symptoms and possibly those with levels below 7 g/dL. Small trials have demonstrated that administering intravenous iron infusions in anemic patients prior to hip and knee replacement surgery reduced the need for postoperative blood product transfusions.

Cognitive decline has been noted following a variety of surgeries. The International Study of Postoperative Cognitive Dysfunction found that 26% of patients older than 60 years who had either intra-abdominal or orthopedic procedures had a significant decline in cognitive function 1 week after surgery. Risk factors included older age, greater use of anesthetics, and postoperative respiratory and infectious complications. In coronary artery bypass surgery, where the aorta is often cross-clamped and a bypass pump is used, embolization of both gas and particulates occurs. As a result, central nervous system ischemic damage is often noted after these procedures. Postoperative cerebral infarcts (many subclinical) are the likely cause of cognitive decline noted with cardiac surgery. Off-pump coronary artery bypass surgery seems to have a lower rate of short-term decline in cognitive function (21% vs 29%), but similar decline is noted at 6 months (31% vs 38%). The risk of further decline in cognitive function should be incorporated into the decision process for patients with underlying dementia who are not undergoing emergent or lifesaving surgery. Finally, postoperative critical pathways involving regimens, including low-dose opiates, early extubation, and an emphasis on accelerated functional recovery, can be safely applied to older patients.

The management of anticoagulants prior to surgery is briefly summarized. For patients on chronic warfarin with an international normalized ratio (INR) goal of 2.0 to 3.0, four scheduled doses should be withheld to allow the INR to normalize to less than 1.5 before surgery. If the INR is typically kept above 3.0, then longer periods without a warfarin dose may be required. The INR should be measured on the day of surgery to ensure that it has reached an acceptable range. If the INR is excessive, a small dose of vitamin K (eg, 1 mg intravenously or 2.5 mg orally) may be given, which will further reverse the INR within 24 hours. If rapid reversal of the INR is required, fresh frozen plasma can be administered. When the INR is less than 2.0, other prophylactic antithrombotic interventions should be considered.

Elective surgery is best avoided for at least 3 months following a DVT or pulmonary embolism (PE) event to ensure adequate duration of anticoagulation treatment. If this is not possible, then anticoagulation bridging with LMWH should be given before and after the procedure for patients on warfarin while the INR is less than 2.0. LMWH should be stopped 24 hours before surgery; restarting LMWH can be considered 24 to 48 hours after surgery, depending on the type of surgery, bleeding risk, and thrombotic risk of the patient. Patients receiving one of the newer oral anticoagulants (eg, dabigatran, rivaroxaban, or apixaban) do not require perioperative bridging therapy given the

relatively short half-life of these agents. These medications can be discontinued 1 to 4 days prior to surgery depending on the patient's risk of thrombosis, surgical bleeding risk, and renal function.

SUMMARY

As our society ages, the need for surgical procedures will continue to increase among older adults. Age alone is not a reliable predictor of operative risk and should not be the sole criteria for deciding who should and who should not have surgery. However, age is associated with a higher prevalence of chronic diseases, which, in turn, are strong predictors of operative risk and help determine who might benefit from surgery and preoperative testing. The AHA and ACC have published updated guidelines, which help guide preoperative cardiac risk assessment. Perioperative care requires a careful medical evaluation and comprehensive postoperative observation that anticipates potential complications. Newer techniques related to minimally invasive surgery appear promising. Besides decreasing recovery time and postoperative pain, there is some suggestion that overall operative risk may be decreased. Future studies examining clinical outcomes of interest in older adults will be an essential component of evaluating the relative risks and benefits of new interventions.

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Chapter 32

Anesthesia

Jeffrey H. Silverstein, Stacie Deiner

Learning Objectives

- Utlitize national guidelines such as the American Heart Association/American College of Cardiology guidelines to risk stratify older adults prior to surgery
- Discuss anesthetic options for different types of surgery
- Understand the difference between general anesthesia, regional anesthesia, and peripheral nerve blocks
- Discuss common postoperative complications experienced by older adults after surgery

Key Clinical Points

1. **The American Society of Anesthesiologists physical score is not a risk calculator but rather a clinician's tool, used to describe a patient's medical comorbidity in light of how it affects function.**
2. **Effective preanesthetic evaluation is best accomplished through good communication between primary and specialist physicians, the surgeon, the anesthesiologist, and the patient.**
3. **The main types of anesthesia are general anesthesia, monitored anesthesia care (sedation), regional anesthesia, and peripheral nerve blocks. A single surgery may require one or several of these techniques.**
4. **Normal physiology of aging and pathophysiology of aging combine to predispose older adults to postoperative complications.**

Perioperative management of the older adult is complex. Anesthetic care itself is challenging, and both preoperative preparation and postoperative care for older adults assume greater importance than for young, healthy adults. Ideally, care is based on a comprehensive plan that integrates the roles of the anesthesiologist, surgeon, geriatrician, primary caregivers, and medical specialists. This chapter provides an overview of the role of the anesthesiologist and anesthesia techniques in pre-, peri-, and postoperative care of the older adult, in order to improve communication with other professionals who provide care to this vulnerable population.

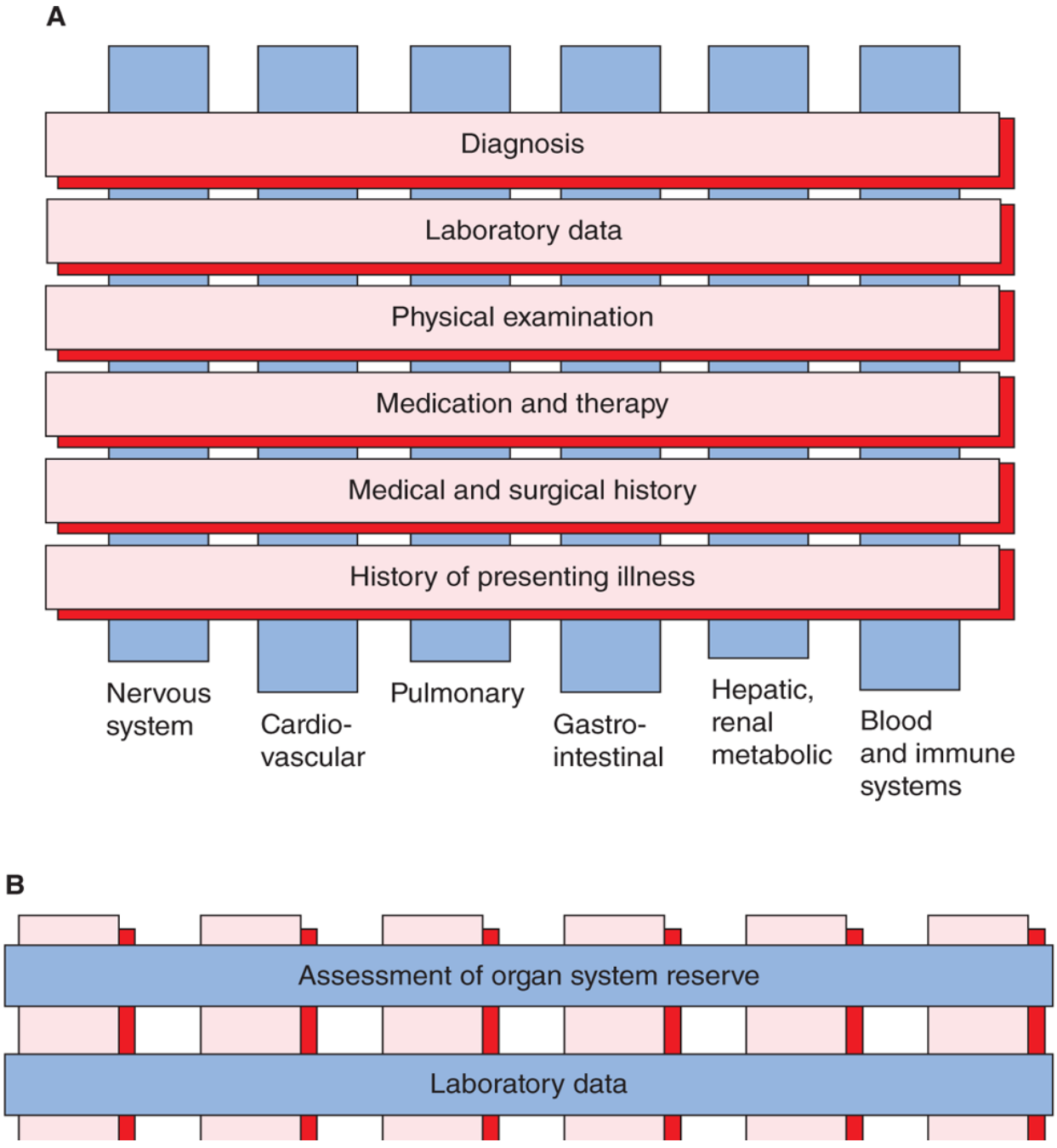
ANESTHESIA AND THE ANESTHESIOLOGIST

Anesthesia is the art and science of controlling physiologic processes in order to permit interventions on the body that would be intolerable owing to normal compensatory mechanisms. Surgery, which involves a direct assault on body tissues, is the standard paradigm for understanding anesthesia. Anesthesiologists perform other valuable services, including sedation for less invasive procedures, management of pain syndromes, and the provision of critical care. European anesthesiologists are also actively involved in emergency care. Anesthesia is based on an understanding of homeostatic mechanisms and their manipulation. *Homeostenosis*, the restricted range and capacity of homeostatic mechanisms associated with aging, provides a challenge to the anesthesiologist. In order to tailor appropriate anesthesia care for an older adult, the anesthesia team must be familiar with the effects of aging on multiple organ systems, particularly the heart, lungs, and brain, and must be familiar with physiologic changes of age, such as changes

in drug sensitivity, increase in body fat, decreased glomerular filtration, and reduced hepatic blood flow, which affect anesthetic drug action and duration.

PREOPERATIVE CARE OF THE OLDER SURGICAL PATIENT

Preoperative care can take place in multiple settings and can occur briefly or over a period of time. The most important goal of preoperative assessment is not the risk assessment, but the improvement of the patient's medical status prior to surgery and planning for the recovery process. The anesthesiologist provides care in a different time frame and uses a different approach than is typical for other specialties. The chief complaint usually takes the form of a request for anesthesia services for a specific operation. The anesthesiologist uses a vertical or systems-based approach, most clearly articulated by Stanley Muravchick (**Figure 32-1**). As part of this approach, the anesthesiologist assigns an American Society of Anesthesiologists (ASA) physical status classification (**Table 32-1**). The American Society of Anesthesiologists score is a clinician's tool, not intended as a predictor of perioperative risk, because, while the American Society of Anesthesiologists score correlates broadly with outcomes, it does not incorporate age or type of operation, both significant influences on outcomes.



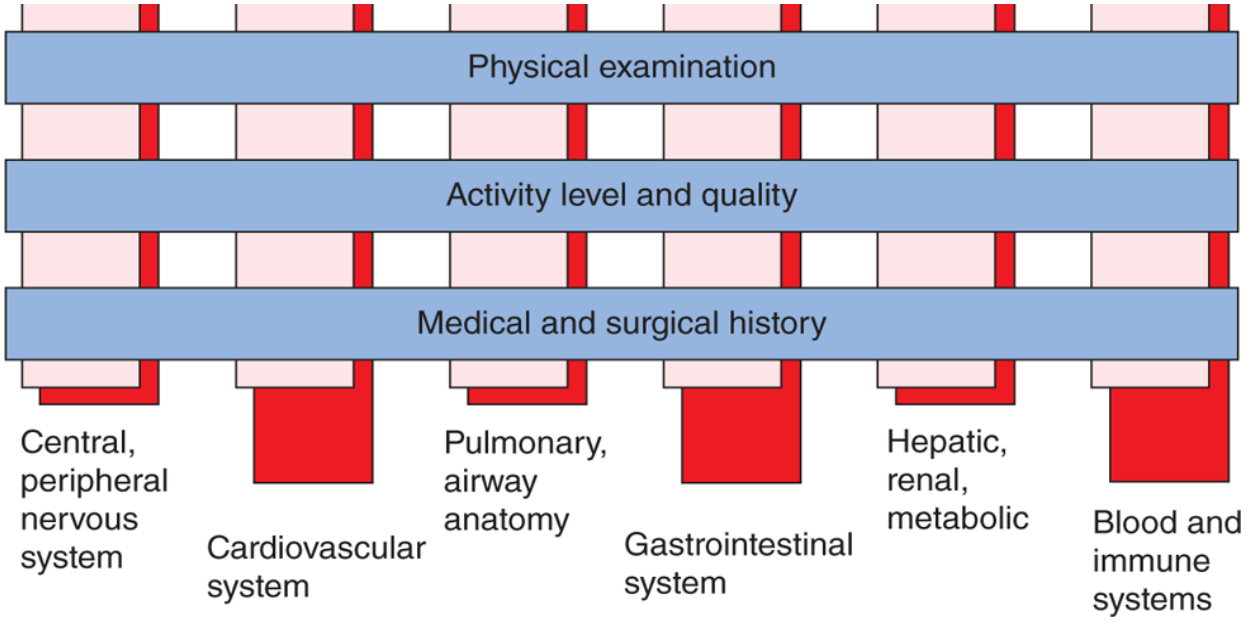


FIGURE 32-1. A. The traditional medical approach to diagnosis can be represented schematically as a series of horizontal techniques of inquiry (open bars) applied across the various organ systems (shaded bars) to consolidate data describing the status of different organs into a unified diagnostic group. **B.** An organ system–based "vertical" approach to preoperative assessment of the older patient by anesthesiologists differs from the traditional diagnostic approach because it applies the various technique of inquiry (shaded bars) sequentially in each major organ system (open bars) in order to assess organ function and functional reserve. The primary objective of preoperative assessment should be evaluation of physical status, rather than the identification of specific underlying disorders. (Used with permission from Muravchick S. *Geroanesthesia: Principles for Management of the Elderly Patient.* St. Louis, MO: Mosby; 1997:17–18.)

TABLE 32-1 AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CATEGORIES

P1	A normal healthy patient
P2	A patient with mild systemic disease
P3	A patient with severe systemic disease
P4	A patient with severe systemic disease that is a constant threat to life
P5	A moribund patient who is not expected to survive without the operation
P6	A declared brain-dead patient whose organs are being removed for donor purposes

In terms of ability to tolerate anesthesia and surgery, physiologic status is more important than chronological age. Aging is a highly variable process; young adults are more similar to each other physiologically than are older adults. While chronological age is insufficient to explain surgical outcomes, it has repeatedly been found to be associated with an increased risk of morbidity, mortality, and poor surgical outcomes. Age appears to be an important modifier of disease load, and the number of diseases (disease burden) appears to be the primary determinant of outcomes. Older adults with limited or low disease load have relatively lower risk of postoperative complications (**Figure 32-2A**), and the combination of high disease load and age is associated with extremely high rates of morbidity and mortality (**Figure 32-2B**). In addition, aging is not uniform across organ systems, and some organ systems may have aged or have been affected by disease more than others. Since aging is so heterogeneous, a careful preoperative evaluation is extremely important in preparing the older adult for surgery.

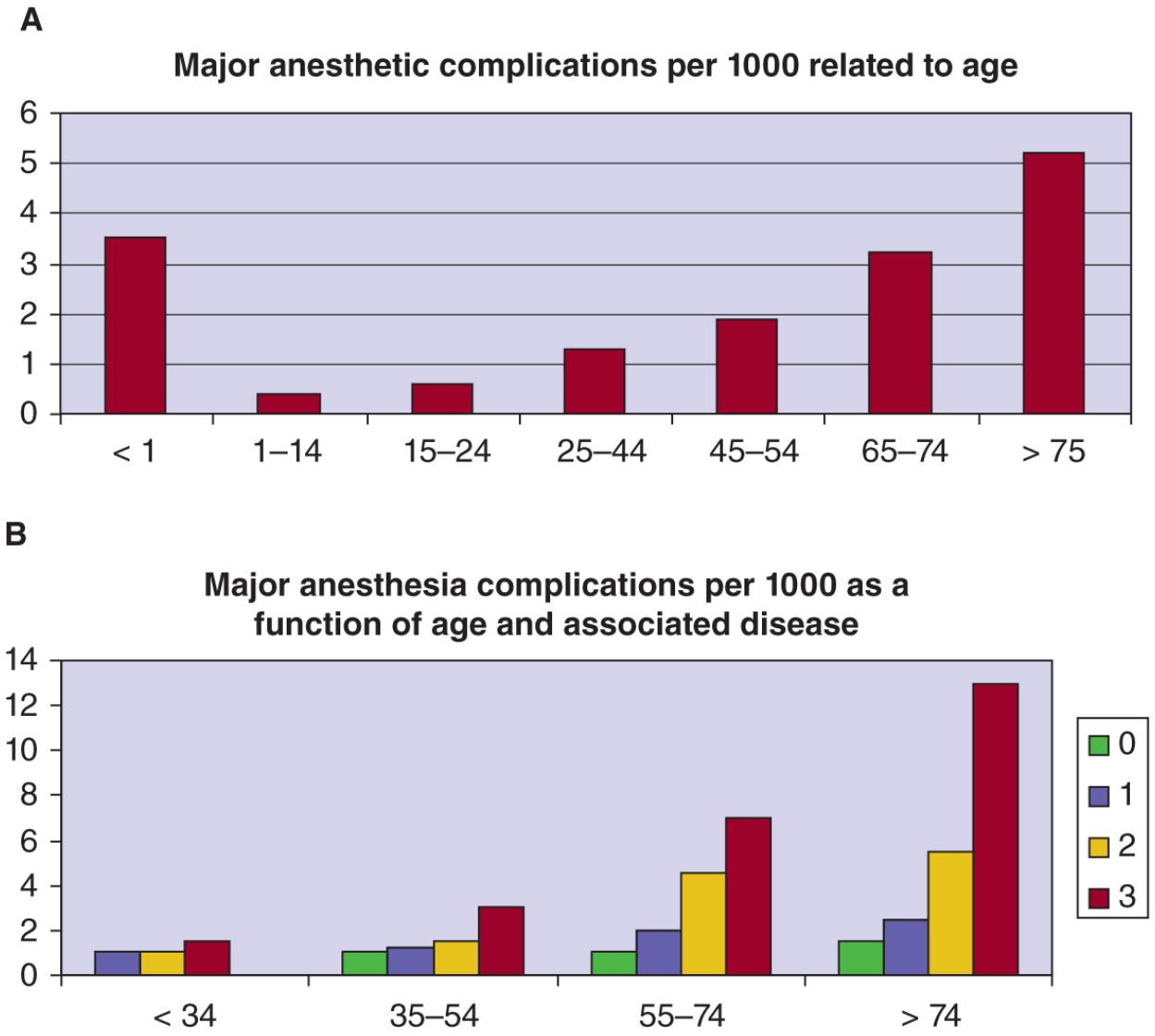
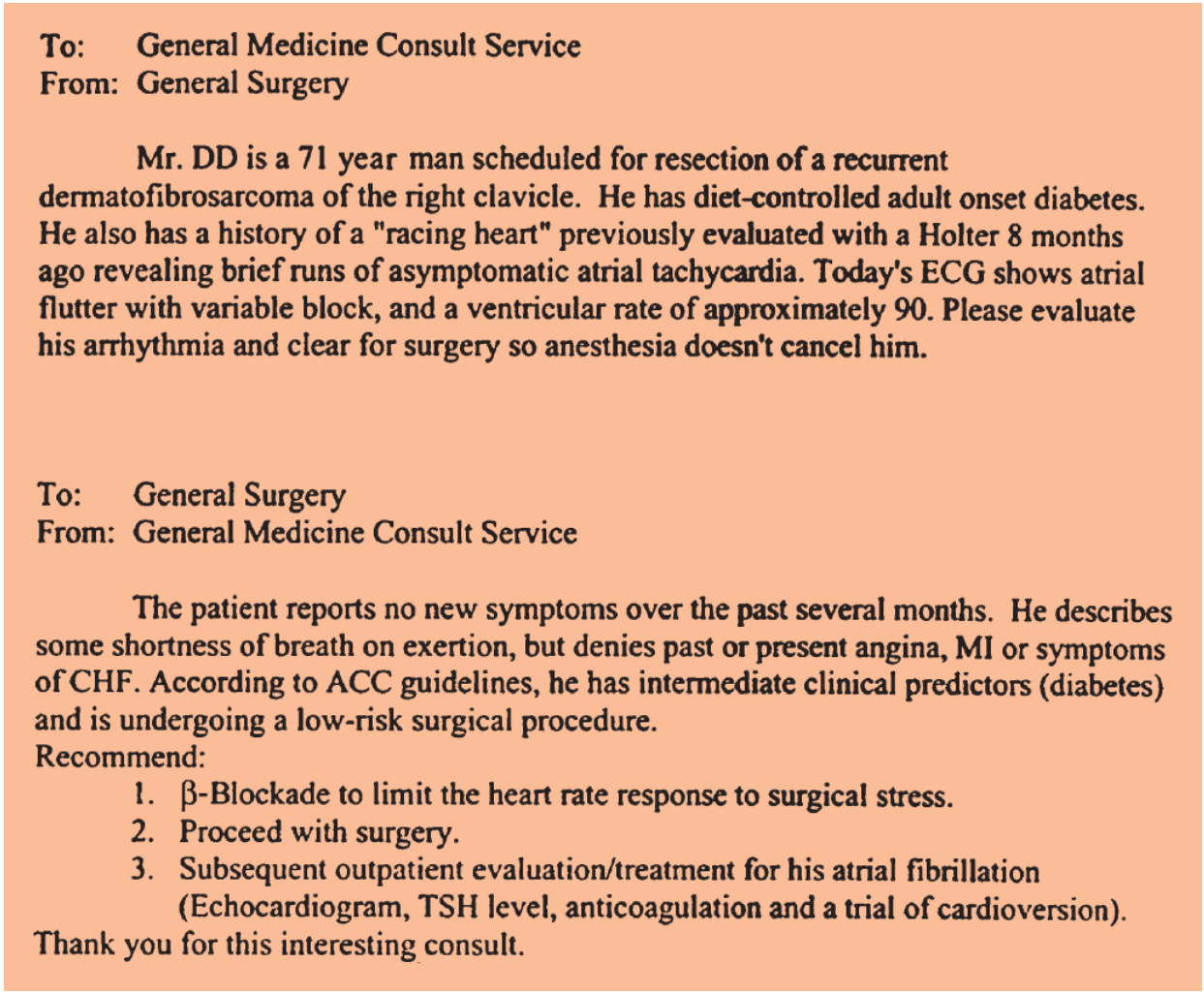


FIGURE 32-2. **A.** Major anesthesia complications per 1000 related to age. **B.** Major anesthesia complications per 1000 as a function of age and associated disease. Legend indicates the number of diseases identified (0 = no disease, 3 = three or more diseases). Note that the disease burden significantly increases the likelihood of major complications as patients age.

Frailty, a concept that has been evolving in geriatrics, has proven useful for additional evaluation of the geriatric surgical patient. Makary and colleagues demonstrated the capacity to improve risk stratification by adding frailty to the ASA physical status score. The concept of stratifying patients to specific surgeries, anesthetics or habilitation regimens is an expanding area of perioperative care. How and when the preoperative evaluation occurs is highly variable. Many modern surgical practices admit patients for major surgery on the day of the operation. In this scenario, the anesthesiologist must perform the preoperative evaluation and discuss the perioperative experience and anesthetic options with the patient in a tight time frame. Alternative approaches include preoperative clinics and telephone calls, which can provide important opportunities to develop an understanding of the patient's physical condition prior to the day of surgery.

The preoperative evaluation is an essential process in developing an anesthetic plan. Just as importantly, it provides an opportunity to answer questions for the patient and family. The most constructive of preoperative evaluations provide plans for minimizing risk in the perioperative period (ie, before, during, and after surgery). As part of the evaluation, a general internist maybe consulted. Institutional policy and practices vary as to whether such input is required or even routine. A generalist's statement that the patient has been "cleared for surgery" is of limited value. Much more useful to the anesthesiologist and surgeon is a complete overview of the patient's medical condition, recent evaluations, and medications along with a plan to manage these in the perioperative period. The more the preoperative evaluator knows and understands, the less often the need for additional consultation. The best plan is based on good communication between the generalist and specialist physicians, the surgeon, the anesthesiologist, and the patient.

Preoperative management of significant medical problems should be agreed upon. Medication regimens (such as anticoagulants, antihypertensive agents [angiotensin-converting enzyme inhibitors and angiotensin receptor blockers], antidiabetic agents, and antiparkinsonian medications) may require modifications and advance planning prior to surgery. Several members of the medical team can lead this effort, but the individual responsible should have a good understanding of the issues that need to be addressed and how they should be handled. Medication management protocols that have been jointly set by surgeons, anesthesiologists, and internists are often useful. When additional consultation is sought, the request should clearly define the issues that need to be addressed and the expected role of the consultant. The example shown in **Figure 32-3** illustrates a reasonable delineation of the problem to be addressed. Anecdotally, an organized preoperative clinic can improve patient satisfaction and decrease the number of perioperative consults.



To: General Medicine Consult Service
From: General Surgery

Mr. DD is a 71 year man scheduled for resection of a recurrent dermatofibrosarcoma of the right clavicle. He has diet-controlled adult onset diabetes. He also has a history of a "racing heart" previously evaluated with a Holter 8 months ago revealing brief runs of asymptomatic atrial tachycardia. Today's ECG shows atrial flutter with variable block, and a ventricular rate of approximately 90. Please evaluate his arrhythmia and clear for surgery so anesthesia doesn't cancel him.

To: General Surgery
From: General Medicine Consult Service

The patient reports no new symptoms over the past several months. He describes some shortness of breath on exertion, but denies past or present angina, MI or symptoms of CHF. According to ACC guidelines, he has intermediate clinical predictors (diabetes) and is undergoing a low-risk surgical procedure.
Recommend:

1. β-Blockade to limit the heart rate response to surgical stress.
2. Proceed with surgery.
3. Subsequent outpatient evaluation/treatment for his atrial fibrillation (Echocardiogram, TSH level, anticoagulation and a trial of cardioversion).

Thank you for this interesting consult.

FIGURE 32-3. An example of a consult request from a surgical service to a medical service.

Risk assessment is a part of the preoperative process. The primary objective of risk assessment is to decide how aggressive one should be in preparing the patient for surgery, rather than deciding that the surgical risk is too high. Risk assessment is most formalized in the form of the American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the evaluation of cardiac disease. The guidelines attempt to integrate severity of comorbid disease, exercise tolerance, and surgical severity into a rational plan, in order to determine who needs to enter an advanced evaluation process or to avoid diagnostic procedures with a risk greater than the proposed surgery itself. In fact, the AHA/ACC guidelines were originally developed specifically to limit the frequency of noninvasive cardiac testing, which has the potential to be used unnecessarily. It is important to remember that the AHA/ACC guidelines have never been formally tested, nor are they meant to supplant clinical judgment. Many medical problems in the older adult cannot be addressed using established guidelines so that decisions are based on clinical judgment. The impact on postoperative outcomes of optimizing medical conditions prior to surgery is usually unknown. Typical conditions that might be optimized preoperatively, even if not seriously unstable, include high blood pressure, diabetes,

reactive airway disease, and coronary artery disease. One of the best examples of medical optimization leading to improved outcome is the use of β-blockade for patients with known or suspected coronary heart disease.

In 2012, the American College of Surgeons and the American Geriatrics Society, in collaboration with a diverse panel of experts, released a document entitled Optimal Preoperative Assessment of the Geriatric Surgical Patient (**Table 32-2**). This document expands on the standard preoperative assessment to include most of the issues that distinguish the assessment of the geriatric patient. The exact choice of instruments, for example, the Mini-Cog test for preoperative cognitive assessment, might be replaced by other instruments, the general approach should be embraced.

TABLE 32-2 ■ CHECKLIST FOR THE OPTIMAL PREOPERATIVE ASSESSMENT OF THE GERIATRIC SURGICAL PATIENT

In addition to conducting a complete history and physical examination of the patient, the following assessments are strongly recommended:

- Assess the patient's cognitive ability and capacity to understand the anticipated surgery.
- Screen the patient for depression.
- Identify the patient's risk factors for developing postoperative delirium.
- Screen for alcohol and other substance abuse/dependence.
- Perform a preoperative cardiac evaluation according to the American College of Cardiology/American Heart Association algorithm for patients undergoing noncardiac surgery.
- Identify the patient's risk factors for postoperative pulmonary complications and implement appropriate strategies for prevention.
- Document functional status and history of falls.
- Determine baseline frailty score.
- Assess patient's nutritional status and consider preoperative interventions if the patient is at severe nutritional risk.
- Take an accurate and detailed medication history and consider appropriate perioperative adjustments. Monitor for polypharmacy.
- Determine the patient's treatment goals and expectations in the context of the possible treatment outcomes.
- Determine patient's family and social support system.
- Order appropriate preoperative diagnostic tests focused on older patients.

Sometimes internists and anesthesiologists disagree on preoperative management, often about whether or not planned diagnostic tests can be delayed until after the surgery. The consult shown in **Figure 32-3** provides an example. In this case, atrial flutter is not a contraindication to surgery. Why should its evaluation delay surgery? Some would argue that if the tests provide useful information or lead to an intervention that improves the patient's status, then the patient will be better off having the tests done prior to elective surgery. In the example in **Figure 32-3**, an echocardiogram provides useful information, even if normal. If a test should be performed, it is reasonable to do it before surgery, unless surgical urgency dictates otherwise. Furthermore, if elective cardioversion is being considered, it should be done before surgery because heart rate control in the intra- and postoperative periods is more easily achieved when the patient is in sinus rhythm. As stated above, there is frequently little evidence upon which to base such judgment but coherent preoperative planning in an older adult can avoid confusion, surgical delay, and requests for emergent consultations that are rarely as complete as elective evaluations.

Geriatrician involvement improves perioperative care but is undervalued in most usual care settings. Comprehensive geriatric assessment (see Chapter 10) has a place in perioperative care because it is the best way to prevent geriatric-specific postoperative issues like delirium and pressure ulcers.

A unique part of the preoperative assessment of the older adult arises when a patient has a "do-not-resuscitate (DNR)" order or other advanced care directives. Many patients have, in consultation with their primary care physicians, elected to forgo resuscitative measures, because of fears that resuscitation will lead to poor outcome, or because they feel that resuscitation measures will be futile. These fears are supported by numerous studies that demonstrate that cardiac arrest in most settings carries a very poor prognosis, because arrests are usually unwitnessed and may be caused by advanced disease states. However, the operating room is a special setting in this regard. In contrast with other in-hospital cardiac arrests, cardiac arrests in the operating room carry a very favorable prognosis, because arrests are often because of reversible causes such as hemorrhage or drug effects, and because they are witnessed events where resuscitation is instituted within seconds. This means that, in the setting of surgery, a patient's DNR order must be reconsidered in light of the different prognostic implications of cardiac arrest during surgery.

Some organizations have standing policies that DNR orders are rescinded in the operating room. The DNR may be reinstituted either upon a physician's order or automatically upon return to the ward. Regardless of the management plan, DNR orders require review and discussion with the patient. While the anesthesiologist should have such discussions with the patient, input from the patient's other physicians can be invaluable.

Sometimes a primary care physician or consultant offers advice on anesthetic management as a part of the anesthesia preoperative referral. These recommendations are usually not helpful. Requests to avoid hypotension and hypoxemia are so obvious as to be unnecessary. Surgical clearance limited to local or regional anesthesia can create problems. These restrictions may not be based on clear evidence. Regional techniques have limitations (see section on "Regional Anesthesia"). Regional anesthetic techniques occasionally fail in the operating room, requiring an immediate alternative. In some cases, local anesthesia may be feasible, but not preferable, as a result of patient characteristics such as apprehension or positioning issues, or because adequate anesthesia would be difficult to achieve with local approaches alone.

ANESTHETIC METHODS AND THE OLDER ADULT

Anesthesiologists have developed two major approaches to the provision of anesthesia. The first is general anesthesia, based on the systemic administration of medications whose principal effects occur in the central nervous system. The provision of various levels of sedation can be thought of as a subtype of general anesthesia. The second major approach is regional anesthesia, based on the use of one of a family of local anesthetics to block nerve conduction. Spinal or epidural anesthesia applies these agents either in or around the spinal canal. Peripheral nerve blocks provide them around nerves subserving specific areas of the body. Local anesthetic agents injected into areas of skin to block the surrounding nerve endings can be thought of as a form of regional anesthesia. The two main forms of anesthesia are not mutually exclusive. A patient undergoing general anesthesia may have a peripheral nerve block to control postoperative pain, and a patient undergoing a procedure with spinal anesthesia is likely to receive hypnotic medications in concentrations that produce sedation. General anesthesia and regional anesthesia work via different mechanisms, so their effects in the older adults are discussed separately below.

GENERAL ANESTHESIA

This section will review the goals of general anesthesia, principles of intraoperative care, types of anesthetic agents, and age-related special management issues. While unconsciousness is the most apparent distinguishing feature of general anesthesia, it has many other important effects. The cardinal features of general anesthesia are (1) lack of consciousness, including amnesia for events that occur under anesthesia, (2) analgesia or absence of pain, (3) lack of movement in response to painful stimuli, and (4) control of the reflex responses to painful stimuli. In the early years of anesthesiology, ether was found to provide all of these properties, although it did cause prolific vomiting following emergence and had a tendency to cause explosions in the operating theater. The observation that ether, a relatively simple molecule, produced an adequate anesthetic state, along with compelling physicochemical evidence suggesting that potency was linked to the length of the carbon chain of the anesthetic, led anesthesiologists to search for a single mechanism or receptor that was responsible for anesthesia. In subsequent years, it has become clear that anesthesia does not result from alterations of a single receptor, but that all available drugs with anesthetic properties have specific targets. General anesthesia results from alterations at multiple receptors and multiple drugs are almost always used to produce general anesthesia.

Intraoperative Anesthesia Care

Standard procedure for anesthetic care is to monitor the electrocardiogram, blood pressure, and oxygen saturation. When general anesthesia is undertaken, end-tidal carbon dioxide monitoring of ventilation is required and temperature should be monitored for most procedures. Intravenous access with large-bore (18 gauge or larger for major surgery) catheters inserted into peripheral veins is almost universally required as part of anesthetic care. The induction of anesthesia is generally accomplished with intravenously administered hypnotic agents. The appropriate dosages of these agents are all decreased with aging. Maintenance of a patent airway and adequate ventilation are primary goals, usually attained via an endotracheal tube and positive-pressure ventilation. In recent years, anesthesiologists have developed a variety of new airway devices, such as the laryngeal mask airway, as alternatives to endotracheal

intubation. The choice of device and backup procedures varies with procedure and practitioner. Spontaneous breathing is also a feasible and potentially desirable alternative to positive-pressure ventilation.

Adjustment of the depth of anesthesia consumes a good deal of the anesthetic manipulations during surgery. How "deep" or "light" the patient is at any moment depends on the balance of drug effects and the surgical stimulus. Titration of the depth of anesthesia is typically a matter of balancing the tendency of the surgical stimulus to activate the brain and stimulate the sympathetic nervous system against the anesthetic's ability to depress brain activity and limit the stimulation of the sympathetic nervous system. Thus, a patient might be fully anesthetized one moment and then be inadequately anesthetized a moment later if the surgical (painful) stimulus suddenly increases. The effective depth of anesthesia can be monitored through a variety of methods. The primary approach for years has been to monitor blood pressure and heart rate. Hemodynamic signs of light anesthesia generally appear long before a patient has any chance of "waking up" or of having postoperative recall. A rise in blood pressure and/or heart rate is typically the first sign of light anesthesia and triggers an increase in the concentration of volatile gas (currently isoflurane, sevoflurane, or desflurane) concentration or administration of a small bolus of a fast-acting opioid such as fentanyl. A safe strategy is to keep blood pressure at or slightly lower than the patient's usual baseline, although this can be quite difficult to accomplish in older patients. The risk of awareness/recall is relatively remote under such circumstances.

Since depth of anesthesia is such a critical issue in perioperative care, and because it can change moment to moment, anesthesiologists have pioneered the use of electroencephalograms to define a brain-based measure of depth of anesthesia. Devices have been developed that use advanced signal processing and computer miniaturization to provide a single number between 0 and 100 that indicates depth of anesthesia. When these devices have been applied to older adults, the findings suggest that the amount of anesthetic typically used to control blood pressure and heart rate frequently results in extremely deep anesthesia for the brain. Excessive depth of anesthesia has been proposed to contribute to poor outcomes. This important area requires further study and might be valuable in the clinical arena in the future.

Patient movement in response to a surgical stimulus, even if very slight, suggests an inadequate depth of anesthesia. Too light anesthesia can result in patient. The amount of movement is usually subtle. Most slight movement does not imply such a light level of anesthesia as to result in awareness or recall. Movement cannot be used as an indicator of depth of anesthesia if a patient is paralyzed by neuromuscular blocking agents that are common adjuvants for abdominal surgical cases or in cases where even minimal movement is surgically unacceptable. Unintentional excessively light anesthesia is most likely to occur when neuromuscular blocking agents produce muscle paralysis in the presence of lighter general anesthetic agents, such as nitrous oxide and opioids, with little or no potent gases. The electroencephalogram monitors described above have an unclear role in preventing awareness during surgery.

Anesthetic Agents

The pharmacokinetics and pharmacodynamics of the intravenous and volatile anesthetic agents are altered in the older adult, so that administration must be adjusted. A general rule of the thumb is that all drugs will have more dramatic and longer-lasting effects in older patients, although this is not universally true. The mechanisms vary with the drug but include changes in protein binding, decreases in initial volume of distribution, alterations in receptor sensitivity, and slowed renal or hepatic metabolism. The therapeutic effect of many intravenous anesthetic agents is not dissipated by metabolism, but by redistribution of the drug from the brain to the fat. These drugs are highly lipid soluble and cross membranes rapidly. On initial injection, the blood levels are very high but will fall as the drug is taken up into fat. The high initial blood levels will promote rapid transfer of the drug into highly perfused organs such as the brain. Even though fat serves as an almost limitless sink for lipid-soluble drugs, blood flow to fat is low and transfer of drug into fat takes time. Transfer time largely dictates the duration of a drug's clinical effect. As blood levels decrease, drug returns to the blood from the more vascular organs and is then transferred to the fat, dissipating the therapeutic effect. Substantial and/or prolonged administration of many drugs results in drug levels in fat that become high enough to sustain a (residual) blood level that has a therapeutic effect. From an anesthetic management viewpoint, the pharmacokinetic and pharmacodynamic changes of aging rarely present a major problem. Patient response to drugs is variable at any age, so, with the exception of induction, drugs are given in small doses and titrated to effect. The trend today in anesthesia practice is to use drugs that are short acting. These drugs either have shorter metabolic half-lives or redistribute to yield very low blood levels with minimal residual effects, or do both. These principles of drug pharmacokinetics apply to patients of all ages, but the ability to use drugs with rapid fat uptake, but minimal residual effects, is particularly helpful in older patients.

Hemodynamic Stability During Anesthesia

Hemodynamic stability is a core goal of anesthesia and one of the more challenging aspects of anesthetic care of the older adult. Many characteristics of aging contribute to the increased vulnerability of older adults to hemodynamic instability (**Table 32-3**). General anesthesia lowers the blood pressure in everyone. This effect is owing to decreased sympathetic tone, which, in turn, may lower heart rate, decrease systemic vascular resistance, and cause peripheral pooling of blood, which will lower cardiac preload. There is also some direct myocardial depression. These effects are exaggerated in older adults. Sympathetic nervous system activity commonly increases with age and so may be more reactive to stimuli than in young people. Chronic hypertension, common in older patients, further exaggerates the vascular response to changes in sympathetic nervous system activity. In particular, the aorta stiffens with age and typically results in left ventricular hypertrophy. Hypertrophy leads to a reduction in the rate of diastolic relaxation, which, in turn, diminishes early diastolic filling. Adequate ventricular preload becomes dependent on passive filling related to left atrial pressure and atrial contraction. Both mechanisms must overcome the increased ventricular stiffness and both require a full atrium. Yet atrial blood volume is difficult to keep constant. Veins also stiffen with age. Venous stiffness reduces the capacity to buffer changes in blood volume, making atrial filling more sensitive to overall volume status as well as to the effects of the sympathetic nervous system on blood distribution. In consequence, older patients are more prone than young patients to both hypotension and hypertension during surgery.

TABLE 32-3 CARDIOVASCULAR AGING AND ANESTHETIC IMPLICATIONS

AGING-INDUCED CARDIOVASCULAR CHANGE	PHYSIOLOGIC CONSEQUENCE	ANESTHETIC AND PERIOPERATIVE IMPLICATION
Loss of sinoatrial node cells and conduction system fibrosis	First-degree block and occasional sick sinus syndrome	Severe bradycardia when coupled with potent opioids
Stiff arteries	Systolic hypertension Impedance mismatching at end ejection, leading to myocardial hypertrophy and impaired diastolic relaxation	Labile blood pressure Diastolic dysfunction and sensitivity to volume status
Myocardial hypertrophy and connective tissue stiffening	Increased ventricular stiffness Ventricular filling dependent on a well-maintained atrial pressure	Failure to maintain filling causes an exaggerated decline in cardiac performance; excessive volume more easily increases filling pressures to congestive failure levels
Decreased β-receptor responsiveness	Limited increases in heart rate and contractility in response to endogenous and exogenous catecholamines Impaired baroreflex control of blood pressure	Increased dependency on Frank-Starling mechanism to maintain cardiac performance. Labile blood pressure
Stiff veins	Decreased buffering of changes in body blood volume impairs ability to maintain constant atrial pressure	Changes in blood volume or body distribution of blood cause exaggerated changes in cardiac filling Hypovolemia more easily impairs cardiac performance, whereas hypervolemia more easily leads to symptoms of congestive failure
Increased sympathetic nervous system activity at rest and in response to stimuli	Basal vascular resistance more dependent on basal sympathetic nervous system	Hypotension from anesthetic blunting of sympathetic tone Increased blood pressure lability from changes in sympathetic tone in response to the surgical stimulus

Management of the inevitable swings in blood pressure can be a challenge. Alterations of blood pressure are particularly common during induction of anesthesia and the laryngoscopy/intubation sequence. Hypertension is usually managed by increasing the depth of anesthesia with more opioid and/or increasing the anesthetic gas concentration. Unfortunately, the surgical stimulus can increase or decrease faster than the depth of the anesthetic can be manipulated. One approach is to complement the anesthetic with β-blockade to minimize the hemodynamic response to the surgical stimulus. Another approach is to use relatively high doses of opioid and relatively less volatile

anesthetic. Opioids produce less intrinsic depression of blood pressure than do volatile anesthetics while preventing significant rise in blood pressure during surgery. If high-dose opioids are used to prevent the hemodynamic response to the surgical stimulus, the primary role of the volatile anesthetic is to produce unconsciousness, requiring approximately half the concentration of gas needed without opioids. An ultra-short-acting opioid, remifentanil, can be employed primarily for short cases that are accompanied by profound simulation in sensitive areas. High doses of moderate-duration opioids (eg, fentanyl or morphine) are limited by residual respiratory depression, which can unacceptably depress ventilatory drive at the end of the surgery. Continuous use of ultrashort agents is not currently encouraged because of cost. Another approach is to use a limited amount of opioids compatible with the surgical procedure and then maintain the volatile anesthetic concentration high enough to block the hemodynamic response to the highest level of surgical stimulus. Such a strategy will minimize hypertension but will also make the patient more prone to hypotension at other, less stimulating, times of the surgery. Sometimes even the minimum level of anesthesia causes an unacceptable depression of blood pressure. In these circumstances, blood pressure must be actively supported. Volume administration can support blood pressure but is of limited utility in older patients. Volume may restore stroke volume but will not compensate for hypotension caused by severe bradycardia or a low vascular resistance. Bradycardia generally responds to glycopyrrolate, an anticholinergic drug that crosses the blood-brain barrier poorly and is presumably less likely to promote postoperative delirium than atropine. Ephedrine stimulates both α- and β-receptors and effectively raises pressure, but tachyphylaxis eventually develops and so it is not used for extended time periods. Phenylephrine, a pure α-agonist, can be conveniently given as either a bolus or a low-dose infusion and effectively maintains blood pressure. On occasion, inotropic infusions (eg, dopamine) are used, especially if bradycardia does not respond to anticholinergics or there is concern over baseline ventricular function. All pressors have potential adverse effects, of course, but serious problems from their use are infrequent.

Intravascular fluid therapy in older adults is a controversial topic. Much has been written, little has been proven, and clinical practice tends to be based more on habit than on science. Much of the science underlying the most standard anesthetic and surgical approach to volume replacement is based on studies undertaken in the 1960s and 1970s. As noted above, cardiovascular aging makes volume administration more difficult. The stiffness of the venous system exaggerates the response to a given volume excess or deficit. Well-anesthetized patients may appear hypovolemic during surgery as a result of the suppression of sympathetic nervous system activity. A common concern of the geriatric anesthesiologist is that large amounts of crystalloid used for blood pressure control may achieve what appears to be normovolemia during surgery, but, when surgery is over and postoperative pain restores sympathetic activity, that volume may shift back to the central circulation and create a volume overload. Recently, the basis for fluid administration has been questioned, and an alternative strategy that uses less fluid has been proposed. To date, this approach to fluid management has not been extensively tested or adopted in the United States. The recent literature on reduced fluid volume has not attended to the special issues of cardiovascular aging. Strategies that limit fluid administration frequently are attended by increased use of vasopressors (phenylephrine, norepinephrine, and vasopressin). Since traditional anesthesia care reserves vasopressor use for when fluid administration has failed to maintain perfusion, vasopressor use can be considered an ominous clinical sign that is frequently cited as an adverse consequence of limited fluid administration. In many cases, volume administration is unavoidable and there are no extant guidelines for managing fluid, particularly in older adults. There is also an extensive literature about the proper content of fluids, particularly comparing crystalloid to colloid solutions. There are no clear-cut guidelines for use in older adults.

Anesthesia and the Pulmonary System

Aging and general anesthesia have important effects on the respiratory system (**Table 32-4**). Closing capacity increases with age because of diminished airway tethering by connective tissue. General anesthesia enhances expiratory muscle tone and diminishes inspiratory muscle tone, thereby decreasing functional residual capacity. Sighs are suppressed. Atelectasis develops more easily because of the increased closing capacity, decreased functional residual capacity, and the loss of sighs. Atelectasis occurs in the great majority of patients undergoing general anesthesia. Mechanical ventilation disturbs the normal pattern of diaphragmatic breathing in the supine patient, altering normal ventilation/perfusion matching. Volatile anesthetics reduce the effectiveness of hypoxic pulmonary vasoconstriction. Both volatile anesthetics and the placement of an endotracheal tube diminish ciliary action of the respiratory tract, an effect that extends into the postoperative period. Opioids diminish the carbon dioxide ventilatory drive. Volatile anesthetics suppress the hypoxic ventilatory drive, even at the low concentrations present postoperatively. Particularly very frail patients are at increased risk of ventilatory failure postoperatively. The increase

in body oxygen consumption during recovery from surgery may exceed the ventilatory reserve that is compromised by increased chest wall stiffness and decreased skeletal muscle mass. Finally, silent regurgitation and aspiration is more common in older patients. At-risk patients will be challenged postoperatively by drugs that may further depress the airway protective reflexes and impair gastric emptying. Aspiration is much more likely to occur postoperatively than intraoperatively. It is important to understand, however, that patients who suffer aspiration to a degree that causes clinical signs or symptoms will present with some evidence of dysfunction (eg, hypoxia) within a few hours of the aspiration. It is unlikely that a patient will aspirate, have no consequences for many hours, and then develop a clinical problem that could be attributed to much earlier aspiration.

TABLE 32-4 PULMONARY AGING AND ANESTHETIC IMPLICATIONS

AGING-INDUCED PULMONARY CHANGE	PHYSIOLOGIC CONSEQUENCE	ANESTHETIC AND PERIOPERATIVE IMPLICATION
Decrease in bony thorax elasticity	Stiff chest that is hard to move, increasing the work of breathing and making it more difficult to increase minute ventilation Increased residual volume	Increased risk of respiratory failure
Loss of muscle mass	Reduced strength to meet the increased minute ventilation requirements secondary to the metabolic demands after surgery	Increased risk of respiratory failure
Decreased lung parenchymal stiffness	Increased lung compliance Decreased “tethering” of small airways, leading to increased closing volume Impaired ventilation-perfusion matching	Increased risk of atelectasis, hypoxia, and pneumonia
Impaired airway-protective reflexes	More frequent aspiration	Increased risk of pneumonia and adult respiratory distress syndrome
Decreased central nervous system responsiveness	Decreased hypercapnic and hypoxic drives	Increased risk of hypoxia Greater sensitivity to anesthetic agents

Intraoperative respiratory management of older patients is straightforward. Bronchospasm is probably the most common intraoperative untoward event. Bronchospasm usually resolves promptly with easily administered treatments. Volatile anesthetic gases themselves produce bronchodilation, and inhaled bronchodilator medications can be administered through the endotracheal tube. Atelectasis prevention strategies during the intraoperative period have been variously successful. Supplemental oxygen is freely used in the operating room, and all patients are monitored by pulse oximetry and frequently with expired gas analysis. This has allowed the anesthesiologist to ensure that all patients are well oxygenated and has markedly decreased the incidence of clinically significant hypoxemia in all age groups.

Most pulmonary problems do not manifest until after surgery. Some degree of hypercarbia is common for at least the immediate postoperative period, especially after considerable opioid administration. This finding usually means nothing more than the presence of good analgesia, so long as supplemental oxygen is administered and the patient can be watched carefully. Supplemental oxygen will likely be necessary for a longer period of time after surgery in older patients. Patients with tenuous respiratory function may need ventilatory support until they are past the acute recovery period. Pneumonia remains an important complication and the ability to prevent its development is limited. Deep breathing and vigorous coughing by the patient are thought to help prevent pneumonia, but postoperative pain may impair these maneuvers. Improved pain control may be one mechanism by which epidural analgesia improves perioperative outcome (see section on “Postoperative Analgesia”). The role of silent aspiration in the development of postoperative pneumonia is unclear and warrants closer examination.

Regional Anesthesia

Regional anesthesia uses a family of pharmacologic agents with unique properties and a range of techniques designed to meet the needs of the surgical plan. This section will review agents first and then techniques. Local anesthetic agents reversibly inhibit the propagation of signals along nerves. When applied to a specific nerve or pathway in sufficient concentration, these agents produce anesthesia (loss of sensation) and paralysis (loss of muscle power). The currently used local anesthetics belong to one of two classes: aminoamide and aminoester local anesthetics. All of these medications are structurally related to cocaine but do not stimulate the sympathoadrenal system and, thus, do not produce hypertension or local vasoconstriction, nor do they have any abuse potential. Local anesthetics vary in their pharmacologic properties. Field and nerve blocks are frequently performed using long-acting drugs such as bupivacaine. This often provides exceptional postoperative analgesia for up to 24 hours. The local anesthetic lidocaine is also used as a Class Ib antiarrhythmic drug. At higher doses, lidocaine and all local anesthetics are arrythmogenic. All agents have limited therapeutic windows, and over-dosage can result in cardiac arrest and death. There are large variations in how aging alters the pharmacokinetics of local anesthetics, and aging per se accounts for less than 20% of variability. There is little suggestion that sensitivity to local anesthetics is altered by aging. Some forms of regional anesthesia can be combined with a light general anesthetic.

Regional anesthesia techniques include topical anesthesia (surface), infiltration, plexus block, epidural (extradural) block, and spinal anesthesia. Topical anesthesia has become the most popular format for minor ocular surgery, such as cataract extraction. As a rule, field and nerve blocks have minimal systemic effects unless there is an untoward event during placement, such as intravascular injection of the local anesthetic, or there is an allergic reaction to the drug. Many procedures, such as cataract surgery, can be accomplished with local anesthetic drops and no additional sedation. Blocks of specific nerves or nerve plexi are associated with anatomically specific side effects and complications. An interscalene block of the cervical plexus provides good anesthesia for operations on the shoulder. It may also result in anesthesia of the ipsilateral phrenic nerve, resulting in hemidiaphragmatic paralysis. An ipsilateral Horner syndrome may also be observed. Field blocks are often placed by the surgeon at the operative site prior to or at the conclusion of surgery.

Neuraxial blocks, including spinal and epidural anesthesia, are considered complete anesthetics; no other supplemental treatment is necessary, although sedation is often provided at the request of the patient or the surgeon. These blocks produce the greatest physiologic effects and are presented here in more detail than other forms of regional anesthesia because their use in older adults is common. Spinal anesthesia differs from epidural anesthesia in the location of anesthetic administration, in the consequences of location of administration on type of nerve affected, and on the resulting clinical manifestations of treatment. With spinal anesthesia, the local anesthetic is injected into the cerebrospinal fluid, inside the dura and arachnoid, where it quickly diffuses into the spinal nerves. Inside the dura and arachnoid, spinal nerves have minimal connective tissue surrounding them so that the local anesthetic effectively blocks all nerve fibers, including motor, touch, and sympathetic nerves. The patient is, thus, provided not only anesthesia but also paralysis and sympathetic blockade. In contrast, an epidural anesthetic is typically administered through a catheter placed just outside the dura. In the epidural space, spinal nerves are covered with a thick connective tissue sheath, which slows the onset of anesthetic effect. By varying the concentration of the injected local anesthetic, nerve types can be differentially blocked. Differential blockade is important for postoperative analgesia, where partial blockade of pain fibers are desired, but touch and motor nerves are to be spared. Unfortunately, it is not possible to fully anesthetize pain fibers without also affecting the sympathetic nerves. When high concentrations of the local anesthetic will be used to achieve full anesthesia, all nerve types will be blocked.

The hemodynamic effects of neuraxial anesthesia stem from the blockade of sympathetic nerves. The hemodynamic response depends on many factors, including how many thoracic dermatomes of sympathetic fibers are affected and how much of a reflex response can be mounted via the vagus nerve and any unblocked sympathetic fibers. In the case of spinal anesthesia, the sympathetic fibers may be at least partially blocked for many dermatomes above the level of sensory blockade, as defined by sharp-dull discrimination. It is not uncommon, therefore, to have a near-total sympathectomy with spinal anesthesia. The hemodynamic consequences can be dramatic. If one accepts the hypothesis that vascular resistance is increased with age because of increased sympathetic tone, then removal of that tone often results in a large decrease in vascular resistance (**Figure 32-4**). Pharmacologic sympathectomy in young adults results in a much smaller decrease in vascular resistance but a similar decrease in cardiac output. In **Figure 32-4**, the sympathectomy also decreased left ventricular filling as blood volume shifted to the legs and mesentery. However, the increase in ejection fraction ameliorated much of what the decrease in preload would have otherwise been expected to do to stroke volume and cardiac output.

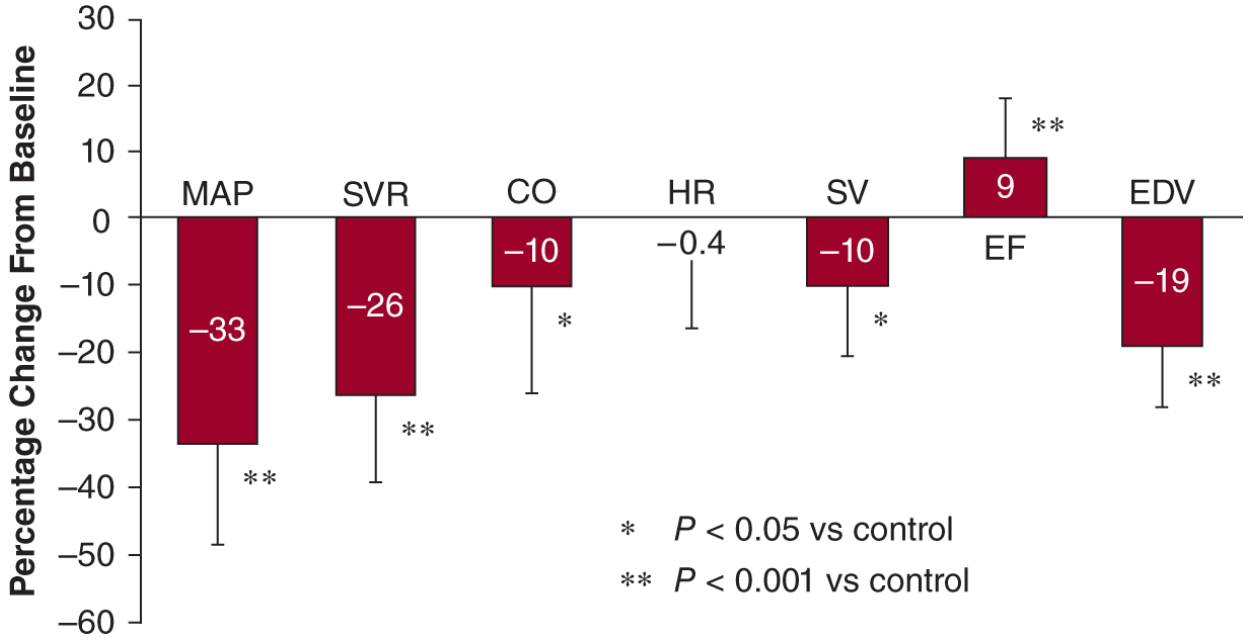


FIGURE 32-4. The hemodynamic response to high spinal anesthesia is shown in 15 older men with cardiac disease. The large decrease in mean arterial blood pressure (MAP) was primarily because of decreases in systemic vascular resistance (SVR) and not decreases in cardiac output (CO). Overall, heart rate (HR) did not change; therefore, the decrease in cardiac output was because of a decrease in stroke volume (SV). The decrease in left ventricular end-diastolic volume (EDV) did not cause a comparable decrease in stroke volume because the ejection fraction (EF) increased. (Adapted with permission from Rooke GA, Freund PR, Jacobson AF. Hemodynamic response and change in organ blood volume during spinal anesthesia in elderly men with cardiac disease. *Anesth Analg.* 1997;85:99–105.)

Many patients request sedation during surgery performed under a regional anesthetic, usually because they are not interested in being aware of the activities in the operating room. Small quantities of midazolam and fentanyl often suffice, but if higher levels of sedation are desired, typically a propofol infusion will be used. Interestingly, older patients commonly fall asleep during spinal anesthesia, even in the absence of any sedative medications. The mechanism behind this phenomenon is unknown but may involve the loss of sensory input to the brain stem. If sedative and analgesic drugs are used, the risk of airway obstruction increases. The combination of sedation plus spinal anesthesia, for example, produces more postoperative hypoxia than sedation or spinal anesthesia alone. With careful monitoring and skill in airway management, the risk of airway obstruction should be minimal. In unskilled hands, however, airway obstruction can rapidly lead to hypoxia and patient injury. This risk to the patient forms the basis for the JCAHO requirement that trained personnel must be present at procedures performed anywhere in the hospital whenever the patient is likely to be sedated to the point of drowsiness that requires verbal stimuli or worse to arouse. The requirements include assigning a person to the sole task of monitoring the patient. Sieber has provided preliminary evidence suggesting that lighter levels of sedation in combination with spinal anesthesia for hip fracture repair are associated with a low incidence of postoperative delirium.

Regional anesthetic techniques can be combined with general anesthesia. Combined general/regional anesthesia involves the provision of primarily a high thoracic epidural anesthetic with subsequent induction of general anesthesia with endotracheal intubation. This approach has been most extensively studied in Denmark in association with a fast-track approach to colonic surgery, which also includes rapid ambulation and food consumption (day of surgery) and early discharge (postoperative day 2). The advantages of the technique combine the ability to use considerably less general anesthetic with resulting rapid emergence, with the complete absence of pain, because the epidural is still active and will be used to manage postoperative pain. The main limitation of the technique is the added difficulty in maintaining blood pressure in the operating room. In addition, it is common to place an epidural catheter exclusively for postoperative pain control, which will only be activated at the end of surgery, that is, it is not used as part of the anesthetic technique.

Regional Versus General Anesthesia

Many anesthesiologists prefer regional anesthesia over general anesthesia. There is something attractive to providing an anesthetic that just blocks nerves but spares direct effects to the brain and other vital organs. Markers of stress such

as cortisol, catecholamines, and cytokines become elevated during and after surgery with a general anesthetic, while spinal and epidural anesthesia markedly attenuate these changes during surgery, and much of the attenuation will continue after surgery if epidural analgesia is continued postoperatively. The presumption has been that the reduction in stress would translate into a reduction in morbidity and mortality, but it has been surprisingly difficult to prove this hypothesis. Early studies centered around the benefits of postoperative analgesia via an epidural catheter typically infused with a dilute local anesthetic plus opioid. These studies employed random group assignment but enrolled small numbers of patients (40–60 each). Perhaps because a high-risk population was recruited, several of the studies demonstrated lower mortality and morbidity with respect to cardiac and pulmonary complications. Other studies have demonstrated additional benefits of regional anesthesia, including less blood loss during hip replacement surgery, a decreased incidence of deep vein thrombosis and pulmonary emboli, and a reduction in early graft thrombosis in peripheral vascular surgery. Not all studies demonstrate consistent benefits, however.

Because the incidence of postoperative complications tends to be low, the numbers of patients required to obtain statistical significance in randomized studies is high. A recent review by Guay of nine Cochrane reviews of the subject suggests that neuraxial **anesthesia** may reduce 0- to 30-day mortality for patient undergoing surgery with an intermediate-to-high cardiac risk. Their conclusion was that large randomized trials are needed. A related review by Kooij suggested that regional **analgesia** does not make a significant difference to outcomes.

It is apparent, then, that the current evidence of the benefit of postoperative epidural analgesia is weak, as is the evidence of the superiority of neuraxial anesthesia over general anesthesia as the primary anesthetic technique. Nevertheless, better pain relief is frequently achieved by regional techniques, and it is still possible that some medical benefits exist. Therefore, these techniques continue to be used, at least in selected circumstances. Given the difficulty in proving a difference in outcome between regional and general anesthesia, it would be surprising if any study could demonstrate a difference in mortality or major morbidity when comparing, for example, different types of general anesthesia. In the absence of compelling outcome data, whether to perform a regional or a general anesthetic depends on many factors. Carotid endarterectomies, for example, may be performed under either a local block with an awake patient or a general anesthesia. Experienced teams of surgeons and anesthesiologists can perform either of these techniques with excellent and equivalent results. Usually, a center chooses one or the other technique. Both the surgeon and the anesthesiologist must be comfortable working with the chosen technique. Patient's physical limitations, including uncomfortable patient positioning for the surgery, may prevent the use of a pure regional technique. For example, total hip replacement surgery requires the patient to lie in a fixed position on their side for the entire procedure. Even with careful positioning and padding, the position can be uncomfortable if only the lower half of the body is anesthetized. Sometimes sedation is adequate to make the procedure tolerable, whereas other patients require sedation bordering on general anesthesia that requires a secured airway. The presence of coagulopathies or the use of preoperative anticoagulation may preclude the use or regional techniques, as a result of the risk of bleeding and, in the case of spinal or epidural anesthesia, the risk of epidural hematoma (see the section below on "Postoperative Analgesia"). Also, the patient must be willing to undergo the regional technique, which will invariably involve placing a needle somewhere into the body. Some patients will not accept needles under any circumstance unless they are totally asleep, but, for safety reasons, most blocks will not be performed under such conditions. Other patients may refuse regional techniques. There is also a common fear of paralysis following spinal anesthesia, which is, for the most part unfounded, representing an extremely unusual complication with multiple potential causes. On the other hand, many patients welcome the opportunity to avoid a general anesthetic and the attendant postoperative sedation and risk of nausea. There is little evidence to suggest that the choice of anesthesia has a significant impact on either cognitive abilities or the incidence of postoperative delirium. All anesthetics should be preceded by a thorough discussion with the patient about anesthetic options, including their benefits, disadvantages, and associated risks. This discussion is best carried out by an anesthesiologist, who is best able to recognize the characteristics of the patient and procedure that will determine which anesthetic options are appropriate, and to explain to the patient the important risks and benefits of each option. In many cases, the choice of anesthetic technique can include patient preference; therefore, it is important to provide patients with comprehensive information and involve them in the decision-making process.

POSTOPERATIVE ANALGESIA

The options for postoperative analgesia have expanded considerably in the past 20 years. Highlighted here are patient-controlled analgesia and peripheral nerve blocks.

Patient-Controlled Analgesia

Patient-controlled analgesia devices are programmable infusion pumps that can provide either basal infusion and/or controlled access on request (usually pushing a button) to an opioid preparation, which is maintained in a locked compartment. The device offers the patient the opportunity to obtain pain medication without having to wait for a busy nurse. The device also provides more smooth analgesia compared to intermittent administration, which produces a cycle of heavy sedation with the initial peak effect, followed by a period of alertness and reasonable analgesia, and ending with increasing pain and anxiety until the next dose comes due. Patient-controlled analgesia allows the patient to finely titrate the analgesia against the opioid side effects, including nausea, sedation, dysphoria, and itching. In recent years, patient-controlled analgesia has become a standard part of postoperative pain management, in which orders follow specific templates. Since there is a tremendous variability in pain tolerance and response among individuals in general, and older adults in particular, effective postoperative pain management programs require a knowledgeable individual to observe the patient on a regular basis, in order to adjust the device properly. While older patients are sensitive to the respiratory depressant effects of narcotic agents, it is impossible to prescribe an age-specific approach to the use of postoperative opioids. Each patient is highly individual, and the therapeutic window for many analgesics is narrowed in older adults.

Peripheral Nerve Blocks

Peripheral nerve blocks performed with long-acting local anesthetics provide up to 24 hours of postoperative analgesia. These blocks provide both significant advantages and risks. These are typically performed in a sedated, but awake and cooperative, patient prior to surgery. The most elaborate technique for postoperative analgesia is provided through indwelling catheters. Given the time involvement for catheter placement and management and the uncertainty of enhanced outcome, this technique is used selectively. Initially, epidural analgesia was nothing more than boluses of morphine through a lumbar catheter. Now the typical formula is low concentrations of both a local anesthetic and an opioid, which are infused continuously through a catheter placed at the dermatome most central to the incision, be it thoracic or lumbar in location. The quality of analgesia afforded by a well-managed epidural catheter is excellent and associated with high levels of satisfaction.

There are significant risks to epidural catheter use. The most common problem is failed placement. The next most common problem is inadvertent dural puncture. As epidural catheters are placed with large-bore needles, the risk of a spinal headache is relatively high. Fortunately, the risk of postdural puncture headache decreases with age. If a thoracic catheter is placed, dural puncture could also lead to direct spinal cord trauma. This complication is rare. The most feared complication is the development of an epidural hematoma. The epidural space has many veins that are occasionally punctured. Generally, any bleeding stops spontaneously and quickly, but if it does not, epidural hematoma may cause cord compression. Permanent paraplegia becomes likely, since the success of emergency laminectomy is poor once symptoms appear. Over the last decade, evidence has accumulated to suggest that a thoracic epidural catheter in surgical patients carries a 10- to 100-fold higher risk, that is, 1 in 1000 to 10,000 for serious complications. Patients who have abnormal coagulation, however, are thought to be at greater risk. The rapid introduction of new agents has made clear guidelines hard to keep current. Most reports of epidural hematoma have been in patients who were anticoagulated when the block was performed or when heparin therapy was instituted less than an hour after the needle placement. The relative risk owing to anticoagulation is unknown, as all reports are anecdotal and do not include a denominator. In the case of epidural catheters, epidural hematomas develop almost as often on catheter removal as on insertion, so the catheter removal must be considered an at-risk event as well. There are case series reports on spinal or epidural block performed in anticoagulated patients, but the largest series involved 1000 patients and is too small to be meaningful despite a zero incidence of hematoma. Even subcutaneous heparin can provide enough anticoagulation to increase risk at its peak effect at around 2 hours after administration. Particularly distressing has been the high number of epidural hematomas reported in patients receiving low-molecular-weight heparin (LMWH). Many of the hematomas developed after catheter removal. In response to these reports of epidural hematoma, it is recommended that any patient with an epidural catheter be given frequent neurologic checks if they receive anticoagulants (warfarin, heparin, LMWH, and antiplatelet agents). Guidelines for catheter placement and removal are given in **Table 32-5**.

TABLE 32-5 GUIDELINES FOR EPIDURAL CATHETERS IN ANTICOAGULATED PATIENTS[a]

MEDICATION	RECOMMENDATIONS

Warfarin	Do not place needle or remove catheter if prothrombin levels are therapeutic. Discontinuation of warfarin must be of sufficient duration to restore all prothrombin factors, not just factor VII. If warfarin is initiated prior to needle placement or catheter removal, check the prothrombin time even if only one dose of warfarin has been given. Anticoagulant therapy must be stopped (ideally 4–5 days before the planned procedure).
Intravenous heparin	Do not place needle or remove catheter if partial thromboplastin time is elevated. Heparin therapy should not be initiated until at least 1 h after needle placement or catheter removal. Catheter removal should be preceded by heparin discontinuation for 2–4 h and evaluation of the coagulation status.
Subcutaneous (mini-dose) heparin	Needle placement and catheter removal is not contraindicated, but it may be wise to avoid doing so at the peak heparin effect at around 2 h after injection.
Low-molecular-weight heparin (LMWH)	Needle placement and catheter removal should occur at least 2 h before, and 10–12 h after, once-a-day LMWH therapy. Twice-a-day LMWH dictates holding one dose, and waiting 20–24 h after the last dose.
Nonsteroidal anti-inflammatory drugs	No evidence of increased risk.
Combination therapy	Little data, but risk may be increased, especially if LMWH is one of the therapies.
Antiplatelet agents	The suggested time interval between discontinuation of thienopyridine therapy and neuraxial blockade is 14 days for ticlopidine and 7 days for clopidogrel. If a neuraxial block is indicated between 5 and 7 days of discontinuation of clopidogrel, normalization of platelet function should be documented.

[a]*For full set of recommendations of the American Society of Regional Anesthesia Consensus Statement, see https://www.asra.com/advisory-guidelines. Accessed March 22, 2015.*

PERIOPERATIVE COMPLICATIONS

The most common surgical indicator of complications is morbidity and mortality within a defined period following a procedure, frequently 30 days. Hamel reported on 26,648 patients aged greater than or equal to 80 (median age 82) and 568,263 patients less than 80 years (median age 62) from the Veterans Administrations National Surgical Quality Improvement Program (NSQIP) database. Mortality is low (< 2%) for many common procedures (transurethral prostatectomy, hernia repair, knee replacement, carotid endarterectomy, vertebral disc surgery, laryngectomy, and radical prostatectomy). The incidence of complications increases and the impact of complications on mortality and functional recovery increases with age. The presence of a complication increased mortality from 4% to 26%. Respiratory and urinary tract complications were most common.

Anesthetic risk is difficult to quantify separately from the risk of surgery, because few people receive an anesthetic in the absence of a surgical procedure. For healthy patients, the risk of death purely caused by the anesthetic has been estimated to be as low as 1 in 250,000. Such a figure is trivial in comparison to the 1 in 500 risk of death associated with surgery and anesthesia overall. Mortality is dependent on patient's age and strongly influenced by the type of surgery. Even in patients older than 90 years, minor surgeries carry a near-zero 30-day mortality, but major abdominal, thoracic, and vascular surgeries are associated with a 20% to 30% mortality. Clearly, comorbid disease, the effects of surgical trauma, and presumably the anesthetic must interact in some way to increase risk. The mechanisms underlying increased risk are poorly understood but are presumed to be influenced by the interaction of age and comorbid disease on reduced physiologic reserve. This reduced reserve is presumed to make the body less able to withstand the various stresses associated with surgery such as pain, a hypermetabolic state, and altered neuroendocrine hormones.

Course of Recovery and Common Perioperative Complications in Older Patients

The influence of age on the course of recovery after surgery has not been a focus of research but a recent study by Lawrence et al. provides valuable insights. Among geriatric patients who had undergone abdominal surgery, recovery of independence in basic activities of daily living (ADLs) took almost 3 months on average. Some measures, such as hand grip strength, had, on average, not returned to baseline even at 6 months. Since recovery from surgery involves patient effort, it is important for the patients to understand their own role in the recovery process and to have a realistic idea of how long it will be before they feel like themselves again.

An exhaustive discussion of complications that may occur in association with anesthesia and surgery is beyond the scope of this chapter. Nevertheless, it is worth commenting on a few complications. The most feared complication from anesthesia is the loss of the ability to ventilate a patient with subsequent hypoxic injury. This type of complication has become rare, and there is nothing to suggest that these events are more common in older patients.

Pulmonary complications are most common in older surgical patients, with postoperative pneumonia carrying a 20% mortality rate. Gag reflexes are decreased in older adults and easily impaired by sedative and analgesic medications. Unless an older adult is specifically assessed as needing prolonged mechanical ventilation following surgery, there is nothing to suggest an advantage delaying extubation based on age. The current practice is to return to spontaneous ventilation and avoid prolonged intubation. Programs to prevent the development of pneumonia have had mixed results to date.

Cardiac events have received intensive focus in the perioperative arena. The nature of perioperative risk has changed during the years, with full Q-wave infarctions becoming less common. The risk of myocardial infarction increases with the prevalence of coronary disease in the patient population examined. In a relatively high-risk group such as patients undergoing peripheral vascular surgery, the incidence of myocardial infarction is approximately 4% and congestive heart failure around 9%. Among patients with a prior history of myocardial infarction, a perioperative myocardial infarction is still associated with approximately 30% mortality. The most common time when myocardial infarctions and congestive heart failure are detected is 2 days after surgery. The use of perioperative β-blockers for patients at risk of myocardial infarction is rapidly becoming a standard of care, and there is no reason to avoid β-blockers solely on the basis of age.

Stroke is a less frequent, but feared, complication of surgery. Perioperative stroke occurs much more frequently than would be expected for the same population in the absence of surgery. The most common cause of stroke in medical patients is thromboembolism, and there is no indication that it is any different perioperatively. In all likelihood, the same changes that increase the risk of myocardial infarction are responsible for the increased risk of stroke. While perhaps widely assumed to be a contributor to surgical stroke risk, hypotension is not a likely cause of stroke in the setting of surgery and anesthesia. There are two main sequences of evidence for this assertion. The first rests on the timing of onset of stroke in the perioperative period, and the second rests on the lack of relationship between duration of hypotension and stroke. The vast majority of strokes occur after the patient recovers from anesthesia and has demonstrated an immediate postoperative unchanged neurologic examination. Intraoperative hypotension is certainly not uncommon in older patients, although it rarely is allowed to persist for long periods of time. It is unlikely that brief periods of intraoperative hypotension are associated with stroke. If brief periods of hypotension caused strokes, then extended periods should, too. Yet no study involving deliberate hypotension for control of blood loss has reported an associated stroke. The best such study, involving 235 patients with an average age of 72 who were randomly assigned to have mean arterial pressure maintained between 45 and 55 mm Hg or 55 and 70 mm Hg during surgery, demonstrated no strokes. Of much greater concern than hypotension as a mechanism for stroke is atrial fibrillation and cardiac emboli, perhaps accentuated by hypercoagulability. The degree to which atrial fibrillation is a risk factor is not well understood, but it raises the issue of how to manage patients who take warfarin chronically for atrial fibrillation or artificial valves. Based on the low risk of stroke in the immediate few days surrounding surgery in the absence of anticoagulation, it seems statistically safe to stop warfarin 4 days before surgery. A heparin infusion does not need to be used unless the patient has a history of arterial embolus or deep vein thrombosis within the previous 3 months. Warfarin therapy should be reinstituted postoperatively as soon as feasible.

There are two neurocognitive syndromes, delirium and postoperative cognitive dysfunction (POCD), that emerge in the postoperative period most commonly in older adults. Postoperative delirium is a change in mental status that consists of the inability to focus, sustain, and shift attention that is accompanied by other cognitive symptoms (eg, disorientation and episodic memory dysfunction), and/or perceptual disturbances (misinterpretations, illusions, or hallucinations). Delirium as an entity is discussed elsewhere in this text. Emergence excitation, frequently called emergence delirium, occurs early, during emergence from general anesthesia. Postoperative delirium on the other hand develops later, usually 24 to 48 hours after an otherwise uneventful recovery from surgery. The risk of postoperative delirium is higher in older adults. For any major general surgery, the incidence is approximately 9% but may be as high as 60% in select surgical populations (major orthopedic and cardiac procedures). In contrast to medical patients, surgical patients rarely have delirium on hospital admission. Approximately a third to a half of the cases of delirium in medical patients are present at admission to the hospital, while only 7% of patients with delirium associated with hip fracture were delirious on admission. The etiology of delirium in general, and in postoperative delirium in particular, remains unknown. Drugs such as meperidine and anticholinergics are potential contributors and should be avoided in older adults, but the risk from opioids is not clear, especially when failure to use such drugs could lead to increased

pain and decreased sleep. One might expect general anesthesia to be a major risk factor for delirium, but multiple studies have all failed to demonstrate any differences in rates of delirium between general and regional anesthesia, even when careful monitoring of attention and cognitive function is performed. Delirium, if present at any time in the hospitalization, is associated with increased rates of complications, significantly prolonged hospital stay, and a decrease in function (eg, ADLs) on hospital discharge. Aggressive management of geriatric patients can result in significant decreases in the incidence of postoperative delirium, as shown primarily by Edward Marcantonio in hip fracture patients (see section below on "Integrated Care"). Both the regular confusion assessment method (CAM) and the CAM-ICU can be used in the perioperative period to detect delirium. As with medical patients, some patients are hyperactive and aggressive, but many delirium patients are hypoactive and quiet, so monitoring programs are required to reliably detect postoperative delirium. Management resembles delirium prevention and care in other settings (see Chapter 47). Practice guidelines for postoperative delirium in older adults have recently been released. POCD is defined as a measurable decline in performance on a battery of neurocognitive tests. POCD appears to be distinct from delirium but may prove to be related. For years, there have been anecdotal reports of cognitive decline following surgery and anesthesia. In 1998, a prospective study tested surgical patients before and at 1 week and 3 months after surgery. A matched set of control subjects not having surgery was selected and tested as well. At 3 months, 10% of the surgical patients had demonstrable cognitive decline, in comparison to only 3% of the control subjects. Subsequent follow-up of this cohort suggested that approximately 1% had a persistent deficit after 2 years. As neurocognitive testing is not routinely done prior to surgery, POCD is primarily a research finding. It appears to be primarily a problem of older adults, in that incidence is minimal below 60 years. POCD is uncommon following minor surgery. POCD following cardiac surgery occurs at a higher rate, approaching 50% at discharge from the hospital. POCD following cardiac surgery had traditionally been attributed to the influence of cardiopulmonary bypass; however, a recent study showed similar levels of cognitive decline among patients undergoing coronary artery bypass with and without cardiopulmonary bypass. Thus, the cause of POCD for both cardiac and noncardiac surgery remains unknown. There are neither strategies to prevent POCD nor treatments once cognitive decline occurs.

MODELS OF COLLABORATIVE CARE FOR THE SURGICAL PATIENT

The most mature literature regarding the role of geriatricians in the care of surgical patients has been focused on patients with fractures of the upper femur. Heyburn and colleagues described four models that have been applied to hip fracture patients: the traditional model in which care is directed by the orthopedic surgeon and medical queries are directed to a consultant, the second is a variation in which multidisciplinary rounds with geriatricians and surgeons increase awareness of cross specialty issues, the third involves early postoperative transfer to a geriatric rehabilitation unit, and the fourth is combined orthogeriatric care in which the patient is admitted to a specialized ward where care is coordinated by geriatricians and orthopedic surgeons. There are clear advantages to patients from these models, the key factor being the implementation of the geriatric parts of the care plan. Marcantonio demonstrated the potential for a marked improvement in outcome in a randomized trial of proactive geriatric consultation based on a structured protocol for patients with hip fractures. The intervention reduced delirium by more than one-third. Some perioperative comprehensive geriatric assessment programs have cut down on length of stay. More complex programs such as the Hospital Elder Life Program are being evaluated for their impact on surgical patients.

CONCLUSION

Since there are more and more older adults, and since surgical procedures are increasingly feasible in complex older adults owing to technical and medical advances, the demand for anesthetic care of older patients is increasing. This care is intricate and carries real risks. Better preoperative preparation and postoperative care are likely to have a greater impact on outcomes than further advances in intraoperative anesthetic management, at least in the near future. The role of postoperative analgesia in improving outcomes and reducing the costs of medical care is still in its infancy. Optimal care of the older adult in the perioperative setting depends on the combined expertise of many specialties and an integrated, comprehensive approach.

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Chapter 33

Surgical Outcomes

Jennifer Kaplan, Emily Finlayson

Learning Objectives

- Describe the effect of surgery on postoperative functional and cognitive status.
- Understand surgical outcomes in specific surgical popu- lation.
- Recognize the future directions in preoperative optimi-zation.

Key Clinical Points

1. **Identifying frailty preoperatively is important for the prediction of postoperative adverse events and mortality.**
2. **Age alone does not predict functional decline after surgery.**
3. **Prehospital rehabilitation is emerging as a strategy to improve postoperative outcomes for frail older adults.**

INTRODUCTION

As the population over the age of 65 grows, so will the proportion of older adults undergoing surgical procedures. Estimates of general surgery workload predict a 32% increase between 2000 and 2020 with a population increase of only 18%, reflecting the larger proportion of older patients. With advances in care and surgical technique, older patients with treatable conditions continue to be referred for surgery; however, operations in frail older adults are associated with a high risk of complications, prolonged hospitalization, and functional decline.

Recently, frailty as a distinct clinical syndrome has been recognized as a surgical risk factor that contributes to adverse surgical outcomes independent of age. Surgical decision making in frail older patients is complex. The balance between high operative risk and the potential benefits of surgery is not always clear. How to effectively prepare frail patients for surgery and identify which patients will benefit most from operative intervention is still a subject of investigation. In this chapter, we will review the risk factors for adverse events and predictors of long-term outcomes of surgery in older patients.

FRAILTY AS A RISK FACTOR

Frailty, or a decreased physiologic reserve with vulnerability to stressors, is an increasingly common focus of surgical research, and is integral to any discussion of surgical outcomes in older adults. The prevalence of frailty in the surgical population is estimated between 40% and 50%. Frailty is independently associated with complications such as postoperative delirium, with an odds ratio (OR) of 1.84. A modified frailty index with points given for comorbidities and functional dependence was found to be associated with mortality in emergency general surgery operations with an OR of 11.7. In multivariate analysis, the association between frailty and mortality was stronger than that observed for increasing age or American Society of Anesthesiologists (ASA) class. Whether to use a particular score or combination of variables (and which variable to use) to define frailty in the surgical population is a subject of debate.

OUTCOMES

Functional Status

For older surgical patients, even transient loss of independence is a major concern; therefore, it is essential to understand the effects of surgery on functional status in the short and long term. In a seminal 2004 study, Lawrence and colleagues described functional recovery after major abdominal surgery in older adults. For several geriatric measures, recovery to baseline after surgery was prolonged: 3 weeks for cognitive status, 6 weeks for Timed Up and Go, 6 weeks to 3 months for activities of daily living (ADLs), 3 to 6 months for instrumental ADLs (IADLs), and over 6 months for grip strength. Factors associated with poor functional recovery included depression, poor preoperative physical performance status, and postoperative complications. Age was not independently associated with functional recovery.

Functional decline after surgery in the frailest old is often substantial and sustained. Among nursing home patients undergoing colectomy, 24% of survivors experienced a decline in their ability to perform ADLs at 1 year. For patients over 70 years undergoing surgery for colorectal cancer, ADLs decreased in 31% and IADLs decreased in 69%. In this analysis, no preoperative factors were independently associated with functional decline. In a separate analysis, only 3% of community-dwelling patients over the age of 75 undergoing elective resections of gastric or colorectal cancer demonstrated functional impairment at 6 months postoperatively, despite 24% having early transient declines. In this cohort, by 6 months after surgery, quality-of-life measurements improved to values higher than preoperatively (0.806 vs 0.769, $p < 0.05$), indicating that in patients with acceptable risk profiles, age should not dictate whether to undergo surgery.

Among frail older patients, procedures aimed at maintaining or improving ambulation may not be successful. Many older patients suffer from peripheral arterial disease, and revascularization procedures are offered to avoid amputations. In a study of nursing home residents undergoing revascularization procedures, of those who were ambulatory prior to surgery, 63% had died or were nonambulatory by 1 year postoperatively. Risk factors for death or nonambulatory status included preoperative nonambulatory status and preoperative declines in ADLs. Hip surgery in older patients has been reported to cause a 61% decrease in functional at 2 years. Patients with cognitive impairment had the greatest risk of functional decline (hazard ratio [HR] 2.64; 95% confidence interval [CI], 1.09–5.85). In a study of hip fracture in nonagenarians, nearly a quarter of patients who could ambulate preoperatively were nonambulatory after surgery. When a similar study was done in nursing home patients, both survival and functional status were poor postoperatively (only 21% of patients who were functionally independent at baseline both survived and were independent at 6 months postoperatively). Preoperative functional and cognitive status are clearly linked to postoperative function and should be addressed with patients and their families during operative planning, especially for those patients already living in nursing facilities. **Table 33-1** summarizes the risk factors for postoperative functional decline.

TABLE 33-1 RISKS FOR FUNCTIONAL DECLINE AFTER SURGERY

SOURCE	PROCEDURE	SAMPLE SIZE	AGE, Y	FOLLOW-UP	OVERALL INCIDENCE NO. (%)	RISK FACTOR	ABSOLUTE RISK (%)	RR (95% CI)
Retrospective cohort								
Finlayson 2012	Colectomy	6822	≥ 65	1 y	24%	Preoperative functional decline	60%	HR 1.21 (1.11–1.32)
Neuman 2014	Hip fracture	52,734	Range not given	6 mo	20.8%	Requires limited assistance at baseline	77.9%[a]	RR 1.09 (1.06–1.11)
Oresanya 2015	Lower extremity revasculari-zation	10,784	> 67	1 y	64%	Cognitive impairment	70%	RR 1.36 (1.27–1.46)
Tay 2014	Hip fracture	64	≥ 90	1 y	50%	Ambulant with aid	17.2%	OR 1.5
Prospective cohort								
Ronning 2014	Colectomy	84	≥ 70	28 mo	31%	Frailty	35%	1.2 (0.1–2.3)
Amemiya 2007	Gastrec-tomy or colectomy	233	≥ 75	6 mo	3%	E-PASS score	NR	1.26 (1.08–1.47)

[a]Composite outcome of death or new total disability in locomotion in patients who were not completely dependent at baseline.
E-PASS, estimation of physical ability and surgical stress; HR, hazard ratio; NR, not reported; OR, odds ratio; RR, risk ratio.

Cognitive Impairment

Postoperative delirium is common in older patients and is associated with long-term cognitive changes. In a study of older patients undergoing operative repair of hip fracture, the risk for postoperative dementia or mild cognitive impairment at 30 months was doubled if a patient had suffered from in-hospital postoperative delirium (risk ratio [RR] 1.9; 95% CI, 1.1–3.3). In a meta-analysis of cognitive function after cardiovascular interventions (including coronary artery bypass, coronary artery bypass graft [CABG], and carotid endarterectomy), long-term cognitive decline was uncommon. One study that compared CABG to medical management found no significant change from baseline in either group at 6 years of follow-up. Cognitive status was not affected by whether the operation was done on or off pump or whether patients were subjected to intraoperative hypothermia or normothermia. Cognition was additionally unaffected in patients undergoing open or endovascular intervention for carotid artery stenosis. More important than the type of operation performed, preoperative cognitive status and postoperative delirium serve as harbingers of later cognitive decline.

Discharge to Facility

Many older patients are unable to return home after surgery and require stays in skilled nursing facilities. Studies of hip fracture patients found cognitive impairment is associated with discharge to a facility (OR 2.18 and HR 7.37). Frailty is also associated with discharge to a facility in patients over 65 undergoing a range of procedures (OR 3.16–13.02). As expected, preoperative residential status is also an important risk factor for discharge to a facility (OR 5.97). Whether these discharges were anticipated preoperatively is unknown. Discharge to a nursing facility should be included in the preoperative discussion of surgical risks in order to set realistic expectations for the patient and their family.

OUTCOMES IN SPECIFIC SURGICAL POPULATIONS

Cancer

As the incidence of many cancers increases with age, older patients are frequently referred for surgical management. Li and coauthors reported a negative impact of postoperative transitional care needs (nonhome discharge destination or home with services) on survival after elective surgical resection of colorectal cancer in older patients. Almost half of patients aged 75 and older required transitional services, with 80% needing rehabilitation. The median overall survival was 4 years less in patients requiring transitional care. In a study of older patients undergoing esophagectomy for esophageal cancer, 5-year cause-specific and overall survival were lowest in patients of 80 year and older; however, this group was less likely to have undergone neoadjuvant chemotherapy and tended to undergo less aggressive intraoperative nodal dissection. Use of neoadjuvant chemotherapy in turn was associated with increased complications in patients aged 75 to 80. These results suggest that in a cohort of healthy older adults, the possibility of more aggressive management must be balanced with the risk of postoperative morbidity.

Cardiovascular

Excellent long-term survival has been demonstrated in octogenarians undergoing valve repair operations that are on par with survival in the general age-matched population. In this study, there was no significant difference in early postoperative mortality between octogenarians and patients aged 60 to 80; however, there were significantly more deaths than in patients under age 60 (5.4% vs 3.2%, $p < 0.001$). Class 4 heart failure, renal failure, respiratory failure, intra-aortic balloon pump requirement, and aortic incompetence were found on multivariate analysis to predict late death, while age was not a factor. Others have found survival after valve surgery to be dependent on discharge destination, with those being sent to a nursing facility versus home or rehab having a higher risk at 1 and 2 years postoperatively (HR 2.6; 95% CI, 1.1–6.1; $p = 0.006$). Predictors of discharge to skilled nursing included increasing age, unmarried status, and a major postoperative complication.

In studies examining the roles of CABG versus percutaneous interventions (PCI) in older populations, both interventions demonstrate improvements in quality of life over medical management. Regardless of procedure, patient frailty is associated with four times higher 3-year mortality (6% vs 28%). Which intervention to choose depends not only on patient goals, but also on existing comorbidities. Older patients with chronic kidney disease may benefit more from PCI, while those with diabetes have shown lower risk of postoperative stroke with CABG. As with any other patient group older patients with stable angina first require optimal medical therapy followed by an honest discussion of surgical risks and benefits.

FUTURE DIRECTIONS

Prehabilitation

Novel strategies to improve surgical outcomes in older adults are receiving increased attention. The prehospital rehabilitation model, or prehabilitation, aims to optimize frail patients prior to their operation with the goal of decreasing complications and preventing a prolonged hospital stay. This builds on the comprehensive geriatric assessment by offering targeted preoperative interventions. One such model includes exercise, nutritional counseling, protein supplements, and anxiety reduction for patients of all ages undergoing colorectal surgery. In a pilot program, patients who underwent “prehabilitation” improved postoperative exercise capacity and functional recovery (mean difference in walking capacity 84 ± 83 m, $p < 0.01$, at 8 weeks postoperatively; 81% of prehabilitation patients recovered vs 40% of controls, $p < 0.01$). Another successful model recruits patients over 65 with significant comorbidities or evidence of frailty, and provides a preoperative comprehensive geriatric assessment, preoperative home therapy if needed, postoperative discharge planning, and connection to postoperative services. By targeting the specific needs of frail patients in a multidisciplinary fashion before they entered the hospital and developing inpatient care pathways, complication rates decreased (pneumonia: 20.4%–3.7%, $p = 0.008$; delirium: 18.5%–5.6%, $p = 0.036$; pressure sores: 18.5%–3.7%, $p = 0.028$), as did length of stay by 4.5 days. Regardless of the prehabilitation model, optimization of functional status, nutrition, and polypharmacy should be attempted preoperatively. Further investigation should seek to determine which components comprise the optimal prehabilitation model and how best to implement interdisciplinary optimization of frail surgical patients.

Preoperative Palliative Care

Despite the necessity of preoperative goals of care discussions, many surgeons may find difficulty doing so in the midst of a busy clinic. For frail patients with significant operative risk, preoperative palliative care consults show

benefit in establishing surgical goals and postoperative expectations. In one study, after the introduction of preoperative palliative care consults to high-risk frail patients, more patients declined surgery and late mortality decreased even with adjusting for whether or not patients had surgery. Thoughtful discussions with a palliative specialist can help patients articulate their goals of care and determine if the planned intervention is in line with these goals. In addition, palliative care specialists can offer effective strategies for symptom management before and after surgery. This model of care requires open communication and collaboration between surgeons and palliative care specialists.

CONCLUSION

Older patients—who are often multimorbid and have geriatric conditions—are at risk for postoperative complications, prolonged length of stay, discharge to skilled nursing facilities, and functional decline. Long-term outcomes in this heterogeneous population, however, are mixed. Individualized risk assessment in older adults is essential to inform surgical decision making in this population. Better preoperative assessments and interventions aimed at improving geriatric syndromes before surgery may continue to improve surgical outcomes.

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Chapter 34

Nutrition and Obesity

Dennis H. Sullivan, Larry E. Johnson

Learning Objectives

- Describe the important interrelationship between diet and physical activity in maintaining or restoring lean body mass (LBM) and the resulting effects this interaction has on total body mass in older adults.
- Describe the changes in body composition that occur over the adult lifespan and what physiologic, dietary, lifestyle, and disease factors are responsible for these changes.
- Describe the changing prevalence of obesity among older adults and be able to assess the impact of excess weight on the health status of older patients.
- Advise older adults about what constitutes an optimal diet and the advisability of using nutrient supplements given their health status.

Key Clinical Points

1. **With advancing age, the ratio of fat to total body mass increases regardless of whether total body weight increases or remains constant.**
2. **Although skeletal muscle mass generally declines with advancing age, the rate of decline in healthy individuals is highly dependent on the individual's habitual level of physical activity and the quality of his/her diet.**
3. **Although the impact of excess weight (ie, body mass index [BMI] > 25 kg/m^2) on long-term survival is highly controversial, there is a strong direct relationship between the level of obesity and the risk of developing disabling chronic diseases such as severe osteo- arthritis, type 2 diabetes, and heart disease.**
4. **There is no evidence of benefit for any micronutrient supplement in healthy older adults who do not have a documented deficiency of the given nutrient or a condition that places them at high risk for the development of such a deficiency. Supplements of vitamins and minerals do not prevent or treat cardiovascular disease (CVD), cancer, or dementia.**
5. **Vitamin and mineral supplements, above the recommended upper limit (UL), increase adverse health outcomes. The Institute of Medicine (IOM) provides evidence-based guidelines for recommended dietary intakes of vitamins and minerals for most individuals.**
6. **Laboratory blood tests of serum proteins (such as albumin and prealbumin) are indicators of inflammatory status, disease severity, and morbidity risk, rather than nutritional status.**

INTRODUCTION

Throughout life, nutrition is an important determinant of health, physical and cognitive function, vitality, overall quality of life, and longevity. The quantity and variety of available foods, as well as the meaningfulness of the social interactions provided by meals, are important to psychological well-being. The composition of the diet and the amount that is consumed are strongly linked to physiologic function. When a well-balanced diet is not maintained, malnutrition may develop with consequent detrimental effects on health and well-being.

Malnutrition can have many manifestations. As outlined in Chapter 35, a diet that is deficient in one or more required nutrients (eg, calories, protein, minerals, fiber, or vitamins) can lead to a state of nutritional deficiency. The greater the magnitude and duration of the nutritional deprivation and the more fragile the individual, the more likely nutritional deficits will produce noticeable body compositional changes, functional impairments, or overt disease. Even borderline dietary deficiencies can have important health consequences such as producing subtle organ system impairments, diminished vitality, or increasing the individual's susceptibility to disease. Protein and protein-energy undernutrition are two of the most common, frequently unrecognized, and potentially serious forms of nutritional deficiency. The prevalence of these conditions is particularly high among chronically ill older individuals and those in hospitals, nursing homes, and other institutional settings. Although there is a complex interrelationship between nutrition, disease, and clinical outcomes, protein and protein-energy undernutrition appear to be significant contributors to disease-related morbidity and mortality in these populations.

At the other end of the spectrum, the persistent consumption of excess quantities of one or more nutrients can have similar untoward consequences. Forms of malnutrition that result from excess consumption include hypercholesterolemia, hypervitaminosis, and obesity. Obesity is the most common nutritional disorder of advanced age in western societies with a high prevalence among noninstitutionalized free-living older adults. Many obese older individuals have other nutritional disorders. Among chronically ill or functionally debilitated obese older individuals, protein undernutrition is a common, serious, and frequently unrecognized problem that can develop for many reasons including an imbalanced diet, disease, and inactivity.

Recognizing and maintaining an optimally balanced diet is an important challenge, particularly as individuals age. The challenge is particularly great for older people who already are malnourished, especially if they have nutritional disorders that developed earlier in life, such as obesity, osteoporosis, or protein undernutrition. Even healthy individuals often fail to maintain an optimal diet due to lack of knowledge, resources, or willpower. The process of aging can introduce other factors including acute and chronic disease, physical disabilities, social isolation, use of multiple medications, depression, impaired cognitive ability, and dysregulation of appetite control that may contribute further to poor eating habits and the development or exacerbation of nutritional disorders. In turn, inappropriate dietary intake and poor nutritional status can impact the progression of many acute and chronic diseases such as coronary heart disease (CHD), cancer, stroke, diabetes, and osteoporosis, which are among the 10 leading causes of death in the United States. Approximately two-thirds of all deaths within the United States are due to diseases associated with poor diets and dietary habits.

Assessing diet quality of the older people is critical to addressing issues relevant to their health and nutritional status. Such an assessment must be based on knowledge of what constitutes a balanced diet for a given individual. The goal of this chapter is to identify an approach to nutrition evaluation and management that takes into account the unique needs, limitations, and desires of each older individual. The chapter examines the interrelationship between nutrition, activity, disease burden, and health outcomes and then focuses on age-related changes in body composition and appetite regulation that effect nutritional status and nutrient requirements. The chapter includes discussion of both undernutrition and obesity as well as specific dietary considerations for optimal health.

THE INTERRELATIONSHIP BETWEEN NUTRITION, ACTIVITY, AND DISEASE

Although nutrition is a vital component of good health, it cannot be evaluated in isolation. The relationship between nutrient intake and health is influenced by other factors, most notably activity level, disease burden, and advancing age. A basic understanding of these interrelationships is essential in order to assess the potential benefits and limitations of nutritional interventions.

Nutrition-Activity Interrelationship

Nutrition and physical activity are closely linked, each having vitally important and interacting effects on body

composition, functional ability, and well-being. The balance between nutrient intake and physical activity is particularly important in determining muscle mass and strength, body fat content and distribution, and bone density and resilience. A detailed description of the importance of physical activity in these relationships is provided in Chapter 115.

To preserve existing muscle mass and strength, it is necessary to maintain both an adequate level of physical activity and a balanced diet that includes sufficient protein, energy, vitamins, and minerals to meet metabolic demands and prevent negative nitrogen balance (as discussed in detail below). It is not known precisely what level of physical activity is needed to prevent loss of existing muscle mass and strength in older adults. However, even a week or two of bed rest or similar degrees of activity restriction can result in noticeable loss of muscle mass, strength, and function even when the diet is adequate and the individual is otherwise healthy. In one study of 12 healthy, moderately active older adults, 10 days of voluntary total bed rest resulted in a 16% loss of strength and a 6% loss of skeletal muscle mass from the lower extremities. Muscle biopsies indicated that muscle protein synthesis declined 30%. Despite the provision of a diet containing the recommended dietary allowance for protein, the participants remained in negative nitrogen balance throughout the study. In contrast, fat mass did not change. The combination of inadequate diet and inactivity can result in an even more rapid loss of muscle. In contrast, overfeeding does not prevent muscle atrophy associated with inactivity and may exacerbate the functional consequences since the excess nutrients are converted to fat.

Consumption of a protein meal stimulates muscle protein synthesis. However, nutrition alone has never been demonstrated to be an effective method of repleting muscle mass, improving strength, or increasing endurance in frail older individuals who have experienced a recent loss of weight. Efforts at repletion should focus on both increasing nutrient intake and exercise. Based on studies of healthy older men, the combination of progressive resistance muscle strength training and a high-protein diet (containing up to 1.6 g of protein/kg body weight/day) may be the most effective method of improving muscle mass. The role of special formula amino acid supplements has yet to be determined.

Exercise and nutrition also play a critical role in maintenance of optimal bone density and strength. As discussed in Chapter 118, the nutrient needs of bone include the correct balance of protein and energy and adequate intake of vitamins and minerals, especially vitamin D and calcium. The importance of exercise for optimal bone health is also described in Chapter 115. Bed rest and weightlessness are associated with a rapid decline in bone mineral density (BMD). Consequently, osteopenia can develop despite an optimal diet if exercise or other weight-bearing activities are not adequate. Because of its apparent beneficial effects on BMD, exercise should be combined with an appropriate diet for both prevention and treatment of osteoporosis and fracture-related disability.

Having both direct and indirect effects on numerous metabolic processes within muscle, bone, and adipose tissues, exercise has a major impact on how nutrients are utilized by the body during health and illness. By inducing an increase in the mass and metabolic capacity of muscle, exercise effects energy expenditure, glucose metabolism, and size of protein reserves in a manner that counteracts some of the effects of aging and thus has important nutritional implications for individuals as they grow older. Total energy expenditure (TEE) represents the sum of basal energy expenditure, postprandial thermogenesis, and the energy expenditure of activity. Muscle represents not only the primary source of energy expenditure during physical activity, it is also the primary contributor to basal energy expenditure, which may represent 50% to 80% of TEE. With advancing age, there is a parallel decline in muscle mass and both basal and total daily energy expenditure that may be partially or fully accounted for by the fact that people tend to become more sedentary as they grow older.

Exercise-induced increases in muscle size and protein content result in greater body protein reserves, which can be critical to survival during episodes of nutritional deprivation that usually accompany profound physiologic stress such as trauma, sepsis, or other acute disease. Such physiologic insults trigger an acute inflammatory response that causes ketogenesis to be suppressed, leaving glucose as the primary energy source available to the body. The problem is invariably compounded by reduced nutrient intake that results as a consequence of the anorexia and gastrointestinal tract dysfunction induced by the inflammatory response. With nutrient intake suppressed, gluconeogenesis becomes the predominant source of glucose. Since the substrate for gluconeogenesis is provided by catabolism of skeletal muscle, LBM becomes an important determinant of survival. Once LBM falls below a critical level, the chance of surviving a serious acute illness diminishes dramatically. Studies conducted within the Warsaw Ghetto, hospital intensive care units, and other settings suggest that a loss of greater than 40% of baseline lean mass is incompatible with life. Indeed, very few healthy people have a LBM that is less than 70% of the mean for that of adults aged 20 to 30.

In addition to inducing muscle hypertrophy, exercise also affects insulin sensitivity and glucose disposal directly and plays a synergistic role with diet in maintaining a healthy weight and a sense of well-being. These effects of

exercise can be important adjuncts to good nutrition in the prevention and treatment of hypertension, diabetes, and osteoporosis.

Nutrition-Disease Interrelationship

There is a complex interrelationship between nutrition, health status, and clinical outcomes. Although a full discussion of this topic is beyond the scope of this chapter, it is important to emphasize several key points. First, nutrient requirements and the ability to metabolize select nutrients are influenced by many disease states. In addition, many diseases compromise the older individual's ability to consume adequate amounts of all nutrients. This can occur through a number of mechanisms including disease-induced suppression of appetite, alteration of the normal swallowing mechanism, maldigestion or absorption, or loss of self-feeding ability.

The detrimental effects of disease on nutrient metabolism often become more pronounced with advancing age. This is particularly true of the many acute and chronic diseases that induce an inflammatory response, including acute and chronic infections, congestive heart failure, chronic pulmonary disease, cancer, end-stage renal disease, and rheumatoid arthritis. As described in detail in Chapter 4, with advancing age, the inflammatory response often becomes dysregulated as indicated by persistently elevated serum concentrations of proinflammatory cytokines and other inflammatory mediators including interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, and possibly IL-8 and others. IL-1, IL-6, and TNF-α all contribute to the loss of skeletal muscle, fat tissue, and bone mass that characterizes inflammation-associated cachexia. Although anorexia is almost always a contributing factor, the inflammation-induced loss of fat and lean mass is often refractory to nutrition support. Through a number of different mechanisms, proinflammatory cytokines create a state of muscle hypercatabolism by suppressing muscle protein synthesis and/or accelerating muscle protein breakdown independent of dietary factors.

Since these potentially deleterious effects of disease can be difficult to predict, older individuals with one or more acute or chronic health problems should have frequent reassessments of their nutritional status and their nutritional care plan revised as necessary. Although nutrient intake may not be adequate to completely reverse inflammation-induced catabolism, a low nutrient intake will accelerate the development of cachexia. Optimally, good nutritional care should be part of the overall plan of medical intervention aimed at treating the underlying pathology as well as addressing protein and energy deficits. Although a number of specific nutrients are being studied to determine their value in counteracting inflammation-induced loss of LBM, there is not yet adequate evidence that any given dietary supplement is more effective than current standard dietary or nutrition support practices.

AGE-RELATED CHANGES THAT AFFECT NUTRITION

Changes in Body Composition

With advancing age, there are significant changes in body composition that affect the nutritional needs of the individual. Weight increases steadily on average from age 30 to 60 years due primarily to an increase in total body fat. After age 60, weight usually stabilizes, and then begins to decline. Improved survival of nonobese individuals during middle age and cohort effects may account for some of the decline in weight with age. However, weight maintenance becomes increasingly difficult in the advanced years of life. The incidence as well as the potential causes of weight loss increase with age, particularly beyond age 75.

Regardless of whether or not weight changes, advancing age is characterized by a progressive loss in LBM, a relative increase in fat mass, and a redistribution of fat from peripheral to central locations within the body. These changes generally begin in the third decade and increase at an accelerated rate after age 65. This late accelerated phase may be a threshold effect brought about by the loss of lean body mass and the increased prevalence of chronic disease in old age. The loss of lean body mass consists predominantly of skeletal muscle, particularly type II or fast twitch fibers. Central lean body mass, such as the liver and other splanchnic organs, is relatively preserved. Muscle mass may decline by up to 45% between the third and eighth decade of life (**Figures 34-1** and **34-2**). The quality of muscle may also change. With advancing age, there is a gradual infiltration or replacement of muscle by fat, as has been documented by computerized tomography. Even accounting for body size, height, and other aspects of body composition, fatty infiltration into muscle is associated with symptomatic functional decline, poorer physical function, and change in strength. The loss of muscle mass with age may be greater in men than women, but this remains controversial.

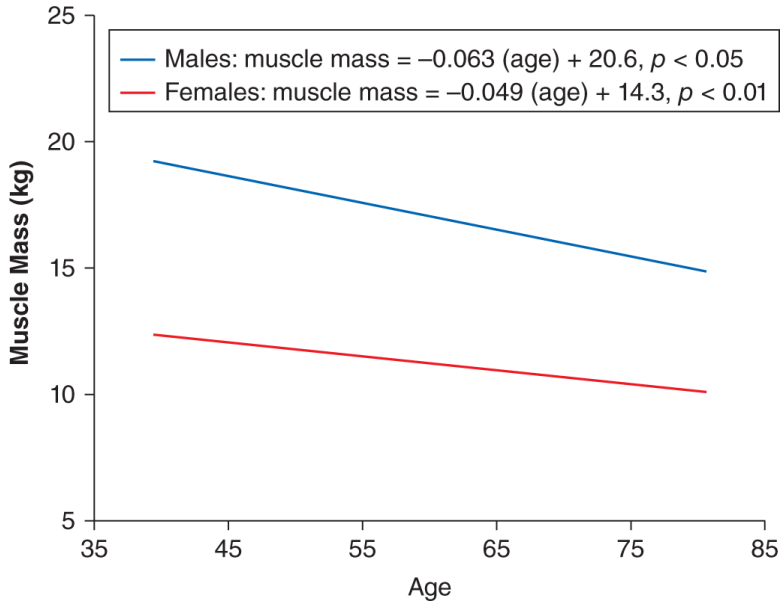


FIGURE 34-1. Declining muscle mass with increasing age. (Data from Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *J Appl Physiol*. 2000;89:81–88.)

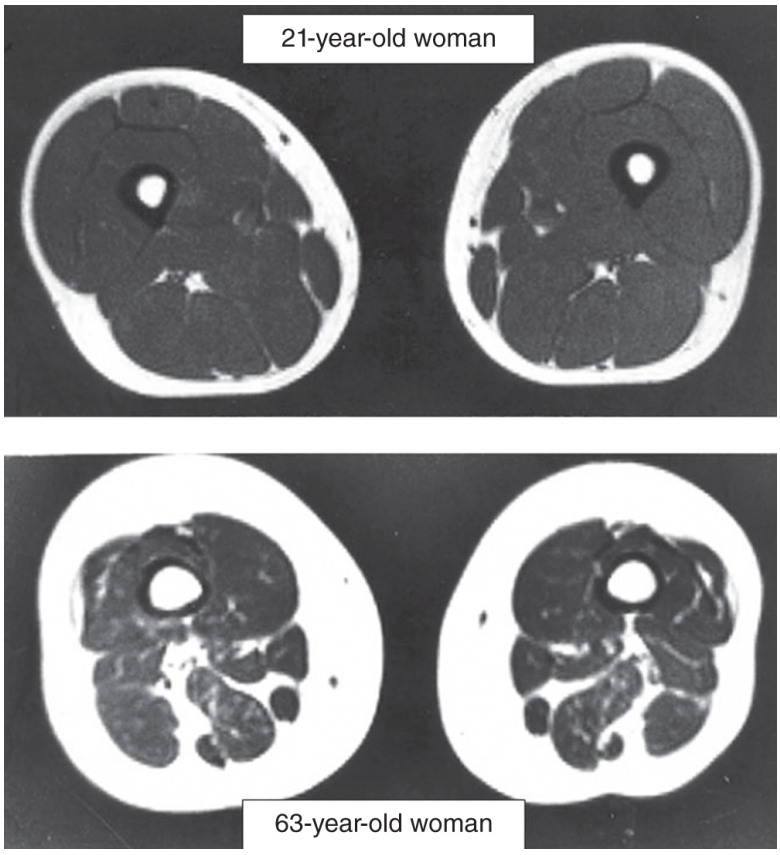


FIGURE 34-2. Cross-sectional computed tomography images of the mid-thighs of a younger and an older woman demonstrating the decline in muscle mass and relative increase in fat mass with age.

The loss of muscle mass with age appears to be the result of multiple interrelated factors including age-related changes in metabolism, function, or structure of organ tissues, disease, medical therapeutics, heritability, and behavior and lifestyle choices of the individual. Notable age-related changes that appear to contribute to loss of muscle include a progressive loss of alpha motor units in the spinal column, a diminution in the intrinsic muscle protein synthetic capacity, and a decline in the production of multiple hormones including testosterone, estrogen, and the insulin-like growth factors. The decline in the intrinsic muscle protein synthetic capacity parallels and may be causally related to a loss of mitochondrial adenosine triphosphate (ATP) production with advancing age. The declines in nutrient

consumption and activity level that often accompany advanced age are possibly modifiable contributors to the loss of muscle mass. Many diseases accelerate the age-related decline, particularly degenerative diseases of the central nervous system (CNS) and those affecting any part of the motor pathway. An accelerated loss of muscle mass can occur when a serious illness requires treatment with steroids or other anti-anabolic drugs or is accompanied by low nutrient intake and the need for prolonged bed rest. In all individuals, the loss of muscle mass with age is closely linked with a reduction in muscle strength and exercise capacity, which contribute to the development of functional impairments and disability. The loss of muscle mass and exercise capacity is also linked to the development of coronary artery disease, diabetes mellitus, and other diseases that contribute further to the decline.

In parallel with the loss of LBM, there is an increase in the relative amount and the distribution of body fat with advancing age. Between the second and ninth decades of life, the percentage of body weight that is fat increases by 35% to 50% in females and to an even greater extent in males. Whether or not total body weight changes, intra-abdominal (visceral) fat increases quantitatively and proportionally more than peripheral fat mass. In females, the accumulation of intra-abdominal fat accelerates at menopause and represents primarily a shift from peripheral sites. In males, the increase in intra-abdominal fat with age represents primarily an increase in total body fat mass. For a given waist circumference, older adults have greater visceral fat than young adults, and men have greater visceral and less subcutaneous fat than women.

Changes in Appetite and Energy Intake Regulation

Maintenance of a stable weight requires a steady balance between nutrient intake and energy expenditure. With advancing age, the metabolic, neural, and humoral pathways that normally maintain this delicate balance by regulating appetite and hunger begin to lose their compensatory responsiveness to changes in energy demands. Psychological, socioeconomic, and cultural influences and numerous disease processes further contribute to the dysregulation. From the third to seventh decade of life, these factors integrate to create an imbalance usually favoring a tendency toward weight gain and increased fat deposition, at least in societies where food is plentiful and the physical demands of life are light. However, after age 70, the risk of losing weight increases steadily with each year of survival. Loss of body weight correlates with low dietary energy intake, which is common among both the healthy and frail older adults. The late-life weight decline is associated with many chronic conditions that increase risk of death in old age, including Alzheimer disease.

Pathophysiologic changes that lead to loss of taste, smell, and appetite with advancing age Numerous pathologic and age-related physiologic changes contribute to the difficulty older people have maintaining a balance between metabolic needs and nutrient intake. The look, smell, taste, and texture of food all contribute to the desirability of a meal and can serve to stimulate or inhibit further consumption. Normal sensory systems are therefore necessary for the full enjoyment of food and are important regulators of nutrient intake. The abilities to smell and taste food are particularly important. The aroma of food can serve as a powerful appetite stimulant. After food enters the mouth, aromatic substances released from the food circulate up through the nasopharynx to the olfactory cleft where they enhance taste. The sensations of smell and taste add to the pleasure of eating while serving as chemosensory signals for food digestion by triggering salivary, gastric, pancreatic, and intestinal secretions. The texture, temperature, and quantity of food in the mouth also contribute to the hedonic qualities of a meal and serve to promote further consumption.

Thus, deterioration in sight, olfactory function, taste sensation, or ability to feel the temperature and texture of food in the mouth can have a deleterious effect on eating habits and the likelihood of maintaining an adequate diet. This becomes an important concern with advanced age. Even healthy older individuals experience a modest deterioration in their ability to detect odors and to differentiate one odor from another. There is a similar pattern to the loss of taste. Much greater losses in taste and smell occur in association with medication usage and other health-related concerns. **Table 34-1** contains a representative listing of medications that can cause appetite suppression and a loss of olfactory function and taste sensation. Poor oral health and many diseases that decrease mastication, salivary flow, or ability to swallow can also lead to deterioration in taste and smell and adversely affect appetite. The grinding and mixing of food with saliva play important roles in the release of volatiles and in bringing substances in contact with taste receptors, while swallowing movements are essential to pump the released volatiles up to the olfactory cleft where they are perceived.

TABLE 34-1 CLASSES OF MEDICATIONS THAT CAN SUPPRESS APPETITE AND ALTER OLFACTORY FUNCTION[a]

Antidepressants
Antiinflammatories
Antihypertensives and other cardiac medications
Lipid-lowering drugs
Antihistamines
Antimicrobials
Antineoplastics
Bronchodilators and other asthma medications
Muscle relaxants
Drugs for the treatment of parkinsonism
Anticonvulsants
Vasodilators

[a]Numerous drugs in each category can alter appetite and olfactory function.

In addition to the special senses, there are various neural and humoral pathways within the gut that may change with advanced age and possibly contribute to the inability of many older individuals to adequately regulate food intake. There are also large numbers of hormones and other gut-derived substances that are thought to influence appetite and food metabolism as shown in **Table 34-2**. It is theorized that the age-related changes in some or all of these substances may adversely affect food intake in older adults.

TABLE 34-2 HORMONES AND CHEMICALS THAT MAY PLAY A ROLE IN APPETITE AND OBESITY

Adiponectin
Amylin
Cholecystokinin (CCK)
Cholesterol and other lipid fractions
Estrogen
Gastrin
Gastrin-releasing peptide (GRP)
Ghrelin
Glucagon
Glucagon-like peptide 1 (GLP-1)
Glucocorticoid hormones
Glucose-dependent insulinotropic polypeptide (GIP)
Growth hormone
Guanylin
Insulin
Leptin
Motilin
Neurotensin
Nonesterified fatty acids (NEFAs)
Oxyntomodulin
Pancreatic polypeptide
Peptide YY
Proopiomelanocortin
Secretin
Serotonin
Sex hormone—binding globulin (SHBG)

Somatostatin
Substance P
Testosterone
Thyroid hormones
Triacylglycerol
Vasoactive intestinal polypeptide (VIP)

Psychological, Socioeconomic, and Cultural Influences on Appetite

After the seventh decade of life, the importance of psychological, socioeconomic, and cultural factors to maintaining an adequate diet increases. Depression is a highly prevalent, frequently unrecognized, and potentially treatable cause of a poor appetite and must always be considered when evaluating an older patient who is losing weight. A correct diagnosis is often difficult to make, particularly when the older individual suffers from other medical problems or dementia. Similarly, bereavement is associated with a lack of appetite. Poverty, lack of education, limited mobility, feeding dependency, and social isolation are also important risks. In healthy adults eating alone may be associated with a lower energy intake than when eating with others. The presence of family and close friends leads to greater nutrient intake than eating with less familiar individuals. Within institutional settings, particularly nursing homes, physical environment and ambience within the dining areas are known to affect appetite. Interventions to ameliorate the dining experience within nursing homes can improve nutrient intakes and promote weight gain. Therapeutic diets (eg, low salt or low cholesterol) are frequently prescribed in nursing homes, often to residents who are losing weight, even though they may add little or nothing to disease management. For these reasons, the American Dietetic Association in collaboration with the Centers for Medicare and Medicaid Services, Pioneer Network, and others published a position statement suggesting that use of therapeutic diets in nursing homes be restricted.

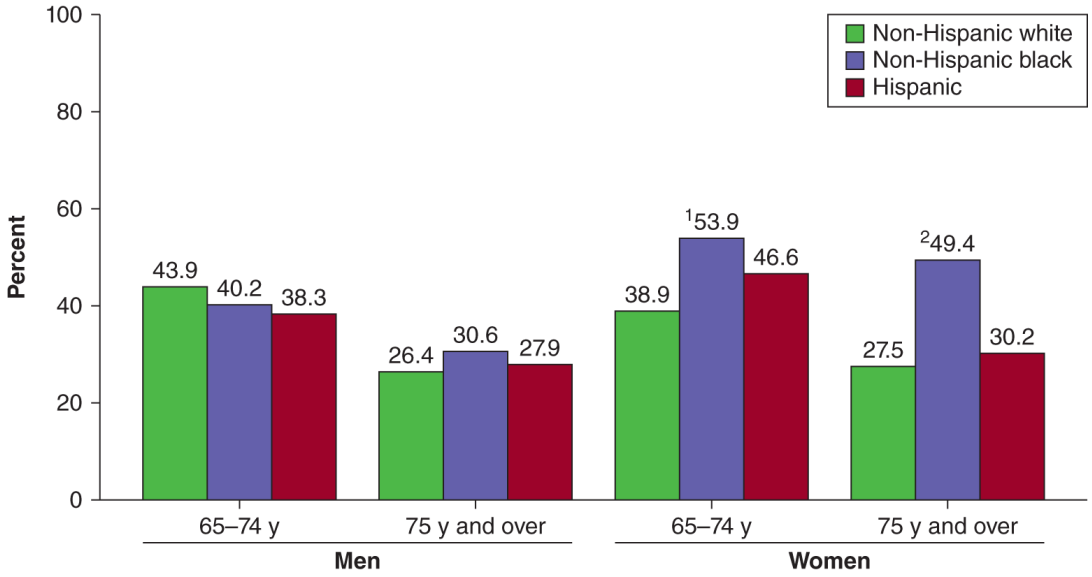
OBESITY

Definition and Prevalence

Obesity is defined as an unhealthy accumulation of body fat, which leads to a higher risk of medical illness and premature death. Although not ideal, BMI and waist circumference are the most widely utilized metrics for classifying overweight and obesity. Both are easily obtained and highly validated measures. BMI is calculated as body weight in kilograms divided by height in meters squared (kg/m^2), while waist circumference is a direct measure obtained halfway between the iliac crest and the lower anterior ribs, with the individual standing, and at the end of expiration.

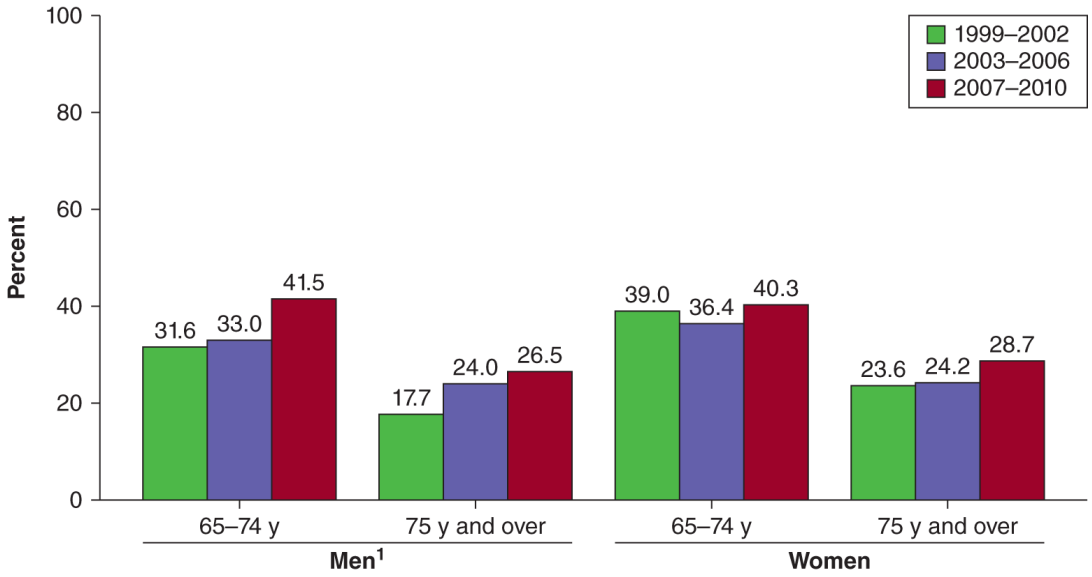
The definition of body weight categories does not currently vary by age or race. Normal weight is considered to be a BMI between 18.5 and 25; overweight, a BMI of 25 to less than 30; and obesity a BMI of 30 or more. Waist circumference is used as an index of central/abdominal adiposity and is clinically useful in further categorizing an individual based on cardiometabolic risk. Traditionally, abdominal obesity is defined as a waist circumference greater than or equal to 89 cm (35 in) for women and greater than or equal to 102 cm (40 in) for men. As with BMI, there is controversy as to whether different reference ranges should be used depending on age and ethnicity. While overweight consistently increases morbidity risk in old age, the data on mortality are less consistent, suggesting that guidelines for both BMI and waist circumference should be liberalized for older individuals.

Based on National Health and Nutrition Examination Survey (NHANES) data and current definitions, obesity is highly prevalent among older adults, especially the young old (ie, individuals between the age of 65 and 80). The variability in rates of obesity by race, gender, and age is shown in **Figure 34-3**. In all race-by-gender groups, the prevalence declines steadily with each decade of life after age 70. In part, this may be a cohort effect. Reflecting trends for the nation as a whole, prevalence rates of obesity in older adults increased significantly between 1999 and 2010, especially among males (**Figure 34-4**). It was only among the oldest-old, those age greater than 80, that the prevalence remained stable during this time.



[1]Significantly different from non-Hispanic white.
[2]Significantly different from non-Hispanic white and Hispanic.
Source: CDC/NCHS, National Health and Nutrition Examination Survery, 2007–2010.

FIGURE 34-3. Prevalence of obesity among adults aged 65 and more, by sex and race and ethnicity: United States, 2007–2010. (National Center for Health Statistics Data Brief No. 106, September 2012, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services.)



[1]Significantly linear trend.
Source: CDC/NCHS, National Health and Nutrition Examination Survery, 2007–2010.

FIGURE 34-4. Trends in the prevalence of obesity among adults aged 65 and more, by sex: United States, 1999–2010. (National Center for Health Statistics Data Brief No. 106, September 2012, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services.)

Potential Benefits and Adverse Consequences of Obesity

There is controversy regarding the potential benefits and adverse consequences of being overweight or obese after age 65. Potential benefits include protection against bone fractures and a possible survival advantage, at least for select populations of older adults. The lower fracture risk associated with obesity is related to several factors. As a result of their increased fat mass, obese older adults place more stress on their bones and convert more androstenedione to estrone than do slimmer individuals of similar age. Both of these factors contribute to the increased BMD in obese older adults. Fat also can serve as a cushion to protect against the impact of a fall, creating further protection against

bone fractures.

Assessing the impact of weight on survival in old age is more complex. The numerous studies and meta-analyses that have examined this relationship in older adult populations have produced inconsistent results. Overweight and obese older adults may have a survival advantage during periods of protracted illness, an effect thought to be the result of their greater energy and protein reserves. In general, obesity is associated with greater lean mass; during periods of catabolic stress, the fat and lean mass serve as a functional nutritional reserve.

The impact of obesity on survival in the general population of community-residing older adults is less clear. Most population-based studies that have examined the relationship between weight categories and survival in older adults have identified a "J-shaped" relationship between BMI and all-cause mortality (**Figure 34-5**). The higher mortality associated with a BMI less than 18.5 is generally consistent across studies. However, this does not necessarily indicate that older adults who have been slender all of their lives are at increased risk of mortality. The high all-cause mortality associated with a low BMI probably reflects the fact that many of the older adults in this weight group had previously lost weight due to disease. However, low protein reserves, whether the result of weight loss or a thinner body habitus, may be the critical factor that is contributing to risk of death in older adults with a low BMI.

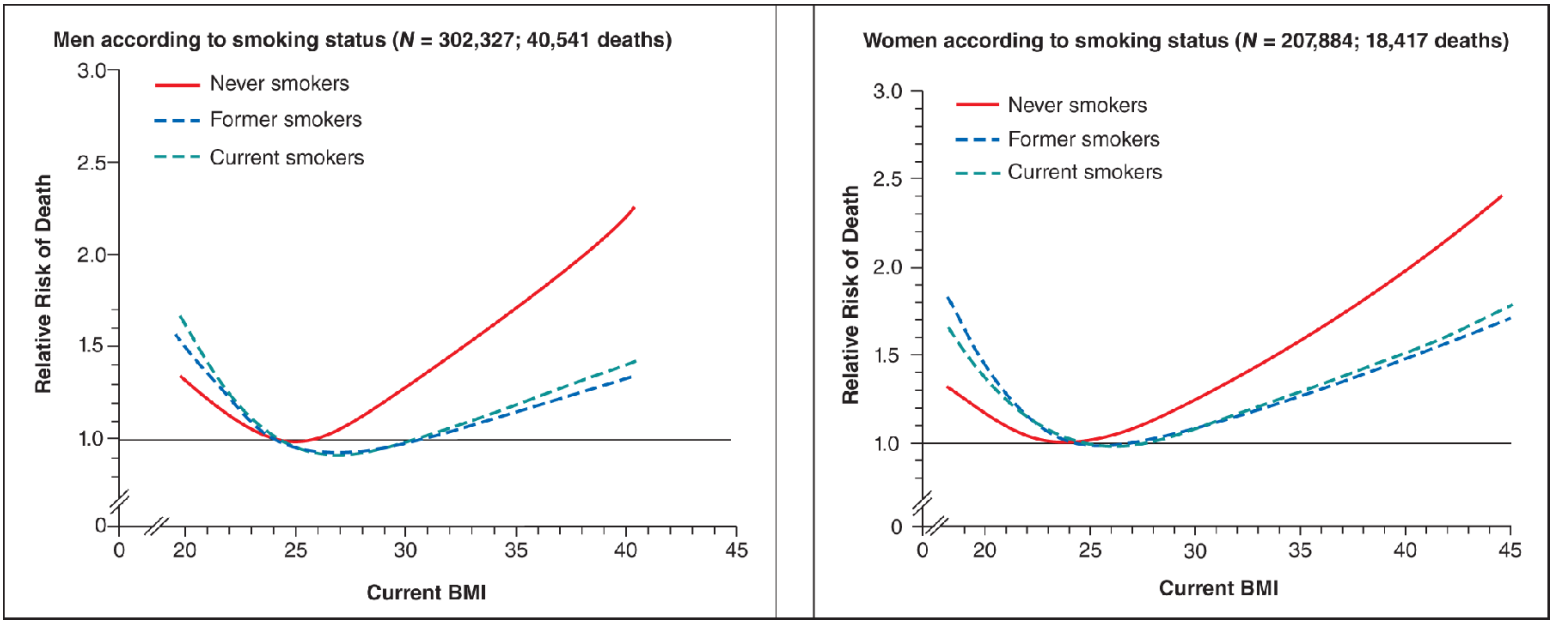


FIGURE 34-5. Data from the National Institutes of Health-AARP cohort aged 50 to 71 years-old and followed for a maximum of 10 years. Men (left) and women (right) shown by smoking status in relation to their current body mass index (BMI). Risks for never smokers are thought to most accurately estimate risk because they remove the effect of smoking on body weight and risk of death. Data adjusted for age, race or ethnic group, level of education, alcohol consumption, and physical activity.

Due to the heterogeneity of study results, it is also unclear what range of BMI is optimal for survival and at what level of obesity all-cause mortality risk begins to increase. Mortality risk appears to be lowest for older adults who are overweight (BMI, 25–30) or even moderately obese (BMI, 30–35), and mortality risk is similar for obese older adults as for age-matched adults who are in the normal weight category. However, when different methodologic approaches are used, which in some cases include controlling for cohort mortality and age-related survey selection bias, all-cause mortality increases in direct relationship with BMI in the range of 25 to greater than 40. Further complicating the issue, mortality risk in old age may relate more to fat distribution than total body mass. For any given body weight, mortality risk increases with increasing waist circumference, or more specifically, increasing intra-abdominal or visceral fat mass as measured by modern imaging modalities. Although waist circumference is strongly correlated with intra-abdominal fat mass, the two metrics are not the same. The relative contribution of mid-abdominal subcutaneous fat to waist circumference varies considerably among older adults. Thus, direct measures of intra-abdominal fat are more powerful indictors of cardiovascular (CV) risk. However, the mortality risk associated with obesity after controlling for intra-abdominal fat mass is also controversial. Given the many uncertainties about the impact of obesity on overall survival, it is important to consider what other effects excess weight has on the health of older adults.

Weight-Associated Morbidity

The impact of obesity on overall health, functional status, and quality of life in older adults is more certain. Overweight in old age is associated with the same risks for disease as in younger populations, and it also exacerbates many age-associated diseases (**Table 34-3**). The higher risk of disease associated with obesity may result as a consequence of the detrimental metabolic effects of excess body fat and/or the adverse mechanical consequences of obesity. With regard to the latter effects, the relative excess in total body weight to muscle mass leads to osteoarthritis and other disabling conditions while increasing the work required to perform many activities of daily living. The result is a lower functional reserve, chronic pain, and an increased risk of disability. Some heavier individuals have relatively less muscle mass than expected on the basis of size, a situation described as sarcopenic obesity; for these individuals, the risk of disability is especially high.

TABLE 34-3 ■ DISORDERS DIRECTLY CAUSED OR EXACERBATED BY OBESITY

Atherosclerotic cerebrovascular disease and stroke
Depression
Hypoventilation/obstructive sleep apnea
Pulmonary hypertension
Heart failure
Coronary heart disease
Peripheral vascular disease
Metabolic syndrome
Varicose veins/venous insufficiency
Hypertension
Dyslipidemia
Type 2 diabetes
Fatty liver diseases
Cholelithiasis
Various forms of cancer
Skin problems
Degenerative disease of large joints
Back pain
Degenerative disc disease
Urinary incontinence
Postoperative complications

The metabolic effects of fat are mediated by a variety of hormones and proteins termed adipokines that are produced and secreted by the adipocytes. The adipokines include leptin, angiotensin, resistin, adiponectin, plasminogen-activator inhibitor 1, and proinflammatory cytokines such as IL-6 and TNF-α. When produced in excess quantities, particularly by visceral fat, these adipokines can have adverse health effects. Obesity is strongly linked to the development of numerous life-threatening diseases such as diabetes, heart disease, stroke, and multiple types of cancer. The adipokines appear to be the causal link between obesity and such diseases. They may play a role in the development of obesity-associated high blood pressure, dyslipidemia, and glucose intolerance, all of which are CV risk factors. The adipokines may also produce insulin resistance, which is seen with higher levels of intra-abdominal fat even in the absence of overt overweight. Intramuscular fat may also contribute to metabolic abnormalities or functional impairments that are mediated by adipokines. Many of the apparent adverse metabolic effects of excess body fat are inadequately studied. In postmenopausal women, overweight and weight gain are associated with risk of breast cancer, and with poorer outcomes for the cancer; overweight also appears to increase the risk of colon cancer. The potential mechanisms that causally link excess fat to these disease outcomes are being investigated.

Because of its many adverse effects on health, obesity is a major risk factor for functional disability with advancing age. Any disease or age-related process that leads to deterioration in central or peripheral nervous system, cardiopulmonary, or musculoskeletal function can contribute to disability. As stated above, obese older adults are at higher risk than age-matched nonobese individuals for developing many of the chronic disabling diseases prevalent

among older adults. As a result of these diseases or the treatments required for their control, obese older adults are far more likely to develop physical impairments or disabilities than are other older adults. Obesity also makes it more challenging to obtain the needed level of care when disabled, all of which can lead to a deterioration in quality of life. For these reasons, interventions specifically targeting obesity are sometimes appropriate in older adults.

Interventions Targeting Obesity

Given the increased risk of disability associated with obesity, controlled weight loss may be an appropriate therapeutic option for select older adults with weight-related problems. Short-term clinical trials in older people show that appropriate interventions can lead to moderate weight loss resulting in improvements in cardiovascular risk factors (such as hypertension, insulin resistance, and metabolic syndrome) and other select clinical outcomes. However, there is a concern that weight loss in older adults could produce more long-term adverse than beneficial results. In fact, there is a strong association between weight loss in older adults and an increased risk of subsequent adverse clinical outcomes such as hospitalization and death. Even among studies that tried to differentiate between voluntary and involuntary weight loss, there were conflicting results as to the risks associated with purported (ie, self-reported) intentional weight loss. Furthermore, when dietary restriction is the primary mechanism for weight loss, the loss of fat is accompanied by loss of both LBM (particularly skeletal muscle mass) and BMD. Although the percentage loss from each of these tissue compartments with dieting is the same in old and young adults, the adverse consequences can be much greater in older people who have low functional reserves and high fracture risk. For this reason, a primary focus of any weight loss intervention in older adults has to be on preserving or improving LBM and BMD. The only approach to date that has proven successful in accomplishing this dual-purpose goal is the combination of an energy-restricted, normal- to high-protein diet with moderate to intense exercise. In obese older adults diet and exercise together can lead to clinically meaningful improvements in key metabolic parameters, physical performance, self-reported physical function, and quality of life; the beneficial effects are greater and the loss of both BMD and LBM less than with either intervention alone. To attain these benefits, only moderate weight loss (in the range of 10%) is required. The target of the weight loss should be improvement in the target weight-related health condition.

Although randomized, highly controlled trials provide strong evidence of benefit, little is known about how best to achieve these results with obese older adults in routine clinical settings. Efforts to increase physical activity and to decrease caloric intake are the best options for older adults, as surgical and pharmacologic options are limited, untested, and generally much riskier. In the absence of relevant long-term clinical trial data on outcomes with weight reduction, advice on weight loss should be guided by symptoms related to the overweight, anticipated short-term health benefits, and the general level of health status of the patient.

To be considered a candidate for a weight loss program, an obese older adult needs to have a weight-related problem that is likely amenable to weight loss plus the motivation to commit to the necessary lifestyle changes that are required to meet program goals. In order to have any lasting benefits, changes in dietary habits and level of physical activity need to be maintained long term. Such a vigorous program would likely require the individual patient to be relatively healthy.

Components of a Weight Loss Program for Older Adults

Upon committing to a weight loss program, an older adult should undergo a careful medical evaluation, which should include a detailed history and physical examination and a very careful assessment of the potential risks and benefits of both exercise and diet. American College of Sports Medicine guidelines should be used to assess the risks of exercise and need for more detailed diagnostic testing such as cardiac stress tests. Successful programs generally include an assessment of the individual's insight, motivation, and readiness to make the necessary lifestyle changes. Using motivational interviewing or other techniques, the individual's personal goals should be illuminated and a personalized intervention strategy devised that includes short- and long-term goals and timelines. Support from, or co-participation by family and significant others can be critical to success.

Ideally, both the dietary and exercise interventions need to be consistent with the individual's lifestyle, abilities, interests, and personal goals. When an established program is not available to which the individual can be referred, input and support from a multidisciplinary team of professionals are crucial. Such a team may include a dietitian/nutritionist, physical therapist, nurse, physician, social worker, or other health professionals. The diet should include adequate protein and micronutrients and only moderate energy restriction (eg, 500–800 kcal/day) with the goal of 1 to 2 lb of weight loss in a week. The exercise intervention should include a combination of endurance and progressive-resistance muscle strength training. Inclusion of flexibility exercises is advisable, but the benefits of these

exercises are not established. The types of exercises incorporated in the personalized plan will need to be predicated on availability of resources, facilities, and equipment and the individual's living environment. The ideal exercise program is one that is conducted in a setting that is safe, accessible, and appropriately equipped and involves activities the individual likes doing. For many older adults, this would necessitate that the exercise program be home-based and require little equipment. Nearly all diet/exercise programs formally investigated have been supervised, institution-based programs, which represent a major access barrier for many older adults.

Once an obese older adult starts an exercise/weight loss program, the quality and frequency of follow-up support become crucial. Early in the intervention, frequent follow-up is often needed, but the intervals between contacts can be gradually extended once the individual demonstrates an acceptable trajectory of success. Follow-up can be accomplished by recurring clinic visits, phone calls, or any of a variety of electronic means. These follow-up visits can be used to monitor progress (eg, checking exercise and weight logs), provide ongoing support and assistance to deal with setbacks and barriers to success, and guidance in advancing exercise intensity or setting new goals. The level of involvement of a nurse or other appropriately trained health professional in the follow-up assessments needs to be determined based on the medical complexity of the participant.

NUTRIENT REQUIREMENTS TO MAINTAIN HEALTH

Energy

Daily energy requirements per kilogram of body weight generally decline with age, dropping as much as 33% between the third and ninth decade of life. Male gender and chronic disease are associated with a greater rate of decline. However, a decrease in energy requirements with age occurs even among those who remain healthy. The primary reason for this decline is the loss of muscle mass that is nearly universal with advanced age. Muscle is much more metabolically active than adipose tissue. As muscle mass is lost, the ratio of fat to lean mass increases leading to a greater drop in the resting or basal metabolic rate (BMR) than predicted by the decrease in total body mass. Since BMR generally accounts for 60% to 75% of TEE, the end result of the muscle loss is a significant decline in TEE and thus energy requirements.

A second mechanism accounting for the decline in energy requirements with age is a decrease in physical activity. Energy expenditure of physical activity (EEA) generally declines with age to the same extent as BMR, accounting for about 15% to 35% of TEE in the majority of older adults. However, EEA can range from 5% in those who are bedridden to 50% in highly active, physically fit older adults. Lifestyle plays a big role in determining physical activity energy expenditure of older people, just as it does in those who are younger. Although the increased prevalence of chronic disabling disease accounts for some of the decline in physical activity with advancing age, even healthy older adults tend to be more sedentary that younger individuals.

Some chronic conditions may result in an increased TEE, although this remains controversial. Individuals with Alzheimer disease who constantly pace would fall into this category, as would individuals with a constant tremor. Even when an individual appears to be rather sedentary, their EEA may be greater than expected, particularly if they have certain disabilities such as a neurologic disorder or amputation. These conditions sometimes result in a loss of neuromuscular energy efficiency and thus exceptional levels of energy expenditure while completing even basic activities of daily living.

The decline in energy requirements with advancing age means that older persons need to consume less food in order to maintain their weight and customary activity level. This places the older individual at risk of developing protein and micronutrient deficiencies, since requirements for other nutrients may not decrease as much as energy. Consequently, it is important that older individuals increase their activity level and change their diet to protein- and micronutrient-rich foods.

Protein

Because of the paucity of high-quality nutrition studies with adequate representation from older age groups, current recommendations for protein intake do not differentiate adults over the age of 65 from those who are younger. The latest (2005) version of the recommended dietary intake (RDI) for protein, released by the Food and Nutrition Board and the Institute of Medicine, is 0.8 g/kg body weight/day for both men and women over age 19. However, the question of whether protein requirements change appreciably with advancing age continues to be debated. Based on their interpretation of available data, some contend that the recommended protein intake for older adults should be 1.0

to 1.25 g/kg/day. Given the variability in estimates of protein requirements in older adults, it may not be possible to resolve this controversy until better measurement techniques become available.

Factors that influence the protein requirements of older individuals The protein requirements of an individual can change with time, being influenced by age, nonprotein content of the diet, activity level, medications, and health status. The energy content of the diet is particularly important. The protein intake required to maintain nitrogen balance increases with decreasing energy intake. Carefully conducted metabolic studies of healthy young males indicate that nitrogen balance cannot be attained at any protein intake when total energy intake is less than 126 kJ/kg (30 kcal/kg). Although comparable data are not available for individuals over the age of 65, the importance of energy intake in older individuals is well recognized. A negative energy balance usually precipitates a negative nitrogen balance, especially in individuals who are ill or who have a low level of activity. Whether progressive resistance muscle strength training, alone or in combination with a high protein diet, can prevent loss of LBM in older individuals during periods of voluntary caloric restriction and weight loss is being investigated. As a general rule, protein requirements increase with high levels of activity such as sustained high-intensity exercise.

Many disease states and medications can induce a catabolic state for protein by altering the normal balance between protein synthesis and degradation. Older individuals who are both confined to bed and have an injury, infection, or another acute inflammatory condition are at particularly high risk of developing a profoundly negative nitrogen balance that can lead to a rapid loss of LBM, particularly skeletal muscle mass. High doses of corticosteroids can have a similar effect. The amount of protein that needs to be consumed in order to minimize loss of LBM and optimize recovery from such disease states is often difficult to determine. In general, older hospitalized patients who are acutely ill or recovering from major surgery or trauma warrant a protein intake of 1.5 g/kg of body weight/day unless they have a condition that necessitates protein restriction such as renal or hepatic insufficiency. Chronically ill and bedridden older residents of long-term care institutions are likely to have similarly high protein requirements. Whether one source of protein is better than another in meeting the nutrient needs of older adults is controversial. Although it is generally recognized that all older adults should consume a diet that provides adequate quantities of all essential amino acids, there is otherwise little consensus as to the importance of the dietary protein source. Several animal and laboratory-based human studies suggest that protein or amino acid supplements containing high concentrations of branched-chain amino acids such as leucine may be more effective than other dietary proteins in stimulating muscle protein synthesis, particularly in sedentary or chronically ill older adults. However, other studies refute these findings.

Fat and Cholesterol

Fat serves as a key source of energy and essential fatty acids as well as a vehicle for transporting fat-soluble vitamins. Even when obesity and elevated cholesterol or triglycerides are a concern, fat intake should not fall below 10% of total energy requirements in order to allow for adequate absorption of fat-soluble vitamins (A, D, E, K), and to ensure that the requirements for the essential fatty acids are met. There are two main types of essential fatty acids, the omega-6 series, derived from linoleic acid (eg, arachidonic acid and γ-linoleic acid), and the omega-3 series, that could be derived from α-linolenic acid (from plant sources) or contained in certain cold water fish (eg, eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]). The essential fatty acids are required for the synthesis of cell membrane phospholipids and eicosanoids, which include prostaglandins, leukotrienes, and hydroxy acids. Cell membrane phospholipids influence the biomechanical properties of the membranes and their membrane-bound receptors. The eicosanoids, derived predominantly from arachidonic acid and EPA, serve many functions including modulation of inflammation and host defenses. It is currently recommended that intake of the omega-6 linoleic acids be at least 1% of total food energy.

Clinical deficiency of these essential fatty acids is rarely seen in adults since Western diets generally provide 8 to 15 g/day and adipose tissue provides a reserve of 0.5 to 1 kg. Omega-6 fatty acids are abundant in many of the foods common to the average American diet including most vegetable oils, nuts, cereals, seeds, and legumes. When a deficiency does develop, it is usually a result of profound cachexia or extensive small bowel disease or necrosis and the inadequate provision of nutrition support. Although current recommendations call for the omega-3 derivatives of α-linolenic acid to be at least 0.2 % of total food energy, many nutritionists suggest higher intakes due to their beneficial effects on lipid metabolism. Oils from a variety of cold water fish species including halibut, mackerel, herring, and salmon are potentially high in the omega-3 fatty acids. Currently, nutritional labeling does not indicate the amount of omega-3 fatty acids that is contained in fresh fish; farm-raised fish may have more or less omega-3 fatty acids than wild caught fish, depending on the food they are fed. Many omega-3 fatty acid supplements are available

commercially, but these provide varying amounts of marine-based EPA and DHA. There is inadequate evidence that these supplements provide the same benefits as consuming fish. α-Linolenic acid, which serves as a precursor of EPA, is also a polyunsaturated omega-3 fatty acid, and is found primarily in plant products such as soybeans, canola oil, flaxseed oil, and walnut oil. However, it is controversial as to how effectively humans can convert α-linolenic acid to EPA; as little as 10% of α-linolenic acid may be converted to EPA.

The optimal fat intake for older adults needs to be determined on an individual basis. Although CHD remains the number one killer of older Americans, the importance of dietary fat after the age of 65 remains controversial. It is not known whether fat- and cholesterol-restricted diets have any beneficial effects in reducing CHD mortality in this age group. In fact such diets may have detrimental consequences, especially in those who are having problems maintaining their weight. Therefore, it seems prudent to limit fat intake only in healthy older individuals who otherwise would not be adversely affected by such dietary restrictions.

Increasing the ratio of monounsaturated and polyunsaturated fat to saturated fat, without changing total fat intake, may be beneficial in some situations. For this reason, some experts support the use of the Mediterranean-style diet, which promotes the use of olive oil, tree nuts and peanuts, fatty fish, seafood, and white meat, and discourages intake of red and processed meats. Concern has also been raised about the use of partially hydrogenated fats rich in trans fatty acids, as these products may have an adverse effect on lipid metabolism. Although more study is needed before any special diet can be recommended, it is probably prudent to emphasize the use of natural fats derived from vegetable oils (predominantly monounsaturated), nuts, and fish while reducing those from animal products and avoiding foods containing trans fatty acids. However, these guidelines may not be applicable to frail older individuals, especially those who are losing weight involuntarily, have a BMI less than 20, or have disease conditions limiting their nutrient intake. Since fats have twice the energy content per gram as carbohydrates and protein, a diet high in fat may be necessary for such frail older individuals in order to meet their maintenance energy requirements or to replete deficits. Restricting the types of foods these individuals consume may have only detrimental consequences.

Carbohydrates

Recommendations for carbohydrate content of the diet are generally based on two considerations, the source of the carbohydrates and the energy requirements of the individual. Ideally, food sources should be rich in fiber (see section on Fiber Content of Diet later) and provide primarily complex carbohydrates rather than simple sugars. The amount of carbohydrates that should be included in the diet is usually determined by default. The energy, protein, and fat requirements of the individual are determined first. Carbohydrate requirements are then determined by subtracting the amount of energy supplied by protein and fat from the total energy requirements. Since protein requirements represent approximately 15% of the total energy content of the diet and fat ideally should be less than 30%, carbohydrates usually represent 55% to 70% of the total. When carbohydrates are totally excluded from the diet, energy requirements of the body are partially met by the incomplete oxidation of fatty acids, which leads to ketosis and may cause lethargy and depression. This ketosis also contributes to anorexia, which is part of the appeal of low-carbohydrate weight loss diets. To prevent ketosis, at least 50 to 100 g of carbohydrates should be consumed each day.

Water

Although fluid requirements do not change appreciably with age in adults, people over the age of 65 have a reduced ability to regulate their fluid intake and are much more likely than young adults to become dehydrated when their health status or environment changes. Aging is associated with a decline in the intensity of the thirst response to fluid deprivation, a delay in correcting the resulting increase in serum osmolarity, and a reduced ability of the kidneys to concentrate the urine despite an increase in serum vasopressin concentration. Urine output increases with age by two- to threefold over younger adults as urine concentrating ability declines. Chronic disease and injuries that cause a deterioration of cognitive or physical function increase the risk of dehydration further by altering the perception of thirst, reducing the ability to express the desire for water, or diminishing the capability to access and drink adequate amounts of fluids. When an acute febrile illness occurs in an older individual who is already physically or cognitively impaired, life-threatening dehydration can develop rapidly. This scenario occurs with alarming frequency in nursing homes. The failure of many health care providers, family members, and personal aid assistants to recognize the risk factors and early warning signs of dehydration contributes to the danger that a frail older individual will become severely dehydrated. Many older adults themselves do not recognize their risks and may inappropriately restrict their fluid intake, sometimes as a method of controlling incontinence.

Care must be taken to prevent dehydration by recognizing those at highest risk, especially older individuals with

cognitive and physical deficits, swallowing problems, ongoing weight loss, diarrhea, fever, or poorly controlled diabetes, or receiving enteral feeding, diuretics, or laxatives. Although there is no DRI for water, the minimum daily intake for inactive adults in moderate climates is estimated to be between 1 and 3 L/day; a reasonable target is roughly 30 mL/kg/day for most healthy older adults. Requirements increase with fever, activity, or prolonged exposure to elevated environmental temperatures. Prolonged exposure to elevated environmental temperatures, such as may occur during heat waves, may also precipitate profound dehydration. Those at high risk for developing dehydration should be given set prescriptions for fluid intake and have their fluid intake monitored closely. Whenever hydration status is in doubt, the subject should be weighed, orthostatic blood pressure reading recorded, and serum electrolytes, urea nitrogen, and creatinine checked. Blood pressure readings should be compared to baseline values as many frail older adults have significant orthostasis even when fully hydrated. In some settings, it may also be appropriate to monitor urine output. Skin turgor is not a reliable indicator of hydration status and should not be used as such in the care of older subjects. Patients, family, and all health care staff, especially in nursing homes, need to be trained to recognize the importance of maintaining an adequate fluid intake at all times, and to carefully monitor intake if there is a change in mental status, activity level, or health status, or if fluid requirements increase, as occurs during heat waves.

Fiber

Dietary fiber is derived from structural components of plant cell walls and consists of plant polysaccharides and lignin, which are resistant to digestion by intestinal enzymes. Many professional health organizations recommend a diet containing 20 to 35 g of fiber a day or 10 to 13 g dietary fiber per 1000 kcal consumed. Although dietary fiber may be associated with health benefits including a decreased rate of certain forms of cancer, diabetes, heart disease, and obesity, the average American diet is very low in fiber with consumption usually in the range of only 10 to 15 g daily.

There are two general categories of dietary fiber: water-insoluble fibers, such as cellulose, hemicellulose, and lignin; and water-soluble fibers, such as gum and pectin. Each category of fiber has a somewhat different spectrum of beneficial effects. Both types lower the energy density of the diet. The added bulk also has a short-term satiety effect, which helps control appetite and prevent overconsumption. Water-insoluble fiber has the further effect of holding water within the intestinal contents, which results in an increased fecal bulk, a decreased gut transit time, and a lower intraluminal pressure within the colon. These properties of water-insoluble fiber make it an important dietary component since it reduces constipation and may help to prevent the formation of colonic diverticula. Sources of insoluble fiber include fruits, vegetables, dried beans, wheat bran, seeds, popcorn, brown rice, and whole grain products such as breads, cereals, and pasta. About two-thirds to three-fourths of the dietary fiber in typical mixed-food diets is water insoluble. There are many excellent web sites that provide tables listing the soluble and insoluble fiber content of foods (eg, http://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/high-fiber-foods/art-20050948, https://www.wehealny.org/healthinfo/dietaryfiber/fibercontentchart.html, https://www.prebiotin.com/resources/fiber-content-of-foods/. Accessed February 9, 2016.).

Water-soluble fiber increases the viscosity of intestinal contents, prolongs gut transit time, and decreases the rate of small intestinal absorption of carbohydrates and bile acids. These effects may have important physiologic implications that can be used to advantage clinically. By slowing the rate of carbohydrate absorption, a very high soluble-fiber diet can be effective in reducing the postprandial surge in the serum glucose, which may be beneficial in the treatment and prevention of diabetes. Through its effects on bile acid absorption, soluble fibers can lower total cholesterol and low-density lipoprotein (LDL) cholesterol by 3% to 10%. There is an inverse association between the total dietary fiber intake and the rate of fatal and nonfatal myocardial infarctions; several meta-analyses demonstrate that higher intake is also associated with decreased all-cause mortality. Most of these effects of soluble fibers were demonstrated using fiber concentrates. Comparable amounts of fiber can be obtained from food sources, such as apples, oranges, pears, peaches, grapes, vegetables, seeds, oat and rice bran, dried beans, oatmeal, barley, and rye. Diets that are high in fiber from food sources also provide essential micronutrients and nonnutritive compounds such as xenobiotics, antioxidants, and phytoestrogens that may have important health-promoting consequences.

As a general rule, a diet rich in fresh fruits, vegetables, legumes, and whole-grain products is recommended. As portrayed in the USDA Choosemyplate.gov, this should include two cups of fruit, 2 1/2 cups of vegetables, and 6 oz of grains each day (**Figure 34-6**). Since most fruits and vegetables contain less than 2 g/serving total fiber and most refined grain products contain less than 1 g/serving, legumes, whole grains, and cereal brans should be substituted for other foods whenever possible in order to increase the amount of both kinds of fiber. Supplementing the diet with any of the commercially available concentrated fiber sources may be necessary, especially in frail older people. Concentrated sources of dietary fiber may also be helpful in the treatment of chronic constipation when a limited

variety of food is available or the amount of food consumed is inadequate. A large increase in fiber over a short period of time may result in bloating, diarrhea, gas, and general discomfort. It is important to add fiber gradually over a period of several weeks to avoid abdominal problems. Fiber supplements should always be taken with adequate fluid in order to avoid worsening constipation.

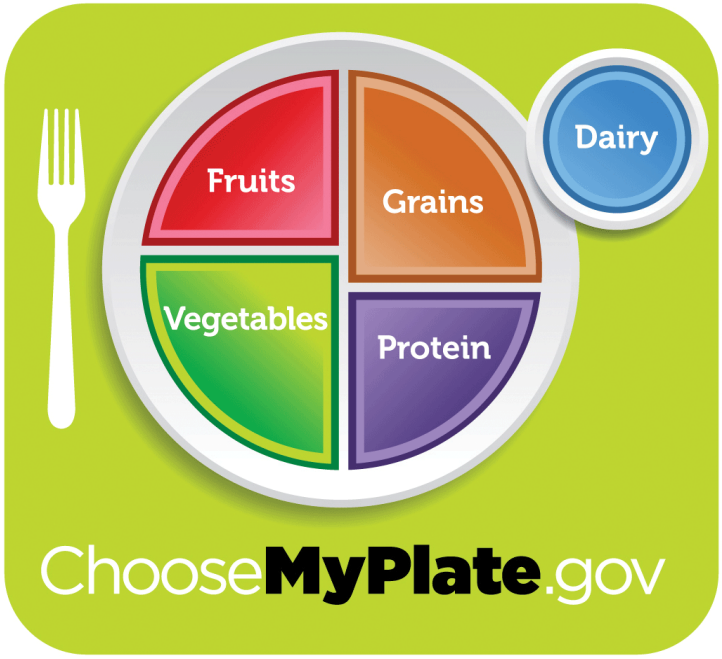


FIGURE 34-6. ChooseMyPlate.gov, U.S. Department of Agriculture, Center for Nutrition Policy and Promotion, June 2, 2011, USDA Center for Nutrition Policy & Promotion (CNPP), http://choosemyplate.gov/. Accessed February 9, 2016.

Vitamins and Minerals

Recommended intakes Between 1997 and 2011, the Food and Nutrition Board of the US National Research Council revised the dietary reference intakes (DRIs), which updated the earlier RDAs for vitamins and minerals. The DRIs include separate intake recommendations for adults aged 51 through 70, and for adults older than 70 years. There are not enough scientific data to calculate requirements for all micronutrients, and any person with a medical disorder may need more or less than the DRI for some nutrients. **Table 34-4** lists the recommended intakes for various vitamins, as well as the recommended tolerable upper intake limits (ULs). Intakes of micronutrients that are lower than the UL usually pose little risk for toxic side effects in healthy people. The UL allows patients and health care workers to understand possible risks if large amounts of vitamins and minerals are consumed. Understanding and consuming the DRI for vitamins and minerals reduces the risk for classic deficiency disorders (like scurvy, pellagra, beriberi, etc), but the ideal intake of vitamins and minerals needed for optimum health, which may be higher than the DRIs or ULs, remains controversial. Changes to the DRIs are often contentious, and they can have major medicolegal and financial implications for fortified foods and the supplement/health food industry.

TABLE 34–4 ■ ADULT DIETARY REFERENCE INTAKES AND TOLERABLE UPPER LIMITS FOR SELECTED VITAMINS AND MINERALS

VITAMIN OR MINERAL	RECOMMENDED DAILY INTAKE[a]	TOLERABLE UPPER LIMIT
Vitamin A (retinol)	900 µg (males) 700 µg (females)	3000 µg
Vitamin D	600 IU (age 9–70) 800 IU (age > 70)	4000 IU
Vitamin E	15 mg 22 IU (natural vitamin E)	1500 IU

	33 IU (synthetic vitamin E)	
Vitamin K	80 µg (males) 65 µg (females)	[b]
Vitamin B_1 (thiamin)	1.2 mg (males) 1.1 mg (females)	[b]
Vitamin B_2 (riboflavin)	1.3 mg (males) 1.1 mg (females)	[b]
Niacin (nicotinamide)	16 mg (males) 14 mg (females)	[b]
Vitamin B_6 (pyridoxine)	1.7 mg (males) 1.3 mg (females)	100 mg
Vitamin B_{12} (cobalamin)	2.4 µg	[b]
Folic acid (folate)	400 µg	1000 µg
Vitamin C (ascorbic acid)	90 mg (males) 75 mg (females) (increase by 35 mg for smokers)	2000 mg
Calcium	1000–1200 mg	2000 mg
Selenium	55 µg	400 µg

[a]The recommended daily intake is the daily intake that will fulfill the nutritional needs of most healthy adults. The tolerable upper limit (UL) is the highest level of daily nutrient intake that is likely to pose no adverse health risk in most people. As intake above the UL occurs, there is an increasing risk of adverse effects.

[b]Tolerable upper limit not yet determined.

Vitamin and mineral supplementation Many older adults, including those who are healthy and living independently as well as those who are frail, ill, or institutionalized, are at risk for micronutrient deficiencies. Several population-based nutritional surveys demonstrate that community-dwelling older adults commonly consume as little as 50% of the RDAs for many vitamins. These findings reflect the fact that even healthy adults do not consistently consume recommended amounts of fortified dairy products, fruits, and vegetables. Risk factors for poor intake, adverse drug-nutrient interactions, and nutrition-related diseases all increase as a function of age, and clinical (and subclinical) deficiencies of vitamins and minerals become more likely, particularly once frailty and the need for institutionalization occurs. The micronutrients most commonly deficient include vitamins C, D, E, B_{12}, thiamine (B_1), and folic acid, and the minerals calcium, magnesium, and zinc. Because of this, many nutritionists recommend that older adults add a daily, iron-free, general vitamin and mineral supplement supplying the DRI for most micronutrients to their diets, although evidence in support of benefit from this recommendation is lacking. Studies of multivitamin supplementation in noninstitutionalized people have found no benefit in reducing cardiovascular or cancer risk. It also remains unclear as to whether intakes of individual micronutrients above the DRI in selected populations are beneficial. High intakes of some micronutrients (such as vitamins A, D, and pyridoxine) are well known to cause toxicity, which may be so subtle and nonspecific that the harmful effects may not be easily diagnosed. High supplemental intakes of other vitamins or provitamins (like vitamin E and β-carotene), which had been thought to be risk free, have now been associated with adverse health consequences. Older adults should be counseled not to exceed the tolerable upper intake limits (see **Table 34-4**) for vitamin intake and to disclose all vitamin and mineral supplement use whenever medications are reviewed by any health professional. Vitamin and mineral supplementation should not substitute for an overall program of healthy nutrition (eg, high fruit, vegetable and whole grain intake and reduced saturated and trans fat intake).

Vitamin B_{12} (cobalamin) Low-serum vitamin B_{12} levels become more common with aging, and about 10% to 15% of older adults have vitamin B_{12} deficiency. Thus, low levels do not represent normal aging. Pernicious anemia, an autoimmune disorder causing decreased gastric intrinsic factor production, is a rare cause of deficiency in the older adult. Cobalamin deficiency in older adults is more commonly due to malabsorption of cobalamin in foods, usually due to atrophic gastritis and hypochlorhydria (**Table 34-5**); supplemental B_{12} in crystalline form is not affected by

atrophic gastritis and continues to be well absorbed. Stomach acid helps to remove the vitamin from food and make it bioavailable. There may be other causes for deficiency in older adults that are not yet known. Disorders that interfere with enterohepatic absorption (such as ileal disease or surgery) will lead to deficiency more rapidly than low intake because the high efficiency of enterohepatic vitamin B_{12} reabsorption will be impaired, and the vitamin lost in the stool.

TABLE 34–5 ■ CAUSES OF VITAMIN B_{12} DEFICIENCY

Atrophic gastritis and hypochlorhydria
Chronic antacid use (histamine-2 blockers, proton pump inhibitors)
Gastric surgery
Ileal surgery
Diseases of the small intestine and terminal ileum: Crohn disease, sprue, malabsorption syndromes
Helicobacter pylori infection
Pancreatic insufficiency
Parasitic infections of the small bowel (eg, fish tapeworm)
Bacterial overgrowth syndromes
Strict vegetarianism
Acquired immune deficiency syndrome (AIDS) and AIDS treatment (eg, zidovudine)
Pernicious anemia
Metformin

Vitamin B_{12} deficiency can present clinically with two relatively independent disorders. There is a hematologic disorder that causes macrocytosis and anemia. And there is a neurologic disorder that can cause a peripheral neuropathy, including paresthesias and numbness; spinal column lesions, including loss of vibration and position sense, sensory ataxia, limb weakness, orthostatic hypotension, and plantar extensor responses; and neuropsychiatric symptoms. These signs and symptoms of vitamin B_{12} deficiency are nonspecific and common in many older adults with comorbid disorders. When there are several possible causes for the neurologic signs and symptoms, vitamin B_{12} supplementation is usually accompanied by disappointing, small measurable neurologic or behavioral improvement. The older the patient is and the more profound the signs and symptoms are, the less likely is the recovery. However, some patients may respond, especially if deficiency is relatively recent. Since patients with more severe hematologic signs often have less neurologic impairment, and vice versa, it is important to consider vitamin B_{12} deficiency even if the patient lacks macrocytosis and anemia. Thus, screening all older adults for vitamin B_{12} deficiency should be considered, and supplementation of all deficient patients is recommended.

Many patients with "low normal" vitamin B_{12} serum levels (< 350 pg/mL) have measurable biochemical abnormalities, including elevated methylmalonic acid (MMA) (> 270 nmol/L) levels, which improve with supplementation. Although these patients often appear to be asymptomatic, it is probable that borderline serum vitamin B_{12} levels represent an early preclinical deficiency state. If this is the case, current laboratory norms for vitamin B_{12} are too low since they may not identify patients with early deficiency. Secondary tests for low B_{12} status are also nonspecific; for example, MMA may also be elevated with renal failure, and homocysteine levels are also affected by folate and vitamin B_6 status. Other tests for vitamin B_{12} deficiency, such as methylcitric acid or holotranscobalamin levels, may prove better (when used with vitamin B_{12} blood levels) but are not yet readily available.

An approach to screening for vitamin B_{12} deficiency, and treatment guidelines are presented in **Table 34-6**. Intramuscular or oral replacement is most common; alternative formulations (such as nasal gels) are more costly and have not been rigorously tested. There is no scientific basis for prescribing vitamin B_{12} supplementation as a general tonic, and it is not recommended.

TABLE 34–6 ■ EVALUATION AND TREATMENT OF VITAMIN B_{12} DEFICIENCY IN OLDER ADULTS

1. Screen with a determination of serum vitamin B_{12} level any older adult who is frail, has macrocytosis or neutrophil hypersegmentation with or without anemia, has peripheral neuropathy or a gait disorder, or has otherwise unexplained neuropsychiatric symptoms.

2. Any patient with a vitamin B_{12} serum level less than 200 pg/mL (150 pmol/L) can be considered to have a deficiency. A serum level between 200 and 350 pg/mL (150–260 pmol/L) indicates a borderline deficiency.
3. Most older adults with a B_{12} deficiency can be treated with supplementation without further investigation. Only in rare cases is it essential to prove that an older patient has pernicious anemia by testing for antibodies to intrinsic factor or performing a Schilling test. Assessing for infection by *Helicobacter pylori* is an additional option.
4. Most older adults with a borderline deficiency can also be treated with supplementation. If it is necessary to obtain further biochemical evidence that a borderline serum vitamin level represents a significant deficiency, the methylmalonic acid (MMA) level (serum or urine) can be determined before and after treatment. (An elevated MMA level should fall to normal with correct treatment.) Assessing for infection by *H pylori* is an additional option.
5. All patients with possible symptoms of vitamin B_{12} deficiency should receive parenteral supplementation. This can be accomplished by giving several intramuscular shots (1000 μg) within several days to weeks and then continuing supplementation indefinitely with monthly injections. Any healthy patient whose deficiency was found incidentally and is otherwise asymptomatic can be given a trial of oral supplementation with 1 mg daily. These patients should have their serum vitamin B_{12} level reassessed in a month to affirm absorption, and periodic (once or twice yearly) screening thereafter.

Folate (folic acid) Folate deficiency is associated with general malnutrition (particularly that accompanying alcohol abuse), or with specific folate antagonists, such as methotrexate, phenytoin, sulfasalazine, primidone, phenobarbital, and triamterene. Like vitamin B_{12} deficiency, it can present as a megaloblastic macrocytic anemia. Folate supplementation alone may improve the macrocytosis and anemia in vitamin B_{12} deficiency, without correcting the ongoing neurologic disorder of vitamin B_{12} deficiency, and may even cause a more rapid neurologic/cognitive deterioration. However, in patients with normal B_{12} status, high folate intake is associated with protection from cognitive impairment. Although measures of both vitamin B_{12} and folate status are often included in the evaluation of macrocytosis, low folate is a rare cause of this disorder. Fortification of grains with folic acid began in the United States in 1998 and has reduced the incidence of neural tube defects in developing fetuses. It was feared that this fortification (about 100 μg folate/day) would mask vitamin B_{12} deficiency, although this has not been proven. Consumption of a diet rich in fruits and vegetables, along with fortified grains, continues to be recommended as the best source for folic acid, but folate in supplements is more bioavailable.

Folate status may be assessed by measuring serum folate if dietary intake (diet or vitamin supplementation) has not recently changed, or with erythrocyte (RBC) folate levels if there has been a recent change in diet (as after hospital admission). Homocysteine levels can be elevated in folic acid deficiency, but may also increase with renal insufficiency, and with vitamin B_{12} or B_6 deficiency.

Vitamin D Vitamin D plays a critical role in maintenance of normal bone health (see Chapter 118). There is evidence that vitamin D has many other physiologic functions beyond those related to bone and calcium metabolism, but the clinical implications of these effects are controversial. Vitamin D receptors are present on many different cell types and through these receptors, vitamin D can play a regulatory role in a number of physiologic processes such as insulin production, myocardial contractility, B and T lymphocyte function, thyroid-stimulating hormone (TSH) secretion, muscle contractility and growth, and CNS function. Vitamin D levels are directly correlated with many clinically important indicators of health and well-being in older adults including muscle strength and mass, physical performance, and the risk for age-related macular degeneration, periodontal disease, and mortality. Although research findings are inconsistent, there is evidence that vitamin D supplementation decreases the risk for falls and fractures in certain high-risk populations such as institutionalized older women. There are ongoing investigations to determine whether supplementation of the diet with vitamin D or vitamin D analogues decreases the risk for other diseases such as diabetes mellitus, inflammatory bowel disease, congestive heart failure, colon and prostate cancers, multiple sclerosis, and rheumatoid arthritis.

The risk of developing vitamin D deficiency increases with advancing age. In humans, vitamin D can be obtained from the diet or manufactured de novo in the skin in response to UV-B light exposure. Both sources of vitamin D can be compromised in older adults. Sunlight is usually the source of UV-B exposure. The capability of the skin to manufacture vitamin D when exposed to unfiltered sunlight decreases with advancing age. Older adults also get less sun exposure than when young; even when outdoors, older adults tend to shield themselves from the sun using clothing, topical sunscreens, or other means. Indeed, such sun protection should be advised to reduce the risk of skin cancer in this population. Sunscreens alone can reduce skin production of vitamin D by as much as 95%. Dark skin pigmentation also reduces the amount of vitamin D produced by the skin in response to sun exposure; this partially

accounts for the higher prevalence of low vitamin D levels in blacks compared to whites. The season of the year is also important. In many parts of the United States, the skin makes very little vitamin D during winter.

Although many foods serve as a source of vitamin D (**Table 34-7**), older adults may not be able to consume enough of these foods to meet their requirements for this nutrient. A cup of fortified milk or fortified orange juice is supposed to contain about 100 IU of vitamin D, although the actual concentration can vary dramatically depending on the quality standards of the manufacturer. Fatty fish, particularly salmon, also have vitamin D, although the amount available in farmed salmon is less certain. Certain diseases and medications can also contribute to the development of a deficiency by decreasing the body's stores or increasing requirements for vitamin D. These include medications such as certain antiepileptic drugs and glucocorticoids, and any disease that causes fat malabsorption or renal failure (glomerular filtration rate [GFR] < 60 mL/min).

TABLE 34-7 DIETARY SOURCES OF VITAMIN D

SOURCE	TYPE [a]	AMOUNT
Salmon	D_3	600–1000 IU per 3.5 oz[b]
Sardines and Tuna	D_3	300 IU per 3.5 oz serving
Cod liver oil	D_3	400–1000 IU per tsp
Shiitake mushrooms	D_2	100 IU per 3.5 oz fresh 1600 IU per 3.5 oz dried
Fortified milk	D_3	100 IU per 8 oz
Fortified cereals	D_3	100 IU per serving

[a] D_3 is of animal origin, D_2 is of plant origin.
[b] May be more or less with farm raised.

Vitamin D status is best assessed by measuring blood levels of 25(OH)D. With chronic kidney disease, a parathyroid hormone (PTH) level would also be important since conversion of 25(OH)D to 1,25(OH)D is often impaired. Serum calcium, ionized calcium, phosphate, alkaline phosphatase, and 1,25(OH)D levels do not adequately identify vitamin D deficiency. There is general consensus that a 25(OH)D level less than 10 ng/mL (25 nmol/L) represents a frank deficiency state. However, the level of vitamin D necessary for optimum health is uncertain. Although some experts feel that a blood level of 25(OH)D less than 20 ng/mL (50 nmol/L) should be used to define a deficiency state, others suggest that blood levels should be much higher, in the range of 30 ng/mL (75 nmol/L) to 60 ng/mL (150 nmol/L). A vitamin D level less than 30 ng/mL is found in as many as 75% of community-living older adults. The health benefits of using vitamin D supplements to achieve levels greater than 30 ng/mL in this population are unproven. Vitamin D is available in two forms, ergocalciferol (vitamin D_2) that comes from plant sources and cholecalciferol (vitamin D_3) that is of animal origin. Vitamin D_2 may be used for fortification, but vitamin D_3 is more potent in raising 25(OH)D levels for longer periods of time, especially in older adults. Thus, vitamin D_3, the form made naturally from sunlight exposure to skin, is the preferred supplemental form. The Institute of Medicine (2011) recommends daily intake of 600 IU vitamin D_3 for healthy adults below age 70 and 800 IU (20 μg) D_3 for healthy adults above age 70. Not all older adults can meet these requirements from food sources. Older adults with conditions that place them at increased risk of vitamin D deficiency may require higher intakes of vitamin D and should probably take vitamin D supplements. Vitamin D deficiency [ie, 25(OH)D ≤ 20 ng/mL] can be treated with 1000 to 2000 IU D_3 daily. This is the safest and most evidence-based approach. Alternatively, an oral dose of 50,000 IU of D_2 can be consumed weekly for 8 weeks. After 8 weeks, further therapy should be guided by results of 25(OH)D, PTH, and calcium levels.

The value of routine screening of healthy older adults with 25(OH)D levels is highly controversial, as there is little consensus about who should consume vitamin D supplements and what is the optimal dose. The US Preventive Services Task Force (USPSTF) (2013) reports that there is insufficient evidence to recommend vitamin D and calcium supplementation for the primary prevention of fractures in pre- and postmenopausal women, and men. The USPSTF (2012) did find evidence to support vitamin D (averaging 800 IU for 12 months) supplementation (and exercise and physical therapy) to prevent falls (but not fractures) in high-risk community-dwelling adults aged 65 and older. Otherwise, decisions should be made on a case-by-case basis recognizing that there is limited evidence on which to base any given recommendation.

Calcium From adolescence onwards, both men and women should consume between 1000 and 1200 mg of elemental calcium daily, unless there are unique nutrition requirements. Many older adults consume far less than this amount. In addition, calcium absorption declines with age and varies depending on dietary source. A cup of milk or yogurt contains about 300 mg of calcium. Green vegetables contain some calcium, but they also contain other phytochemicals that interfere with calcium absorption. Therefore calcium bioavailability from vegetables may be limited. Because of dietary limitations or other factors, many older adults are unable to consistently obtain the recommended intake of calcium from natural sources and may need to take calcium supplements. Some brands of orange juice and candy now contain added calcium, which can add to dietary sources of this element. Calcium is also available in pill form. Calcium carbonate is least expensive, but should be consumed with food (although high-fiber foods may reduce absorption somewhat). Some other formulations, such as calcium citrate, are better absorbed but may cost more, and have less calcium per pill. Calcium supplements can increase constipation in some individuals. Persons who develop calcium oxalate kidney stones should not drastically limit their calcium intake from foods, as dietary calcium can bind with and reduce food oxalate absorption and decrease risk of stone formation. Observational studies have identified a possible association between calcium supplementation and increased risk for CVD. Until this issue is clarified, emphasis should be placed on maximizing calcium intake from food sources.

SPECIFIC DIETARY CONSIDERATIONS FOR OPTIMAL HEALTH

Vitamins and Cognition

Although numerous vitamins have been linked to cognitive decline with advancing age and to the pathogenesis of Alzheimer disease, most of this evidence is from observational studies. For example, there are associations between dietary intake of foods high in carotenoids and a diminished risk of cognitive impairment. A theorized mechanism by which carotenoids may preserve cognitive function is by decreasing small vessel disease in the brain. Similarly, an association between neurocognitive dysfunction (including cognitive impairment without dementia, Alzheimer disease, and vascular dementia) and elevated plasma homocysteine has been identified, which suggests a potential role for folate and B vitamins in preserving cognitive function with advancing age. These findings highlight the potential importance of maintaining a well-balanced diet, but do not provide evidence of benefit of using supplements containing these particular vitamins. Likewise, there is an association between 25 (OH)D serum levels and cognitive function. However, there is no evidence that vitamin D supplementation improves cognition or delays further cognitive decline.

As stated previously, it is known that B_{12} deficiency can lead to a deterioration of multiple structures within the CNS. The investigation of reversible causes for dementia has routinely included the assessment of folic acid and vitamin B_{12} status. Vitamin B_{12} deficiency can cause neuropsychiatric symptoms, including delirium manifesting as slowed thinking, depression, confusion, memory loss, and poorer language comprehension and expression that is difficult to differentiate from early Alzheimer disease. Low serum folate is associated with atrophy of the cerebral cortex, perhaps as a result of hyperhomocysteinemia. Among nondemented persons over 75 years of age, those with low levels of either vitamin B_{12} or folate had increased risk for developing Alzheimer disease over 3 years. There are very rare case reports of neuropathy associated with folate deficiency. Slowed mental processing, including poorer performance on mental status testing, and depressive symptoms (particularly impaired motivation and social withdrawal) have been described in patients with folic acid deficiency. While deficiency of vitamin B_{12} is common in frail older adults with cognitive disorders, vitamin B_{12} (or folic acid) supplementation almost never affects the course of slowly progressive cognitive decline. The effectiveness of B_{12} replacement therapy to reverse the neurologic pathology may relate to timing of diagnosis and treatment.

One multicenter randomized, controlled trial found a small but significant effect of vitamin E supplementation (2000 IU/day of α-tocopherol) in slowing functional decline and decreasing caregiver burden in older adults with mild to moderate Alzheimer disease. Whether vitamin E supplementation should become a standard of care for this patient population will needed to be determined, weighing the potential benefits and harms of such a policy. There is no evidence that other nutritional supplements, including multivitamins, have a clinically significant effect on preserving cognition.

Nutrition and Cardiovascular Disease and Cancer

There is a growing body of evidence that nutrition plays an important role in CVD prevention. Diets that are low in

saturated fat, contain poly- and monounsaturated fatty acids, and include an abundance of fruits and vegetables are associated with a reduced risk of cardiovascular events. A number of dietary regimens fall into this category including the so called Mediterranean diet, which reduced major CV events in persons at high CV risk. The Mediterranean diet emphasizes olive oil, tree nuts and peanuts, fresh fruits and vegetables and legumes, fatty fish and seafood, and white meat, and less commercial bakery goods, pastries, and red and processed meats. The benefits of the various types of oils, especially those containing poly- and monounsaturated omega-3 essential fatty acids, have already been discussed. Various theories have been formulated to explain the beneficial effects of increased consumption of vegetables and fruits. These include the fact that many vegetables and fruits are low in saturated fats and contain ample amounts of vitamins, dietary fiber, and plant polyphenols, which represent a large group of natural antioxidants. In addition to their antioxidant properties, polyphenols elicit several interesting effects in animal models and in vitro systems; they trap and scavenge free radicals, regulate nitric oxide, decrease leukocyte immobilization, induce apoptosis, inhibit cell proliferation and angiogenesis, and exhibit phytoestrogenic activity. Whether these properties of polyphenols are important in human nutrition or contribute to the role of fruits and vegetables in CVD protection remains to be determined.

Antioxidants have also been promoted as protective for cardiovascular disease. The rate of cardiac death is lower in people who consume a diet rich in the antioxidant vitamins and minerals, particularly vitamins E and C, and carotenoids. High levels of serum carotenoids are associated with a lower risk of periventricular white matter lesions on magnetic resonance imaging (MRI), particularly in smokers. These findings are difficult to interpret as diets rich in antioxidants are also higher in fiber and lower in cholesterol and saturated fat, and people who consume large amounts of fruits and vegetables, or who take vitamin supplements often have healthier lifestyles. Meta-analyses of randomized clinical trials for primary prevention of cardiovascular disease have not confirmed a beneficial effect of any vitamin, antioxidant mineral, or fish oil supplement. In fact, increased morbidity or mortality was found with the use of supplemental β-carotene, vitamin E, and selenium; high supplemental vitamin E may increase risk for hemorrhagic stroke and all-cause mortality.

An indirect association between the concentration of antioxidants in the diet (which typically includes diets high in fruits and vegetables) and lower cancer rates has been observed. Similar to studies of antioxidants and CVD, it is difficult to determine whether these findings are due to the antioxidant nutrients themselves or to other reasons. There is currently no convincing evidence that any vitamin, mineral, or antioxidant supplementation prevents cancer.

It is very likely that people with cancer or other serious illnesses will try alternative therapies, including megavitamin and mineral supplements, and herbal or folk remedies. Although it is generally thought that the toxicity of antioxidant vitamins and most B vitamins is low for intakes below the UL, there is increasing evidence of potential harms. Some of this evidence has come from intervention trials which have reported an increased incidence of lung cancer in high-risk patients treated with β-carotene supplements, an association between selenium supplementation and skin cancer, and an increased incidence of prostate cancer in men who took vitamin E. Folic acid supplementation has been linked to an increased risk for colon cancer. Certain subgroups, like smokers, persons with uncontrolled hypertension, and those with other risk factors for the development of cancer appear to be at higher risk for such adverse effects. These risks should be discussed proactively with patients so that they can have the best information available to make their decisions and toxic side effects can be prevented. Tolerable ULs should not be exceeded.

Nutrition and Age-Related Eye Diseases

Evidence to support a protective effect of individual vitamin and mineral supplements on age-related eye diseases is conflicting. The Age-Related Eye Disease Study (AREDS) found a slight reduction in progression (not prevention) of age-related macular degeneration (AMD) using a combination of higher-dose vitamins C and E, β-carotene, zinc, and cupric oxide. In the AREDS2 study, the addition of omega-3 fatty acids (DHA and EPA), and/or lutein and zeaxanthin (macular xanthophylls), and removal of β-carotene, did not decrease AMD progression. The AREDS2 supplementation also did not reduce the risk of cardiovascular disease in the older adult participants. Observation studies have identified an association between dietary antioxidant content and a lower risk of age-related cataracts. However, there is also no evidence that regular high doses of antioxidant vitamin and mineral supplements are effective in preventing cataracts.

ASSESSMENT OF NUTRITIONAL STATUS

Initial Screening Assessment

The risk of developing one or more nutritional disorders increases as a function of age, paralleling the age-associated increase in the prevalence of disease and disability that are often causally related to the development of protein, energy, and micronutrient deficiency states as well as obesity. Prevention and early intervention are the best approaches to keeping older individuals optimally nourished because many forms of malnutrition, particularly protein and energy undernutrition, are very difficult to reverse.

Providers should routinely screen their older patients to determine if they have or are at risk of developing nutritional problems. Ideally this should be done as part of a general health maintenance program that is automatically scheduled at least annually and whenever there is a change in the patient's health state. Like other screening instruments, the nutritional screen should use simple criteria, be relatively easy to complete, have relatively low attendant costs, and provide a valid assessment of nutritional risk with a reasonable degree of sensitivity and specificity. Components of the screening evaluation can be self-administered, completed by associate staff, or gleaned from other assessments including a routine history and physical examination. Individuals identified by the screen to be at risk of having or developing nutritional disorders should be scheduled for a more in-depth assessment.

For the purpose of the initial screening assessment, older individuals who have experienced a recent deterioration in their socioeconomic or health status should be considered at risk for the development of subsequent nutritional problems. For this reason, it is important to carefully assess for new health concerns and change in socioeconomic status as part of a nutritional screening assessment. Since many older individuals facing financial hardship do not volunteer this information, it is always important to assess whether financial resources are inadequate to meet living expenses, including the purchase and preparation of an appropriate variety and quantity of foods. When the older person is dependent on others for meal preparation or feeding assistance, the resources, health status, and dedication of the caregivers become important. Caregiver neglect and other forms of abuse can pose serious threats to nutritional health and often require careful vigilance to identify. The nutritional screen should also look for psychological stressors that can have a detrimental effect on nutritional status, particularly the loss of a spouse or other family members. Older individuals should always be evaluated for depression since this is a common cause of nutritional deterioration in this age group. Alcohol and drug abuse are serious but frequently unrecognized problems that can cause a variety of nutritional disorders. Screening for alcohol abuse with the University of North Carolina CAGE questionnaire or a similar instrument can be included as part of the nutritional assessment.

Other known risk factors for the development of nutritional problems include a recent deterioration in physical or cognitive function and a change in the number or type of medications prescribed. The effects that these disabilities can have on appetite and food intake have been described previously. The list of medications that can adversely affect nutrient intake is very long. As a general rule, any drug that is being taken should be considered suspect when nutrient intake declines, especially when the individual is having other health problems. Many drugs produce subtle side effects that older individuals may tolerate when feeling well. However, these same side effects, which may include alterations in appetite, taste sensation or salivary secretion, nausea, constipation, diarrhea, or a depressed sensorium, can contribute to the development of anorexia during periods of ill health. Swallowing problems can also adversely affect nutrient intake. Although patients with dysphagia classically present with the complaint of choking or coughing during meals or when consuming liquids, the signs and symptoms are often far more subtle and can include only food avoidance necessitating a high index of suspicion, and a comprehensive dysphagia evaluation, to make the diagnosis. As mentioned previously, older patients who are hospitalized due to an acute illness or surgical problem are at very high risk of developing nutritional deficits prior to discharge. Prolonged bed rest, acute inflammation, and inadequate nutrient intake, which are common during hospitalization, rapidly lead to the depletion of both lean and total body mass placing the older patient at high risk for subsequent mortality. For this reason, any acute hospitalization should be recognized as a nutritional risk factor and prompt a more in-depth assessment.

A careful weight history, possibly the most important and specific component of the nutrition screen, should be obtained from all older patients. If prior weights are available from the medical record, these should be utilized since patients often provide inaccurate accounts of their weight history. A weight loss of 5% or more within the prior 6 months or 10% or more within the prior 3 years should be considered indicative of a potentially serious nutritional problem unless the weight fluctuation can be ascribed with certainty to alterations in fluid balance. There is a clear and direct correlation between the amount of weight that is lost and an increased risk of subsequent mortality (**Figure 34-7**). This is true even if the older individual states that they voluntarily lost the weight. Voluntary weight loss in frail older adults has the same adverse implications as involuntary weight loss. This probably relates to the fact that few older individuals are successful in their efforts to volitionally lose weight and to keep the weight off while healthy. Voluntary weight loss is probably the result of underlying pathology in many older individuals.

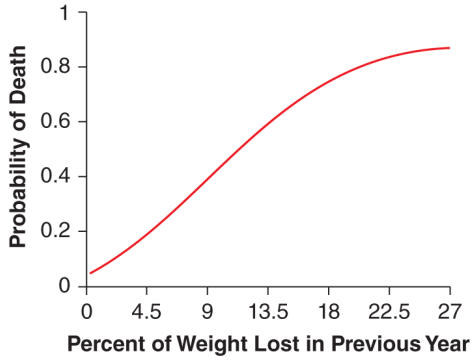


FIGURE 34-7. The relationship between the amount of weight that was lost in the previous year and the estimated risk of mortality within the subsequent year. Based on a study of 750 patients aged 65 and older discharged from an acute-care hospital.

As part of the general physical examination, a weight and height should be obtained. If significant kyphosis or scoliosis is present, the patient's estimate of peak adult height can be utilized for current height. From the weight and height measurements, the patient's BMI, weight as a percentage of ideal, and weight as a percentage of usual weight can be calculated using standard formulas. Signs of dry skin, thinning hair and nails, and other dermatologic findings are very nonspecific and probably of no value in the nutritional assessment other than indicating the need for careful review of appetite and eating patterns. Since poor oral health may contribute to the development of nutritional problems, a careful oral examination is indicated.

Comprehensive Nutritional Assessment

Anthropometrics Although poor reliability limits their usefulness for monitoring change over time, anthropometric measurements provide a prognostically important assessment of an older individual's nutritional status when skillfully obtained. Whereas skinfold measurements (biceps, triceps, suprailiac, subscapular, and mid-thigh) provide a rough indication of the adequacy of subcutaneous fat stores, arm and arm muscle circumferences are indicators of both muscle mass and subcutaneous fat. There is an inverse correlation between both types of anthropometric measurements and an increased risk of subsequent mortality. Values below the 10th percentile for age for any of these measures should prompt a careful assessment of both nutrient intake and functional status or activity level.

Neither BMI nor the skinfold measurements are good measures of total body fat mass if there is significant intra-abdominal fat accumulation, as often occurs with advanced age. Waist circumference and the waist-to-hip ratio are reasonably useful indicators of abdominal fatness. These measurements can be obtained easily in most clinical settings and provide a useful indication of nutritional status when viewed in conjunction with the other anthropometric measures. A waist-to-hip ratio greater than 1.0 in males and 0.8 in females or a waist circumference greater than 40 in (102 cm) in males and greater than 35 in (88 cm) in females are indicators of central obesity and an increased risk of diabetes and cardiovascular disease.

Laboratory assessment Although serum albumin, transferrin, prealbumin, and cholesterol are commonly utilized as indicators of nutritional status, considerable caution must be exercised when interpreting the results of these serum measurements. With advancing age, it becomes increasingly difficult to differentiate the interrelated effects of natural aging, disease, and nutritive state on the physiologic processes that determine the serum concentrations of these substances. Consequently, random determinations may have marginal clinical value. However, when used to supplement other data, these measurements often provide valuable clues as to the patient's overall health status, which influences nutritional risk and prognosis. Interpretation of these measures is aided by knowledge of what physiologic and pathologic factors influence their serum concentration.

Albumin A random serum albumin, interpreted without regard to clinical context, has low sensitivity and specificity and only limited clinical utility as a nutritional indicator. While albumin synthesis decreases by 30% to 50% after only 24 to 48 hours of protein and energy deprivation, there may be little change in the serum albumin concentration even after a much more prolonged period of fasting in an otherwise healthy individual. During periods of inadequate nutrient intake, a decreased rate of albumin degradation and mobilization of albumin from the extravascular space may contribute to the maintenance of a normal serum albumin concentration. For these reasons, albumin is not a very sensitive screening test for early stages of nutritional deterioration. Conversely, a low albumin concentration has low specificity as an indicator of protein-energy undernutrition. Acute and even chronic subclinical inflammation and other

disease conditions are usually the primary contributors to the development and maintenance of a low serum albumin. Although in healthy individuals serum albumin has a half-life of approximately 20 days, during periods of acute physiologic stress (such as major surgery or sepsis), the serum concentration can decline by up 30 g/L within a few days. This effect on the albumin concentration is probably mediated by cytokines (such as tumor necrosis factor and interleukin-6) that are believed to increase vascular permeability to albumin. The concentration of albumin is normally much greater within the intravascular compared to the extravascular space (35–50 g/L compared to ~ 10 g/L). With inflammation induced changes in vascular permeability, there is a rapid loss of the normal concentration gradient between the intra- and extravascular space and an apparent sequestration of albumin in extravascular sites. These same cytokines also suppress albumin synthesis and may trigger an increased rate of albumin degradation with a resultant drop in the serum concentration to 25 g/L or less. Prolonged hypoalbuminemia can also develop in association with advanced liver disease (cirrhosis), severe congestive heart failure, nephrotic syndrome, and protein-losing enteropathies. When these conditions are not present, a persistently low serum albumin probably represents ongoing inflammation and is associated with a high risk of adverse outcomes, including death. The independent effect of nutritional deprivation on low albumin is unclear. Since it is not currently possible to differentiate the effects of inflammation from those of nutritional deprivation, a low albumin indicates only that the patient is at risk for being undernourished. Unexplained hypoalbuminemia should trigger a more in-depth evaluation of the patient to identify other evidence of protein-energy undernutrition and to determine whether nutrient intake is adequate. Serum albumin does not increase rapidly with refeeding and should not be utilized as an indicator of the adequacy of nutritional support.

Prealbumin and the Prealbumin–Retinol-Binding Protein Complex Although it has limited specificity as a nutritional indicator, prealbumin may respond to changes in nutrient intake if there is no persistent inflammation or other active disease processes that are keeping the serum levels suppressed. Prealbumin can be used to monitor for change in a patient's clinical status and to identify risk for the development of nutritional deficits. Despite its name, prealbumin is not a precursor to albumin. Its more descriptive name is transthyretin, because it *trans*ports both *thyr*oxine and *retin*ol (vitamin A). In health, prealbumin has a half-life of 2 to 3 days and a much smaller volume of distribution compared to albumin. Like albumin, prealbumin and the prealbumin–retinol-binding protein complex are negative acute-phase reactants. In response to systemic inflammation, liver production declines and the serum concentration drops rapidly. Low levels are also found in association with end-stage liver disease, iron deficiency, and nutrient deprivation. Renal failure (which results in a decreased catabolism of both prealbumin and retinol-binding protein by the kidney) and high-dose steroid therapy are associated with elevated prealbumin concentrations. Because of its relative short half-life, prealbumin is more sensitive to changes in nutrient intake and disease activity than is albumin. The serum concentration begins to drop after 3 to 5 days of very low nutrient intake in an otherwise healthy individual and can decline by 50% or more subsequent to a major physiologic insult. In the latter case, the nadir value is usually reached within 3 to 5 days and corresponds to the period of maximal negative nitrogen balance. With resolution of the inflammatory process, the serum concentration will climb rapidly to the normal range if nutrient intake is adequate. A rising prealbumin correlates with positive nitrogen balance. This fact can be used to advantage to assess the adequacy of nutrition support. Failure of the serum concentration to increase by at least 20 mg/L in 1 week is considered an indication of inadequate nutrient intake and/or ongoing inflammation and should prompt a careful assessment of the patient and the nutrient regimen being employed.

Assessment of nutrient intake Although frequently difficult to obtain, a detailed nutrient intake assessment is often the most critically needed part of the nutritional assessment. In the outpatient setting where both over- and undernutrition may be a concern, a 24-hour recall or a 3-day food intake diary can be effective tools for estimating nutrient intake and identifying where dietary modifications need to be made, especially if a dietitian or comparably skilled health care provider gives the patient and the family adequate instructions on how to collect the needed data. The employment of more accurate methods of measuring nutrient intake is often especially necessary within hospitals and nursing homes.

Unfortunately, many older patients are maintained throughout their hospitalization on nutrient intakes that are far less than their estimated maintenance energy requirements. Contributing to the problem, the attending health care team often overestimates how much food the older patient is consuming. In one study, over 20% of nonterminally ill older hospitalized patients had an average daily nutrient intake while hospitalized that was less than 50% of their maintenance energy requirements. This lack of adequate nutrient intake was associated with a significant deterioration in protein-energy nutritional status by discharge and a sevenfold increased risk of mortality. Low nutrient intake may be an even more widespread problem within nursing homes. Only by carefully monitoring each older individual's

nutrient intake during their institutional stay can this problem be recognized. However, resources are often not available to support monitoring efforts at the required level of intensity. For this reason, careful selection of older individuals to be monitored is essential. Within the hospital setting, older patients who are not recovering as rapidly as expected, have been placed on clear liquids or nothing by mouth for more than 24 hours, have a persistently low serum prealbumin, or are unexpectedly losing weight, should have their nutrient intake measured each day until they resume an adequate diet. A dedicated team of appropriately trained staff members may be needed to perform this daily nutrient intake assessment, since accuracy often suffers when the regular nursing and dietary staff performs this function. Within extended care facilities, any resident experiencing an acute illness, change in mental status, loss of weight, or decline in functional status should have their nutrient intake monitored in a similar fashion.

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Chapter 35

Malnutrition and Enteral/Parenteral Alimentation

Jeffrey I. Wallace

Learning Objectives

- Describe common factors contributing to undernutrition in older adults.
- Identify the three most common causes of weight loss in older adults.
- Determine appropriate nutritional support interventions for persons with protein-energy malnutrition (PEM).

Key Clinical Points

1. **Weight loss of 5% or more of baseline body weight over 6 to 12 months is associated with increased morbidity and mortality and should prompt clinical investigation.**
2. **When malignancy is the cause of weight loss, the diagnosis is usually readily made with standard evaluations that include a careful history, physical examination, and basic laboratory tests.**
3. **High-protein, high-calorie oral nutritional supplements may reduce morbidity and mortality when provided to hospitalized, malnourished patients age 75 or older.**
4. **Enteral nutrition (EN) is preferred over parenteral nutrition (PN) for patients who are in need of nutritional support and have a functional gastrointestinal (GI) tract.**

MALNUTRITION

Definition

Protein-energy malnutrition (PEM) is present when insufficient energy and/or protein is available to meet metabolic demands. PEM may develop because of poor dietary protein or caloric intake, increased metabolic demands as a result of illness or trauma, or increased nutrient losses. Proposed clinical criteria from the Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition to diagnose adult malnutrition are listed in **Table 35-1**.

TABLE 35-1 CLINICAL CHARACTERISTICS RECOMMENDED FOR THE DIAGNOSIS OF ADULT MALNUTRITION[a]

Insufficient energy intake
Weight loss
Loss of muscle mass (eg, temporal wasting, reduced pectoralis, deltoid, quadriceps, other muscle)
Loss of subcutaneous fat (eg, orbital, triceps, fat overlying ribs)
Localized or generalized fluid accumulation (eg, extremity or genital edema, ascites)
Decreased functional status as measured by reduced handgrip strength

[a]A minimum of two or more characteristics is recommended to diagnose malnutrition.

Epidemiology

Prevalence data, relying on a variety of measures of nutritional adequacy, suggest that deficiencies in macronutrients (protein-energy) and micronutrients (vitamins and minerals) are very common among older adults. National survey data indicate that 40% to 50% of noninstitutionalized older adults are at moderate to high risk for nutritional problems, and up to 40% have diets deficient in three or more nutrients. Prevalence estimates in selected populations over 65 years indicate that 9% to 15% of older persons seen in outpatient clinics, 12% to 50% of hospitalized older persons, and 25% to 60% of older persons residing in institutional settings have one or more nutritional inadequacies—with PEM being the most common. Physical and psychosocial factors that may lead to inadequate nutrition are listed in **Table 35-2**.

TABLE 35-2 FACTORS CONTRIBUTING TO INADEQUATE NUTRITION IN OLDER ADULTS

SOCIOECONOMIC	PHYSIOLOGIC
Fixed income	Impaired strength/aerobic capacity
Reduced access to food	Impaired mobility/dexterity (arthritis, stroke)
Social isolation	Impaired sensory input (smell, taste, sight)
Inadequate storage facilities	Poor dentition/oral health
Inadequate cooking facilities	Malabsorption
Poor knowledge of nutrition	Chronic illness (via anorexia, altered metabolism)
Dependence on others	Alcohol
Caretakers	Drugs (eg, SSRIs,[a] NSAIDs,[b] digoxin, opiates, levodopa, antibiotics, metformin, iron, others)
Institutions	
PSYCHOLOGICAL	**ACUTE ILLNESS/HOSPITALIZATION**
Depression	Failure to monitor dietary intake and record weights
Bereavement	Failure to consider increased metabolic requirements
Anxiety, fear, paranoia	Iatrogenic starvation (eg, NPO[c] for diagnostic tests)
Dementia	Delay in instituting nutritional support

[a]Selective serotonin reuptake inhibitors.
[b]Nonsteroidal anti-inflammatory drugs.
[c]Nothing by mouth.

Energy intake declines significantly with age, attributable in part to decrements in lean body mass and physical activity that often accompany aging. A still greater reduction in caloric intake to levels that may be below daily requirements has been a consistent finding of nutritional surveys conducted among community-dwelling older adults. The National Health and Nutrition Examination Survey (NHANES III) found that the mean daily energy intake of persons aged 70 and older was approximately 1800 kcal/day for men and 1400 kcal/day for women, and more than 10% of older people reported consuming less than 1000 kcal/day. Even if this limited energy intake met the caloric needs of some less-active older adults, it is unlikely that all noncaloric nutrient needs (vitamins and minerals) would be met unless the diet was extremely diverse and rich in nutrients. Although micronutrient deficiencies are common when PEM is moderate to severe, it is the PEM that tends to have the greater clinical impact. Accordingly, this section focuses primarily on PEM, with particular attention to prevention and management of PEM in the acute-care setting.

Poor nutritional status and PEM are associated with altered immunity, impaired wound healing, reduced functional status, increased health care use, and increased mortality. Despite the confounding effect of coexisting nonnutritional factors, poor nutrition remains an independent source of increased morbidity and mortality after adjustment for nonnutritional factors. Although the efficacy of nutritional support to improve outcomes in many circumstances is unproven, there is growing evidence of measurable benefits from interventions to correct or prevent nutritional deficits.

Pathophysiology

PEM may occur as a consequence of inadequate intake alone (eg, starvation) or in association with disease-activated physiologic mechanisms that affect body metabolism, composition, and appetite (ie, cachexia). In the former (primary

caloric deficiency state), the body adapts by using fat stores while conserving protein and muscle, and the resulting physiologic changes are often reversible with resumption of usual intake and activity. Cachexia is a complex metabolic syndrome that is associated with elevated inflammatory cytokines (eg, tumor necrosis factor-α [TNF-α] and interleukin-6 [IL-6]) and increased protein and muscle degradation that may not be readily reversed by refeeding. Although cachexia is usually associated with specific chronic disease conditions (eg, cancer, renal failure, chronic obstructive pulmonary disease [COPD]), this state may develop in older persons without obvious underlying disease. To some extent these physiologic changes may be adaptive. Thus, caution is necessary when devising strategies to halt the lean body mass loss and functional decline that often accompanies cachexia.

Presentation and Evaluation

Despite its apparent clinical importance, physician recognition of malnutrition is often lacking. Effective management of frail or ill older adults mandates an evaluation of nutritional status to better allow for early recognition of PEM and consideration of appropriate interventions. Assessment of nutritional status by standard anthropometric, biochemical, and immunologic measures can be complex, as both nutrient intake and nonnutrition-related factors can affect these parameters. The use of such measurements (eg, body mass index, skinfold thickness, muscle circumferences, serum concentrations of proteins, and lymphocyte counts) to detect the presence of poor nutrition is often advocated, but may not result in earlier or more effective intervention than can be achieved by a careful history and physical examination. The close monitoring of body weight, a readily obtainable measure that reflects imbalance between caloric intake and energy requirements, is a simple and reliable way to screen for malnutrition, particularly in the outpatient setting. Body weight should be recorded at all patient visits. Weight change should be expressed as a percentage of change from past to current weight, because proportional weight change helps account for variability in baseline weight and appears to be the most clinically relevant measure. Although weight gain caused by excessive energy intake is a common form of malnutrition, only undernutrition and weight loss caused by deficits in energy balance are considered here. Weight loss of 5% or more of usual body weight over 6 to 12 months is associated with increased morbidity and mortality in the outpatient setting, and so should prompt investigation. Illness-related weight loss exceeding 10% of preillness weight is associated with functional decline and poor clinical outcomes. Weight loss of 15% to 20% or more of usual body weight implies severe malnutrition.

In the hospital setting, where acute illness or injury often coexists with inadequate intake, alterations in nutritional parameters associated with PEM may develop rapidly. Elevated levels of inflammatory mediators appear to be responsible for the greater losses in lean body mass and the rapid declines in albumin that often accompany PEM in physiologically stressed patients. While serial weight measures remain clinically relevant, early detection and correction of PEM in acutely ill hospitalized patients is enhanced by determination of dietary intake relative to metabolic requirements. Although registered dietitians often provide this information, physicians should be aware of dietary intake and can readily estimate caloric and protein requirements using formulas presented in **Table 35-3**. Biochemical and immunologic measures (eg, albumin, prealbumin, transferrin, and lymphocyte counts) are useful adjuncts in the assessment of nutritional status and can provide prognostic information, but their lack of specificity limits their utility as markers of PEM. Anthropometric measures of fat stores (skinfolds) and muscle mass (midarm muscle area) may help in the assessment of PEM, but clinicians are generally not well versed in obtaining these measures and interrater variability can be high. Although less sensitive, clinical evaluation for loss of skin turgor and the presence of atrophy in hand interosseous or head temporalis muscles can help assess for losses in subcutaneous fat and muscle mass. Because all of these parameters may be affected by nonnutrition-related factors, an effective assessment of nutritional status requires synthesis of information provided from the dietary history, physical examination, and biochemical data. There are no definitive criteria for classifying degrees of PEM. However, when weight loss exceeds 20% of premorbid weight, serum albumin is less than 21 g/L, transferrin is less than 1 g/L, and total lymphocyte count is less than 800/μL, PEM is generally considered to be severe.

TABLE 35-3 ESTIMATION OF DAILY ENERGY AND PROTEIN NEEDS

I. Daily energy requirements (kcal/d)

A. Quick estimate: maintenance 25–30 kcal/kg; stress 30–40 kcal/kg; sepsis 40–50 kcal/kg (tends to overestimate requirements for older and obese patients)

B. Estimates based on resting metabolic rate (RMR, kcal/d):

1. First estimate RMR (using either equation below)

a. Harris-Benedict: $RMR_{women} = 655 + [9.5 \times wt(kg)] + [1.8 \times ht(cm)] - (4.7 \times age)$

$RMR_{men} = 66 + [13.7 \times wt(kg)] + [5 \times ht(cm)] - (6.8 \times age)$

b. Schofield: $RMR_{women} = [wt\ (kg) \times 9.1] + 659$

$RMR_{men} = [wt\ (kg) \times 11.7] + 588$

2. Then multiply RMR by adjustment factor to estimate total energy requirement:

Total daily energy requirement = RMR × 1.3 for mild illness/injury

= RMR × 1.5 moderate illness/injury

= RMR × 1.7 - 1.8 severe illness/injury

II. Daily protein requirements (g/d) (may overestimate if patient obese)

RDA healthy nonpregnant adults	0.8 g/kg
Minimally stressed patients	1.0 g/kg
Injury/illness	1.2-1.4 g/kg
Severe stress/sepsis	1.4-1.8 g/kg

Assessment for Causes of Weight Loss

Initial management of patients with PEM and/or weight loss should include a thorough evaluation to identify underlying causes, and if found, to aggressively attempt to correct potentially remediable factors. In the acute-care setting the cause(s) of malnutrition are often readily evident, although depression may be a contributing factor that is frequently overlooked. In contrast, reasons for poor nutrition and weight loss among community-dwelling older persons may be multiple and not as readily discernible. Depression, GI maladies (eg, peptic ulcer, motility, or malabsorption disorders), and cancer are the three most common causes of weight loss in older adults (**Table 35-4**). When cancer is the cause of weight loss, the diagnosis is rarely obscure. Most diagnoses are readily made after standard evaluations that include a careful history and physical examination and basic screening tests (urinalysis, complete blood count, serum electrolyte, renal, liver, and thyroid function tests, stool hemoccults, and a chest radiograph), with additional tests only as directed by signs and symptoms. If the initial basic evaluation is unrevealing, as will occur in around 25% of cases, it is best to enter a period of "watchful waiting" rather than pursue more extensive undirected testing. A diagnostic algorithm (**Figure 35-1**) focusing first on verifying actual weight loss (patients may inaccurately report a history of weight loss) and then on whether caloric intake is adequate can help guide an appropriate work-up.

TABLE 35-4 ■ DIAGNOSTIC SPECTRUM OF INVOLUNTARY WEIGHT LOSS

	STUDY (STUDY SIZE)								
	MARTON ET AL. (*N* = 91)	RABINOVITZ ET AL. (*N* = 154)	HUERTA ET AL. (*N* = 50)	LANKISCH ET AL. (*N* = 158)	LEVINE ET AL. (*N* = 107)	THOMPSON ET AL. (*N* = 45)	METALIDIS ET AL. (*N* = 101)	BILBAO-GARAY ET AL. (*N* = 78)	WU ET AL. (*N* = 136)
Study population	70% Inpatient 30% Outpatient	Inpatient	Inpatient	Inpatient	Outpatient	Outpatient	57% Inpatient 43% Outpatient	Outpatient	Inpatient
Weight loss definition[a]	≥ 5%/6 mo	≥ 5%/not stated	≥ 10%/6 mo	≥ 5%/6 mo	≥ 5%/6 mo	≥ 7.5%/6 mo	≥ 5%/6–12 mo	> 5%/3 mo or > 10%/6 mo	≥5%/6–12 mo
Mean age (range)	59 ± 17[b]	64 (27–88)	59 (18–83)	68 (27–92)	62 (17–91)	72 (63–83)	64 (51–71)	59 ± 19[b]	80 ± 6[b]
Gender (% male)	100%	45%	64%	44%	53%	33%	46%	49%	81%
Diagnosis %									
Neoplasm	19	36	10	24	6	16	22	23	17
Gastrointestinal	14	17	18	19	6	11	15	6	
Psychiatric	9	10	42	11	22	18	16	33	24
Endocrine	4	4	10	11	5	9	2	6	
Cardiopulmonary	14	—	2	10	9	—	5	3	
Other medical diagnoses[c]	18	9	8	8	16	22	13	17	34
Unknown	26	23	10	16	36	24	28	11	26

a

Weight loss study definition: percent body weight lost per time interval in months.

[b]Mean age in years ± standard deviation (age range not reported).

[c]Neurologic, infectious, alcohol, medication, renal, inflammatory disease, multifactorial. Wu study did not report specific medical diagnoses separately.

Data from Bilbao-Garay J, Barba R, Losa-García JE, et al. Assessing clinical probability of organic disease in patients with involuntary weight loss. Eur J Intern Med. 2002;13:24; Huerta G, Viniegra L. Involuntary weight loss as a clinical problem. Rev Invest Clin (Spanish). 1989;41(1):5; Lankisch PG, Gerzmann M, Gerzmann JF, Lehnick D.. Unintentional weight loss: diagnosis and prognosis. J Intern Med. 2001;249:41; Levine MA. Unintentional weight loss in the ambulatory setting: etiologies and outcomes. [Personal communication and abstract]. Clin Res 1991;39(2):580A; Marton KI, Sox HC Jr, Krupp JR.. Involuntary weight loss: diagnostic and prognostic significance. Ann Intern Med. 1981;95:568; Metalidis C, Knockaert DC, Bobbaers H, Vanderschueren S. Involuntary weight loss. Does a negative baseline evaluation provide adequate reassurance? Eur J Intern Med. 2008;19:345; Rabinowitz M, Pitlik SD, Leifer M, Garty M, Rosenfeld JB. Unintentional weight loss. Arch Int Med. 1986;146:186. Thompson MP, Morris LK. Unexplained weight loss in the ambulatory elderly. J Am Geriatr Soc. 1991;39:497; Wu JM, Lin MH, Peng LN, Chen LK, Hwang SJ. Evaluating diagnostic strategy of older patients with unexplained unintentional body weight loss. Arch Gerontol Geriatr. 2011;53:e51.

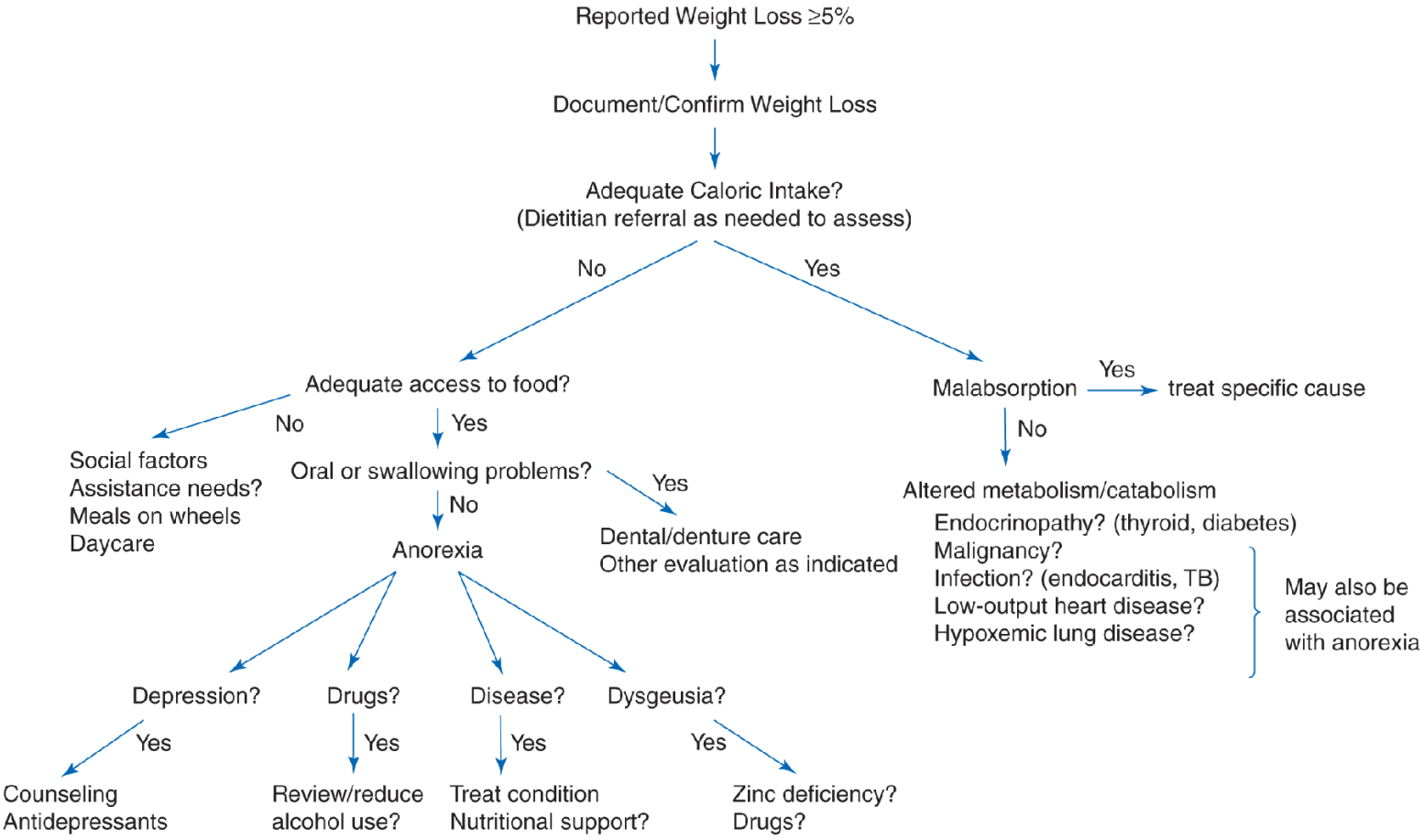


FIGURE 35-1. Weight loss evaluation algorithm.

Management

General considerations Older persons who are not meeting their protein and caloric requirements through oral intake should be considered for nutritional support. **Table 35-5** outlines approaches to nutritional support and factors to consider in deciding whether to pursue specific interventions. The urgency for nutritional interventions relates to the degree of protein-calorie depletion at the time of diagnosis coupled with the expected magnitude and duration of inadequate nutrition. In the hospital setting, clinicians must consider that patients may have been suffering from PEM for some time prior to admission. Therefore, delay in instituting appropriate nutritional support while waiting for improved intake should be avoided. One approach is to intervene after a period of 5 to 7 days of severely limited intake, or for weight loss more than 10% of preillness weight in hospitalized patients. However, attempts should be

made to prevent PEM rather than wait for this degree of PEM to develop because weight loss and undernutrition are associated with worse clinical outcomes and recovery of lost lean body mass is often difficult. This is particularly important in severe stress states (eg, sepsis, major injury) where protein catabolism can lead to losses of lean body mass that approach 0.6 kg/day. In support of early intervention when the development of PEM is likely, a trial of enteral nutrition among patients with major injury found that early (within 24 hours) enteral feeding had clinical benefits over tube feeding started later in the course of hospitalization.

TABLE 35-5 APPROACHES TO IMPLEMENTING NUTRITIONAL SUPPORT

AVAILABLE INTERVENTIONS	FACTORS TO CONSIDER
Enhance oral intake Frequent meals, snacks Provide favorite foods, fortified foods, minimize/remove dietary restrictions Feeding assistance, company at meals Protein-calorie supplements Multivitamins Appetite stimulants?	Degree of baseline protein-calorie depletion Current intake relative to requirements Expected duration of inadequate nutrition Effect of intervention on clinical outcomes Potential benefits Potential adverse effects Burden of intervention
Anabolic agents	Potential for reversibility
Enteral nutrition	Quality of life
Parenteral nutrition	Patient care preferences

Patient preference The effect of the planned intervention on the patient's quality and/or quantity of life should be addressed before proceeding with nutritional support. Although nutritional support interventions may improve weight and other nutritional parameters, their ability to improve clinical outcomes is still limited, particularly when PEM is associated with serious (eg, critically ill intensive care unit [ICU] patients) or irreversible underlying disease (eg, cancer). While efforts to improve nutrition, even in patients with serious underlying disease, are often warranted, late in the course of disease appropriate palliative care may include, if not mandate, discontinuing such efforts. Determination of the care preferences of the patient is a critical component of the decision-making process. Patient and family counseling prior to implementing nutritional support should include a review of the interventions being considered and their potential for adverse, as well as beneficial, effects. **Figure 35-2** shows an algorithm to help guide nutritional support decisions.

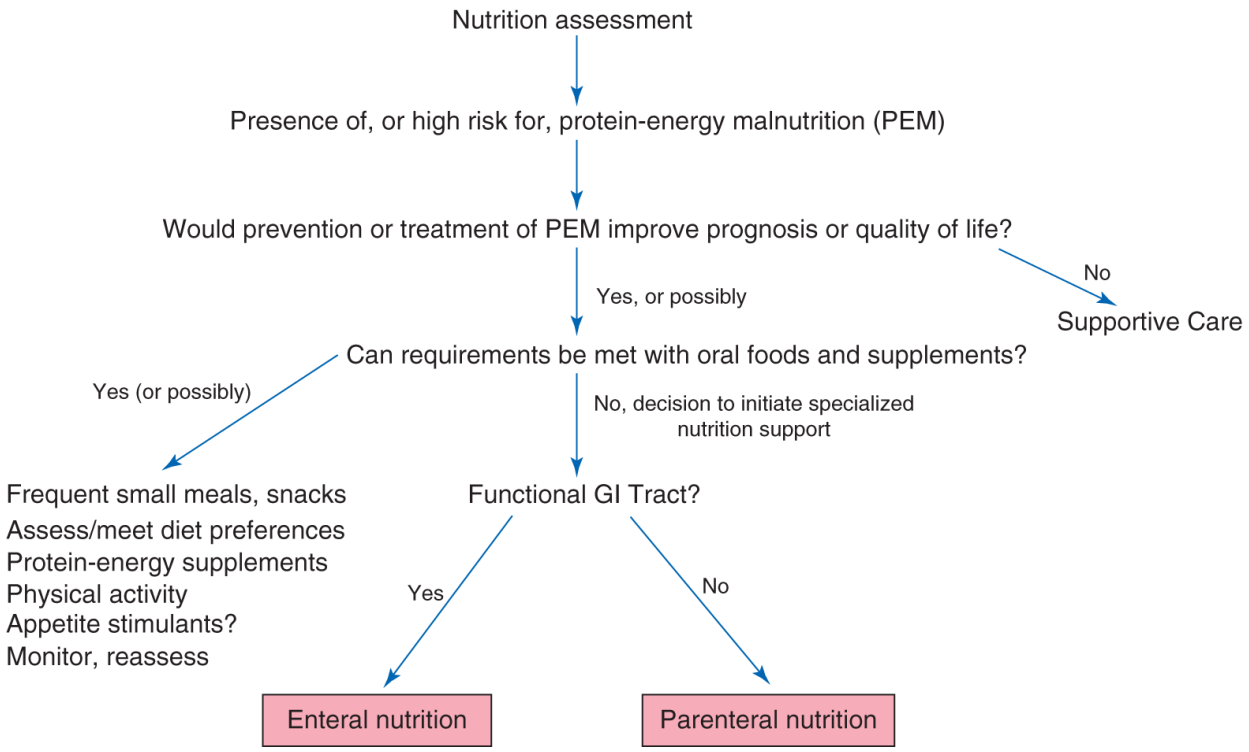


FIGURE 35-2. An algorithmic approach to nutritional support.

Enhancing oral intake

Nonpharmacologic Approaches Although it is uncommon for hospitalized older persons with PEM to be able to increase their food consumption sufficiently to correct their nutritional deficits, trials of strategies to improve voluntary intake are reasonable for stable patients with mild PEM (no definitive criteria exist, but parameters consistent with mild-moderate PEM include weight 85%–90% of premorbid weight, albumin 25–30 g/L, transferrin 1.5–2.0 g/L, total lymphocyte count 800–1200/μL). As previously outlined, underlying causative or contributing condition(s) to PEM should be sought, identified, and addressed. Strategies to help overcome anorexia and improve oral intake include assessing and meeting food preferences, providing frequent small meals and snacks, use of fortified and flavor-enhanced foods, providing company at meals and feeding assistance as needed, and minimizing dietary restrictions. Dietitians may aid greatly in these efforts.

The exact role for high-protein, high-calorie oral nutritional supplements is not clear. Some studies have demonstrated meaningful clinical benefits in malnourished older adults, but the effects are less clear in persons with dementia or other progressive illnesses, particularly in the outpatient setting. A Cochrane Library review concluded that oral nutritional supplements produce modest (2% on average) weight gain, may reduce mortality in undernourished individuals and may reduce hospital complications, but evidence for functional benefits or reduced length of hospital stay is lacking. As the greatest mortality impact was found in hospitalized malnourished patients age 75 or older who received high-calorie supplements, it seems reasonable to recommend such supplements in older hospitalized patients with, or at high risk for, PEM. Higher-calorie “plus” variety nutritional supplements (1.5–2.0 kcal/mL) are preferred over standard (1 kcal/mL) formulas. Costs are only slightly higher, and because they deliver higher–calorie content per milliliter ingested, patients do not need to drink as much volume to improve caloric intake. Supplements should be provided between, rather than with, meals as this appears to result in less compensatory decreases in food intake at mealtime, thereby more effectively increasing total daily caloric intake. However, even if total caloric intake is only marginally improved, the provision of energy from nutritionally dense supplement sources may be beneficial due to improved protein and micronutrient intake.

A standard multivitamin supplement should also be considered for all older adults with poor intake. Although study results are not consistent, improving micronutrition with multivitamins, particularly in malnourished or at-risk persons, may improve clinical outcomes (eg, infection rates). Increased physical activity is an important adjunct that can help maintain lean body mass, improve appetite and sense of well-being, thereby leading to improved caloric intake and functional status.

Drugs Pharmacologic approaches to stimulate appetite and promote weight gain can be considered on an individual

basis with the knowledge that the few agents (megestrol acetate [MA], dronabinol, cyproheptadine) that may improve intake in some patient populations (eg, cancer, human immunodeficiency virus [HIV], anorexia nervosa) have not been shown to be effective in older adults and have the potential to cause important side effects. Further, the weight gain that has been observed with these agents has usually been small, disproportionately fat mass, and not associated with improved function, quality of life, or decreased morbidity and mortality. MA increases risks of thrombotic events, fluid retention and mortality, and was added to the American Geriatrics Society's Beers Criteria list of potentially inappropriate medications for older adults in 2012. Dronabinol has not been well-studied in older adults and at best has shown limited promise in small nonrandomized trials conducted in nursing home patients. A head-to-head comparison trial in cancer patients found MA to be more effective than dronabinol in improving appetite and promoting weight gain. MA's mechanism of action may involve suppression of inflammatory cytokines (eg, IL-6 and TNF-α), consistent with the observation that this agent appears most effective in persons with elevated cytokine levels (eg, cancer or acquired immunodeficiency syndrome [AIDS] patients). If initiated, MA may not have a demonstrable effect on appetite for several weeks, but if no effect is seen by the eighth week, MA should be discontinued. If positive effects are demonstrated without significant side effects, MA may be continued for up to 12 weeks. Treatment for more than 8 to 12 weeks can suppress the adrenal-pituitary axis resulting in adrenal insufficiency and insufficient response to acute stressors. MA also appears to blunt the beneficial effects of progressive resistance exercise, consistent with an undesirable glucocorticoid-like catabolic effect.

If depression is felt to be a likely, or possible, contributing factor to poor intake, a trial of therapy is usually warranted. Selective serotonin reuptake inhibitors (SSRIs) are first-line antidepressant agents, and improve appetite by improving depression. Mirtazapine generally leads to more weight gain than SSRI antidepressants, but it is not clear that mirtazapine has a significant advantage over other antidepressants when weight loss is a predominant presenting sign in a depressed older adult. There is no high-quality evidence to support the use of mirtazapine for weight gain in the absence of depression.

Maintaining lean body mass and functional status

Anabolic Agents Anabolic hormones (eg, growth hormone [GH], testosterone, oxandrolone) have received considerable attention in the search to find strategies to help preserve or increase lean body mass in patients with malnutrition and weight loss. Although adequate nutrition is essential for patients with weight loss, a physiologically stressed catabolic patient may lose significant lean body mass despite aggressive nutritional support (and the weight gain that does occur with nutritional support and appetite stimulants may be primarily fat and water). GH has generally failed to demonstrate benefits on muscle mass or muscle strength in older adults, even in association with resistance training. The use of GH in intensive care and congestive heart failure patients has also yielded disappointing results with evidence of increased mortality. The cost, need for injection, and potential side effects of GH (eg, arthralgias, edema, insulin resistance, tumor growth) further limit its clinical utility. Testosterone increases muscle protein synthesis, mass and strength, and improvements in functional outcomes have been observed in small controlled trials in selected male populations (eg, older men after knee replacement surgery, deconditioned older men on a Geriatric Evaluation and Management unit). Although testosterone might be considered in men with documented clinical hypogonadism, its role in the setting of malnutrition and/or cachexia remains to be clarified, especially in light of known safety concerns (in particular cardiovascular). In terms of future possibilities, selective androgen receptor modulators (SARMs) have the potential to provide desirable anabolic effects on muscle and bone without undesirable effects on other organs but these agents are still under study and not available clinically. Oxandrolone, a synthetic testosterone derivative with an increased anabolic to androgenic effect ratio, has shown some utility for patients with weight loss in association with AIDS/HIV or burns, and preliminary data also suggest benefit in patients with COPD. This agent can cause hepatitis, hirsutism, and fluid retention, and is contraindicated in patients with breast or prostate cancer. Further research is needed to define the clinical role of oxandrolone as a pharmacologic intervention to be used in combination with nutrition therapy in older adults. Other anabolic agents that are under study include myostatin inhibitors. Myostatin is expressed in skeletal muscle and inhibits muscle protein synthesis and promotes fibrosis. Blocking these effects may provide a novel approach to prevent muscle loss and promote muscle growth.

Physical Activity Efforts to increase physical activity are an important adjunct to any nutritional intervention, as positive effects of exercise include enhanced appetite and improved functional status. The benefits (and safety) of exercise in older populations are reviewed in Chapter 115.

NUTRITIONAL SUPPORT

Enteral Nutrition

Enteral nutrition is defined as the nonvolitional delivery of nutrients by tube into the GI tract. EN should be considered for patients with PEM, or at high risk for it, who cannot meet their nutritional requirements through oral intake. However, specific indications regarding if and when to provide EN are not clearly established, and patient prognosis and preference are critical factors that must be taken into account. EN requires a functional GI tract and is contraindicated in patients with bowel obstruction, inadequate bowel surface area, major upper GI bleeding, GI ischemia, paralytic ileus, or intractable vomiting or diarrhea. Purported benefits of enteral tube feedings relative to PN include the maintenance of GI structure and function, more physiologic delivery and use of nutrients, less risk of overfeeding and hyperglycemia, and lower costs. Although these advantages may be more theoretical than actual, EN is preferred when GI function is felt to be adequate. However, EN and PN should not be considered mutually exclusive. For patients unable to fully meet their nutritional requirements through EN, a mixture of PN and EN is preferable to moving to PN alone.

Efficacy Enteral nutrition can improve prognostically important intermediate nutritional parameters, but the effects of EN on clinical outcomes (eg, functional status, medical complications, mortality) are unclear owing to limited and/or mixed data. EN is often not initiated until advanced undernutrition is present, which is a clear impediment to the potential positive effects of nutritional therapy. There is prospective clinical trial evidence among older undernourished hip fracture patients that EN can improve both nutritional parameters and clinical outcomes (eg, length of stay, infectious complications, and mortality). Further study is needed to determine which older hospitalized patients might benefit most from aggressive nutritional support. In the interim, sufficient rationale exists to consider EN for patients who are undernourished or at high risk for undernutrition, and cannot meet their nutritional needs with oral intake.

Tube placement The route selected for tube feeding depends on the anticipated duration of feeding, the potential for aspiration, and the condition of the gastrointestinal tract (eg, esophageal obstruction). Nasogastric (NG) or nasointestinal tubes provide the simplest approach for patients requiring relatively short-term EN (< 30 days). Patient comfort is often problematic and tolerance is best when a small-diameter, soft feeding tube is used rather than a standard large-bore NG tube. The use of longer specialized feeding tubes also allows the tube to reach beyond the pylorus into the distal duodenum or jejunum (ie, beyond the ligament of Treitz), which is the preferred site of placement for patients who are critically ill, have delayed gastric emptying, or are at high risk for aspiration. Methods to promote passage of the tube past the pylorus when postpyloric feeding is desired include ensuring adequate tube length, having the patient lie on their right side, and prescribing erythromycin or metoclopramide. If these methods fail and the risk of aspiration is felt to be very high, tube placement into the duodenum or jejunum can be performed endoscopically or under fluoroscopic guidance. After placement, the desired tube position should be verified radiologically before starting feedings and the tube should be marked at its exit point to help identify if subsequent movement occurs.

Percutaneous tube placement (gastrostomy, gastrojejunostomy, jejunostomy) is indicated when long-term tube feeding is anticipated (> 4 weeks). However, it may also be appropriately considered earlier, especially when EN is likely to exceed 2 weeks, because such a tube is better tolerated, allows more consistent nutrition delivery, and has less treatment failures than nasointestinal tubes. Percutaneous placement of gastrostomy tubes (G-tubes) can be performed either endoscopically or under radiographic guidance. The risks of major complications with either procedure are generally low, but infection, hemorrhage, and peritonitis have each been reported at rates of 1% to 3%.

Tube feeding is associated with an increased incidence of aspiration. However, most aspiration pneumonias are the result of difficulty handling endogenous (oropharyngeal or gastric) secretions rather than aspiration of material introduced through tube feeding. Thus it is not entirely surprising that although postpyloric feeding tube placement is generally advised in older and sicker patients, evidence is not definitive that such placement reduces rates of aspiration pneumonia. Postpyloric feeding may offer other advantages such as less gastric residual problems in persons with gastric dysmotility and reduced esophageal reflux symptoms. Placement of a feeding tube directly into the jejunum may be required for a patient with an abnormal or inaccessible stomach (eg, gastrectomy, duodenal obstruction). Although direct jejunostomy tube (J-tube) placement can be accomplished using percutaneous methods, a J-tube traditionally requires an open surgical procedure and is often placed at the time of laparotomy when the need for prolonged nutritional support is anticipated.

Formula selection Adult enteral formulas fall into one of the following categories: standard, concentrated, predigested (previously called elemental or semielemental) and disease specific. All consist of varying mixtures of

protein (often casein), carbohydrate (often cornstarch), and fat (usually vegetable oils), and most do not contain lactose. Formula variability includes nutrient composition, nutrient density, fiber content, digestibility, viscosity, osmolality, and cost (cost tends to be substantially higher for disease-specific specialty formulas, and up to 10-fold higher for critical care and predigested elemental specialty formulas). Isotonic standard formulas with caloric densities of 1 to 1.2 kcal/mL are usually the initial products of choice. Higher-caloric density formulas (1.5–2.0 kcal/mL) may be useful when volume restriction is paramount (eg, in patients with renal failure), but their higher viscosity increases the risk of tube clogging and their higher osmolality may be less well tolerated if delivered rapidly via tubes placed beyond the pylorus. There is no evidence that routine supplementation of EN with fiber prevents diarrhea, but formulas with higher fiber content may be tried if patients receiving EN are having problems with diarrhea or constipation. In predigested or elemental formulas, carbohydrates are supplied primarily as oligosaccharides and proteins have been partially or fully hydrolyzed to peptides and amino acids. Although they are promoted for patients with diminished ability to digest nutrients, it is uncommon for patients to be incapable of digesting and absorbing standard formulas unless they have significantly impaired gastrointestinal function (assuming appropriate adjustments are made in rates of feedings, osmolality, and fiber content). Elemental diets can also cause, rather than reduce, diarrhea because of their high osmolality.

Disease-specific/specialty formulas are available for patients with renal failure, liver failure, diabetes mellitus, pulmonary disease, gastrointestinal dysfunction, and critical illness. However, as costs are usually substantially higher and no clear clinical benefits have been consistently demonstrated, disease-specific formulations are not routinely recommended. Renal formulas do have a place in renal failure patients who have need for fluid and/or electrolyte restrictions. Renal disease formulas are low in protein, low in electrolytes, and dense in calories to assist in fluid restriction. These formulas may be useful before dialysis but are not necessary for most patients once on dialysis. Formulas have been developed for diabetic patients, but use of cheaper standard formulas with adjustments in glucose control regimens as necessary is adequate for most diabetic patients. Formulas for pulmonary patients have higher fat content, because energy utilization from fat results in less carbon dioxide production relative to the metabolism of carbohydrate energy sources. Although possibly useful for patients being weaned from ventilators, these formulas are of questionable clinical importance for most patients with chronic lung disease. Hepatic formulas have specific amino acid mixtures (high in branched-chain, low in aromatic amino acids) that are less likely to cause or exacerbate hepatic encephalopathy. They are indicated when, in spite of appropriate medical therapy, hepatic encephalopathy limits the delivery of adequate protein to a patient with liver disease.

A number of specialty formulations have been designed for critically ill patients. Some of these products are enriched with glutamine (an amino acid associated with improved nitrogen balance and gut barrier function as well as immune-modulating effects when delivered parenterally), arginine (an amino acid associated with improved nitrogen balance and immune function), and/or other immune modulators (eg, antioxidants, selenium, omega-3 fatty acids). However, meta-analyses have not shown convincing clinical benefits and a large trial of such “immunonutrition” in an ICU population found that early provision of glutamine or antioxidants did not improve clinical outcomes, and glutamine was associated with increased mortality. Pending further study use of these amino acids in enteric formulas is not advocated.

Administration guidelines After desired tube placement location is confirmed, tube feeds can be started at a rate of 10 to 30 mL/h. Isotonic formulas can be started at full strength, whereas hyperosmolar formulas are usually diluted to half strength to improve initial tolerance. Although standard clinical practice had been to monitor gastric residuals at regular intervals, this practice does not reduce aspiration pneumonia risk and is associated with decreased caloric delivery. Nonetheless, the most recent (2009) recommendations from the American Society of Parenteral and Enteral Nutrition advise gastric residual monitoring, and such monitoring is appropriate if there are concerns regarding GI motility or delayed gastric emptying. An evaluation for remediable factors (eg, medications, high-fat content formulas) should be conducted if gastric residual volume exceeds 250 mL, and feedings should be held if residuals exceed 500 mL. In non-ICU settings feeding rates can be advanced 25 mL/h every 8 to 12 hours based on individual tolerance, until target rate is reached. A large study in mechanically ventilated ICU patients indicated that EN was better tolerated (eg, less vomiting, lower mean plasma glucose levels, lower insulin requirement, reduced use of prokinetic agents) and clinical outcomes were similar when feeding rates were kept low (10–30 mL/h, roughly 30% of target rate) for 6 days before increasing by 25 mL/h every 6 hours as tolerated to target rate. Once daily requirements are reached, further adjustments to deliver nutrients primarily at night are often desirable to allow more freedom of movement during the day. Nocturnal feeds probably offer little benefit in terms of decreased satiety and improved intake during the day relative to continuous feeds. Larger-bore NG and gastrostomy tubes allow for intermittent gastric feedings without

requirement of a pump. Although this offers convenience advantages and it is more physiologic for food to be placed into the stomach, intermittent bolus feedings are generally avoided in persons with delayed gastric emptying and those at high risk for aspiration.

Attention must also be paid to water and electrolyte requirements. Basal free-water requirements for hospitalized patients are roughly 30 mL/kg per day, or about 1 mL/kcal delivered. Free water will need to be increased if excess fluid loss is occurring as a consequence of diarrhea, urinary, or increased insensible losses. For patients with fever, an additional 300 to 400 mL of water is needed for each degree centigrade of temperature elevation. Monitoring of weight and electrolytes can help direct any necessary adjustments, with additional free-water needs given in divided boluses three or four times a day.

Risks and complications Proper consideration of whether to proceed with EN entails an understanding of common adverse effects (**Table 35-6**). NG tubes are often not well tolerated, with patient agitation and self-extubation being particularly common among patients with cognitive impairment or delirium. The subsequent need for physical or chemical restraints can increase complications and appropriately dampen enthusiasm for NG tube feedings. Also, EN in actual practice often involves delayed and inadequate nutritional support because of frequent problems with tubes (eg, self-extubation, plugging) or GI intolerance (eg, high residuals, bloating, diarrhea). These factors may explain why attempts to provide EN to older persons are often abandoned after only a short course of therapy. Some have advocated for an early switch to PN, or even starting with PN, particularly if patients are confused or delirious and the expected duration of therapy is short (1–2 weeks). If longer-term support is likely, early use of a percutaneous gastrostomy tube, which tends to be better tolerated by uncooperative or confused patients, may be considered (along with a reevaluation of overall patient care preferences and intervention goals before proceeding with this more invasive approach).

TABLE 35-6 ADVERSE EFFECTS OF ENTERAL NUTRITION AND MANAGEMENT APPROACHES

ADVERSE EFFECTS	MANAGEMENT
Poor tolerance	Consider
Frequent self-extubation	Parenteral nutrition
Agitation	Percutaneous gastrostomy tubes
Pulmonary	Elevate head of bed ≥ 30° (ideally 45°)
Aspiration	Monitor gastric residuals, ↓ rate as needed
	Nasointestinal, G-J, J-tubes
Gastrointestinal	Low-fat formula, metaclopramide
Gastric retention	Nasointestinal, G-J, J-tubes
Nausea/vomiting	↓ Delivery rate, ↑ fiber, antidiarrheals
Diarrhea	
Metabolic complications	Routine monitoring glucose, electrolytes
Hyperglycemia	Monitor weight, volume status, free water
Fluid and electrolytes	Monitor phosphate, magnesium, potassium
Refeeding syndrome[a]	
Mechanical problems	Local skin care
Insertion site irritation/infection	
Tube plugging	Warm water or pancreatic enzyme flushes
G-tube, J-tube extubation	See text
Nasopharyngitis, sinusitis, local pain, epistaxis	Use small-bore flexible tube and avoid prolonged nasal intubation (> 4–6 wk)
Drug interaction considerations	
Tube feeds ↓ bioavailability (eg, ciprofloxacin, azithromycin)	Hold feedings 15 min before and after medications
Frequent medications interrupt nutrition	Alternate medication routes (IV, IM, rectally, transdermal)

[a]

Abrupt, often large drops in serum potassium, phosphorous, magnesium, which may accompany initiation of nutritional support in malnourished patients.

Pulmonary aspiration is a relatively common complication of EN, but unless aspiration causes an overt clinical event (eg, aspiration of a large volume), it is not clear that aspiration causes untoward clinical outcomes such as higher rates of pneumonia. Nonetheless, strategies to reduce aspiration are generally advised. Patients with gastric retention, decreased gag reflex, and altered levels of consciousness are at increased risk for aspiration, and mechanically ventilated patients should not be considered protected by the presence of an endotracheal cuff. The risk of aspiration can be reduced as outlined in **Table 35-6**.

EN-related GI issues include gastric retention and diarrhea. Gastric retention problems may respond to a change to a low-fat formula or to pharmacologic intervention with metoclopramide. When significant diarrhea occurs, infectious causes (particularly *Clostridium difficile*) must first be excluded. The possibility of intolerance to formulas with high osmolality or high fat content should also be considered. Interventions to reduce diarrhea include slowing the rate of infusions, diluting hypertonic formulas, increasing formula fiber content, and the use of antidiarrheal agents. In addition to the electrolyte abnormalities that can be caused by diarrhea, hyperglycemia and other metabolic abnormalities may develop related to tube feedings. Potassium and phosphorous requirements can be very high in the first few days after nutritional support is started because of extracellular to intracellular shifts that accompany nutrient utilization, particularly among very malnourished patients (“refeeding syndrome”). Fluid retention problems are common in older adults with impaired renal or cardiac function. To minimize these problems, monitoring protocols should include frequent evaluations of GI tolerance, daily weights, and daily monitoring of glucose and electrolytes (including phosphorus, calcium, and magnesium) until stable.

Increased problems with tube clogging often occur when more viscous higher-calorie formulas and medications (especially fiber and calcium supplements) are passed via small-bore (smaller than no. 10 Fr) catheters. Tube maintenance with regular flushing every 4 to 8 hours for patients on continuous feeds, and before and after the delivery of intermittent tube feeds or medications (with 30 mL warm water), can reduce clogging problems. When possible, medications should be given by mouth rather than by feeding tube. If clogging occurs try flushing with 30 to 60 mL of warm water, or a solution containing pancreatic enzymes. Cola or cranberry juice flushes are not consistently effective for resolving occlusions, and when used, their dried residuals can narrow the lumen of the tube and contribute to clogging. Another common mechanical problem is the replacement of a gastrostomy or jejunostomy tube that has fallen out. Feeding tube fistula tracts are generally not well established for at least 1 to 2 weeks after placement (and often substantially longer given malnutrition’s adverse effect on wound healing). Tubes that come out early (in the first 2–3 weeks after placement) require replacement by the original specialist. If the fistula tract is well established, patients or care providers should be able to gently replace tubes that have fallen out, and delay in doing so for more than 6 to 12 hours risks spontaneous closure of the tract. However, feeding should not be resumed until proper tube placement is radiologically confirmed.

Parenteral Nutrition

PN, the delivery of required nutrients by vein, is generally indicated to prevent the adverse effects of malnutrition in patients who are unable to obtain adequate nutrients by oral or enteric routes (ie, EN is not possible). However, specific indications regarding if and when to institute PN, as well as the utility of PN once instituted, have not been clearly delineated. In general, the decision to institute PN depends on the severity and expected course of the underlying disease(s) and the severity of preexisting and anticipated undernutrition. The duration of undernutrition that can be tolerated before adverse effects occur is not clear. For critically ill patients who are adequately nourished on admission and have contraindications to EN, guidelines recommend against PN during the first week as early PN may increase risk of infections and other complications. If a critically ill patient has evidence of PEM at admission and EN is not possible, PN initiation within the first few days should be considered. The European Society for Clinical Nutrition and Metabolism guidelines for PN in geriatric patients recommend initiating PN support in older persons facing a period of starvation of more than 3 days when oral nutrition or EN is not possible, or when oral nutrition or EN is likely to be insufficient for more than 7 to 10 days. Decisions to institute PN require careful consideration of the patient’s clinical condition and prognosis, clinical judgment about the patient’s ability to tolerate undernutrition, and insight regarding patient care needs and preferences.

Efficacy The European Society for Clinical Nutrition and Metabolism concluded that PN can reduce morbidity and mortality in geriatric patients, but the evidence that PN improves clinical outcomes in older adults is not robust. The limited data that PN can have beneficial effects comes primarily from the following settings: perioperative PN in

patients with GI cancers; severely malnourished patients (defined in the reference study by a low nutritional risk index score, which generally was reached if weight loss exceeded 10%–15% and serum albumin level was < 33 g/L, or, in the absence of weight loss, if albumin was < 28 g/L) undergoing major elective surgery; and bone marrow transplant recipients, malnourished critically ill patients, and patients with short bowel syndrome. Overall there is a paucity of studies and many unanswered questions about the efficacy and safety of PN in older adults. Furthermore, detrimental clinical outcomes observed with routine PN for cancer chemotherapy patients, along with the cost and invasiveness of PN, indicate that risks and benefits must be reviewed carefully for each patient. That PN may be of some benefit when used in cancer patients who are severely malnourished affirms the importance of patient selection and the identification of clear goals of therapy before instituting PN.

Administration guidelines

Intravenous Access Total parenteral nutrition (TPN), the delivery of all required nutrients by vein, requires the use of hypertonic solutions that can only be tolerated when delivered into large venous vessels, preferably into the superior vena cava. Because peripheral veins are limited to solutions containing lower concentrations of amino acids and dextrose (< 10% dextrose), peripheral parenteral nutrition (PPN) usually cannot deliver nutrients in sufficient quantity to meet all requirements. Although the infusion of lipids can improve energy delivery and vessel tolerance to PPN, its role in PN is extremely limited given the uncertain clinical benefits of short-term PPN and the ease of obtaining central venous access to proceed to TPN. Short-term TPN in the hospital setting is generally delivered through a subclavian or internal jugular venous catheter or via a peripherally inserted central catheter (PICC). PICC lines offer reduced risks of central placement complications (eg, pneumothorax, inadvertent arterial puncture, and hemorrhage) and may have a reduced risk of infectious complications. Tunneled central venous catheters (eg, Hickman or Groshong catheter) are generally preferred over PICCs for long-term TPN (eg, home TPN) owing to lower infection rates. Regardless of the placement method used, proper line position needs to be confirmed by x-ray before initiating TPN.

TPN Composition Standard TPN solutions contain carbohydrate (dextrose) and protein (amino acid) concentrates, fat emulsions (soybean or safflower oil with egg phospholipids), micronutrients, and electrolytes. Although clinicians should have a basic knowledge of usual TPN formula composition (**Table 35-7**), PN should be initiated and monitored by a team (usually physicians, nutrition specialists, and pharmacists) with an advanced understanding of factors such as nutrient metabolism and solute compatibility. Clinicians should also be aware that electrolyte requirements are highly variable and often require adjustments, as they are influenced by the patient's underlying disease (eg, heart failure, renal dysfunction) and factors such as renal or GI fluid losses. Standard packages of vitamins and trace elements are added to TPN solutions daily to prevent the development of micronutrient deficiencies. Because patients on warfarin should not receive vitamin K, it is not included in standard vitamin packages and must be given separately in doses of 5 to 10 mg/week.

TABLE 35-7 "AVERAGE" TPN FORMULA COMPOSITION AND PARAMETERS FOR DAILY VITAMIN, MINERAL, AND ELECTROLYTE REQUIREMENTS

MACRONUTRIENTS[a]	15%
Protein	55%–65%
Carbohydrate	20%–30%
Fat	
MICRONUTRIENTS	
Vitamins	
Vitamin A	3300 IU
Vitamin D	200 IU
Vitamin E	10 IU
Thiamine (B_1)	6 mg
Riboflavin (B_2)	3.6 mg
Niacin (B_3)	40 mg
Pantothenic acid (B_5)	15 mg
Pyridoxine (B_6)	4 mg
	60 µg

Biotin (B_7)	600 µg
Folic acid (B_9)	5 µg
Cobalamin (B_{12})	200 mg
Vitamin C	
Trace Elements	
Zinc	5 mg
Copper	1 mg
Chromium	10 µg
Manganese	0.5 µg
Selenium	60 µg
Electrolytes	
Sodium	60–150 mEq
Potassium	40–100 mEq
Chloride	Equal to sodium
Magnesium	16 mEq
Phosphorus	10–30 mmol
Calcium	10 mEq

[a]Percentage of total calories.

The optimal proportions of fat and carbohydrate to meet energy needs are controversial. All standard formulas contain hypertonic glucose (10%–70% dextrose before mixing), but because glucose tolerance declines with age, slow upward titration in delivery rates is necessary in older adults. Aggressive glucose monitoring and treatment is important as hyperglycemia is associated with increased infection risk and worse clinical outcomes in critically ill patients. Glucose infusion rates should not exceed 5 mg/kg/min (about 500 g/day for a 70-kg person on continuous TPN) because the rate at which stressed patients can metabolize glucose as energy is limited. Overfeeding with glucose results in increased risks of hyperglycemia, increased carbon dioxide production, and the conversion of excess glucose calories into fat (which requires energy and contributes to fatty liver changes).

Lipids in the form of 10% to 20% fat emulsions are added to TPN as a source of concentrated energy and to supply essential fatty acids. Delivery of fat emulsions two to three times a week is usually adequate to prevent essential fatty acid deficiency. Fat emulsions are isotonic and are generally well tolerated, but patients occasionally develop hyperlipidemia and, less frequently, have allergic reactions (usually to the egg phospholipid component). Increasing the proportion of energy supplied by fat can reduce hyperglycemia and carbon dioxide production, but fat delivery should not exceed 2.5 g/kg/day (or 50%–60% of nonprotein calories) to avoid possible adverse consequences associated with fat overload. The fat overload syndrome is characterized by hyperlipidemia with diffuse fat deposition that can cause organ and reticuloendothelial system dysfunction and increased risk of sepsis. Lipid emulsions containing fish oil may have anti-inflammatory and antioxidant properties that could be beneficial during critical illness, but to date, evidence is inadequate to recommend their routine use.

Formula Delivery Initial infusion rates should be at a rate of 25 to 50 mL/h and increased every 8 to 12 hours as metabolic status allows until fluid and nutrition goals are met. At some institutions carbohydrate, fat, and protein TPN components are mixed together into a single bag (total nutrient admixture or 3-in-1 formula), which may have cost and convenience benefits compared to traditional TPN administration of dextrose and amino acids (2-in-1) with separate IV fat emulsion infusions. In most circumstances, daily TPN volumes are infused continuously over the full 24 hours. This allows slower delivery of carbohydrate (which can help reduce hyperglycemia), and the continuous flow may decrease the risk of catheter occlusion while avoiding interruptions that might lead to hypoglycemia. Shorter infusion schedules with brief periods off TPN (cyclic TPN) are occasionally desirable, but this is more of an issue for long-term TPN in the home care setting. Because TPN formulas (especially the lipid component) can suppress appetite, it may be desirable to reduce or hold lipid emulsions for a few days to help improve intake prior to planned discontinuation of TPN.

Patient monitoring and complications Older persons receiving TPN should be monitored closely (**Table 35-8**),

with adjustments made in frequency of monitoring depending on the patient's acuity and stability. **Table 35-9** details common complications and their prevention and/or treatment. Correction of dehydration and volume depletion can most readily be accomplished with standard intravenous fluids, which can be infused separately or added to TPN bags for convenience. Fluid overload can be managed by using higher concentrations of macronutrients to limit total volumes infused, with diuretics added as needed. Although insulin can be added directly to TPN solutions to help control hyperglycemia, it is best to give intravenous insulin separately until caloric delivery and glucose control are stabilized. Intravenous insulin is preferred over subcutaneous insulin owing to the latter's potential for erratic absorption in malnourished patients. Infection and volume depletion need to be considered if hyperglycemia is a persistent problem. As with EN, potassium and phosphate must be monitored closely because they may drop precipitously after initiating TPN in malnourished patients. In most cases, electrolyte requirements stabilize within 1 week. The relative amounts of chloride (which can lead to metabolic acidosis) and acetate (which can be metabolized to bicarbonate and lead to metabolic alkalosis) can be adjusted as needed depending on the patient's acid-base balance. Patient monitoring should also include clinical (eg, weight, functional status) and laboratory (eg, albumin, prealbumin) assessment of the efficacy of nutritional support.

TABLE 35-8 GUIDELINES FOR MONITORING PATIENTS ON TPN

CLINICAL DATA	LABORATORY DATA
Vital signs three times per day until stable	Glucose chemsticks QID until stable
Daily weights	Daily: Electrolytes, glucose, creatinine, blood urea nitrogen, calcium, phosphorus, magnesium until stable, then twice weekly
Daily fluid input and output	Weekly: LFTs, albumin, CBC, PT, triglyceride
Daily line and skin inspection	
Efficacy of nutritional support	

CBC, complete blood count; LFTs, liver function tests (alanine and aspartate aminotransferase, alkaline phosphatase, bilirubin); PT, prothrombin time.

TABLE 35-9 TPN COMPLICATIONS AND POTENTIAL CORRECTIVE MEASURES

CONDITION	PREVENTION/MANAGEMENT
Metabolic	
Fluid overload	Restrict fluid by ↑ macronutrient concentrations
Hyperglycemia	↓ Carbohydrate delivery (rate, concentration), insulin IV; consider ↑ proportion energy from fat
Hypoglycemia	Avoid sudden cessation/interruption of TPN
Refeeding syndrome	Start/titrate TPN slowly, avoid overfeeding
Hypertriglyceridemia	↓ Fat infusion rates and/or frequency of lipids
Hyperchloremic metabolic acidosis	↑ Acetate/↓ chloride; consider renal/gastrointestinal causes
Metabolic alkalosis	Consider renal/gastrointestinal causes; replete K+; ↓ acetate
Respiratory (hypercarbia)	↓ Total calories, ↑ proportion energy from fat
Nonmetabolic	
Line infection	Hand hygiene and maximal barrier precautions during insertion, single-lumen catheter; dedicated TPN line; aseptic line
Hepatic	
Steatosis/↑ LFTs	Avoid carbohydrate overfeeding; rule out other causes
Biliary (cholestasis)	Enteral feed if possible; rule out other causes
Catheter occlusion	Regular flushes; no line blood draws; urokinase

LFTs, liver function tests.

Infection of the access line is uncommon in the first 72 hours, so early fevers are usually a result of other causes.

The risk of infection can be reduced by following optimal insertion techniques and providing aseptic vigilant catheter care. The line site should be monitored daily for erythema, tenderness, or discharge. Positive line cultures in the absence of other sources are usually an indication for line removal. The increased rates of sepsis that have been observed in some trials of TPN (and which possibly diminished the potential for TPN trials to demonstrate improved clinical outcomes) may have been related to overfeeding and hyperglycemia. Avoidance of hyperglycemia (in particular glucose levels > 200 mg/dL) may decrease the risk of TPN-associated infections. Liver abnormalities that can occur with TPN include fatty liver with elevated liver function tests (often occurs early, likely related to carbohydrate overfeeding, generally benign/reversible) and cholestasis (tends to occur later, after 3+ weeks). EN, even in small amounts, may reduce problems with cholestasis.

Special Issues

Comorbidity Responses to nutritional support efforts may vary substantially owing to heterogeneity in underlying disease states associated with PEM (particularly the presence and severity of inflammatory/catabolic states). Limited data on the interaction between nutritional support and specific comorbid conditions and care settings include the following:

Hip Fracture As many as half of all older patients who present with hip fractures are malnourished. Undernutrition may directly contribute to hip fracture events via increased presence of osteoporosis, increased risk of falls as a consequence of reduced lean body mass and strength, and reduced fat to "cushion" a fall. Oral nutritional supplements may improve energy balance and reduce complications and hospital length of stay following hip fracture. While a Cochrane review found the quality of the evidence to be weak, the risks and costs of oral protein energy supplementation are relatively low and as such should be considered for all undernourished patients after hip fracture. Trials of EN after hip fracture indicate that NG feedings were not well tolerated and did not improve mortality, so consideration of EN should probably be reserved for patients with more severe levels of malnutrition with poor intakes not responsive to oral supplementation.

Chronic Obstructive Pulmonary Disease Prevalence estimates of malnutrition in patients with COPD range from 20% to 70%. Causes are likely multifactorial and include increased inflammatory activity, higher metabolic rate due to work of breathing and diminished intake due to dyspnea, chronic sputum (can alter taste), flattened diaphragm (may contribute to early satiety), and medication side effects (eg, adverse GI effects). Although one meta-analysis concluded that energy supplementation does not have significant clinical effects in patients with *stable* COPD, another review indicated that 10 of 12 randomized controlled trials have noted positive effects of nutritional support (mostly oral supplements providing 400–1000 kcal/day) on anthropometric, immune, muscular strength, and respiratory function outcome measures. Given the relative low cost and potential for benefit, nutritional support should be considered for all patients with COPD and evidence of PEM.

Nursing Home Care Setting Very high prevalence rates of PEM and weight loss have been documented in nursing home settings. Because conditions associated with reduced intake are common in nursing home residents (eg, dental, chewing, swallowing problems, depression, cognitive impairment, and dependence on others for feeding), it is likely that the proportion of patients with PEM caused by reduced intake (without inflammatory/cachexia states) is higher than among hospitalized patients. In this setting, simple interventions such as fortified foods, high-calorie snacks, nutritional supplements, and assisted feeding can improve nutritional parameters and help to stabilize weight. Although it is not clear that improvements in nutritional parameters translate to improved clinical outcomes, such interventions may enhance quality of life and are likely reasonable and appropriate for most nursing home residents.

Dementia Use of tube feeds in patients with advanced dementia is not advised. Tube feeding patients with advanced dementia does not appear to improve nutritional status, decrease pressure sores or infections, reduce aspiration problems, or improve functional status or survival. Potential adverse effects of tube feeds in these patients include increased risk of aspiration, discomfort and complications from tube placement, agitation with increased use of physical and chemical restraints, worsening pressure ulcers from increased urine and fecal output, and diminished quality of life from decreased interaction at mealtime and loss of gustatory pleasure from food intake. The lack of demonstrable benefits, combined with considerable potential for harm, led the American Geriatrics Society to advise clinicians not to recommend percutaneous feeding tubes in patients with advanced dementia and instead to offer oral assisted feeding with food as the preferred nutrient.

Future directions An increased understanding of the physiologic mechanisms underlying appetite, inflammatory and other systemic responses to acute stressors, illness and aging, is leading to new approaches that may help to attenuate the adverse outcomes associated with undernutrition and cachexia. Such approaches are needed. Despite aggressive nutritional support, it is often difficult to lessen the catabolic effects that occur in response to illness or injury. Also, anthropometric measures indicate that when body weight does increase with nutritional support, gains are mostly in the form of fat and water, whereas greater increases in lean body mass might lead to better functional and overall clinical outcomes. Strategies under investigation to better prevent protein catabolism and/or promote anabolism include enriched delivery of certain nutrients (eg, glutamine, arginine) that may have positive immunomodulating action independent of their role as nutritional substrates; agents with anti-inflammatory effects (eg, omega-3 fatty acids, thalidomide); agents with anticytokine activity (eg, inhibitors of TNF-α production, antibodies to TNF-α or to IL-6); and anabolic agents with more favorable benefit-to-risk profiles (eg, SARMs, myostatin inhibitors). Other approaches to prevent or ameliorate weight loss and cachexia may focus on overcoming anorexia by modulating effects of peptides and hormones involved in appetite and energy regulation such as ghrelin, neuropeptide Y, and leptin. Although promising, such strategies to increase appetite, anabolism, and/or decrease catabolism require further study to better define their efficacy and safety in various disease states before they can be considered for clinical use.

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Chapter 36

Disorders of Swallowing

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Learning Objectives

- To understand the anatomy and physiology of the normal swallowing process.
- To distinguish between *presby*phagia (healthy age-associated changes in swallowing) and *dys*phagia.
- To identify age-related diseases and conditions most commonly associated with the development of dysphagia.
- To describe screening and assessment techniques, instrumental and noninstrumental, for identifying and characterizing dysphagia.
- To summarize options available for treatment of dysphagia, including compensatory and rehabilitative approaches.

Key Clinical Points

1. **Changes in swallowing that occur with healthy aging, termed presbyphagia, combined with age-associated diseases and conditions place older adults at risk for the development of dysphagia.**
2. **Swallowing is a complex patterned response that involves coordination of 30 oral and pharyngeal muscle pairs across both the cranial and spinal nerve systems.**
3. **An interdisciplinary team approach to early identification and comprehensive assessment of dysphagia will allow for effective treatment through both compensatory and rehabilitative techniques.**

INTRODUCTION

Demographic changes related to aging necessitate that clinicians have the resources to address eating and swallowing difficulties present in older adults. The capacity to effectively and safely eat or swallow is one of the most basic human needs and also can be a great pleasure. Therefore the loss of this capacity can have far-reaching implications. Many would argue that swallowing is one of the cardinal behaviors needed to sustain life. The process of swallowing requires orchestration of a complex series of psychological, sensory, and motor behaviors that are both voluntary and involuntary. Dysphagia refers to difficulty swallowing that may include oropharyngeal or esophageal problems. More specifically, there may be difficulty in oral preparation for swallowing and/or moving material from the mouth to the esophagus and from the esophagus to the stomach.

Although age-related changes place older adults at risk for dysphagia, an older adult's swallow is not inherently impaired. *Presbyphagia* refers to characteristic changes in the mechanism of swallowing of otherwise healthy older adults. Clinicians need to be able to distinguish among *dysphagia*, presbyphagia, and other related diagnoses such as globus hystericus to avoid overdiagnosis and overtreatment of dysphagia. Older adults can be more vulnerable and, with additional stressors such as acute illness and certain medications, they can cross over from having a healthy older swallow (*presby*phagia) to experiencing *dys*phagia. This chapter reviews the normal swallowing process and presbyphagia, as a healthy aging evolution, dysphagia outcomes, multidisciplinary approaches to diagnosing and managing dysphagia, and rehabilitation strategies for dysphagia care.

IMPACT OF DYSPHAGIA

Dysphagia prevalence depends on the specific population sampled, with community-dwelling and more independent individuals having rates near 15%. Upward of 40% of people living in institutional settings such as assisted living and nursing homes are dysphagic. Given the projected increases in the geriatric population over the next several decades, the prevalence of dysphagia is expected to increase substantially. With a greater number of individuals in nursing homes, there is a compelling need to address dysphagia not only in ambulatory and acute care settings but also in long-term care settings.

The consequences of dysphagia vary from social isolation because of the embarrassment associated with choking or coughing at mealtime to physical discomfort (eg, food sticking in the chest) to potentially life-threatening conditions. The more ominous sequelae include dehydration, malnutrition, and both overt and silent aspiration precipitating pulmonary complications. For the purposes of this chapter, aspiration is defined as the entry of material into the airway *below* the level of the true vocal folds. Silent aspiration refers to the circumstance in which a bolus comprising saliva, food, liquid, medication, or any foreign material enters the airway below the vocal folds *without* triggering overt symptoms such as coughing or throat clearing. Both overt and silent aspiration occur more frequently in older adults and may lead to pneumonitis, pneumonia, exacerbation of chronic lung disease, or even asphyxiation and death.

Pneumonia is the fifth leading cause of infectious death in those aged 65 and older and the third leading cause of death in those aged 85 and older, with a financial impact exceeding $8 billion annually. A high proportion of hospital admissions related to aspiration pneumonia occurred in individuals over the age of 65. Dysphagia is an independent risk factor for the development of aspiration pneumonia. The reported prevalence of dysphagia in older patients hospitalized for pneumonia ranges from 55% to 86%. Dysphagia is also an independent risk factor for hospital readmission due to aspiration and nonaspiration pneumonia in patients 70 or older discharged from an acute geriatric unit. These patients had an 80% increased risk of being readmitted for pneumonia, a 40% increased risk for nonaspiration pneumonia, and a 400% increased risk for aspiration pneumonia. In light of an International Association of Gerontology report calling for improved recognition and treatment of malnutrition in older adults, it is important to note that dysphagia is an independent risk factor for malnutrition as well.

To gain a better understanding of the effect that these consequences have on older adults and the impact of dysphagia interventions, research in this area has aimed to develop more meaningful outcome measures. Assessments focused on pathophysiology, function, and health services are now being conducted to create more evidence-based practices in dysphagia care.

Insofar as dysphagia is a biomechanical disorder of bolus flow, signs of flow abnormality, using videofluoroscopy, have been well detailed. These include (1) the duration, direction, and completeness of bolus flow; (2) the duration and extent (range) of anatomic structural movements; and (3) the relationship between bolus flow and structural movements as well as between physiologic and anatomic parameters such as pressure generation and muscle/fat structure. Bulbar innervated swallowing mechanisms may provide targets specific for novel treatment paradigms aimed at improving swallowing function. Other clinical outcomes of dysphagia have become important end points in assessing interventions that aim to make it possible for patients to eat and drink adequately and safely. These include measures of hydration, nutrition, aspiration episodes, and emotional sequelae. Other measures target what and how dysphagic adults eat and drink. Most of these scales are directly applicable to older adults (**Table 36-1**). Additionally, pneumonitis, overt aspiration pneumonia, and other forms of pulmonary damage are monitored. Nonetheless, it has been difficult to attribute mortality directly to dysphagia because it is often a secondary rather than a primary diagnosis.

TABLE 36-1 ■ SUMMARY DESCRIPTIONS OF SELECTED TOOLS FOR ASSESSING EATING AND DRINKING FUNCTION

TOOL	COMPONENTS
American Speech Language Hearing Association Scale (1996)	1. Oral versus nonoral 2. Need for supervision 3. Need for special techniques 4. Need for extra time
Rehabilitation Institute of Chicago Clinical Evaluation of Dysphagia (Cherney et al., 1986)	1. Oral versus nonoral 2. Need for and type of supervision

	3. Need for special techniques 4. Type of diet 5. Episodes of choking
Amyotrophic Lateral Sclerosis Severity Scale (Hillel et al., 1989)	1. Oral versus nonoral 2. Type of diet 3. Time to eat 4. Patient symptoms 5. Choking
Dysphagia Disability Index (Silbergleit et al., in progress)	1. Emotional reactions 2. Time to eat 3. Need for compensations 4. Need for special food and liquid 5. Coughing 6. Choking 7. Other influences on behavior
Dysphagia Severity Rating Scale (Waxman et al., 1990)	1. Findings from videofluoroscopy 2. Oral versus nonoral 3. Time to eat 4. Consistency of food and liquid 5. Need for cueing and compensation
Functional Outcome Swallowing Scale (Salassa, 1997)	1. Findings from videofluoroscopy 2. Variety of medical consequences 3. Oral versus nonoral 4. Coughing, choking, and other symptoms
Functional Outcome Assessment of Swallowing (Wisconsin Speech and Hearing Association, 1996)	1. Percent oral and nonoral 2. Food/liquid consistency 3. Need for cueing 4. Need for strategies 5. Time to eat

Adapted from McHorney CA, Rosenbeck JC. Functional outcome assessment of adults with oropharyngeal dysphagia. Semin Speech Lang. 1998;19(3):235.

Dysphagia profoundly influences quality of life (QOL). Patients with swallowing difficulties, especially those who relinquish oral eating, manifest significant changes in psychosocial status, functional status, and emotional well-being. Eating and drinking are social events that relate to friendship, acceptance, entertainment, and communication. As such, major adjustments in the process of feeding and eating can lead to distressing responses such as shame, anxiety, depression, and isolation. Practical dysphagia-specific, comprehensive, QOL measures are now available. By monitoring functional outcomes in clinical practice, physicians and other health care providers may be able to better assess and adjust their treatment of dysphagia.

SWALLOWING PROCESS

Swallowing is an orchestrated activity that balances the competing behaviors of ingestion, speaking, and breathing. Approximately 30 oral and pharyngeal muscle pairs and multiple nerves must perform precisely on cue so that the upper aerodigestive tract is reconfigured from a mechanism that channels air for breathing and speaking (**Figure 36-1**) to a food-propelling mechanism that accomplishes ingestion (**Figure 36-2**). The four morphologic regions serving these purposes are the oral cavity, pharynx, larynx, and esophagus. Of these, the first three collectively are termed the upper aerodigestive tract because they also serve the airway-dependent functions of respiration and speech production.

In humans, with our upright posture, it is the adjacent position of the anatomy for breathing to the anatomy for food passage that facilitates gravitational influences on food to flow into an unprotected airway. Such anatomy and physiology require precision to satisfy the delicate balance between swallowing physiology and breathing—each a life-sustaining function that must occur during cessation of its counterpart. Thus, a basic understanding of the relationship between the anatomic components and the functional interaction of this mechanism is essential to an understanding of normal swallowing and the effects of age and age-related diseases on it.

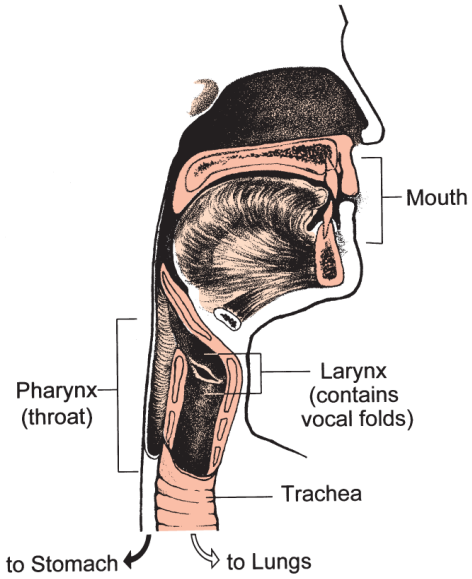


FIGURE 36-1. Aerodigestive tract channeling air for breathing from the nose and mouth through the open larynx into the lungs and back up and out. For speaking, air is channeled similarly, but the vocal folds vibrate to produce voice. (Adapted with permission from Weihofen D et al. *The Easy to Swallow, Easy to Chew Cookbook.* New York, NY: John Wiley and Sons; 2002.)

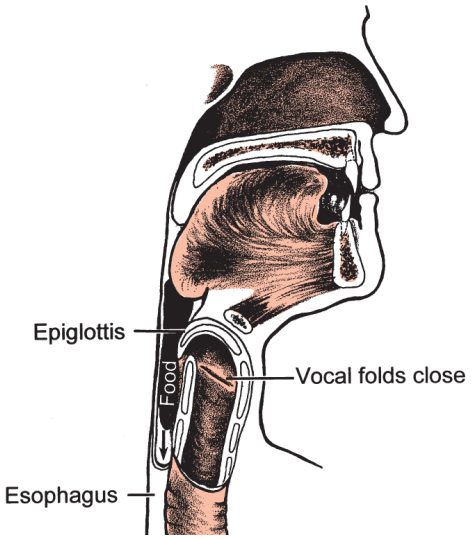


FIGURE 36-2. Aerodigestive tract reconfigured from an air channel to a food-propelling mechanism during swallowing. The tongue propels food into the throat; the epiglottis covers the larynx, which is the airway entrance; and the vocal folds close to protect the trachea and lungs from foreign material. (Adapted with permission from Weihofen D et al. *The Easy to Swallow, Easy to Chew Cookbook.* New York, NY: John Wiley and Sons; 2002.)

Normal Swallowing

Swallowing is an integrated neuromuscular process consisting of a combination of volitional and relatively automatic movements. Although normal swallowing is usually conceptualized as a continuous sequence of events, the process of deglutition has been conveniently described as occurring in two, three, or four phases or stages. Moreover, the system engaged in swallowing can be divided into two basic structural subsystems, horizontal and vertical (**Figure 36-3**), that

mirror the direction of bolus flow and the potential for gravitational influence on it.

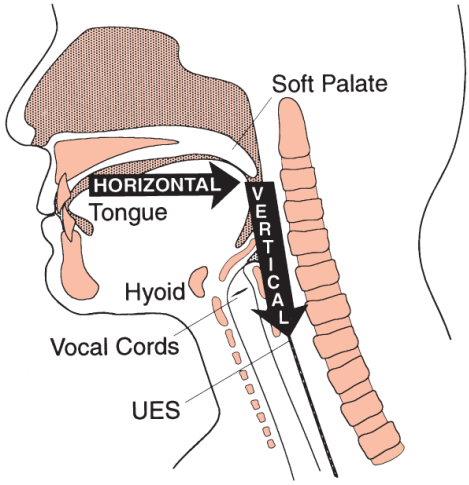


FIGURE 36-3. The oropharyngeal swallowing mechanism can be divided into two basic structural subsystems, horizontal and vertical, that mirror the direction of bolus flow. UES, upper esophageal sphincter. (Adapted with permission from Robbins J. Normal swallowing and aging. *Semin Neurol*. 1996;16(4):309–317.)

Horizontal subsystem The oral cavity components comprise the horizontal subsystem. As such, this subsystem is involved in the initial, largely volitional, processing, and transport phases of swallowing—the swallow preparatory phase and the oral transport phase. The swal low preparatory phase is characterized by food acceptance, containment, and manipulation. The lips and the buccal musculature act in complex patterns, varying the size and shape of the oral opening to allow acceptance and/or containment of food within the oral cavity. The process of chemically changing the material requires that numerous labial and lingual glands secrete into the oral cavity an enzyme-rich fluid that maintains and lubricates the mucosa and is directly incorporated into the food. Textural manipulation of food and the mechanical formation of a bolus once it is modified by saliva are accomplished largely by the tongue. The tongue positions the bolus between the teeth and moves in a complex three-dimensional chewing pattern if the bolus requires mastication. The moistening of the food in the oral cavity is essential for normal bolus transit and/or flow and clearance, particularly because gravity provides no assistance until the vertical phases of swallowing.

The oral transport phase comprises movement of the cohesive bolus (masticated if necessary) posteriorly (and horizontally when the subject is in a normal upright seated posture) to the inlet of the superior aspect of the vertical subsystem, the pharynx (**Figure 36-4**). The intrinsic tongue muscles change the shape of the tongue, forming grooves along its body and anterior and lateral seals to facilitate containment. The extrinsic tongue muscles change the position of the tongue within the oral cavity and assist in changing its shape (**Figure 36-4A**), and then progressively arching the tongue posteriorly to transport the bolus to the vertical subsystem (**Figures 36-4B and C**).

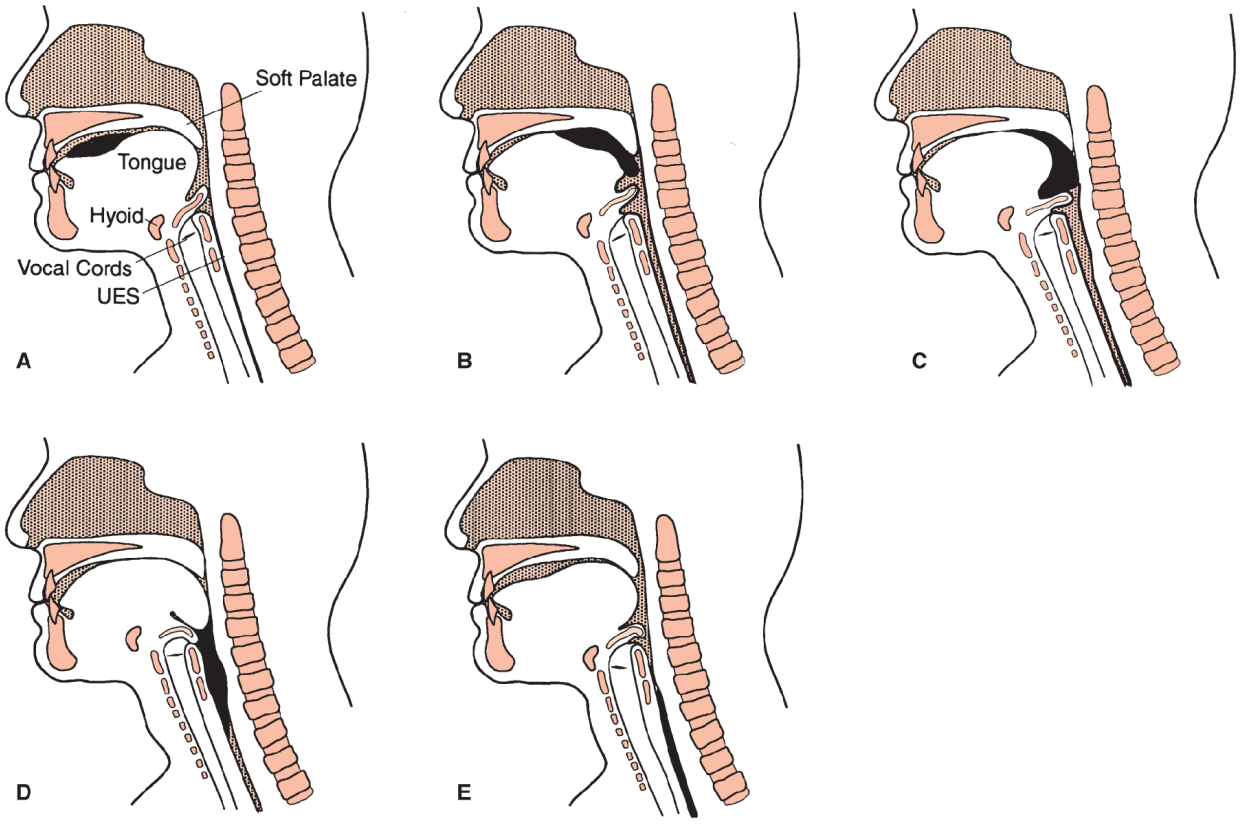


FIGURE 36-4. Lateral view of bolus propulsion during swallowing. **A.** Voluntary initiation of the swallow by tongue "loading." **B.** Bolus propulsion by tongue dorsum and upper esophageal sphincter (UES) opening anticipating bolus arrival. **C.** Bolus entry into pharynx associated with epiglottal downward tilt, hyolaryngeal excursion, and UES opening. **D.** Linguapharyngeal contact facilitating bolus passage through the pharynx. **E.** UES closing and completion of oropharyngeal swallowing; then the entire bolus is in the esophagus. (Adapted from Robbins J. Normal swallowing and aging. *Semin Neurol*. 1996;16(4):309–317.)

Vertical subsystem The pharyngeal and laryngeal components, in conjunction with the tongue dorsum, comprise the superior aspect of the vertical subsystem, where gravity begins to assist in the transport of the bolus. The anatomic juxtaposition of the entrance to the airway (laryngeal vestibule) and the pharyngeal aspect of the upper digestive tract demand biomechanical precision to ensure simultaneous airway protection and bolus transfer or propulsion through the pharynx. To this end, the pharyngeal transport phase is characterized by a sequence of rapid, highly coordinated neuromuscular events that cause pressure changes critical to bolus transport or transit in a safe, timely, efficient manner.

Linguapalatal contact sequentially moves the bolus against the posterior pharyngeal wall, contributing to the positive pressures imparted to the bolus and propelling it downward. Simultaneously, the pharyngeal constrictors begin to contract in a descending sequence, first elevating and widening the entire pharynx to engulf the bolus (**Figures 36-4D and E**), and clean up residue after swallowing is completed. A descending peristaltic wave then cleanses the pharynx of residue. Tight closure of the velopharynx during the pharyngeal transport phase provides a seal at the superior aspect of the vertical system, preventing nasal leakage of the bolus and contributing to the generation of high positive pressures, which are applied to the bolus.

Several mechanisms ensure the redundancy by which airway protection is accomplished. Three levels of sphincteric closure include (1) the aryepiglottic folds, (2) the false vocal folds, and (3) the true vocal folds, with closure of the true vocal folds (the lowest of the three sphincters) providing "the last line of defense" to prevent aspiration of invasive material. The hyolaryngeal complex is lifted upward and forward by the combined contraction of the suprahyoid muscles, thyrohyoid muscles, and pharyngeal elevators. This hyolaryngeal elevation and anterior movement, coupled with retraction of the tongue base, covers the laryngeal vestibule and diverts the bolus laterally around the airway. Timely relaxation and opening of the upper esophageal sphincter (UES) permits continuous vertical passage of the bolus into the esophagus. The UES functions as a mechanical valve. For it to open normally, four criteria must be met: (1) relaxation of muscle tone, (2) compliant tissue, (3) traction force provided by sufficient hyolaryngeal excursion, and (4) pulsion force imparted by the bolus. In normal swallowing, UES relaxation and opening occur prior to bolus arrival at the hypopharynx.

Neurophysiology of Oropharyngeal Swallowing

Historically, swallowing was largely viewed as a sequence of pharyngeal and esophageal events and was defined as reflexive. However, it is now clear that normal swallowing is a patterned response rather than a traditional reflex.

Sensorimotor control of swallowing requires the coordinated activity to be distributed across both the cranial and spinal nerve systems, including the peripheral nerves, their central nuclei, and their neural centers. More specifically, the neural control of swallowing involves five major components: (1) afferent sensory fibers contained in cranial nerves, (2) cerebral and midbrain fibers that synapse with the brainstem swallowing centers, (3) paired swallowing centers in the brain stem, (4) efferent motor fibers contained in cranial nerves and the ansa cervicalis, and (5) muscle and end organs. Indeed, this neural network spans all levels of the neuraxis from the cerebrum superiorly to the brain stem and spinal nerves inferiorly and muscles and end organs at the periphery. This relatively diffuse network is designed to integrate and sequence both the volitional and automatic actions of swallowing.

Healthy persons depend on a highly automated neuromuscular sensorimotor process that intricately coordinates the activities of chewing, swallowing, and airway protection. To accomplish a normal swallow, which occurs in 2 seconds or less, the muscles of chewing interact with 26 pairs of striated pharyngeal and laryngeal muscles. The muscles involved in chewing include the masseters, temporalis, and pterygoids (innervated by cranial nerve V); the lip and buccal musculature, the orbicularis oris, and the buccinator (innervated by cranial nerve VII); and the intrinsic and extrinsic lingual muscles (innervated by cranial nerve XII). Optimal structural integrity and precise neural mediation result in continuous, rapid bolus flow from the mouth to the esophagus (**Figures 36-5A, B, and C**) that accommodates variations in bolus size, texture, and temperature and the individual's intent to swallow, chew, or just hold the bolus in the mouth.

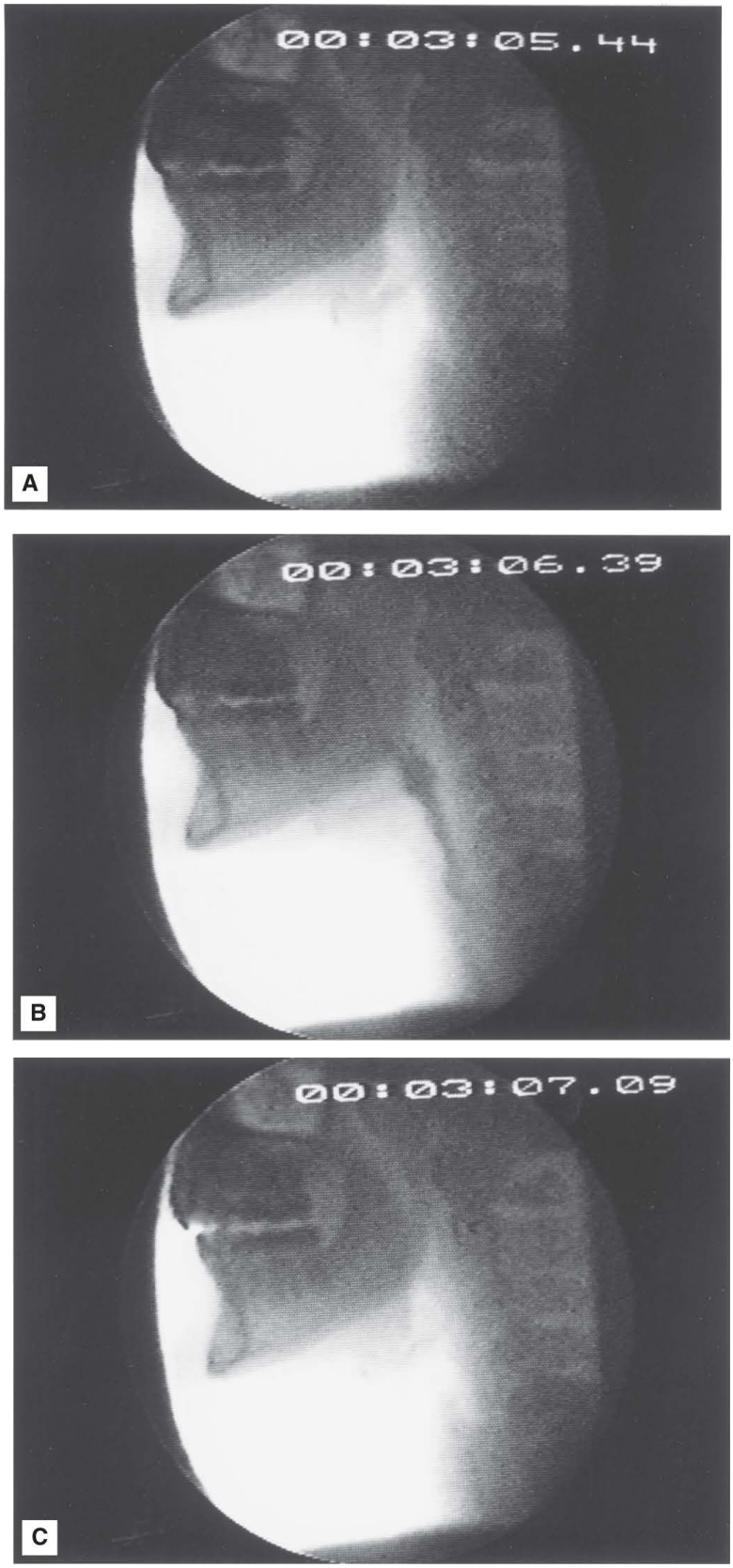


FIGURE 36-5. Healthy young swallowing documented with videofluoroscopy. **A.** Bolus in oral cavity, ready to be swallowed. **B.** Bolus appears as a "column" of material swiftly moving through the pharynx. **C.** Oropharynx cleared of material when the swallow is completed. (Adapted with permission from Robbins J. Normal swallowing and aging. *Semin Neurol*. 1996;16(4):309–317.)

Complex underlying neural substrates can explain how willful control during the early stage of swallowing allows access to the patterned response. Behavioral and sensory interventions attempting to modify a response have considerably more treatment potential than if they are aimed at a reflex. Accessing mechanisms of neural plasticity, defined as the ability of the brain to change, is becoming a focus to elicit neuroprotection relative to aging effects or

recovery from dysphagia following injury such as stroke.

SENESCENT SWALLOWING

Traditional thinking suggests that the causes of dysphagia are always disease related, with direct or indirect damage to effector end-organ systems of swallowing. However, swallowing changes occur even with healthy aging. Progressive changes of the anatomy and physiology of the oropharyngeal swallowing mechanism put the older population at increased risk for dysphagia (**Figure 36-6**). These changes are particularly relevant when an older healthy adult with diminished functional reserve is faced with increased stressors such as central nervous system (CNS)-altering medications, mechanical perturbations (eg, a nasogastric [NG] tube or a tracheostomy), or chronic medical conditions (eg, frailty) that elicit dysphagia only in a vulnerable individual. Translation of this understanding into clinical practice will provide safeguards against the overdiagnosis and overtreatment of dysphagia in the older adult population.

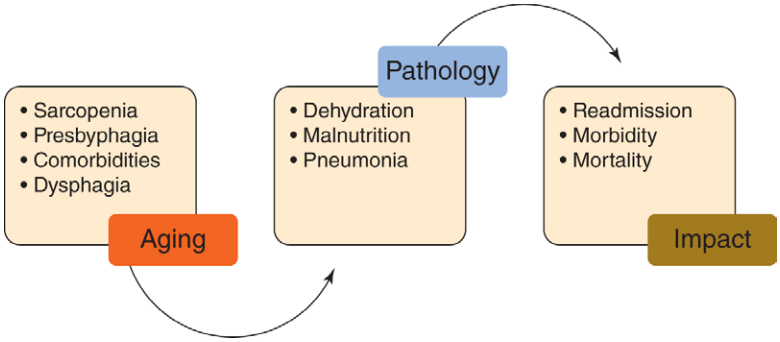


FIGURE 36-6. The onset of sarcopenia along with other factors leads to *presby*phagia, or age-associated changes in swallowing, in healthy older adults. When older adults experience comorbid age-related disease or conditions, such as stroke or dementia, they are at increased risk for the development of *dys*phagia. Dysphagia is associated with a variety of negative health outcomes, including dehydration, malnutrition, and pneumonia, that increase the risk for hospital readmissions, morbidity, and even death.

Age-Associated Changes in Swallowing

A major characteristic of older healthy swallowing is that it occurs more slowly. In people older than 65 years, the initiation of laryngeal and pharyngeal events, including laryngeal vestibule closure, maximal hyolaryngeal excursion, and upper UES opening, takes longer than in adults younger than 45 years. Although the specific neural underpinning has not been confirmed, oral events may become uncoupled from the pharyngeal response. Thus, in older healthy adults, the bolus may remain adjacent to an open airway by pooling or pocketing in the pharyngeal recesses longer than in younger adults (**Figure 36-7**).

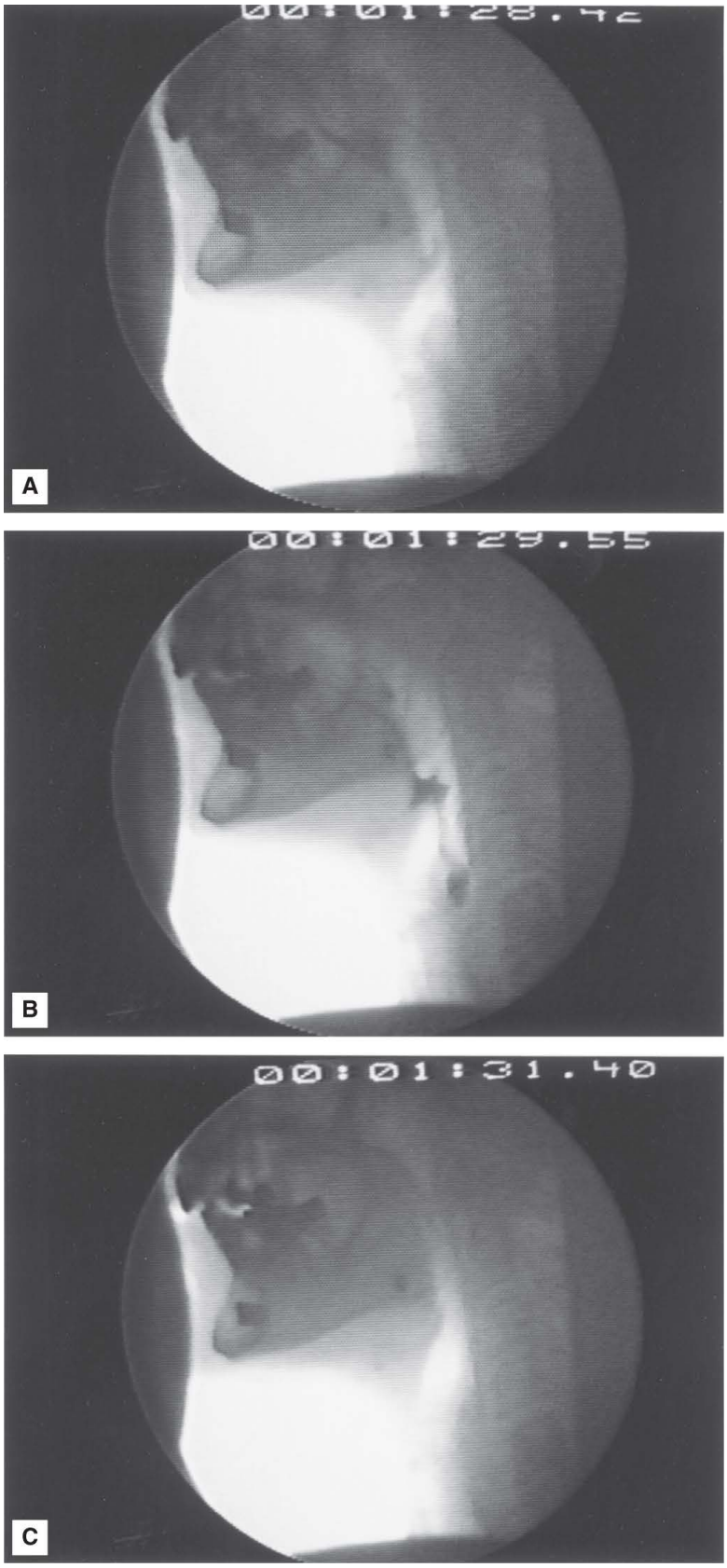


FIGURE 36-7. Healthy old swallowing documented with videofluoroscopy. **A.** Bolus in mouth ready for swallowing. **B.** Bolus pooled in vallecula and pyriform sinus during delayed onset of pharyngeal response. **C.** Bolus cleared of material when the swallow is completed. (Adapted with permission from Robbins J. Normal swallowing and aging. *Semin Neurol*. 1996;16(4):309–317.)

Aspiration and airway penetration are believed to be the most significant adverse clinical outcomes of misdirected bolus flow, as reflected in the high rates of pneumonia with increasing age and disease. However, airway invasion in healthy adults is commonly believed to be largely absent. The use of an eight-point scale (**Table 36-2**) that discretely

quantifies the occurrence, the depth, and the person's reaction to airway penetration or aspiration found no difference between young (21- to 32-year-olds) and old (63- to 84-year-olds) age groups in scale scores on three repeat swallows. However, when a greater number of swallows were performed, aspiration did occur in the older group, indicating fatigue or change in endurance as a possible factor that may relate in a very practical sense to eating meals.

TABLE 36-2 ■ MULTIDIMENSIONAL DEPTH OF AIRWAY INVASION AND RESIDUE, SINGLE-DIGIT SCORING SYSTEM FOR THE PENETRATION-ASPIRATION SCALE

CATEGORY	SCORE	DESCRIPTION
No penetration or aspiration		
PENETRATION	1	Contrast does not enter the airway
	2	Contrast enters the airway, remains above vocal folds, no residue
	3	Contrast remains above vocal folds, visible residue remains
	4	Contrast contacts vocal folds, no residue
	5	Contrast contacts vocal folds, visible residue remains
ASPIRATION	6	Contrast passes glottis, no subglottic residue visible
	7	Contrast passes glottis, visible subglottic residue despite patient's response
	8	Contrast passes glottis, visible subglottic residue, absent patient response

From *Robbins JA, Coyle JC, Roecker EB, Rosenbek JC, Woody GL. Differentiation of normal and abnormal airway protection during swallowing using the penetration aspiration scale. Dysphagia. 1999;14(4):228–232.*

Using simultaneous videofluoroscopy and manometry (manofluoroscopy) and a tube through the nasopharynx similar in size to a "garden variety" NG tube, an interaction was found for tube by age. That is, liquid penetrated the airway more frequently when the tube was in place only in the *oldest* group of men and women (older than 70 years). Thus, it appears that under demanding conditions (eg, endurance = demanding, or NG tube placement), older individuals are less able to compensate and are more at risk for aspiration. Findings such as these differentiate presbyphagia, from clinically abnormal swallowing.

Age-related changes in the generation of lingual pressure also define presbyphagia. Healthy older individuals have reduced isometric tongue pressures compared with younger individuals. In contrast, the generation of maximal lingual pressure during swallowing (which requires submaximal pressures) remains "young" in magnitude but slows in the time necessary to achieve those "young" swallowing pressures. The relationship between maximum isometric pressure and peak swallowing pressures can be considered an indication of the functional reserve available for swallowing. As people get older, slower swallowing may allow time to recruit the necessary number of motor units required for pressures critical for adequate bolus propulsion through the oropharynx. However, fluids of low viscosity (eg, water, tea), by their composition, are likely to move more quickly than the physiology to handle them safely and thus put older people at increased risk for aspiration.

Neurophysiologic Correlates of Senescent Swallowing

Neuroimaging studies using cranial magnetic resonance imaging (MRI) in normal adults have shown a relationship between slower swallowing and an increase in the number and severity of periventricular white-matter hyperintensities (PVHs) in the brain, supporting the concept that voluntary control of swallowing is mediated by corticobulbar pathways traveling within the periventricular white matter. The occurrence and degree of PVHs increase with age and may explain, at least in part, the relatively asymptomatic decline in oropharyngeal motor performance observed in older people. Cerebral atrophy, a common finding in asymptomatic older individuals, may be another contributing factor to presbyphagia.

Changes in the periphery also occur with age and may be a function of changes in various sensory mechanisms or caused by muscle atrophy. Similar to the age-related loss of limb skeletal muscle, there are changes with age in fiber density, muscle tension, muscle strength, and muscle contraction in facial, masticatory, and lingual musculature. Rather than reflecting CNS deterioration, slowed swallowing that remains coordinated and effective, as found in most healthy old people, may represent a compensatory strategy for achieving pressure-generation values that may be critical to successful bolus propulsion.

DIFFERENTIAL CONSIDERATIONS FOR DYSPHAGIA AND ASPIRATION

Etiologies

Older adults are at increased risk for developing dysphagia because of a number of age-associated phenomena. Several factors and comorbid processes increase the chances that older adults will suffer the adverse consequences of dysphagia: dehydration, malnutrition, and aspiration pneumonia. By targeting high-risk groups and intervening with acceptable compensatory and rehabilitative approaches, it is hoped that the ultimate burden of dysphagia on the geriatric population will decline.

A decreased physiologic reserve can combine with a number of age-related, disease-related, or iatrogenic changes to transform an at-risk individual into an older adult with dysphagia. The concept of homeostenosis, or decreased physiologic reserve, is being recognized as a crucial covariable with dysphagia. Frailty or sarcopenia may be outward manifestations of this poor reserve. Sarcopenia in the limb musculature is described in detail in Chapter 46, and is now known to affect the head and neck musculature involved in swallowing. In fact, anterior and posterior isometric tongue pressure positively correlates with hand grip strength. Anterior tongue pressures also correlate positively with jump height and power (as measured with jumping mechanography). Furthermore, the presence of sarcopenia (diagnosed using the Asian Working Group for Sarcopenia criteria) was found to be an independent predictor of dysphagia in a group of older adults.

Several anatomic or pathologic perturbations occurring throughout the orobuccal cavity, the laryngopharyngeal region, and the esophagus are also important cofactors in the onset of dysphagia. Additionally, age-related alterations in the neural coupling between respiration and swallowing result in more frequent occurrences of swallowing during the inspiratory phase in older adults. When the inspiratory phase is interrupted for swallowing rather than the expiratory phase, there is an increased risk for entry of material into the airway once inhalation is resumed.

Age-related conditions Age-related changes throughout the upper aerodigestive tract can influence swallowing integrity. Oral risks are also discussed in Chapter 37. During the oral phase, the food bolus may be inadequately prepared because of poor or absent dentition, periodontal disease, ill-fitting dentures, or inappropriate salivation caused by xerostomia. Salivary flow rate declines with advancing age and is exacerbated by xerostomia-inducing medications often prescribed to older adults. Certain organic components within whole saliva, including secretory immunoglobulin A and mucoglycoproteins, also are reduced in older adults thereby altering the compositional makeup of saliva and affecting oral health. This decline in mucous properties can change the viscoelastic properties of saliva that may be important for bolus formation.

Musculoskeletal factors such as weakness of the muscles of mastication, arthritis of the temporomandibular joint or larynx, osteoporosis of the jaw, or changes in tongue strength and coordination of the oropharyngeal events can deter efficient swallowing. Sensory input for taste, temperature, and tactile sensation changes in many older adults. This disruption of sensory-cortical-motor feedback loops may interfere with proper bolus formation and timely response of the swallowing motoric sequence and detract from the pleasure of eating. Controversy exists regarding the predictive value of an absent gag reflex for aspiration, although many clinicians still use this criterion to screen for altered

pharyngeal sensation. In one study 43% of healthy older people and 27% of healthy younger people had an absent gag while all but one had intact pharyngeal sensation.

Material can penetrate into the upper airway in normal individuals if the bolus is not properly prepared, if the timing of the swallow is delayed, or if the intake is too rapid. Important risk factors for aspiration include altered level of attention during feeding (eg, delirium), altered sensory discrimination in the oropharynx, feeding problems, mechanical ventilation, and feeding tube placement. In the latter circumstance, the rate of tube feeding, the position of the patient, altered intestinal transit times, and the ability of the patient to protect their airway all influence the occurrence of reflux and aspiration and are discussed in detail in Chapter 35. There are subtle changes in lower esophageal sphincter (LES) function even in asymptomatic older individuals. Gastroesophageal reflux caused by LES incompetence as well as intraesophageal reflux (defined as material moving proximally within the esophagus prior to crossing the LES) also predisposes individuals to micro- or macroaspiration.

Age-related disease Neurologic and neuromuscular disorders are principal risks for dysphagia (**Table 36-3**). Neurologic diseases rise in prevalence in older cohorts of the population. Stroke, brain injury, Alzheimer disease, other dementia syndromes, and Parkinsonism all place older adults at increased risk for dysphagia with its incipient consequences.

TABLE 36-3 NEUROLOGIC DISORDERS CAUSING DYSPHAGIA

Stroke
Head trauma
Parkinsonism and other movement and neurodegenerative disorders
Progressive supranuclear palsy
Olivopontocerebellar atrophy
Huntington disease
Wilson disease
Torticollis
Tardive dyskinesia
Alzheimer disease and other dementias
Motor neuron disease (amyotrophic lateral sclerosis)
Guillain-Barré syndrome and other polyneuropathies
Neoplasms and other structural disorders
Primary brain tumors
Intrinsic and extrinsic brainstem tumors
Base of skull tumors
Syringobulbia
Arnold-Chiari malformation
Neoplastic meningitis
Multiple sclerosis
Postpolio myelitis syndrome
Infectious disorders
Chronic infectious meningitis
Syphilis and Lyme disease
Diphtheria
Botulism
Viral encephalitis, including rabies
Myasthenia gravis

Myopathy
Polymyositis, dermatomyositis, inclusion body myositis, and sarcoidosis
Myotonic and oculopharyngeal muscular dystrophy
Hyper- and hypothyroidism
Cushing syndrome
Iatrogenic conditions
Medication side effects
Postsurgical neurogenic dysphagia
Neck surgery
Posterior fossa surgery
Irradiation of the head and neck

Because cognitive function and/or communication may be impaired, it is important for the practitioner to note the warning signs associated with dysphagia and risk of aspiration (**Table 36-4**). The entire eating process, which includes self-feeding (transferring food from the table to the mouth) in addition to swallowing, is affected in patients with dementia. The inability to eat safely is one of the most life-threatening impairments for these patients, with approximately 50% of those with Alzheimer disease losing the ability to feed themselves within 8 years following their diagnosis. Between 50% and 75% of patients who have had a recent acute stroke develop eating and swallowing problems, with ensuing complications of aspiration developing in 50%, malnutrition in 45%, and pneumonia in 35%. Other delayed adverse consequences have also been reported, with up to 15% of patients who have suffered a cerebrovascular accident (CVA) developing pneumonia within 1 year of the acute insult. Brainstem or bilateral hemispheric strokes predictably produce dysphagia, but unilateral lesions also can contribute to dysphagia. Six clinical features associated with an increased risk for aspiration poststroke include (1) an abnormal volitional cough, (2) an abnormal gag reflex, (3) dysarthria, (4) dysphonia, (5) a cough following a trial swallow, and (6) a voice change following a trial swallow. The presence of any two of these findings had a sensitivity of 92% and a specificity of 67% in predicting penetration and aspiration of material by videofluoroscopy.

TABLE 36-4 WARNING SIGNS ASSOCIATED WITH DYSPHAGIA AND ASPIRATION RISK

Decreased alertness or cognitive dysfunction
Stupor, coma, heavy sedation, delirium, “sundowning,” dementia, agitation
Playing with food, inappropriate size of bites, talking or emotional lability during attempts to swallow
Changes in approach to food
Avoidance of eating in company
Increase in amount of food remaining on plate
Special physical preparation of food or avoidance of foods of specific consistency
Prolonged mealtime, intermittent cessation of intake, frequent “wash downs”
Compensatory measures (head and neck movements)
Laborious chewing, repetitive swallowing
Coughing and choking on swallowing, increased need to clear throat
Manifestations of impaired oropharyngeal functions
Dysarthria
Wet, hoarse voice and other voice changes
Dysfunction of focal musculature (facial asymmetries, abnormal reflexes or dystonia, dyskinesias or fasciculations)
Drooling or oral spillage, pooling and pocketing of food
Frequent throat clearing
Patient complaints or observations of
Difficulty initiating a swallow

Sensation of obstruction of bolus in the throat or chest
Regurgitation of food or acid
Inability to handle secretions
Unexplained weight loss
Impaired breathing during meals or immediately after eating
Pain on swallowing
Leakage of food or saliva from a tracheostomy site

A host of common problems involving the head and neck can directly damage the effector muscles of swallowing and increase the risk for dysphagia. Head and neck injury, carcinoma, complex infections, thyroid conditions, and diabetes are associated with age-related dysphagia. Although vertebral osteophytes are common, these bony growths alone rarely cause dysphagia. Dysphagia more commonly results from the presence of osteophytes in conjunction with neuromuscular weakness or discoordination. This can be caused by combinations of several underlying conditions or comorbidities such as diabetes, chronic obstructive pulmonary disease, congestive heart failure, renal failure, an immunocompromised status, and/or cachexia for which an individual no longer can draw an adequate reserve to effectively compensate.

Sometimes dysphagia can be a direct consequence of a treatment provided for another disease process. Health care interventions can result in drug-induced delirium, protracted hospital stays, and ultimately malnutrition. Indwelling NG tubes, airway intubation, and medication effects may all predispose a frail older adult with borderline airway protection to develop frank aspiration. Understanding the iatrogenic causes of dysphagia can alter medical practice and may reduce its incidence and complications.

Older adults are much more likely to be taking medications for multiple medical conditions. These medications can influence salivary flow, intestinal peristalsis, cognition, or psychomotor status, thereby interfering with normal oropharyngoesophageal function or altering airway protection. More than 2000 drugs can cause xerostomia or reduced salivary flow via anticholinergic mechanisms. The list is extensive and can include common antidepressants, antihistamines, antipsychotics, and antihypertensive agents. Likewise, a number of delirium-promoting therapies exist and similarly produce adverse consequences through either anticholinergic or other central mind-altering effects. Certain agents can directly relax the LES and increase acid reflux and esophageal problems. Finally several psychotropic drugs can produce delayed neuromuscular responses or extrapyramidal effects, thereby influencing the tongue and bulbar musculature. **Table 36-5** provides a partial list of these agents and how they can contribute to dysphagia.

TABLE 36-5 MECHANISMS BY WHICH COMMON MEDICATIONS CONTRIBUTE TO DYSPHAGIA

Xerostomia
Anticholinergic effects
Tricyclic antidepressants
Antipsychotic agents
Antihistamine drugs
Antispasmodic drugs
Antiparkinsonism drugs
Antimetic drugs
Other mechanisms
Antihypertensives (eg, diuretics, calcium channel blockers)
Reduction in esophageal and/or laryngeal peristalsis
Antihypertensive drugs (eg, dihydropyridine calcium channel blockers)
Antianginal drugs (eg, nitrates)
Delayed neuromuscular responses
Drugs that promote delirium (eg, anticholinergic agents, opiates, benzodiazepines)

Drugs that have extrapyramidal side effects (eg, antipsychotic drugs)
Esophageal injury and/or inflammation
Drugs that relax the lower esophageal sphincter (eg, calcium channel blockers, nitrates)
Large pills that have incomplete esophageal transit

An altered level of attention and cognition may also produce special concerns with regard to safe eating and swallowing. Those who are not oriented to person, place, or time are at 31% increased risk for liquid aspiration. The inability to follow single-step verbal commands raises the risk for liquid and puree aspiration by 57% and 48%, respectively. As described in Chapter 47, delirium is frequently underrecognized and undertreated in both hospital and institutional settings. In general, testing an inattentive adult for dysphagia results in the poorest evaluation. If swallowing is assessed during one of these episodes, aspiration is likely to occur. If a staff member at a hospital or nursing home feeds a patient during one of these intervals, the outcome may be disastrous.

Several different treatments can either directly or indirectly damage swallowing effector organs as described previously. Head and neck cancer surgeries, some spinal cord surgeries, thyroid surgeries, and any intervention that can jeopardize the recurrent laryngeal nerve may result in dysphagia. A number of chemotherapy and radiotherapy regimes can cause oropharyngeal injury. The prospective outcome of dysphagia should be incorporated into the risk-benefit discussions of these procedures.

Symptoms

Medical history plays a critical role in establishing a diagnosis of dysphagia (**Table 36-6**). A detailed history can elucidate the proper diagnosis in some dysphagic adults and is an important first step in the evaluation process. Recognizing the classic complaints associated with dysphagia and differentiating them from symptoms of common age-related diseases can be challenging. Nevertheless, a careful history may avert increased testing and potential iatrogenic complications in frail older patients. Dysphagia may also present in a more subtle fashion, without symptoms, but with recurring exacerbations of an underlying disease such as chronic obstructive pulmonary disease.

TABLE 36-6 HISTORICAL DATA USED FOR CLINICAL DIAGNOSIS OF DYSPHAGIA

Site or timing of impairment
Oral (problems with chewing, bolus gathering, initiation of swallow)
Pharyngeal (problem immediately on swallowing, choking after a long delay, suggestive of passage of residue from the pharynx into the larynx)
Esophageal (seconds after swallow, behind chest bone)
Onset, frequency, and progression
Duration, sudden onset related to a specific event (stroke, pill impaction, etc), or gradual
Frequency (constant, intermittent)
Progression and severity (including more and more foods and impairing nutrition and hydration)
Aggravating factors and compensatory mechanisms
Food consistency (solids and/or liquids)
Temperature
Usefulness of sucking, turning, and tilting of head, and so on
Intermittent, constant, or fatiguing symptoms
Associated symptoms
Change in speech or voice
Weakness; lack of control of musculature, particularly of the head and neck
Choking or coughing
Repetitive swallows or increased need to clear the throat
Regurgitation (pharyngeal and nasal, or esophageal and gastric; immediately on swallow, or long delay, undigested food, putrefied or secretions?)

Fullness/tightness in the throat (globus sensation)
Pain, localized or radiating
Odynophagia (pain on passage of bolus)
Ancillary symptoms and evidence of complications
Loss of weight or loss of energy (including from dehydration)
Change in appetite; attitude toward food, toward eating in company; preparation of foods
Respiratory problems (cough, increased sputum production, shortness of breath, pneumonias and other respiratory infections)
Sleep disturbances (secondary to secretion management or regurgitation)
Changes in salivation (water brash or dry mouth)

Patients may initially complain of difficulty swallowing liquids, solid food, or pills. Caregivers or nursing personnel may note such difficulties experienced by the patient including "pocketing" of pills within the oral cavity. The patient may report more effort needed while eating. The patient or the patient's observant family members may complain of the increased time needed to complete a meal. The patient or the practitioner may identify weight loss without any other localizing explanation. However, clinicians must distinguish these dysphagia or aspiration symptoms from a myriad of other common health problems that may mimic dysphagia in older adults. For example, in frail individuals, depression or early parkinsonism may be manifested solely by weight loss and slowed eating. Without a complete history, these patients may be sent for a dysphagia work-up before an attempt is made to manage their "root problem."

Symptoms of esophageal dysphagia include food "hanging up" behind the sternum, neck pain, chest pain, and heartburn. This issue is also addressed in Chapter 93, which includes a discussion of esophageal disorders. A specific problem with solid food dysphagia suggests a mechanical obstruction. If the symptoms are intermittent, a lower esophageal ring may be present. If the symptoms are progressive, a peptic stricture or carcinoma is more likely. If there are difficulties in ingesting solids and liquids, a neuromuscular or dysmotility etiology must be considered.

SCREENING ACROSS A CONTINUUM OF CARE SETTINGS

Dysphagia evaluation varies depending on the clinical setting. The comprehensive diagnostic approaches available for hospitalized older patients with dysphagia may not be logistically feasible for bedbound nursing home residents. Likewise, interdisciplinary dysphagia teams are frequently available in academic settings or in larger hospital systems and less common in other settings. When such a team is not available, the responsibility for screening for swallowing problems falls on the primary provider or the hospital staff. Speech language pathologists, who are usually the swallowing therapists, are well trained to conduct bedside (also referred to as noninstrumental) examinations that include history-taking, oral motor assessment, voice evaluation, and assessment of trial swallows. Prior to this referral though, clinicians can provide a focused secondary screening during their encounter with the patient. A number of attempts have been made to identify a simple screening tool for use in ambulatory clinics or at the patient's bedside. A systematic review focused on dysphagia screening techniques for inpatients 65 years or older without stroke or Parkinson disease concluded that existing evidence is not sufficient to recommend the use of bedside tests in a general older population. While none of these approaches has proven altogether effective, certain approaches warrant mention.

A 3-oz water swallow test can be performed at the bedside. The clinician auscultates over the patient's trachea before and after the water is swallowed. Overt coughing, choking, or a change in the character of breath sounds suggests aspiration. The Toronto Bedside Swallowing Screening Test (TOR-BSST) has high sensitivity and a high negative predictive value for detection of dysphagia in patients poststroke. It includes the 3-oz water swallow test as well as assessment of voice quality before and after the swallow and evaluation of tongue movement. However, along with the risk of false negatives, bedside screening provides no information about the underlying pathophysiology of the swallow or for selecting specific interventions.

Despite these issues, owing to the high prevalence of swallowing difficulties in geriatric patients, some mechanism of primary screening needs to take place within a primary care clinic setting. An example of a dysphagia screening form is provided in **Table 36-7**. Because swallowing is not something a patient usually mentions, it may be necessary to ask related questions until a particular word or phrase triggers an association with the patient's experience (eg, swallowing, chewing, moving food to the throat, coughing, choking).

TABLE 36-7 ■ DYSPHAGIA SCREENING FORM–UNIVERSITY OF WISCONSIN AND MADISON GRECC

Patient Name: _____

Medical record # _____ or Social Security # _____

Primary Diagnosis: _____

1. Do you have difficulty swallowing? Yes No Chewing? Yes No
2. Do you have difficulty moving food/liquid out of your mouth into your throat to swallow? Yes No
3. Does food/liquid remain in your mouth after you finish swallowing? Yes No
4. Do you cough or choke when drinking or eating? Yes No

   If so, how often does this occur:
   - Infrequently
   - Once a day
   - 1 or more times per meal

5. Does food/liquid feel like it remains in your throat after you finish swallowing? Yes No
6. Does food/liquid feel like it stays in your chest (esophagus) after you finish swallowing or eating a meal? Yes No
7. Do you bring back up food or liquid after you've swallowed it? Yes No
   If so, how many minutes or hours after swallowing does it come back up?
8. Do you have any pain when swallowing? Yes No If so, where?
9. Is your mouth dry? Yes No
10. Any difficulty swallowing your saliva? Yes No
11. Have you noticed any drooling? Yes No Wet pillow in the morning? Yes No
12. Is it taking longer to eat a meal? Yes No
13. Do you eat everything you want to eat? Yes No
14. What have you stopped eating because of difficulty?
15. What type of foods are easiest for you to swallow:
    A. All kinds of foods
    B. Soft solids (eg, pasta, soft vegetables)
    C. Pureed
    D. Liquids
16. Are you hungry? Yes No
17. Current weight: _____
    Occurrence of weight loss over past 3 months: Yes No
    If so, please specify amount: _____
18. Are you congested in your chest, throat, or nose? Yes No
    How often do you have a head cold or chest cold?

Many forms of comprehensive geriatric assessment now include nutritional screening, which can be used as a surrogate screening for dysphagia. Some geriatric clinics now incorporate questions about difficulties with eating or swallowing that are included in periodic screening questionnaires. The simple question, "Do you have difficulty swallowing food?" was reported to have 100% sensitivity and 75% specificity in detecting swallowing difficulties in patients with parkinsonism. Alternatively, a practitioner's recognition of the relationship among symptoms of weight loss, cough or respiratory decompensation, and dysphagia may serve as a start in addressing this common problem. Nonetheless, once dysphagia is suspected, a more complete assessment is necessary not only to validate its presence

but also to define and construct a treatment plan that modifies the underlying sensorimotor pathophysiology.

TEAM APPROACH TO DYSPHAGIA

Interdisciplinary health care teams play a vital role in the care of complex older adults with dysphagia. This cross-disciplinary focus helps to address not only the medical but also the functional and psychosocial consequences of this problem. The team approach offers the stated advantage of a more efficient comprehensive assessment with shared responsibility for interventions and often makes timely consultation possible. The responsibilities of team members are often divided among disciplines and can include reviewing health issues, obtaining pertinent swallowing history, and an examination (which may include instrumental studies), providing education and counseling to the patient and to the family or the care provider, conducting psychosocial screening, and reviewing advance directives. Teams can be either formal or informal in composition. Core teams frequently include a speech language pathologist, a dietitian, and either a physician or a nurse practitioner.

Focused Assessment of Swallowing

A major function of the swallowing team is to perform a thorough assessment of the swallowing mechanism and its function. Most commonly, the speech language pathologist plays a major role, performing a two-part examination consisting first of a clinical (bedside) noninstrumental evaluation often followed by an instrumental assessment of swallowing. A brief description of both methods follows.

Noninstrumental Swallowing Assessment

The clinical evaluation is noninstrumental and although often referred to as a "bedside" procedure can be performed in a variety of environmental settings including an outpatient office. It usually involves four types of assessment: (1) history-taking; (2) speech and voice assessment; (3) oral motor assessment; and (4) performance on trial swallows. The specific methods and measures preferred and most frequently used by clinicians when working with dysphagia of neurogenic origin, which is frequently the case in older patients, are shown in **Table 36-8**.

TABLE 36-8 CLINICAL AND BEDSIDE SWALLOWING METHODS AND MEASURES

History	**Oral motor**
Patient report of problem	Tongue strength/range of motion
Family report of problem	Lip seal/pucker
History of pneumonia	Jaw strength/lateralization
Type of neurologic insult	Soft palate movement/symmetry
Nutritional status	Dysarthria
Gastrointestinal anomaly	Speech intelligibility
Structural abnormality	Oral apraxia
Previous surgery	Volitional cough
Other disease	Ability to follow directions
Medications	Management of secretions
Voice	**Trial swallows**
Breathiness	*Bolus type:*
Harshness	Thin liquid
Wet/gurgly	Thick liquid
Strained/strangled	Puree
Overall dysphonia/aphonia	Solid
Resonance	*Swallowing-related events:*
	Oral transit estimate
	Estimate swallow duration

	Laryngeal elevation
	Voice quality after swallow
	Ability to feed self
	Swallows per bolus
	Spontaneous cough
	Estimate of penetration/aspiration
	Estimate of oral stasis
	Observation of meal

Adapted from McCullough GH, Wertz RT, Rosenbek JC, Dinneen C. Clinicians' preferences and practices in conducting clinical/bedside and videofluoroscopic swallowing examination in an adult/neurogenic population. Am J Speech Lang Pathol. 1999;8(2):149.

Although a noninstrumental assessment provides a breadth of information, it can only increase the suspicion of aspiration through findings such as increased secretions or a wet and/or gurgly voice quality. Given the possibility of silent aspiration as a result of decreased cognition or diminished sensation in older people, coughing and throat clearing, which are the characteristic signs of aspiration, may be absent. To rule out aspiration with an acceptable level of confidence, an instrumental assessment is often necessary. Moreover, effective dysphagia intervention relies on an accurate diagnosis of the specific pathophysiology. That is, the underlying movement disorder that results in disordered bolus flow in terms of direction, duration, and clearance, must be defined and remediated in order to eliminate or minimize the dysphagia. Most frequently, instrumental methods are necessary to clarify the aspects of the swallowing sequence that must be modified to effect safe and efficient bolus flow. Although clinicians must pursue a complete oropharyngeal and esophageal assessment of many dysphagic patients, this section focuses on oropharyngeal dysphagia, and the reader is referred to Chapter 93 for a discussion of the esophagus.

Instrumental Examination

To obtain the most useful and valid representation of swallowing, an instrumental diagnostic test should do the following:

1. Depict soft tissues, air, fluid-filled cavities, and surrounding bone
2. Produce clear images of functional changes in multiple planes and real time
3. Allow viewing of the entire swallow
4. Be noninvasive and risk free
5. Detect and quantify aspiration
6. Allow objective and repeatable measurements
7. Estimate prognosis and treatment potential

A variety of imaging methods are available for studying the swallow, including ultrasound, MRI, computed tomography scanning, and scintigraphy. The two most commonly used techniques are described in the following sections.

Oropharyngeal videofluoroscopic swallowing evaluation An oropharyngeal videofluoroscopic swallowing evaluation is most commonly used to assess the integrity of the oropharyngeal anatomy, swallowing physiology, and bolus flow. Structural abnormalities and mucosal lesions are identified by the barium that is swallowed and used to outline the soft tissue structures it passes. In this manner, webs, pharyngeal diverticula, masses, and other soft tissue anomalies are revealed. Structural anomalies such as postsurgically modified anatomy, scar tissue, and osteophytes can be elucidated by radiographic means. Perhaps the two greatest strengths of the videofluoroscopic swallow evaluation are that the swallow is recorded in motion and preserved digitally or on videotape for replay.

This method permits viewing of the dynamic swallow. All oropharyngeal structures can be examined with regard to their contribution to the coordinated (or uncoordinated) swallow in terms of timing and range of motion. Their impact on bolus flow is made apparent. Therefore, the specific pathophysiology and its impact on bolus flow are clarified and can be targeted for treatment.

An oropharyngeal videofluoroscopic swallow study is not designed simply to determine if a patient is aspirating or

even why a patient is aspirating or retaining residue. It is designed also to assist a clinician in determining if a patient can safely receive oral nourishment and allows for trials of proposed interventions to maximize efficacy and safety. During the study, the clinician often varies bolus characteristics sufficiently to be able to offer a diet recommendation (such as thickened liquid or semisolid). Additional recommendations may be simple postural adjustments, such as tucking the chin, which are shown under fluoroscopy to improve direction or efficiency of bolus flow.

Although videofluoroscopy is the instrumental method most commonly used to assess swallowing, it is limited in the following ways:

1. The amount of information obtained is restricted to a few minutes in an effort to limit radiation exposure.
2. The environment can be distracting for patients with cognitive deficits.
3. The material ingested is barium, not food, and may not simulate the swallow evoked when real food is used as a stimulus (taste, smell).

Despite these limitations and exposure to a small amount of radiation (equivalent to 2 years of natural background radiation or a set of dental x-rays), videofluoroscopy is preferred for the breadth of information it provides with regard to anatomy, physiology, bolus flow, and assessment of trial intervention.

In addition, a fluoroscopic examination can easily be extended to the esophagus when indicated. Merging of the videofluoroscopic swallow study directly into esophagraphy, which results in a distinct third test referred to as an oropharyngeal esophagram, may reveal anatomic or physiologic findings for the referred sensation. Findings may include a Schatzki ring, an esophagus-narrowing web or stricture, a delay in LES opening or esophageal stasis, or other esophageal etiologies for the dysphagia. Thus, an oropharyngeal esophagram permits a more organized, efficient, cost-effective process for professional personnel and for the patient. Most importantly, it optimizes the potential for comprehensive findings and facilitates immediate intervention.

Fiberoptic endoscopic evaluation of swallowing Fiberoptic endoscopic evaluation of swallowing (FEES) is second to videofluoroscopy in frequency of instrumental approaches used with older patients. It combines the traditional endoscopic examination, in which the flexible scope allows direct visualization of the nasal cavity, the entire nasopharynx, the oropharynx, the larynx, and the hypopharynx, with dynamic recording of swallowing. Although FEES permits only limited observation of the pharyngeal swallow because it is “whited out” or visually obliterated during swallowing caused by constriction of the anatomy, the method provides a valuable alternative to a noninstrumental clinical assessment. It is being used with increased frequency in long-term care facilities where videofluoroscopy is unavailable and also with bariatric patients or those who cannot be moved to radiology because of medical instability. Other advantages are its repeatability, the use of real food and fluid during the assessment, and its potential as a biofeedback tool.

In addition to limited visualization of the dynamic oropharyngeal swallow, the limitations of FEES involve risks related to endoscopy, which include nosebleed, mucosal injury, gagging, allergic reaction to the topical anesthesia, laryngospasm, and vasovagal response. Laryngospasm is reported most often as patients are being extubated or by a sudden flow of refluxed gastric contents. Aspiration of food or liquid also might trigger laryngospasm. Patients with a history of significant aspiration, patients who require supplemental oxygen, and patients with acute mental status depression may be at increased risk if they are functioning on the edge of adequate respiratory status and cannot tolerate the minor laryngopulmonary trauma caused by the endoscope. Finally, a vasovagal response, commonly manifested as fainting, is a fairly uncommon event but can be dangerous. The unlikely possibility of encountering an adverse reaction during a flexible endoscope examination must be balanced against the daily risks faced by patients with dysphagia.

DYSPHAGIA INTERVENTION

Dysphagia clinicians and researchers have historically felt most comfortable with physiologic outcomes (movement parameters such as range of motion) and the effect on bolus flow direction, duration, and clearance as indicators of the success of an intervention. Attitudes are changing as reflected by increased concern about QOL and the development of SWAL-QOL, a dysphagia-specific patient-centered QOL instrument. Through focus group methodology, SWAL-QOL was designed to represent the patient’s perspective in measuring QOL attributable to dysphagia. The questionnaire, comprising 10 domains, is completed by patients in 10 minutes on an average.

The intent is for advances in QOL measurement such as SWAL-QOL to fill a void in dysphagia care, including understanding how variations in treatment affect the human experience of living with a swallowing difficulty and documenting the effectiveness of any given treatment in terms of both physiologic function and QOL. Once data are obtained clarifying how QOL varies with treatment, the dysphagia-specific tool can be used to facilitate decision making by patients and clinicians and to monitor the longitudinal course of individual patient treatment outcomes.

Adherence to dysphagia-related recommendations, whether thickened liquids or an exercise regimen, is known to be problematic. Reasons include poor insight into the extent of swallowing-related deficits, a lack of understanding regarding the importance of treatment for dysphagia, and inadequate patient education on the part of the clinician. A variety of patient-reported outcome measures, including the SWAL-QOL, Eating Assessment Tool (EAT-10), and MD Anderson Dysphagia Inventory, allow clinicians to gauge the patient's perspective of his or her swallowing impairment in order to tailor treatment to the needs of the patient, thereby supporting improved adherence.

Treatment for dysphagia is usually compensatory, rehabilitative, or a combination of the two approaches. Compensatory interventions avoid or reduce the effects of impaired structures or neuropathology and resultant disordered physiology and biomechanics on bolus flow. Rehabilitative interventions have the capacity to directly improve dysphagia at the biological level. That is, the targets of therapy are aspects of anatomic structures (eg, muscle) or neural circuitry that may have a direct influence on physiology, biomechanics, and bolus flow.

Compensatory Dysphagia Interventions

Traditionally, interventions for dysphagia in older patients are compensatory in nature and are directed at modifying bolus flow by targeting neuromuscularly induced pathobiomechanics or by adapting the environment. Compensatory strategies are believed by clinicians to be less demanding on the patient in terms of effort, and many of these strategies can be imposed on a relatively passive patient. Examples of compensatory strategies include postural adjustment, slowing the rate of eating, limiting bolus size, adaptive equipment, and the most commonly used environment adaptation, diet modification.

Postural adjustments Postural adjustments are relatively simple to teach to a patient, require little effort to employ, and can eliminate misdirection of bolus flow through biomechanical adjustment. A general postural rule for facilitating safe swallowing is to eat in an upright posture so that the vertical phase of the oropharyngeal swallow capitalizes on gravitational forces at work when the patient is sitting with the torso and neck at a 90-degree angle to the horizon and the head in line with the horizon. This posture also can assist in precluding early spillage of food or liquid from the horizontal oral phase into the pharynx and a potentially open airway as well as diminishing the probability of nasal regurgitation. A less obvious postural adjustment is useful for patients with hemiparesis. For this group of patients, a common strategy is a head turn toward the hemiparetic side, effectively closing off that side to bolus entry and facilitating bolus transit through the nonparetic pharyngeal channel. If the pathophysiologic condition is the uncoupling of the oral from the pharyngeal phase of the swallow, a simple chin tuck (45 degrees) reduces the speed of bolus passage, thereby giving the neural system the time it needs to initiate the pharyngeal and airway protection events prior to bolus entry. Other postural adjustments facilitate safe swallowing and are designed to specifically compensate for pathophysiologic conditions analyzed and treated by a swallowing clinician on referral for a swallowing assessment and treatment.

Food and liquid rate and amounts Although we live in a "fast food" society, older individuals and especially those with dysphagia take longer to eat. Eating an adequate amount of food becomes a challenge not only because of the increased time required to do so but also because fatigue frequently becomes an issue. Typically, smaller amounts per swallow are less likely to enter or block the airway, but in individuals who experience a sensory loss in the mouth or throat, larger amounts of food or liquid may be necessary to trigger a swallow. To promote a safe, efficient swallow in most individuals with swallowing and chewing difficulties, the following recommendations are useful:

- Eat slowly and allow enough time for a meal.
- Do not eat or drink when rushed or tired.
- Take small amounts of food or liquid into the mouth—use a teaspoon rather than a tablespoon.
- Concentrate on swallowing—eliminate distractions like television.
- Avoid mixing solid food and liquid in the same mouthful.
- Place the food on the stronger side of the mouth if there is unilateral weakness.
- Alternate between liquids and solids.

Use sauces, condiments, and gravies to facilitate cohesive bolus formation and prevent pocketing or small food particles from entering the airway.

Adaptive equipment Eating and drinking aids can assist in placing, directing, and controlling the bolus of food or liquid and in maintaining proper head posture while eating. For example, modified cups with cutout rims (placed over the bridge of the nose) or straws prevent a backward head tilt when drinking to the bottom of a cup. A backward head tilt, which results in neck extension, should be avoided in most cases because when the head is tilted back, food and liquid are more likely to be misdirected into the airway. Spoons with narrow, shallow bowls, or glossectomy feeding spoons (spoons developed for moving food to the back of the tongue) are useful to individuals who require assistance in placing food in certain locations in the mouth. More importantly, these utensils and devices promote independence in eating and drinking. A speech pathologist or swallowing clinician can make suggestions regarding appropriate aids for optimizing swallowing safety and satisfaction. Occupational therapists are experts in the area of adaptive equipment and can be helpful in obtaining products that are often available only commercially.

Diet modification The most common compensatory intervention is diet modification, a totally passive environmental adaptation. Withholding thin liquids such as water, tea, or coffee, which are most easily aspirated by older adults, and restricting liquid intake to thickened liquids is almost routine in nursing homes in an attempt to minimize or eliminate thin-liquid aspiration, presumably the precedent to the long-term related outcome, which is pneumonia. Despite the huge impact these seemingly unappealing practices may have on patient QOL, they have been commonly implemented in the absence of efficacy data.

A large National Institutes of Health (NIH)-funded multisite, randomized clinical trial (RCT) was designed as two sequential RCTs to compare the efficacy of two of the most commonly prescribed dysphagia interventions: chin-down posture and thickened liquids (nectar and honey viscosity) for patients with Parkinson disease and/or dementia in the short term and over a longer period of time. The short-term arm of the study used videofluoroscopy and showed that aspiration was reduced with honey-thick liquids as compared with both nectar-thick and chin-down posture interventions. The long-term follow-up showed equal value for chin-down posture and thickened liquids in pneumonia prevention over 3 months. Patients with dementia (with or without Parkinson disease), regardless of intervention, had a higher incidence of pneumonia than patients with Parkinson disease only. Patients who aspirated more frequently with all of the interventions during the videofluoroscopic evaluation of swallowing also were more likely to incur pneumonia over 3 months. Of the individuals who did get pneumonia, those randomized to drink honey-thick liquids (defined as 3000 centipoise, which is very thick) for 3 months were hospitalized for an average of 13 days longer than patients drinking nectar-thick liquids (4 days) or those performing the chin-down posture (6 days) while drinking.

With the development of patient-reported outcome measures specific to dysphagia, some of these ongoing practices can be evaluated from the patient's perspective as well as by the clinicians who, with good intent, recommend them. In the NIH RCT, more patients who were cognitively intact reported preferring chin-down posture with thin liquids over nectar- or honey-thickened fluids. Comparing the thickened fluids, the patients reported nectar more satisfactory, or pleasant to drink, than honey.

Additional diet modifications include a pureed diet, and a soft food diet in which the bolus maintains itself in a cohesive mass during transit but has more texture than the pureed diet. The use of sauces and gravies to minimize the formation of dry particles that may easily be misdirected into the airway is a common practice. Other strategies within this category as interventions are available, and the dietitian should work closely with the team to ensure that the safest diet is provided and that it is effective in maintaining adequate nutrition and hydration, while also acceptable to patients in order to enhance compliance.

Knowing the Heimlich maneuver Educating care providers and family members about the signs of choking and the standard first aid technique for clearing the airway, namely, the Heimlich maneuver, is essential. While the Heimlich maneuver can be self-administered, it is recommended that individuals with dysphagia eat in the company of someone who knows this first aid technique. Family members should be trained in emergency techniques for clearing the airway.

Rehabilitative Dysphagia Interventions

Rehabilitative exercises are, by nature, more active and rigorous. Often a rehabilitative approach to dysphagia intervention is withheld from older patients because such a demanding activity is assumed to deplete any limited remaining swallowing reserve, thus potentially exacerbating dysphagia symptoms. Sufficient treatment efficacy data are unavailable, and so assumption-based patterns of practice prevail.

Although progressive resistance training appears to be safe and effective for limb musculature in older adults, such training has only begun to be systematically applied to the muscles of swallowing. Below is a description of two different exercise regimens that are supported with efficacy data for improving swallowing-related function in older patients.

One is a simple isotonic/isometric neck exercise performed over a 6-week period in which the patient simply lies flat on his back and lifts his head (keeping shoulders flat) for a specified number of repetitions. The improved physiologic outcome of UES opening that affects swallowing is speculated to result from strengthening the mylohyoid/geniohyoid muscle groups and possibly the anterior segment of the digastric muscle.

Another exercise regimen demonstrating effectiveness in older dysphagic patients comprises an 8-week isometric resistance exercise for the tongue. This regimen improves swallowing safety in acute and chronic stroke patients by reducing airway invasion, increasing lingual pressure generation both isometrically and during swallowing and increasing lingual structure, specifically volume or size, as measured via MRI. Use of the same 8-week isometric resistance therapy program in Veterans with dysphagia resulting from a variety of medical etiologies led to improvements in lingual pressures, SWAL-QOL scores, amount and variety of oral intake, body mass index, and perceived swallowing-related effort. Some improvements in levels of airway invasion as well as reductions in hospital admissions and pneumonia diagnoses were observed as well. Such findings suggest that older, dysphagic individuals are able to benefit from rehabilitative exercises focused on bulbar-innervated head and neck musculature. The methods hold promise for not only influencing safe, efficient bolus flow with significant functional gains but also may restore overall health and improve QOL as well.

OPTIMIZING SWALLOWING AND RELATED HEALTH THROUGH PREVENTION

Medications

Minimizing medications that may, most often in combination, put a patient at risk for dysphagia is an important goal. Furthermore, pills are often described by patients as being difficult to swallow. Patients should be informed about medications that can be crushed, can be mixed with foods, or are available in liquid form. Pill-induced damage to the esophagus can occur if pills are taken when lying down or with inadequate amounts of liquid.

On the other hand, some medicines can enhance the swallow. For example, in parkinsonism, the timing of medication can be adjusted to decrease bradykinesia, thereby achieving the greatest effect in improving swallowing coordination at mealtimes.

Oral Hygiene

Poor oral hygiene is a risk factor for pneumonia, and aspiration of saliva, whether or not it is combined with food or fluid, can increase the likelihood of infection. The risk for periodontal disease as well as dental caries increases with age. Age-related decreases in saliva production with alterations in salivary viscoelasticity contribute to this risk. Therefore, patients should be encouraged to perform oral hygiene several times a day and undergo periodic dental examinations. Furthermore, products to relieve oral dryness in the form of saliva substitutes, as well as alcohol-free mouth care products, can be recommended.

TuBe or Not TuBe—Oral Versus Nonoral Intake

Oropharyngeal dysphagia is potentially life threatening. In the older population, critical decisions often must be made that impact on the patient's safety, health, and QOL. Among these perplexing issues is the question of continuing oral intake or providing nonoral enteral or parenteral nutrition. This dilemma is also reviewed in Chapter 35.

Enteral nutrition, the delivery of nutritive products to the digestive system through nonoral means, is often selected for the temporary prevention of aspiration in acutely ill patients. It also is chosen for permanent replacement in patients whose disease process results in confirmed or suspected swallowing-related aspiration or malnutrition and dehydration. In the case of longer-term or permanent nutritive supplementation, the clinician's impressions often direct decisions relating to tube feeding for weeks, months, or even years in older patients whose chronic disease processes are overlaid on reduced functional reserve for safe, sufficient swallowing. Rabenek et al. wrote "No explicit guidelines for percutaneous endoscopic gastrostomy (PEG) tube placement are available to guide clinical decision making. In the absence of such guidelines, the decision to place a PEG tube focuses mainly on the patient's ability to take food by mouth." However, it would clearly be narrow and short-sighted to make decisions with such an impact solely on the

basis of empirical swallowing abilities or even instrumental physiologic and bolus flow test results. For an issue that may be a critical source of a patient's sense of autonomy, self-respect, dignity, and QOL, swallowing ability is merely one factor in a decision-making formula that is yet to be determined. Unfortunately, the current situation remains as stated by Logemann: "An important decision is whether the patient should continue to be fed orally, or be placed on a nasogastric tube or given some type of gastrostomy or jejunostomy. At this time, there are no absolute guidelines the clinician can use to make the decision."

Therefore, both published evidence and the practitioner's own clinical experience must contribute to such decision making. One study of older people followed for 11 months documented the incidence of complications of tube feeding. At 2 weeks postintubation, 43% of patients fed by NG tube and 56% of those fed by gastric (G) tube had been diagnosed with aspiration pneumonia. Sixty-seven percent of patients fed by NG tube and 44% of those fed by G tube had become agitated and/or self-extubated, requiring restraints or sedative medications to maintain the integrity of enteral nutrition. Late complications in patients in the NG tube group included a 44% incidence of aspiration pneumonia and a 39% incidence of self-extubation, whereas a 56% incidence of aspiration occurred in the gastrostomy group.

These data and others have led to comparisons between the outcomes of parenteral (intravenous) and enteral modes of feeding. Parenteral modes of feeding appear to have advantages in safety and somewhat equivocal physiologic and clinical outcomes, whereas costs may be less for the enteral modes.

In summary, while oropharyngeal dysphagia may be life threatening, so are the alternatives, particularly for frail older patients. Therefore, contributions by all team members are valuable in this challenging decision-making process. The patient's family or care provider's point of view is also critical but second, of course, to that of the competent patient, himself. The state of the evidence calls for more research, including RCTs in this area. Until then, the many behavioral, dietary, and environmental modifications described in this chapter and being further refined are compassionate and, in many cases, preferred alternatives to the always present option of tube feeding.

FURTHER READING

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Chapter 37

Oral Health

Joseph M. Calabrese, Judith A. Jones

Learning Objectives

- Describe the differences between normal healthy hard and soft tissue and nonhealthy tissue or lesions in the oral cavity.
- List the primary barriers to professional oral health care: finances, perceived need, access to care, and the clinician's inability to care for the challenges that face this population.
- Identify limitations that patients have that decrease their ability to perform oral hygiene and home care.
- Understand the importance of being part of an interdisciplinary team along with an oral health care group (dentist, dental specialist, dental hygienist, dental assistant, home health and nurse aides) to ensure good oral health in long-term care.
- Understand the oral health challenges that a frail medically compromised homebound patient will face.
- Understand when to refer and what criteria are most important when referring a geriatric dental patient to a dental health care professional.

Key Clinical Points

1. **Comprehensive oral health screening should be part of the patient's initial history and physical.**
2. **Tools used in a preventive model of oral health care for geriatric dental patients include fluoride-containing gels, varnishes, rinses and paste, antibacterial rinses, electric tooth brushes, floss threaders, and other adaptive methods.**
3. **Many common medications can have negative effects on the oral cavity and oral health.**
4. **Disease in the oral cavity can diminish a patient's overall health and quality of life.**
5. **Common systemic medical conditions may affect oral health and affect the treatment options in the oral cavity.**

INTRODUCTION

The centrality of the mouth to human health, function, and behavior is clear. The ability to eat, smile, speak, and interact with other people depends on an intact oral cavity. The initiation of alimentation and protection of the host are essential functions. The purpose of this chapter is to present the contributions of the mouth to health and function in an older person's life. The components of the oral cavity will be described along with age- and disease-related changes, how to evaluate geriatric patients' oral conditions, and when to refer. The impacts of oral conditions on quality of life are described, as are disparities in access to and outcomes of oral health care and the importance of prevention in health status. Goals of long-term oral health care are described, along with options for providing long-term oral health care.

ESSENTIAL FUNCTIONS OF THE ORAL CAVITY

Many specialized tissues have evolved in the orofacial region that allow us to speak, process food, and protect us from pathogens and trauma (**Table 37-1**). The teeth, the periodontium, and the muscles of mastication prepare food for swallowing. The tongue plays a central role in communication and is a key participant in food bolus preparation and translocation. Salivary glands provide secretions with multiple functions; saliva lubricates oral mucosal tissues to keep them intact and pliable, and moistens the food bolus, permitting it to be fashioned into a swallow-acceptable form. Because these tissue activities are finely coordinated, a disturbance in any one tissue function can compromise speech and/or alimentation and diminish the quality of a patient's life (**Table 37-2**).

TABLE 37-1 ORAL TISSUES AND THEIR FUNCTIONS

ORAL TISSUE	FUNCTION
Teeth	Mastication, bone regeneration
Periodontium	Mastication, bone regeneration, host defense
Salivary glands	Lubrication, buffering acids, antimicrobial activity, mechanical cleansing, mediation of taste, remineralization of teeth, oral mucosal repair
Taste buds	Taste, host defense
Oral mucosa	Host defense, mastication, swallowing, speech
Muscles of mastication and facial expression	Mastication, swallowing, speech, posture

TABLE 37-2 ORAL-PHARYNGEAL PROCESSES IN OLDER ADULTS

PROCESS	HEALTHY OLDER ADULTS	MEDICALLY COMPLEX OLDER ADULTS
Taste	Unaffected	Diminished
Smell	Diminished	Diminished
Food enjoyment	Unaffected	Diminished
Salivary output	Unaffected	Diminished
Chewing efficiency	Slightly diminished	Diminished
Swallowing	Slightly diminished	Diminished

The oral cavity is exposed to the external world and is vulnerable to infectious, traumatic, and environmental insults. Multiple types of local infections that can affect the oral cavity are summarized in **Table 37-3**. Mechanisms have evolved to protect the mouth and permit normal oral function. The oral cavity is richly endowed with sensory systems that contribute to the enjoyment of food and alert an individual to potential problems. These systems include mechanisms for taste (and its inextricable relationship with smell); thermal, textural, and tactile sensation; and pain discrimination. Saliva plays an important protective role and contains a broad spectrum of antiviral, antibacterial, and antifungal proteins that modulate oral microbial colonization. Biomarkers of systemic and oral inflammation are present in saliva. Other proteins maintain the functional integrity of the teeth by keeping saliva supersaturated with respect to calcium and phosphate salts and provide the first role in repairing incipient dental caries (tooth decay) via a remineralization process.

TABLE 37-3 CLINICAL MANIFESTATIONS OF ORAL INFECTIONS

DISEASE	ORAL MANIFESTATIONS
Dental and periodontal infections	
Dental caries	Soft to hard discolored defect on tooth surface
Gingivitis and periodontitis	Erythematous, edematous, and hemorrhagic gingiva, which may be accompanied by gingival recession and tooth mobility
Viral infections	

Primary herpes simplex infection	Clear to yellow vesicles that rupture and form shallow, painful ulcers on all mucosal surfaces; gingival tissues inflamed, edematous, and painful
Recurrent herpes simplex infection	Burning or tingling prodrome in lesion sites (lip, hard palate, attached gingiva); whitish-gray vesicles rupture to form painful ulcers, which then develop a crust
Herpes zoster	Unilateral vesicular eruptions in areas following the distribution of ophthalmic, maxillary, or mandibular divisions of trigeminal sensory nerves
Cytomegalovirus	Mononucleosis-like symptoms, petechial hemorrhages, enlarged salivary glands, pharyngotonsillitis
Fungal infections	
Pseudomembranous candidiasis	Soft, white or yellow plaques that can be wiped off to expose an underlying erythematous mucosa
Hyperplastic candidiasis	Leukoplakic or keratotic lesions that cannot be removed by scraping
Erythemic or atrophic candidiasis	Painful erythematous oral mucosal lesions; tongue appears “bald”; diffuse inflammation of denture-bearing areas
Angular cheilitis	Erythematous cracked or fissured lesions at the lip commissures
Salivary gland infections	
Acute sialoadenitis	Tender salivary gland swelling with purulent discharge on palpation of the gland duct
Chronic sialoadenitis	Recurrent, tender swellings of salivary gland progressing to a firm and atrophic gland

TOOTH LOSS AND DENTAL CARIES

The loss of teeth has long been associated with aging. However, older adults lose teeth not because of age per se, but because of dental diseases. National surveys in the United States (NHES, NHANES) demonstrate that each successive age cohort has less tooth loss than the prior one. Thus, the percent of 65- to 74-year-olds who had lost all their teeth decreased from 55% in 1958 to 1959 to 29% in 1988 to 1994 to 24% in 1999 to 2004.

Tooth loss has two major causes: dental caries (discussed later) and periodontal diseases (discussed in the next section). Dental caries affect the exposed tooth surfaces, and periodontal diseases are confined to the supporting bony and ligamentous dental structures. With the current trends toward increasing tooth retention in aging populations, there is a correspondingly greater risk for the development of both of these disease entities.

A tooth consists of several mineralized and nonmineralized components supported by the periodontal ligament and the alveolar bone (**Figure 37-1**). The outer dental structure is enamel and is the hardest, most mineralized component, consisting of approximately 95% hydroxyapatite. Enamel covers the coronal aspect of the tooth and is the first hard tissue exposed to caries-causing bacteria. Dentin, approximately 72% mineralized, constitutes the main portion of the tooth structure, extending almost the entire length of a tooth. It is covered by enamel on the crown and by cementum on the root. Cementum is the least mineralized of the three components (~ 50%) and is the component most susceptible to caries-causing bacteria. The central, nonmineralized portion is the dental pulp, which houses the vascular, lymphatic, and neuronal supply to the tooth. Stem cells are present in pulpal tissues.

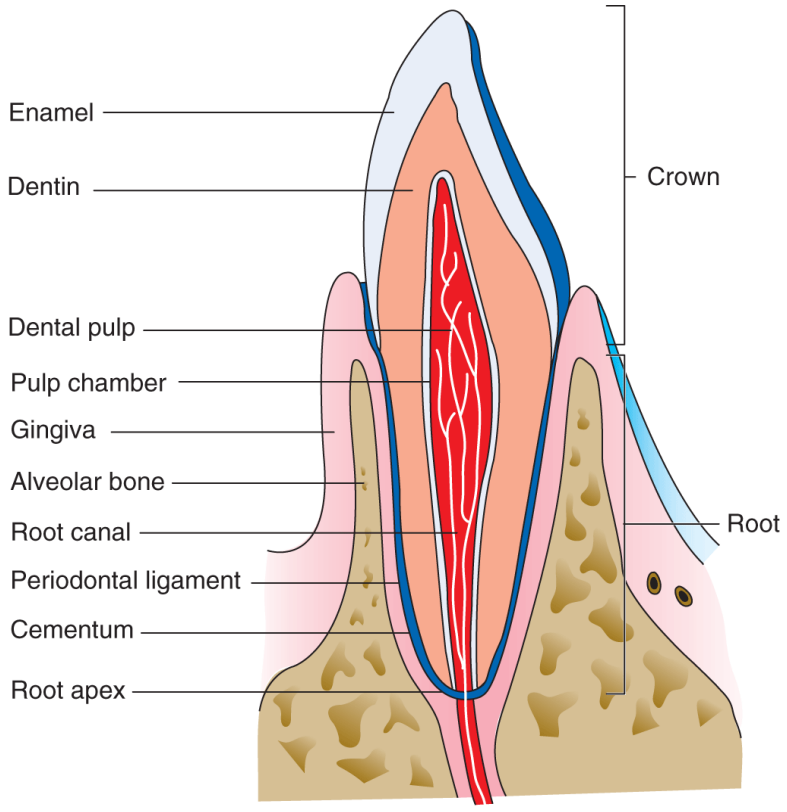


FIGURE 37-1. Cross-section of tooth.

There are two classifications of dental caries, depending on the tooth surface affected. Coronal caries occurs when the enamel and dentin of the crown portion of the tooth (usually above the gums) are affected. In older adults, if gingival recession or periodontal disease causes the root surfaces of the tooth to become exposed to the oral environment, root surface caries may occur.

The primary caries-causing microorganisms are *Streptococcus mutans*; oral streptococci, *Actinomyces*, and lactobacilli are also associated with coronal and root surface lesions. These bacteria reside on the tooth surface in dental plaque, a soft, firmly adherent mass that contains bacteria, food debris, desquamated cells, and bacterial products. Acid production by plaque bacteria dissolves the mineral content of the enamel, dentin, or cementum. The exposed proteins are destroyed by hydrolytic enzymes, resulting in the start of dental caries. Dental plaque is considered a primary etiologic factor in dental caries, as well as a principal source of pathogenic organisms in periodontal diseases.

As older adults live longer and maintain their teeth, there is susceptibility to coronal caries as a result of recurrent decay around existing fillings and the prevalence of root surfaces caries increases. There are many risk indicators for root surface caries: increased age, decreased exposure to fluoride, coronal caries, periodontal attachment loss, diminished oral-motor skills required for proper oral hygiene and additional medical, behavioral, and social factors.

For an older adult with teeth, dental caries is a significant concern and may be a source of pain, infection, and malnutrition. Dental caries will appear as orange to dark brown lesions that frequently are associated with dental plaque (**Figure 37-2**). Long-standing dental caries ultimately result in the destruction of the tooth with the possibility of local or disseminated infection in the maxillofacial tissues, space infections in the head and neck, and in the systemic circulation (septicemia). Once teeth have been destroyed from dental caries or periodontal disease, mastication, phonation, and swallowing are perturbed. Finally, social contact and nutritional status may be affected in an edentulous aging individual.

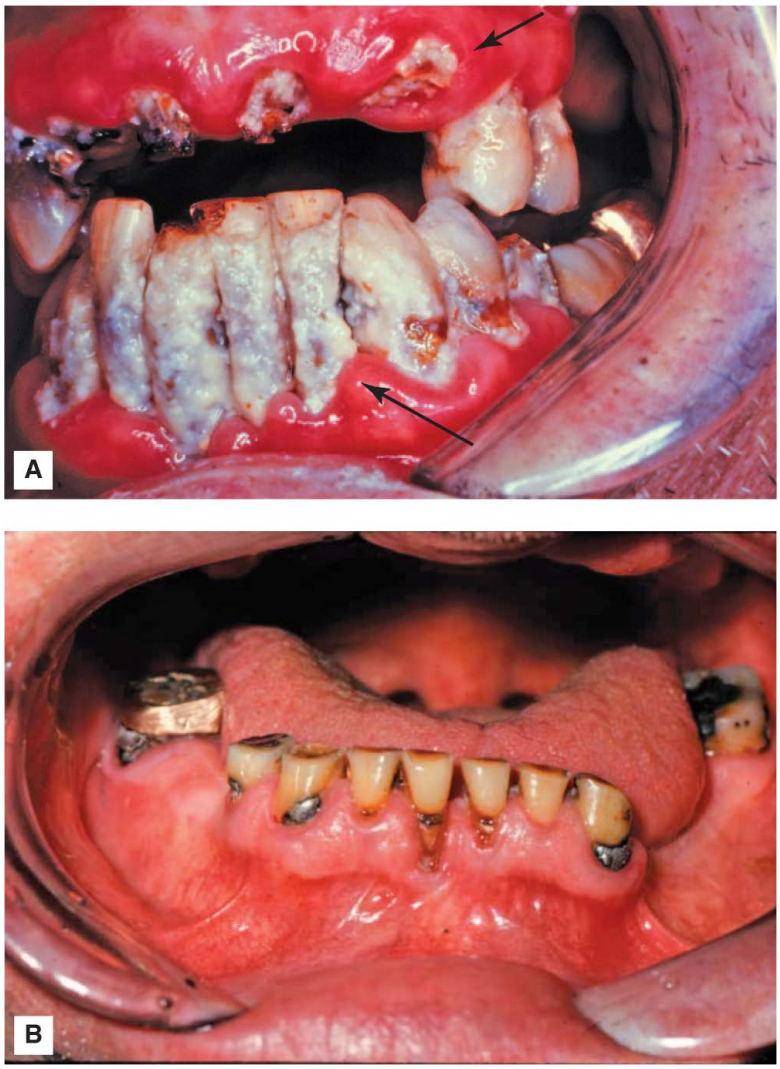


FIGURE 37-2. Dental caries, dental plaque (arrows in A), and gingival recession in two patients with dementia.

The prevention of dental caries in an older adult includes use of fluoride in many forms: daily effective oral hygiene and regular visits to dental professionals. Tooth surfaces can become resistant to decalcification and decay through repeated exposure to fluoride in water supplies, toothpaste, rinses, high-strength prescription gels, and varnishes. However, even resistant tooth surfaces can become carious when oral hygiene is inadequate and the mouth is dry and/or exposed repeatedly to fermentable carbohydrates. When detected early, dental caries can be debrided from a tooth, and the missing tooth structure can be restored with a wear-resistant, insoluble restorative material (eg, amalgam or composite resin). Some restorative materials contain fluoride (glass ionomer cements) and can help reduce caries risk. Replacements for lost teeth are available with removable prostheses (complete or partial dentures) or fixed prosthodontic appliances (crowns, bridges, implants).

PERIODONTIUM AND PERIODONTAL DISEASES

The periodontium consists of the tissues that invest and support the teeth. It is divided into the gingival unit (gums) and the attachment apparatus (cementum, periodontal ligament, and alveolar bony process) (see **Figure 37-1**). Gingivitis occurs when the gingival unit alone is inflamed. Periodontitis (or periodontal disease) exists when there is inflammation, infection, and an appreciable loss of the attachment apparatus as a result of the presence of pathogenic microorganisms. Microbial species (eg, *Porphyromonas gingivalis*, *Bacteroides*, *Fusobacterium*, *Prevotella*, *Actinobacillus*, *Actinomyces*, *Capnocytophaga*, and *Streptococcus*) cross into and through the gingival epithelium and enter subepithelial tissues, where they activate host defense mechanisms. Eventually, this causes tissue destruction, including bone loss, mobility, pain on eating, and tooth loss.

Periodontal diseases are more prevalent in the aging population than younger adults. Sixty-four percent of persons in the United States aged 65 and above have moderate or severe periodontal diseases. Older persons experience greater

gingival recession and loss of periodontal attachment (**Figure 37-3**). Periodontal disease proceeds through a series of episodic attacks rather than occurring as a slowly progressing continuous process. Periodontal bone destruction results from an overly aggressive local immune reaction to the pathogenic organisms, triggering a cascade of cytokine and immunologic events that can produce irreversible loss of alveolar bone. It is not known whether older age cohorts are more susceptible to periodontal destruction than are younger populations. Among healthy adults, periodontal attachment loss occurs at small increments in all age cohorts and does not occur in greater amounts in older healthy adults. However, many systemic diseases and therapeutic regimens commonly found in older individuals may adversely affect periodontal health. Therefore, an older, medically compromised adult is especially susceptible to developing periodontal diseases and is at risk for associated dental-alveolar infections, pain, and tooth loss.

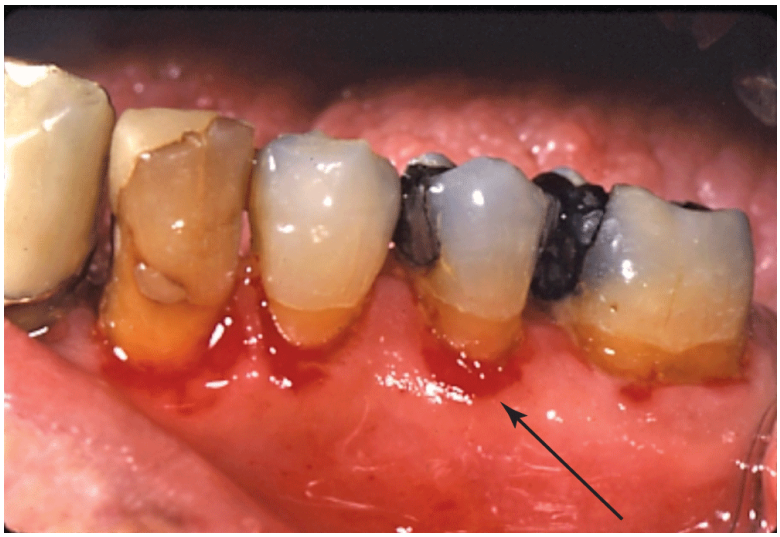


FIGURE 37-3. Periodontal and gingival disease.

Medication-induced changes: Several classes of medications commonly prescribed for older people are associated with gingival enlargement and hyperplasia, a condition that if left untreated, predisposes to both dental caries and destructive periodontitis. Some calcium channel blockers can cause this unwanted drug side effect, which may require periodontal surgery for definitive treatment. The antiseizure medication phenytoin and the immunosuppressant cyclosporine have also been associated with gingival enlargement.

Periodontal-systemic connections: Periodontal diseases have oral and systemic effects on health. They are directly associated with halitosis, gingival bleeding, tooth mobility, and tooth loss. Untreated periodontitis has been reported to interfere with blood glucose control in patients with diabetes; and cardiovascular disease is associated with periodontitis after controlling for traditional risk factors such as body mass index (BMI), gender, tobacco use, age, and blood lipid levels. Gram-negative bacteria are implicated in the pathogenesis of periodontal disease, and colonization of the oropharynx with gram-negative bacilli predisposes a patient to pneumonia. Aspiration pneumonia can occur when oropharyngeal secretions are aspirated into the lungs, causing infection. Bacteria from the gingival sulcus in persons with periodontitis have been isolated from patients with pneumonia. Risk factors for aspiration pneumonia include older age, immunocompromised state, mechanical ventilation, feeding problems and/or feeding tubes, deteriorating health status, and wearing dentures during sleep. Importantly, debilitated older patients who do not have adequate oral hygiene care are highly susceptible to aspiration pneumonia.

Treatment of gingivitis and periodontitis starts with good oral hygiene in the form of tooth brushing for 2 minutes twice daily and flossing daily. Electric toothbrushes can assist older patients who have arthritis, motor, and/or cognitive disorders. Periodontal therapy ranges from local (eg, dental prophylaxis, local debridement, scaling, and root planing) to pharmacologic (eg, use of intrasulcular antimicrobial solutions, systemic low-dose doxycycline as an immunomodulator) to surgical techniques (eg, debridement, excision of hyperplastic tissue), depending on the extent of periodontal infection and bony destruction. Several antimicrobial and anticollagenase drugs have been approved for treatment: oral rinses (eg, chlorhexidine 0.12%), subgingival antimicrobials (eg, minocycline hydrochloride 1-mg microspheres), short-term antimicrobials (eg, clindamycin 300 mg QID or metronidazole 400 mg TID for 7–10 days), or anticollagenases (eg, doxycycline 20 mg). While periodontal healing after surgery tends to be slower even in healthy older persons, the long-term results of periodontal therapy are indistinguishable from those in younger adults. The decision either to save the dentition and restore periodontal health or to extract teeth with moderate periodontal

disease should be determined after all oral and systemic factors have been evaluated. Therefore, the health and functional status of a person, rather than age per se, should determine the extent of periodontal treatment.

SALIVARY GLANDS, HYPOFUNCTION, AND XEROSTOMIA

There are three major pairs of salivary glands (parotid, submandibular, and sublingual) and numerous groups of minor glands (eg, labial, palatal, and buccal), all of whose principal function is the exocrine production of saliva. Each gland type makes a unique secretion derived from either mucous or serous cell types, forming the fluid in the mouth termed *whole saliva*. Saliva includes many constituents that are critical to the maintenance of oral health. Saliva lubricates the oral mucosa, promotes the remineralization of teeth, and protects against microbial infections. Although the role of saliva in digestion is limited, saliva helps prepare the food bolus for deglutition, dissolves foods, and delivers tastants to the taste buds.

It was previously thought that salivary output diminishes with increasing age. This was based on the clinical observation that older individuals frequently have a dry mouth and complain of xerostomia. However, in general, there is no substantial diminution in salivary production across the human lifespan in healthy adults. Thus, in the absence of complicating factors (eg, many systemic diseases, medications), there is no generalized age-related decrease in the production of salivary fluid. In addition, there appear to be no significant alterations in the composition of saliva in older, healthy persons.

The physiologic findings contrast with the morphologic changes seen in aging salivary glands. Major salivary glands lose approximately 30% of their parenchymal tissue over the adult lifespan. The loss primarily involves acinar or fluid-producing components, while proportional increases are seen in ductal cells and in fat, vascular and connective tissues. Because acinar components are primarily responsible for the secretion of saliva, it is not known why, in the presence of a significant reduction in the gland acinar volume, total fluid production does not diminish with increasing age. Current thinking is that salivary glands possess a functional reserve capacity that enables them to maintain fluid output throughout the human adult lifespan. There is evidence that with a reduced reserve capacity, additional burdens placed on aging salivary glands (eg, anticholinergic medications) increase their vulnerability to functional decline. Therefore, salivary hypofunction (the objective finding) and complaints of a dry mouth (xerostomia—the subjective finding) should not be considered normal sequelae of aging but instead are indicative of a variety of diseases and their treatments (**Table 37-4**). Many medications taken by older adults reduce or alter salivary gland performance, as can dehydration. In addition, radiation for head and neck neoplasms and cytotoxic chemotherapy can have direct and dramatic deleterious effects on salivary glands.

TABLE 37-4 CAUSES OF SALIVARY HYPOFUNCTION IN OLDER ADULTS

CATEGORY	EXAMPLES
Medications	Anticholinergics Antidepressants Antihistaminics Antihypertensives Anti-Parkinson disease Anxiolytics Diuretics
Oncologic therapy	Cytotoxic chemotherapy Head and neck radiotherapy
Oral conditions	Bacterial and viral infections Salivary gland obstructions Traumatic lesions Neoplasms
Other conditions	Alzheimer disease Cerebrovascular accidents

	Dehydration Diabetes mellitus Late-stage liver disease Sjögren syndrome Systemic lupus erythematosus Thyroid disorders (hyper and hypo)

The most common disease affecting salivary glands is Sjögren syndrome, an autoimmune exocrinopathy that occurs predominantly in postmenopausal women. Alzheimer disease, diabetes, dehydration, rheumatoid arthritis, and cerebrovascular accidents may also affect salivary output. Several oral inflammatory and obstructive salivary gland disorders (eg, bacterial infections, sialoliths, trauma, neoplasms) result in salivary dysfunction, as well as benign and malignant salivary tumors.

A clinician is likely to encounter many older patients with oral complaints related to salivary gland hypofunction. A brief clinical examination should include palpation of all major glands and inspection of the duct orifices while milking the glands to ensure gland patency. The application of a mild solution of citric acid or lemon juice to the tongue can help determine whether a patient's salivary glands will respond to a gustatory stimulus. Regardless of etiology, any of the major oral physiologic roles influenced by saliva (see **Table 37-1**) may be affected adversely. With impaired glandular output, dental caries will increase, increasing the possibility of tooth loss. The oral mucosa becomes desiccated and cracked, leaving the host more susceptible to microbial infection (**Figure 37-4**). Older adults with salivary gland hypofunction may experience difficulty in swallowing or speaking at length, pain (which may arise from either the teeth or the oral soft tissues), impaired denture use, altered taste, and diminished food enjoyment.

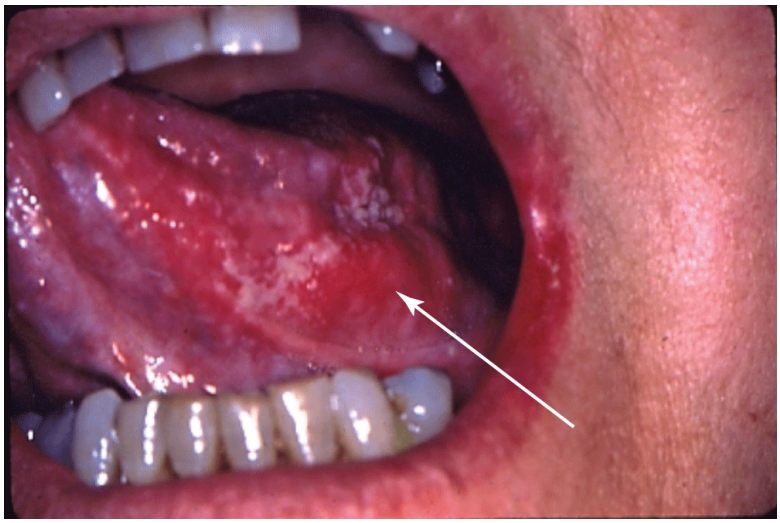


FIGURE 37-4. Candidiasis of lateral border of tongue.

Treatment of salivary dysfunction starts with identification of the etiology. Medication-induced salivary problems can be eliminated by stopping unnecessary medicines, modifying drug use and dose, or substituting one drug with another drug that has fewer anticholinergic side effects. Even when no reduction in the daily dose is recommended, the splitting of a dose into several smaller and more frequently taken doses may alleviate or diminish the sensation of oral dryness. To enhance salivary production, gustatory (*sugar-free* mints, candies), masticatory (*sugar-free* gums), and pharmacologic (pilocarpine 5 mg TID and qhs, cevimeline 30 mg TID) stimulants can be useful in a patient who has remaining salivary function. Salivary substitutes, rinses, and moisturizing gels can assist a patient who has little or no remaining salivary function. Prevention of dry mouth is essential and can be achieved with the frequent use of noncarbonated, caffeine- and sugar-free beverages, topical fluoride, and routine oral hygiene no less than twice daily. Removable dentures and partials must be kept clean and out of the mouth during sleeping hours. Frequent lubrication of the lips helps prevent lip cracking and infections.

SENSORY FUNCTIONS

To the extent that food enjoyment, recognition, and sensory function decline in an older person, significant nutritional deficits can result. The question of whether there is a true anorexia (loss of appetite) associated with aging is confounded by the many comorbidities, common in older people, that may cause anorexia, as well as other social and psychological factors that may reduce oral food and fluid intake. Perturbations in taste, smell, and other oral sensory modalities can occur with age and with dental/periodontal problems, thereby reducing the rewards of eating and contributing to a diminished interest in food by some older persons.

The taste receptors of the human gustatory system are distributed throughout the oropharynx and are innervated by three cranial nerves: VII, IX, and X. The number of lingual taste buds does not diminish with age. The registration of a taste phenomenon is complex, because multiple factors are involved: gustation, olfaction, and central nervous system function. The ability to taste is often evaluated at two levels: (1) *threshold*, the most common measure, a "molecular-level" event, which reflects the lowest concentrations of a tastant that an individual can recognize as being different from water, and (2) *suprathreshold*, a measure that is reflective of the ability to taste the intensity of substances at functional concentrations encountered in daily life. In addition to detection, recognition, and intensity, the normal sensation of taste involves a hedonic component: the degree of pleasantness.

Taste function among generally healthy, community-dwelling persons changes modestly with increased age. In contrast, a threefold increase in the frequency of subjective taste complaints has been observed among older persons who take prescription medications. Objective threshold and suprathreshold evaluations of gustatory function in healthy older adults have been reported for all four taste qualities (sweet, sour, salty, and bitter). In general, the changes detected with increased age have been modest and taste-quality-specific. For example, the ability of older adults to detect salt decreases slightly with age, while no changes in the detection threshold for sucrose (sweet) are noted. The importance of medication usage and place of residence in the evaluation of taste dysfunction has been confirmed in clinical studies in which institutionalized persons and those using more prescription medications had elevated taste thresholds.

Older adults perform less well in the more complicated problems of flavor perception, food recognition, and food preference. This is probably a result of diminished olfactory performance rather than the modest changes that accompany taste function with aging. Olfactory performance data show declines in thresholds, suprathreshold intensity judgments, and odor recognition in both men and women with increasing age. Among older adults, average thresholds are higher, the ability to perceive suprathreshold intensities is blunted, odor recognition is impaired, and the judgment of pleasantness is reduced compared with younger subjects. Moreover, longitudinal studies demonstrate that as people get older, recognition decrements become even more severe.

Normal chemosensory function does not operate independently of good oral health. Numerous oral conditions can directly or indirectly affect smell and taste by altering the underlying biology of the taste or smell system or by introducing exogenous stimuli into the mouth or nose. Many oral conditions, including fungal/bacterial/viral infections, vesiculobullous diseases, salivary gland hypofunction, poorly fitting prostheses, and oral manifestations of systemic diseases, can cause chemosensory dysfunction. Inadequate removal of food particles can allow their breakdown or metabolic conversion by oral microorganisms to noxious, unpleasant substances. Periodontal diseases can result in accumulations of putrefied acidic materials that may leak into the oral cavity and alter taste sensation. Similarly, dental-alveolar bacterial infections with subsequent fistula formation may contribute continuously low levels of purulent matter in the mouth.

The complaint of a smell or taste problem may be indicative of a chemosensory disorder or could be the manifestation of an oral and/or systemic medical problem. For example, the sudden loss of either smell or taste may be a sign of brain tumor. Alternatively, gradual diminishment in food enjoyment may be related to multiple sources. Examples include a poorly fitting removable prosthesis (**Figure 37-5**), an oral fungal infection (see **Figure 37-4**), decreased smell identification, or use of a new drug. A patient should be asked if he or she can specifically identify the four basic tastants and distinguish between different odorants; such patients can be given the University of Pennsylvania Smell Identification Test. A thorough multidisciplinary approach is required for a patient presenting with chemosensory complaints because of the wide range of potential oral, systemic, physiologic, cognitive, and pathologic factors that are involved in oral sensory functioning.

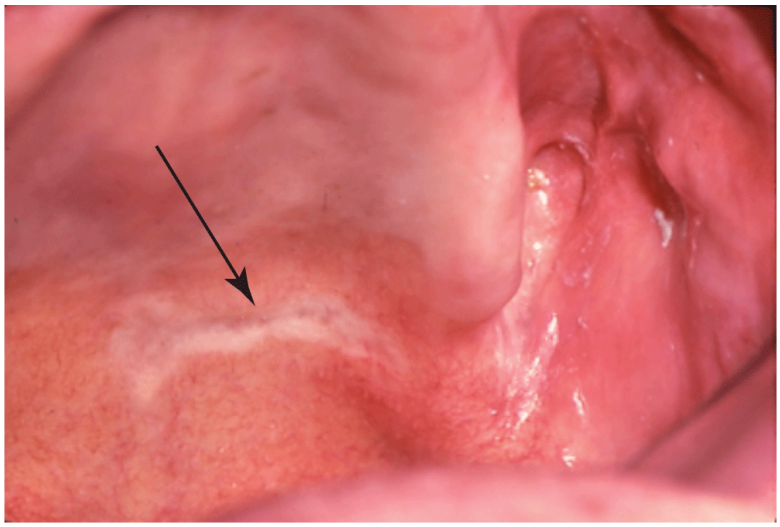


FIGURE 37-5. Denture scar on palate in patient with dry mouth. Arrow points to denture scar on palate.

ORAL MUCOSA

The soft tissue lining of the mouth may be characterized by three general types: (1) well-keratinized tissue with a dense layer of connective tissue and firmly attached to underlying bone (eg, marginal gingiva, palatal mucosa), (2) slightly keratinized and freely movable tissue (eg, labial and buccal mucosa, floor of the mouth), and (3) specialized mucosa (eg, dorsum of the tongue). The primary function of the oral mucosa is to act as a barrier to protect the underlying structures from desiccation, noxious chemicals, trauma, thermal stress, and infection. The oral mucosa plays a key role in the defense of the oral cavity.

Aging can be associated with changes in the oral mucosa similar to those in the skin, with the epithelium becoming thinner, less hydrated, and more susceptible to injury. The reasons for these changes are complex and include alterations in protein synthesis and responsiveness to growth factors and other regulatory mediators. Cell renewal (ie, mitotic rates) and the synthesis of proteins associated with oral mucosal keratinization occur at a slower rate in aging individuals. Alternatively, the normal tissue architecture and patterns of histodifferentiation, which probably are dependent on complex interactions with the underlying connective tissue, do not display any changes with age. Overall, changes in the vascularity of oral mucosa likely contribute to alterations in mucosal integrity because of reductions in cellular access to nutrients and oxygenation. Mucosal, alveolar, and gingival arteries demonstrate the effects of arteriosclerosis. Varicosities on the floor of the mouth and the lateral and ventral surfaces of the tongue (comparable to varicosities on the lower extremities) are also observable in geriatric patients.

The maintenance of mucosal integrity depends on the ability of the oral epithelium to respond to an insult. Insults can be caused by physical factors (trauma), exposure to chemical or microbiological toxins, microbial infections, and oral and/or systemic conditions. Many studies have documented that the immune system undergoes a decline with age (see Chapter 3); it is unknown whether this decline extends to mucosal immunity. If so, the oral mucosa may be more susceptible to transmission of infectious diseases as well as delayed wound healing. Similar findings have been reported for healing gingival tissues.

Although age has no effect on the clinical appearance of the oral mucosa, the use of removable prostheses has a potentially adverse effect on the health of the oral mucosa. The denture-bearing mucosa of aged maxillary and mandibular ridges shows significant morphologic changes. Ill-fitting dentures can produce mechanical trauma to the oral tissues (see **Figure 37-5**) and cause mucosal hyperplasia. Oral candidiasis can frequently be found on denture-bearing areas in an edentulous individual, often occurring with angular cheilitis (deep fissuring and ulceration of the epithelium at the commissures of the mouth). Therefore, the clinician should ask the patient to remove all removable dentures before conducting an oral screening.

Oral mucosal alterations in an older person are often a result of multiple oral and systemic factors (**Table 37-5**). Many medications have been associated with oral mucosal changes, and long-term use of antibiotics frequently results in oral candidal infections, while drugs with xerostomic side effects (see earlier) increase the potential for mucosal injury. Bisphosphonate drugs used for cancer metastasis and osteoporosis (especially those administered intravenously [IV], but possibly those delivered orally) are associated with increased risk for osteonecrosis, a severe destruction of

oral mucosa and bone. However, risk for the rare event of osteonecrosis must be balanced against the benefit of bisphosphonate drugs for common osteoporosis-related fractures. Drugs used in older patients for arthritic conditions, hypertension, cardiac arrhythmias, seizures, and dementia are associated with lichenoid-like reactions. The withdrawal of a causative drug usually results in complete resolution of the lesion within 2 to 3 weeks, but if there is no clinical improvement, a definitive diagnosis should be obtained with a biopsy specimen.

TABLE 37-5 CONDITIONS ASSOCIATED WITH ORAL MUCOSAL CHANGES

CLASSIFICATION	DISEASE/DISORDER	EXAMPLES
Oral conditions	Infections	Candidiasis, herpes simplex, herpes zoster
	Ulcerative conditions	Recurrent aphthous stomatitis
	Cancer	Oral squamous cell carcinoma
	Periodontal diseases	Gingivitis, periodontitis
	Prosthodontic problems	Poorly fitting dentures, denture stomatitis
	Salivary gland hypofunction	Dessicated oral tissues
	Food allergies	Lichenoid changes
	Trauma	Traumatic fibroma, mucocele
Systemic diseases	Dermatologic disorders	Systemic lupus erythematosus, lichen planus, pemphigus vulgaris, cicatricial pemphigoid, erythema multiforme
	Endocrine disorders	Diabetes mellitus
	Neurologic disorders	Alzheimer, Parkinson, CVA
	Immunocompromising disorders	HIV, AIDS, rheumatoid arthritis
Medical therapies	Medications	Diuretics, calcium channel blockers, antibiotics, antiseizures, immunomodulating drugs, bisphosphonates
	Radiotherapy	Head and neck radiotherapy
	Cytotoxic chemotherapy	Methotrexate, 5-FU, cyclosporine

AIDS, acquired immunodeficiency syndrome; CVA, cerebrovascular accident; 5-FU, 5-fluorouracil; HIV, human immunodeficiency virus.

Many oral mucosal disorders can affect older people, ranging from benign (eg, recurrent aphthous ulcers and traumatic lesions) to malignant (eg, squamous cell carcinomas) (**Figure 37-6**). The diagnosis of mucosal diseases requires a detailed history and a thorough head and neck and oral examination, including all mucosal tissues. For vesiculobullous and erosive diseases, a simple three-item classification is helpful: (1) acute multiple lesions (eg, erythema multiforme, herpes simplex, herpes zoster, allergic reaction), (2) recurring oral ulcers (eg, recurrent aphthous stomatitis, traumatic ulcer), and (3) chronic multiple lesions (eg, pemphigus vulgaris, mucous membrane pemphigoid, lupus erythematosus, lichen planus, dysplasia, squamous cell carcinoma). If a lesion does not resolve after 2 to 3 weeks, a tissue biopsy is required. For lesions that are suspected to be oral manifestations of autoimmune connective tissue disorders (eg, pemphigus, pemphigoid, lichen planus), biopsies should also include specimens for direct immunofluorescence. If trauma from an injury or an ill-fitting denture is suspected, removal of the etiology should allow the lesion to heal. Many of these conditions have an immunologic etiology, and therefore management strategies involve topical and/or systemic immunomodulating agents (**Table 37-6**).

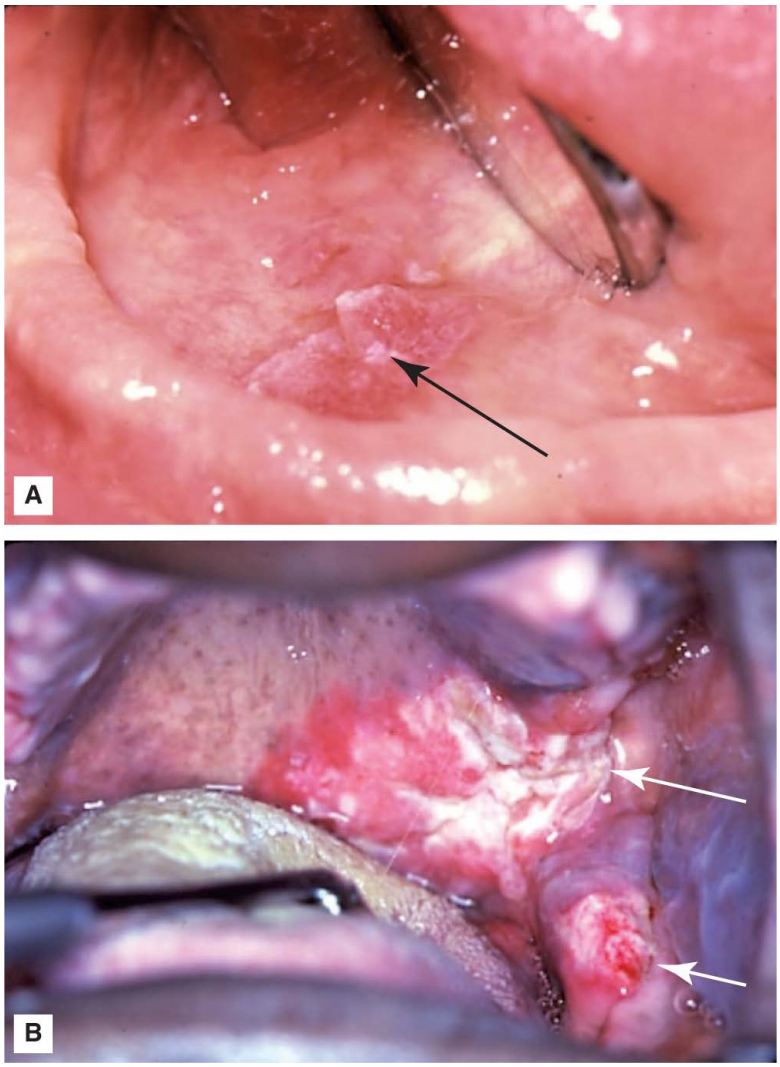


FIGURE 37-6. **A.** Squamous cell carcinoma, floor of the mouth. **B.** Squamous cell carcinoma, soft palate, retromolar pad.

TABLE 37-6 TREATMENT OF COMMON VESICULOBULLOUS AND EROSIVE DISEASES IN OLDER ADULTS

MEDICATION	REGIMEN
Topical treatments[a,b,c,d]	
Fluocinonide gel 0.05%	Apply to affected regions TID and qhs
Triamcinolone acetonide in gel base 0.1%	
Clobetasol propionate gel 0.05%	
Oral rinses[b,c,e]	
Dexamethasone elixir 0.5 mg/5 mL	Rinse and spit 10 mL QID for 5 min
Diphenhydramine elixir 12.5 mg/5 mL	
Systemic medications[b,f,g]	
Prednisone 5 mg	12 tabs qod × 2 days, decreasing by 2 tabs every other day
Azathioprine 50 mg	1 tab BID

[a]If extensive gingival lesions are present, use with a custom-fabricated tray.
[b]Oral candidiasis may result, and concomitant antifungal therapy may be necessary.
[c]Taper as indicated by clinical response.
[d]Can be combined in a 1:1 mixture with orabase.
[e]Can be combined in a 1:1 mixture with sucralfate, Kaopectate, or Maalox.
[f]

Dose and duration depend on severity of disease and concomitant systemic diseases.
[g]Azathioprine in combination with prednisone permits use of lower doses of prednisone.

ORAL CANCER

The oral mucosal disease with the greatest potential morbidity and mortality is cancer (see **Figure 37-6**). Oral cancers represent 2.4% of all cancers. There were an estimated 42,440 new oral and pharyngeal cancers in the United States in 2014 and 8390 cancer deaths. The 5-year survival rate is 62.7%. Median age at diagnosis is 62; 72% of new cancers occur after age 55; and median age at death is 67. Five-year survival for localized cancers (31% of oral and pharyngeal cancers) is 83%, for cancers that spread to regional nodes (47%) is 60%, and for metastatic oral and pharyngeal cancers (18%) is 37%. The three greatest risk factors for developing oral cancer are age, tobacco, and heavy alcohol use. Males are more than twice as likely to develop oral cancer as females.

Carcinoma should be considered part of the differential diagnosis of any oral lesion. Any oral lesion that does not heal* completely *in 2 to 3 weeks after removal of suspected etiologies (eg, ill-fitting denture, change in medication) should undergo a diagnostic biopsy procedure.

The treatment of oral cancers involves head and neck surgery, radiotherapy, chemotherapy, or a combination of any of these three modalities, depending on the tumor's histopathology and stage. Before receiving definitive therapy, the patient should have a comprehensive oral examination so that focal areas of infection or potential infection (dental caries, periodontal disease, dental-alveolar infections, soft and hard tissues lesions) can be treated *before* surgery, radiotherapy, or chemotherapy. The patient must be educated about many potential risks: surgery-related sensory, esthetic, and functional problems; radiotherapy-induced mucositis, salivary gland hypofunction, and osteoradionecrosis; and chemotherapy-induced mucositis and immunosuppression.

MOTOR FUNCTION

The oral motor apparatus is involved in routine yet intricate functions (speech, posture, mastication, and swallowing). Regulation of these activities may occur at three levels: the local neuromuscular unit, central neuronal pathways, and systemic influences. While aging is associated with changes in neuromuscular systems, animal studies suggest that age-associated deficiencies in motor function are unrelated to the composition and contractile function of skeletal muscles. Rather, these changes probably are related to other factors such as neuromuscular transmission and propagation of nerve impulses.

Dentition status (the number of teeth) and not age, influences mastication. While older adults with an intact dentition prepare food more slowly for swallowing than do younger individuals, and minor alterations in performance (mastication, swallowing, oral muscular posture, and tone) can be expected with increased age, changes are more common among completely or partially edentulous persons rather than among persons with a natural dentition. Any diminution in masticatory efficiency can be exacerbated in individuals with a compromised dentition (persons with dental caries, periodontitis, missing teeth, and removable dentures).

Swallowing changes in older persons are usually caused by sensory, muscular, and neurologic deterioration. A thorough review of swallowing problems in older people is provided in Chapter 36. Normal aging has minor adverse effects on swallowing, although in a healthy older person, even advanced age does not appear to cause any clinically important dysfunction. However, a host of conditions common in the older adult population can cause clinically significant swallowing deficiencies. Salivary hypofunction (described earlier) impairs swallowing times and under severe conditions increases the likelihood of aspiration. Patients with neuropathies have been reported to have oral swallow times four- to sixfold longer than those in healthy controls; these persons may not even be able to produce the recognizable characteristics of an oral swallow. Neurovascular conditions (eg, cerebrovascular accidents, dementia, motor neuron disease) are likely to cause dysphagia and predispose a person to the danger of aspiration.

The temporomandibular joint (TMJ) is located between the glenoid fossa and the condylar process of the mandible, and exhibits a functionally unique gliding and hinge movement. It is of particular interest to clinicians, for it is the focus of several craniofacial pain disorders. Radiographic and postmortem evaluations suggest that the components of this joint undergo degenerative alterations with increasing age. However, TMJ functional impairment is not a "normal" age-associated event. Rather, temporomandibular disorders (TMD) in older adults are linked with many common oral and systemic conditions. Orofacial pain in an older patient may be a result of a variety of problems of the

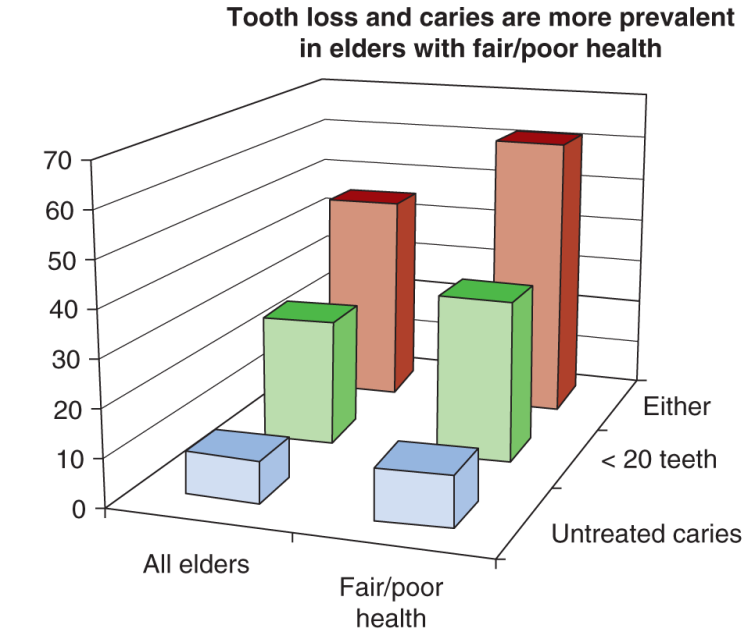
craniomandibular-oral complex and other extraoral diseases, making diagnosis and treatment challenging and frequently requiring a multidisciplinary approach.

In general, two types of pathology are associated with the TMJ: *articular*, related to the joint itself, and *nonarticular*, pathology occurring in structures unrelated to the joint but causing similar or referred symptomatology. Articular abnormalities common to all joints may also affect the TMJ, for example, trauma, ankylosis, dislocation, and arthritis. Nonarticular disorders may result from trigeminal neuralgia, headache, migraine, otitis, dentoalveolar pain/infection, and masticatory myalgia. Orofacial habits (eg, jaw clenching and tooth grinding) and poor head and neck posture can produce muscle fatigue and spasm. Psychological conditions (stress and depression) can exacerbate underlying articular and nonarticular disorders. Clinically, the patient will present with pain in many regions: TMJ, temporal, neck, masticatory muscles, and the oral cavity. Diagnosis is challenging because symptoms primarily occur in any of these sites with regular, irregular, or no pain referred to the TMJ region. Limited jaw opening (< 40 mm from the maxillary central incisor to the mandibular central incisor) and pain on mastication or during jaw movements may be indicative of TMD. Treatment, as with other arthritic or muscular disorders, requires the elucidation of an appropriate diagnosis and ranges from conservative and reversible regimens (anti-inflammatories, analgesics, muscle relaxants, physical therapy, oral bite splints) to more invasive procedures for unresolved painful conditions (eg, TMJ surgery). Pain in the jaws and/or face is present in 3% to 6% of persons age 65 and older.

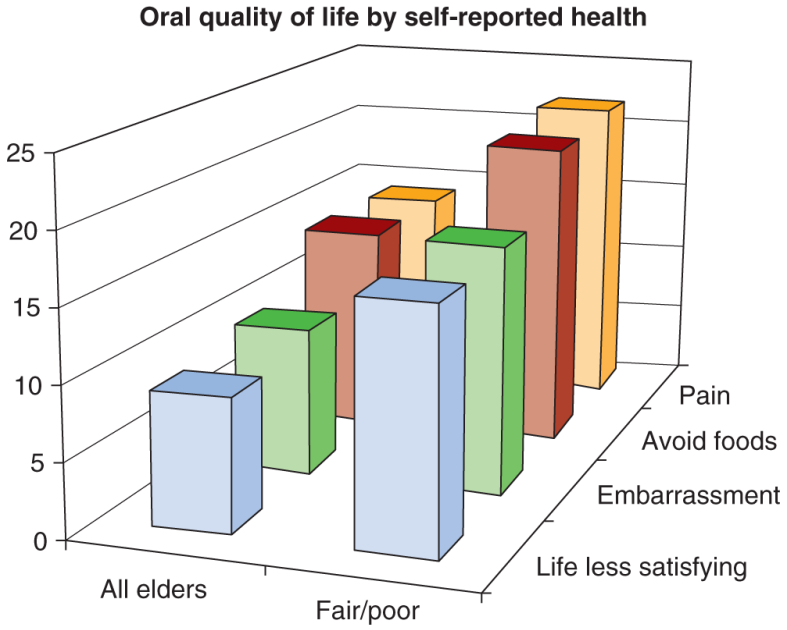
Speech is another function of the oral structures; speech undergoes changes with increasing age, including shape of the tongue and its function during sound production and frequency variability. Among healthy older persons, these changes do not compromise or alter speech in any perceptible way. Tongue strength decreases with age, even among healthy adults, yet tongue endurance is similar between younger and older persons. There are also age-associated alterations in intraoral and maxillofacial posture. Drooping of the lower face and lips in the older adult results from the loss of supporting hard tissues and diminished tone of the circumoral muscles. The latter changes may elicit esthetic concerns and can lead to embarrassment from drooling or food spills caused by the inability of an older individual to close the lips competently while eating or speaking. Often, drooling caused by reduced circumoral muscle tone can result in complaints of excess salivation. Finally, oral motor disorders also may result from a number of therapeutic drug regimens, such as the frequent association of tardive dyskinesia with phenothiazine therapy. These dyskinesias may include diminished performance and speech pathoses as well as alteration in movement (eg, chorea).

ORAL CONDITIONS AND QUALITY OF LIFE IN OLDER ADULTS

Poor oral health diminishes the quality of life among persons with poor general health. There is a strong association between poor general health and poor oral health (**Figure 37-7**). Persons who report poor general health are more likely to have complete tooth loss compared to older people reporting good or better general health. Older adults with teeth reporting poor general health also have two to four fewer teeth than persons reporting good or better general health. Further, the mean number of teeth in persons 50 years and older reporting poor general health is below the threshold for a functional dentition (20 teeth are considered the minimum for a functional dentition). Persons reporting poor general health are also more likely to report painful aching in their mouth. Conditions that increase the likelihood of reporting pain include arthritis, chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), diabetes, and low/no vision. One in five adults aged 65 to 74 who report poor general health also report avoiding particular foods because of poor oral health (problems with their teeth, dentures, or mouth).



A (NHANES 2005–2008; Griffin et al.)



B (NHANES 2005–2008; Griffin et al.)

FIGURE 37-7. **A.** Tooth loss and caries are more prevalent in elders with fair/poor health. **B.** Oral quality of life by self-reported health.

POLICY CONSIDERATIONS: DISPARITIES IN ACCESS TO AND OUTCOMES OF ORAL HEALTH CARE

Nearly 73 million baby boomers will turn 65 by 2030. Most will lose dental insurance upon retirement. **Medicare** does not cover dental care except in very narrowly prescribed circumstances. **Medicaid** coverage varies by state; in 2011, 22 states provided "comprehensive," 7 provided limited, 14 provided emergency, and 7 provided no dental coverage for adults. However, Medicaid is only for people at or below the poverty level. Thus, a large "middle" group of older people are on a fixed income with limited access to sponsored dental care coverage. Such people need private dental coverage and/or effective, community-based prevention programs.

There are important disparities in access to dental care, tooth loss, unfilled caries, periodontal diseases, and oral cancers among the poor, near poor, and racial and ethnic minorities. Insurance affects access for persons aged 65 and

over: “54% of adults with private health care coverage had visited dental professional within the past 6 months, compared with 41% of adults who had only Medicare and 25% who had Medicare plus Medicaid” (CDC, 2014). Thus, the so-called dual eligibles are the most likely group of elders to not have access to dental care. Non-Hispanic whites are more likely to use dental care than non-Hispanic African Americans and Hispanics, even after controlling for income (**Figure 37-8A**).

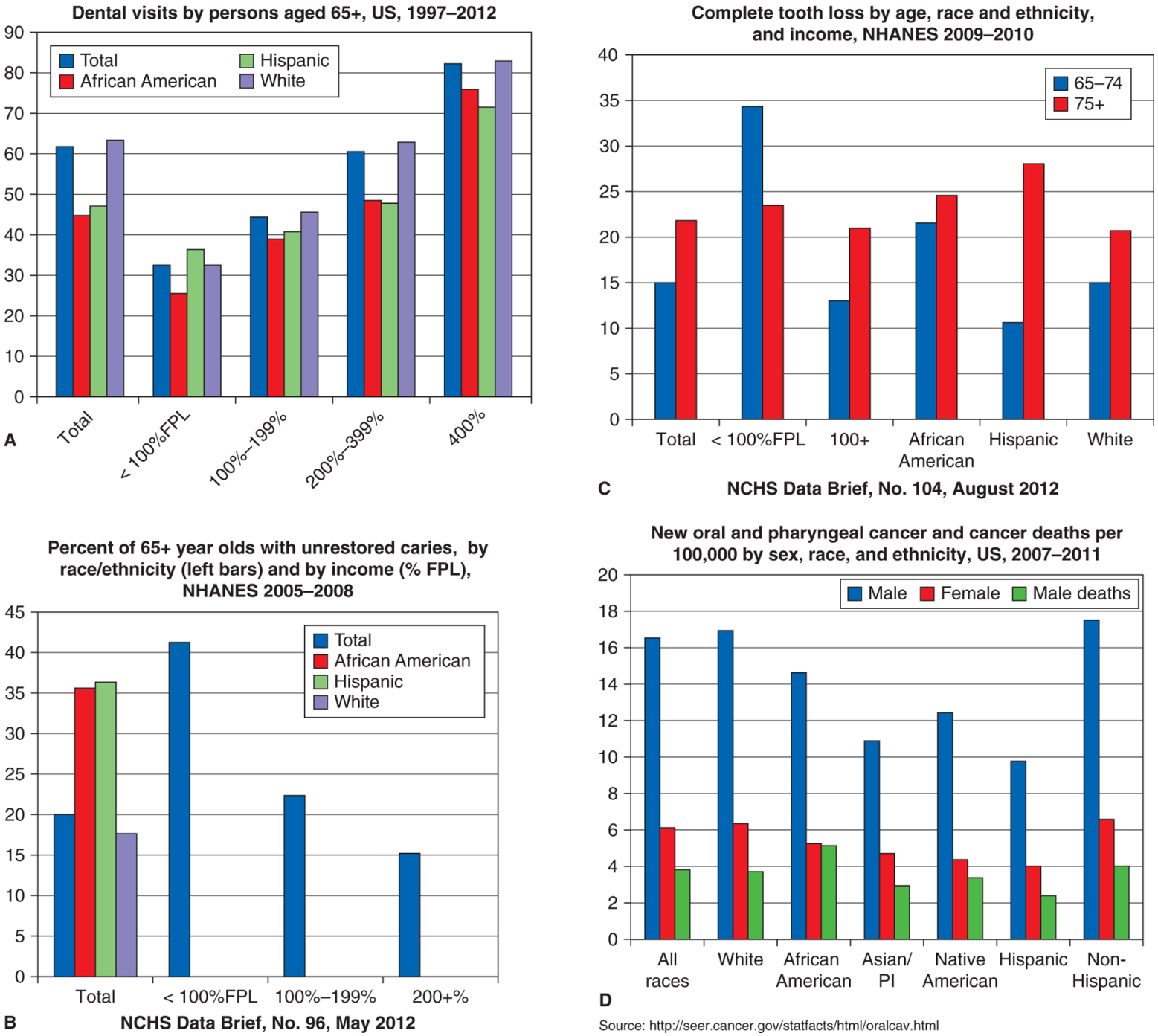


FIGURE 37-8. A. Percemtage of people with a dental visit in the past year by race and ethnicity, United States, 1997–2012. **B.** Unfilled dental caries, United States. **C.** Percentage of people with complete tooth loss, United States, 2009–2010. **D.** Oral and pharyngeal cancer per 100,000 by sex, race, and ethnicity, United States, 2007–2011. AI, American Indian; AN, Alaskan native; FPL, Federal Poverty Level; PI, Pacific Islander.

Baby boomers will be keeping their teeth longer and in greater numbers than ever before; however, dental caries are now as much of a problem in older adults as in children. NHANES caries data from 2005 to 2008 (**Figure 37-8B**) showed that among persons age 65 and over, rates of unfilled caries were highest among the poor (42%) versus nonpoor (17%). Unfilled caries also varied by race and ethnicity: 36% of non-Hispanic black and Hispanic elders had

unfilled caries versus 18% in non-Hispanic whites. Disparities in access and unfilled caries are the most stark in nursing homes and senior centers; in Massachusetts "35% of elders at meal sites had unfilled caries with 17% having major to urgent dental needs, and 59% of elders in long-term care facilities had unfilled caries with 34% having major to urgent dental needs" (Massachusetts Department of Oral Health, 2010).

Complete tooth loss is lowest among whites and highest among the poor, African-American elders, and Hispanics age 75+ (**Figure 37-8C**). New oral and pharyngeal cancer rates are highest among male whites and non-Hispanics, yet death rates are highest among African-American men (**Figure 37-8D**).

COMPREHENSIVE ORAL HEALTH SCREENING

The initial examination and radiographic series by an oral health professional can yield the greatest diagnostic value. This information will not only serve as a diagnostic tool for the immediate treatment needs but also as a baseline that can be used to map the progression of disease or a decline in the patient's oral health. For frail medically compromised (homebound or institutionalized) older adults, subsequent visits can be more challenging when there has been an overall decline in the patient's medical and physical condition or psychological state.

For nondental health professionals on the interdisciplinary geriatric team, it is important to take a few minutes to complete a brief intraoral examination. The specifics of such an examination are described in the next section. Any clinical findings that differ from the routine normal color and structure are indications for referral for a consultation by a dental health professional. Along with the clinical intraoral evaluation, it can be very helpful for the nondental health professional to ask two simple and straightforward questions:

"Do you have any pain or discomfort in your mouth?"
"Do you have any trouble biting or chewing your food?"

Although these questions are subjective in nature, a positive response to one or both predict need for treatment. Any combination of positive responses to these questions should also trigger a referral for consultation to a dental health professional with specialty training or experience with special needs adults or geriatric dental medicine. Often the most important step is the early identification of the clinical problem, and referral. Better to request the referral than to not refer and miss the opportunity to aid the patient with their oral health needs. And, the interdisciplinary team working together can ensure that the needs of the patient are addressed in a timely and thorough manner. An important interaction is between the physician, nurse practitioner, physician's assistant, and the dentist. One key goal is to determine the need for antibiotic premedication prior to dental intervention for a patient with risk for endocarditis, autoimmune disease, chemotherapy, joint replacement, or heart murmur. Another goal is to establish appropriate antianxiety premedication regimes for patients with psychiatric, social, and medical conditions to ensure that optimal dental treatment can be rendered.

KEY FEATURES OF AN ORAL EXAMINATION FOR NONDENTAL CLINICIANS

When performing an intraoral assessment, the clinician should use a strong light source and take the time to systematically review all of the anatomic landmarks in the oral cavity. An instrument such as a dental mirror or tongue blade plus use of fingers with a dry 2x2 gauze can be used to isolate by retraction tissues within the oral cavity to properly evaluate each structure. For example, it is impossible to evaluate the floor of the mouth without physically retracting the tongue and gaining direct vision on the area in question. At a minimum oral health screening should include the hard palate, soft palate, uvula, tongue, cheek, lips, floor of the mouth, gingiva/gums, and teeth. It is important to document and report any findings in any referral for dental treatment. This report should include any mobile, decayed, or fractured teeth along with any structure that is loose or does not follow normal size, color, or texture. Any sign or symptom of an abscess or infection in the oral cavity should be reported immediately. If a physician starts the patient on a course of antibiotic for a dental infection, that should also be noted to avoid repetition of the antibiotic.

ORAL HEALTH IN LONG-TERM CARE

By the time people get to nursing homes for long-term care, dental care needs are already great. There is a clear need for community-based prevention *before* older people require long-term care. However, significant gaps remain in our knowledge base regarding prevention of caries in older adults. Prior to embarking on programs to prevent caries and other oral diseases in older people using, for example, fluoride varnish, patient navigation and patient-centered counseling, it is important to take a community-based participatory approach to find out what older people want, and what would be acceptable options for preventive care.

As the end of life draws near either in the long-term care setting or at home, goals of dental care may shift from aggressive treatment to a focus on comfort, safety, dignity, and preservation of function. In a Delphi study of the goals of oral health in long-term care, the 10 most important goals are shown in **Table 37-7**.

TABLE 37-7 TOP 10 ORAL HEALTH OUTCOMES IN LONG-TERM CARE

Patient will be free from oral pain.
Patient will not be at risk for aspiration of teeth, crowns, dentures, and dental material.
Emergency dental treatment will be available when needed.
Prevent mouth infections.
Daily mouth care is as much a part of daily care as shaving or brushing hair.
Prevent discomfort from loose teeth or sore gums.
Teeth will be brushed thoroughly once a day.
Staff will be able to provide oral hygiene care as needed.
Provide dental care to prevent problems eating.
Recognize oral problems early.

The overall goal in these special populations is to be proactive as opposed to waiting for problems to arise. Prevention and early detection are paramount to avoid more complex problems that may require a more invasive treatment plan for the patient and in many cases a greater financial burden for the patient, the family, or the facility.

First, it is important to identify any limitations the patient may have. Oral health care should ideally be practiced in the morning when the patient wakes up, after each meal, and at their hour of sleep. In some cases patients are not able to gain access to care at each of these points in a day due to the lack of available assistance. When assistance is available the oral hygiene should be practiced as often as possible, but *no less than twice daily*.

When obstacles are introduced, such as a patient with arthritis who is unable to hold the small handle of a tooth brush, the plan needs to be modified so it is doable. The solution to this example could be as simple as creating a larger handle by wrapping a sponge around the brush and securing it with medical tape, placing two small slits in a tennis or racquet ball and sliding the brush into the slits, securing the brush in a bicycle handle or purchasing an electric toothbrush with a larger handle. In most cases the action of the electric brush can take the place of many of the movements that once were accomplished by the patient.

It is also important to continue to see the oral health team on a regular basis. The number of visits needed for older adults could range from quarterly to semiannual or an annual evaluation for the edentulous patient. These routine visits along with a strong care plan for twice-daily oral hygiene will greatly decrease the risk of complex problems arising in the oral cavity. It is important for the physician to communicate any major health changes to the oral health team, who will be able to assist in finding solutions for new barriers. When delivering oral health care within a long-term facility it is important to consider the cooperation and participation of the staff, patients, their families, and the administration. Without the support of the administration, delivery of oral health care is very difficult. There are many models that can be designed to best fit the needs of each specific population. At a minimum the facility should provide the space and time required to properly treat each patient and allow access to the staff to allow for the in-service training as required by the facility.

ACKNOWLEDGMENTS

The late Dr. Jonathan Ship wrote this chapter in the 6th edition. We regret not being able to include him as an author in this chapter as much of the material from that chapter has been retained in this edition. The authors are grateful for Dr. Ship’s enduring leadership and lifetime contributions to the field of geriatric dental medicine and oral health in the

older population.

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Chapter 38

Low Vision: Assessment and Rehabilitation

Gale R. Watson

Learning Objectives

- Understand the prevalence of vision impairment among older adults, its functional implications, as well as the costs to the older adult who develops it, to the family, and to society.
- Understand the normal age-related vision changes, and the functional indications and losses of the most prevalent age-related eye diseases.
- Care for older adults who have vision loss with evaluations, recommendations, supportive education, and appropriate referrals to eye care and rehabilitation providers.
- Assure that older adults with low vision who are in long-term and palliative care have their specific visual needs addressed.

Key Clinical Points

1. **Visual impairment among older adults is treated through examination, prescription and recommendation of assistive devices and interventions, rehabilitation training, and education of family and other health professionals.**
2. **Vision loss among older adults is associated with depression, comorbid health problems, and other disabilities. Treatment and rehabilitation for vision loss increase independence and mental health.**
3. **Geriatricians can play an important role in assuring that older adults receive low-vision rehabilitation, and supporting the full range of services that can be provided.**
4. **Addressing visual impairment and assuring that older adults maintain their visual abilities and strategies can be included as a part of long-term and palliative care plans.**

DEMOGRAPHICS

Population Studies

Many large, population-based, cross-sectional studies have documented the increase in prevalence of eye disease and visual impairment with increasing age, particularly in people over the age of 75. The Centers for Disease Control and Prevention (CDC) and the National Centers for Health Statistics (NCHS) estimate the prevalence of significant visual impairment among Americans age 18 to 44 with vision loss is 5.5%; the prevalence in those age 45 to 74 is approximately 12% and is rising to more than 15% for those 75 and over. After age 85, one in four older people are vision-impaired—unable to read, drive, recognize faces, and perform everyday activities without assistive devices and

rehabilitation training.

Cost of Age-Related Vision Loss

Age-related visual impairment is not only challenging to the person who develops it, but also affects society as a whole. For the year 2004, the total financial cost to the United States of four common eye disorders (age-related macular degeneration, cataract, diabetic retinopathy, and glaucoma), refractive error, visual impairment, and blindness in US residents aged 40 and older was estimated at $35.4 billion. (This includes direct medical costs, direct nonmedical costs, and lost productivity.)

Medicare beneficiaries with coded diagnoses of vision loss have also been shown to incur an additional $2.14 billion in non–eye-related medical costs, incurring significantly higher costs than those with normal vision. Additional eye-related costs per patient yearly are approximately $345 for those with moderate vision loss, $407 for those with severe vision loss, and $237 for those who are blind. Additional non–eye-related costs per patient yearly are $2193, $3301, and $4443, respectively. Health utility (distress, pain, depression, lack of mobility, social limitations) was converted into quality-adjusted life years and the total lost value for this factor was $10.5 billion. Thus, preventing vision loss and disability among older people is not only a medical imperative, but also an economic one.

Related Impairments

Vision loss is reason enough for a decline in function among older people, but vision loss has also been associated with cognitive decline, heart disease, arthritis, hypertension, falls and hip fracture, depression, reduced overall quality of life, and mortality. Older visually impaired people are twice as likely to have difficulty walking as do sighted peers, three times more likely to have difficulty getting outside, more than twice as likely to have difficulty getting in and out of a bed/chair, and three times more likely to have difficulty preparing a meal.

The most prevalent age-related causes of visual impairment in the United States are macular degeneration, diabetic retinopathy, glaucoma, and cataract. Approximately 60% of people with visual impairments who are not institutionalized have one or more additional impairments. These include the loss of hearing, impaired mobility, decreased energy and stamina from respiratory and heart disease, and cognitive changes resulting from stroke or dementia. Vision loss has been ranked third, behind arthritis and heart disease, among the most common chronic conditions causing older people to require assistance with activities of daily living (ADLs). Because the majority of people with visual impairments have useful vision, rehabilitation services and vision-enhancing techniques and devices offer opportunities to increase their visual and general functional capacity.

AGING AND LOSS OF VISION

Normal Age-Related Changes in Vision

Every older person experiences age-related changes in vision. **Table 38-1** summarizes the age-related changes that cause functional declines for older people. Decreased transmission of the ocular media, increased scatter in the cornea, lens, vitreous body, and retina as well as decreased pupil size are related to anatomic changes in the aging eye. The age-related changes discussed here are those that have the greatest impact on function in daily life. These common changes in vision function must be taken in account when considering the daily living, quality of life, and the design of facilities for all older people.

TABLE 38-1 NORMAL AGE-RELATED CHANGES IN VISION

CHANGES	REASON	IMPLICATIONS FOR DAILY LIFE
Loss of accommodation	• Crystalline lenses lose flexibility • Ciliary muscles lose tone	Increasing inability to focus on close targets beginning around age 45. Plus lenses prescribed in a bifocal, reading glasses, or contact lenses; required to compensate for loss of accommodative ability.
Loss of low-contrast acuity	• Decreased transmission of ocular media • Decreased pupil size	Functional loss of acuity under glare or low lighting may cause small targets to be missed,

		bumping or tripping into low-lying objects.
Increased sensitivity to glare	• Increased light scatter in cornea, lenses, vitreous body, and retina	Discomfort even in low glare conditions such as cloudy days. High glare causes decreased acuity and difficulty in seeing targets in the environment. Sun lenses, hats, visors, and umbrellas provide more comfort outdoors; tinted lenses may be prescribed for indoors.
Increased difficulty with dark adaptation	• Losses in ocular transmittance and pupillary miosis	Difficulty moving from bright to dim environments. Risk for stumbling or falling is greater under these circumstances. Fear of balance problems or falling may cause compensatory behaviors such as shuffling, reaching for hand-holds, etc. Change environmental lighting to avoid light/dim areas. If not possible, wear sunglasses outdoors and remove coming indoors. When emerging into disabling light, wait before ambulating.
Loss of color discrimination	• Smaller pupil diameter, reduced light transmission through the lens, changes in photoreceptors and neural pathways	Difficulty detecting differences in dark colors and pastels; adding lamps or matching colors near a sunny window helps.
Loss of attentional visual field	• Decline of higher-order visual processes such as selective and divided attention and rapid processing speed	Risk factor for balance and mobility problems and vehicle crashes in driving. Training improves performance.
Increased difficulty with visual reading ability	• Related to attentional visual field, low-contrast acuity and slower saccadic performance in eye movements.	Reading speed of older readers reduced by one-third that of younger readers; text navigation skills decline with age. Training improves performance.

Accommodation The ability to accommodate for focus on visual targets from distance to near, which is dependent on a flexible crystalline lens and the ciliary muscle, is altered with age, beginning around age 45. During this change, an increasing amount of plus in a concave lens (usually prescribed in bifocal lenses or reading glasses) is required to boost the focusing power of the eye to compensate for the loss in refracting ability of the lens for near tasks.

Visual acuity The visual acuity of normally sighted older people shows only a modest decrease under high-contrast conditions, but reducing the illumination of an acuity chart, reducing the contrast of the acuity chart, and/or adding surrounding glare, produces drastic age-related acuity losses, as compared to young observers. For example, in a sample of 900 older observers, for those at age 82, the median high-contrast visual acuity was 20/30, low-contrast high-luminance acuity was 20/55, low-contrast, low-luminance acuity was 20/120, and low-contrast acuity in glare conditions was 20/160. A young observer loses only about one line of acuity under similar conditions.

Adaptation to changing lighting conditions Because of anatomic changes in the eye and media, older people are more sensitive to glare in the environment, are more likely to experience disabling glare, and have reduced glare recovery time. This may have the most impact on activities such as walking outdoors or driving, but may also affect indoor activities as well, if very bright and dim environments are adjacent, such as restaurants, movie theaters, and atriums. Visual discomfort may arise because of glare, and disabling glare may hide important targets that must be viewed for the sake of safety. Glare sensitivity has been associated with motor vehicle accidents for older drivers.

Attentional visual field Attentional visual field, the visual field area over which one can process rapidly presented visual information, declines with age. Unlike conventional measures of visual field that assess visual sensory sensitivity (such as static flashing lights), attentional visual field relies on higher-order processing skills such as selective and divided attention and rapid processing speed. Decreased attentional visual field has been correlated to a greater incidence of driving accidents and is related to a greater risk for balance and mobility problems for normally sighted older people. Attentional visual field can be improved with training, but such training is not widely available.

Reading rate Visual reading ability decreases with age as well. The reading rate of older people who are normally sighted and have good high-contrast visual acuity decreases by as much as a third of that of young readers. Accuracy of reading, however, can remain comparable to that of younger readers. Reading performance among older people with good acuity (20/30) is highly correlated with attentional visual field; those with good reading performance into very old age also retain good attentional fields as well. Low-contrast visual acuity is also correlated with reading performance for this population; older people with poor low-contrast acuity tend to read more slowly. Even when high-contrast acuity is good, older people, especially the oldest old, are at risk for reading difficulties that may arise from a combination of reduced attentional visual field, slower saccadic performance in eye movements, and poor low-contrast visual acuity. Reading rate for normally sighted older adults with good high-contrast acuity and good comprehension skills can be improved with training. Training in reading efficiency that emphasizes improvements in eye movements for reading similar to those exercises used to improve reading for school children has given good results for this population. Such training, however, is not widely available.

Color discrimination Color discrimination is another aspect of vision that declines with advancing age. People who are older have greater difficulty detecting differences between dark colors such as brown, black, or navy, and also have difficulty with pastels. Loss of color vision in old age is related to smaller pupil diameter, reduced light transmission through the lens, and changes in photoreceptors and neural pathways.

Dark adaptation Dark adaptation declines as a result of losses in ocular transmittance and pupillary miosis resulting from the aging process. Difficulty with dark adaptation can be limiting to older adults moving from light to dim environments and vice versa. The risk for stumbling or falling may be greater under these circumstances. The normally sighted older person may function as if severely visually impaired when first adjusted to a drastic change in illumination.

Spectacles and falls risk Although not related to a change in vision per se, care must be taken in providing refractive correction in spectacle form for geriatric patients. Multifocal spectacle lenses either in the form of bifocals or varifocals are commonly prescribed but are associated with a higher risk of “edge of step” accidents, and multifocal lens wearers are twice as likely to fall as single focus lens wearers. A large percentage of the falls are reported to occur outside the home, perhaps as a result of tripping or stumbling resulting from obstacles not seen in the near-vision correction of the lower visual field. The bifocal portion of a spectacle correction provides additional dioptric power to provide vision at near distance for reading, etc. This means that objects outside this near-focal range, such as steps, curbs, stairs, house cats, etc are blurred and indistinct. This effect is greatest in older patients, as the need for extra dioptric power for near vision increases with age. Patients with multifocal correction are encouraged to tuck their chins and look over the top of the bifocal correction when moving so that they can look through the distance correction in the upper portion of the lenses, but head flexion significantly increases postural instability. Encouraging those who are at risk for falling to explore these issues with their eye care specialists can be an important aspect of falls prevention.

Prevalent Age-Related Causes of Visual Impairment

Age-related macular degeneration Functional vision loss due to age-related macular degeneration may include metamorphopsia (visual images appear distorted and wavy), relative scotomas, as well as dense central scotomas for those whose pathology progresses to visual impairment. Individuals with central scotomas in both eyes usually develop a strongly preferred retinal locus or loci (PRL) that performs as the primary fixation reference, although the patient may not always be aware that there is a scotoma present. The loss of central visual field results in loss of visual acuity and contrast sensitivity. The ability to use the PRL that develops for fixation may be difficult for many people. The effects of macular degeneration on daily life include difficulty with reading print, inability to recognize faces (that can lead to reluctance to participate in social activities), difficulty with distance and depth cues (that adversely affect safe mobility), and loss of color and contrast sensitivity (that interfere with a variety of household and work/leisure tasks) (**Table 38-2**).

TABLE 38-2 AGE-RELATED CAUSES OF VISUAL IMPAIRMENT

CONDITION	COMMON CLINICAL PRESENTATION	IMPLICATIONS FOR REHABILITATION
Macular degeneration	• Reduced visual acuity • Loss of central visual field and contrast	Difficulty with tasks requiring fine detail vision such as reading, inability to recognize faces,

	sensitivity	distortion or disappearance of the visual field straight ahead, loss of color and contrast perception, mobility difficulties related to loss of depth and contrast cues.
Diabetic retinopathy	• Reduced visual acuity • Scattered central scotomas • Peripheral and midpheripheral scotomas • Macular edema	Difficulty with tasks requiring fine detail vision such as reading, distorted central vision, fluctuating vision, loss of color perception, mobility problems because of loss of depth and contrast cues.
Cataract	• Reduced visual acuity • Light scatter • Sensitivity to glare • Altered color perception • Loss of contrast sensitivity • Image distortion • Possible myopia	Usually remedied by lens extraction and implant, except in extreme cases. If not managed by implant, difficulty with detail vision, difficulty with bright and changing light, color perception, decreased contrast perception, some mobility problems caused by loss of perception of depth and distance, sensitivity to glare, and loss of contrast.
Glaucoma	• Degeneration of optic disk • Loss of peripheral visual fields	If not managed by medication or surgery, reduced peripheral fields result. Reading and mobility problems because of restricted visual fields. People suddenly appearing in the small visual field seen as "jack in the box."
Traumatic brain injury and stroke	• Loss of hemi/quadrant visual field, or paracentral scotoma • Possible visual neglect • Visual perceptual difficulties • Visual agnosia	Mobility and reading problems due to visual field loss and spatial perceptual difficulties that reduce ability to drive, reach accurately, and execute eye movements related to reading; difficulty with visual and cognitive processing. Visual neglect may include inability to complete shaving and/or dressing. Difficulty completing other rehabilitation assessments and interventions because visual impairment may not be recognized as disabling.

Diabetic retinopathy The progression of diabetic retinopathy includes macular edema that may cause blurred vision if the fovea is involved, retinal hemorrhages (and/or laser treatments), which may result in scattered central, peripheral, and/or midperipheral scotomas, and retinal detachment, which can cause larger areas of field loss if not reattached. Diabetic retinopathy can progress to total blindness. Loss of function can include decreased visual acuity, scattered field loss over the retina, metamorphopsia across the retina, increased sensitivity to glare, and loss of color and contrast sensitivity. If the fovea is lost to scotoma, then a PRL or multiple PRLs will likely develop. Vision fluctuations can be manifested over time as macular swelling increases or subsides, and can also be related to hemorrhage. Sudden vision loss is common following hemorrhage, with the patient describing episodes of smoky vision, a dropped veil over the eye(s), or seeing black or red strings across the field of view. Treatment and absorption of blood can improve acuity, though not usually to normal levels. The effects on daily life include difficulty reading print materials, difficulty recognizing faces, increased sensitivity to glare and light/dark adaptation, difficulty with distance and depth cues, loss of color and contrast sensitivity, and fluctuating vision.

Cataract Age-related cataract is manifested by gradual opacity of the lens, which interferes with the passage of light, causing reduced visual acuity, light scatter, sensitivity to glare, altered color perception, and image distortion (straight lines appear wavy). People with cataracts may experience trouble with glare and loss of contrast, may have decreased acuity, and report areas of metamorphopsia or small scotomas in the visual field. When the cataract has begun to interfere with lifestyle, surgery may be performed to remove either the entire lens or the posterior portion. Correction for the removal of the lens is provided primarily through intraocular lens implants, but occasionally eyeglasses, or contact lens are used instead. Cataract surgery is the most common major surgical procedure done for people older than age 65 who are receiving Medicare funding. Cataract surgery with lens implantation is associated with improved objective and subjective measures of function in ADLs, as well as improved levels of vision to normal acuity in most cases.

Glaucoma Glaucoma is an increase in intraocular pressure caused by an abnormality in flow of aqueous fluid from the anterior chamber. It can cause a degeneration of the optic disk, loss of visual fields, and severe visual impairment. When left untreated, or if treatment is not successful, glaucoma results in a loss of peripheral fields and can lead to blindness. The effect of peripheral field loss on daily life is most problematic in safe ambulation. Because of field restrictions, the patients may not see objects in their path and may bump into objects that fall outside the field of view in any direction (street signs, tree branches, other people, etc). In addition, a person outside the patient's field of view may suddenly be seen as a "jack-in-the-box" and create a startle effect. Peripheral field loss may also create problems in reading and writing as only a small portion of the page can be seen at once.

Traumatic brain injury Head injury to older adults from falls or automobile accidents resulting in traumatic brain injury (TBI), as well as brain injury due to strokes, can lead to visual impairment. Between 20% and 40% of strokes result in visual disorder that can inhibit cognitive functioning and may reduce the effectiveness of rehabilitation of the traumatic brain injury. Visual field disorders can result from injury to the visual pathway anyway between the retina and the striate cortex. The optic chiasm is an anatomic landmark that differentiates the peripheral (prechiasmatic) and the central (postchiasmatic) visual pathway. Unilateral injury to the prechiasmatic pathway affects the ipsilesional field only, but postchiasmatic injury causes visual deficits in both monocular hemifields that are referred to as homonymous. Visual field disorders must be discerned by visual field measurement techniques called perimetry. Patients are often unaware of field loss and may not report the lost visual field/s, but they may suffer from their effects, for example, bumping into objects, tripping, falling, being unable to read, etc. Vision can be completely lost in the missing field, or some vision function (eg, light detection) may remain. The most common visual field losses are hemianopsia (loss of half the visual field), followed by quadranopsia (loss of one quadrant) and paracentral scotoma (island of vision loss in the parafoveal region). Recovery of some visual field following injury may be spontaneous, and some patients learn spontaneously to adapt to visual field loss by oculomotor strategies; shifting gaze may reveal what is missing in the field of view of a street scene (such as an oncoming car) or the missing portion of a line of text. Systematic training in oculomotor adaptation and visual perceptual training can improve vision function and has the ability to improve the perceived visual field. Visual field loss may also be accompanied by visual neglect. Older adults with neglect may not spontaneously be able to attend to the neglected side. TBI may also result in disorders of visual space perception, which affect reach (over- or underreaching for objects, knocking objects over), driving (accidents resulting from inability to judge distance and depth), and reading (inability to plan and execute accurate eye movements). Visuospatial localization and orientation may be improved through training, but may not reach pre-TBI thresholds. Visual agnosia, a failure to visually recognize an object because of "mistaken identity," is a disorder that is based in both visual-perceptual and visual-cognitive functions. Typically, misidentifications result from the incomplete or inappropriate use of object features such as size, shape, or color. Older adults with TBI may be unaware that they are ignoring other features that might assist with correct identification. Cognitive and/or communication disorders can make visual impairment more difficult to detect following TBI. Undetected or untreated visual impairment in TBI can limit the effectiveness of other TBI rehabilitation. For example, many cognitive and functional assessments use visual items that cannot be appropriately identified by older people with vision loss; visual motor assessments require eye-hand coordination. If TBI vision loss is not detected and treated to the extent possible, the examiner or therapist may get a false-negative impression of the level of TBI disability. In addition, the TBI patient will be frustrated and troubled unduly by participating in rehabilitation that does not simultaneously address the vision deficit.

ROLE OF THE GERIATRICIAN IN VISION REHABILITATION

After diagnosis and medical management of the patient's vision loss, the geriatrician can play an important role in assuring that visually impaired people receive rehabilitation services that are of high quality, are sought in a timely manner, and provide all the benefit that the patients might be able to derive from them.

A geriatrician can provide the following services for their patients related to vision rehabilitation:

1. A visual acuity evaluation. Current best practice includes the use of a logarithmic visual acuity chart.
2. A contrast sensitivity function evaluation. The Pelli-Robson chart is recommended for its ease of use and reliability.
3. A referral to a low-vision eye care specialist (ophthalmologist or optometrist) for the appropriate clinical low-vision evaluation and prescription of optical low-vision devices for tasks the older person can no longer perform,

such as reading, writing, watching television, and recognizing street signs.

4. A referral to vision rehabilitation professionals for assessment and instruction of vision, and assistive devices for literacy, ADLs, safe travel, hobbies, etc. These therapists can also provide environmental analyses and teach the use of environmental cues.
5. Assistance to patients in preparing for rehabilitation by providing information and encouraging them to consider the goals they would like to achieve. **Table 38-3** provides the questions and rating scale for the VA Low-Vision Visual Functioning Questionnaire-20 (VFQ-20). The VA VFQ-20 is a modified 20-item questionnaire that is effective in assessing the impact of vision impairment on quality of life and is helpful in assisting patients in setting goals for rehabilitation.
6. Counseling or referral for coping with psychosocial issues related to visual impairment. Patients may not be forthcoming about these issues, so the physician must ask. Adjustment disorder and depression are associated with visual impairment for older people. When patients are dealing with loss of independence and control, lowered self-esteem, and strained social relations, counseling and/or psychotherapy may be recommended for both patients and family members.
7. Reinforcement of simple strategies to improve abilities, such as the use of saturated colors and contrast in the home environment, and the use of simple devices, such as sun lenses outdoors and brighter indoor environments.
8. Providing information to the patient and family about the variable nature of low vision, its effect on daily life tasks, and the variable nature of visual abilities according to fluctuations of light and contrast.
9. Sponsorship of, or referral to, support groups where older people with vision loss and their families can discuss problems, coping, and rehabilitation strategies they have learned with other patients.
10. Assistance in community awareness about the prevalence, treatment, and rehabilitation of visual impairment among older people.

TABLE 38-3 VA LOW-VISION VISUAL FUNCTIONING QUESTIONNAIRE-20 (WITHOUT OVERALL SCORING)

Directions: Select one of the responses listed below to indicate the level of difficulty for each activity which pertains to the following question: "Is it difficult to_____?"

1. Not difficult
2. Slightly/moderately difficult
3. Extremely difficult
4. Impossible

U. Unscored/don't do because of *nonvisual* reasons

Note: *If you use a low-vision device, adaptive device, or an adaptive technique to assist with the activity, respond as though you were using the device or technique.*

ACTIVITY	LEVEL OF DIFFICULTY
1. Read newspaper or magazine articles	
2. Read mail	
3. Read menus	
4. Read small print on package label	
5. Keep your place while reading	
6. Read street signs and store names	
7. Read print on TV	
8. See photos	
9. Find something on a crowded shelf	
10. Identify medicine	
11. Tell time	
12. Watch TV	
13. Handle finances	
14. Get around outdoors in places you know	
15. Adjust to bright light	
16. Take a message	

17. Prepare meals
18. Use appliance dials
19. Groom yourself
20. Eat and drink neatly

Patients likely to benefit from vision rehabilitation include those with reduced acuity of less than 20/50 in the better-seeing eye, central or peripheral field loss with intact visual acuity, reduced contrast sensitivity, glare sensitivity, and/or light/dark adaptation difficulties as well as those with traumatic brain injury. Candidates for cataract surgery with macular disease might also benefit from preoperative low-vision assessment and coincident rehabilitation training that enhances postoperative visual performance and satisfaction with a cataract procedure.

ADAPTATIONS OF CLINICAL AND FUNCTIONAL EVALUATIONS FOR OLDER ADULTS

The clinical and functional low-vision examinations for older people should distinguish aging from treatable disease processes; focus holistically; be multidisciplinary; incorporate family and caregiver support; and identify and set realistic goals to improve functional status and quality of life.

In health care service delivery to older adults with low vision, certain aspects of the examination sequence are adapted to accommodate these principles.

Case History Interview

Because most age-related visual impairments result in a central scotoma, most patient complaints will be related to the loss of acuity, loss of central visual field, and resultant decrease in contrast sensitivity and color sensitivity. Patient goals for rehabilitation will usually include reading, writing, independence in ADLs such as meal preparation and household maintenance, management of glare and other illumination concerns, leisure activities, and safe independent movement and travel. Older people may also have specific health-related activities that require the use of vision (eg, loading a syringe with insulin, changing an ostomy bag); these will be goals as well.

This information may be taken by a preexamination telephone interview to lessen the amount of time the first examination visit might require. Because low-vision rehabilitation requires a great deal of energy and motivation from the patient, it will be guided by their personal goals for rehabilitation and by those tasks that are difficult or impossible to perform because of low vision. In this regard, the intake interviewer may find that some education is necessary in order to set reasonable goals for low-vision treatment. Because most low-vision interventions and assistive devices are “task specific,” it is important to state treatment goals as specifically as possible.

Because of the nature of the older person’s vision loss, professionals should become familiar with some of the courtesies and accessibility issues that assist in providing quality health care, such as the following:

- Unless there is a problem with the person’s hearing, always speak directly to the older adult with visual impairment.
- Allow the older adult to take your arm when moving from place to place in the environment, and use appropriate sighted guide techniques. If you are guiding a person with visual impairment by having the person take your arm, you are responsible for assuring that the path you are taking is wide enough to accommodate both of you. If the path is not wide enough (eg, a crowded hallway), ask the person to step behind you, while still holding your arm when walking.
- Say your name when first coming into the room, and tell the older adult when you are leaving the room.
- Do not leave the older adult with low vision standing alone in a hallway or room without a wall or furniture near to touch for orientation and balance.
- Avoid using directional cues that are visual in nature such as pointing or giving directional references that are unclear to those with low vision. For example, instead of saying, “take that chair over there,” say, “take the red chair against the white wall to your immediate right.”

Clinical Low-Vision Evaluation

The low-vision eye care specialist (who may be an ophthalmologist or an optometrist) must be flexible and adaptable

to a variety of different environments, schedules, and communication styles. The conventional pattern of the low-vision examination will be followed including distance and near acuities; internal and external ocular health examination; retinoscopy; tonometry and slit-lamp biomicroscopy; ophthalmoscopy; ophthalmometry; determination of central and peripheral fields; color vision and contrast-sensitivity testing; glare testing; and near and distance testing of vision-enhancing devices, including optical, electronic, and nonoptical devices. For many older adults, especially those in long-term care facilities, a careful refraction and update of conventional spectacles may provide significant improvement in vision. **Table 38-4** summarizes the aspects of the clinical low-vision examination.

TABLE 38-4 CLINICAL LOW-VISION EXAMINATION

Settings for the examination	• Long-term care facilities • Individual's home • Community service agency • Rehabilitation center
Aspects of the examination	• Distance/near acuities • Internal/external health examination • Retinoscopy • Tonometry • Slit-lamp biomicroscopy • Ophthalmoscopy • Ophthalmometry • Central/peripheral field measurement • Color vision testing • Contrast-sensitivity testing • Evaluation of low-vision devices (optical, nonoptical, and electronic)

Because of the nature of medical and long-term care service delivery to older adults, the low-vision examination and therapeutic intervention is often taken out of the office or clinical setting. There is a growing trend of providing low-vision services as a part of outpatient hospital care, comprehensive outpatient rehabilitation facilities, and long-term care facilities, such as nursing homes and private homes of older adults.

Long-Term Care Facilities

Despite the fact as many as half the people in nursing homes have visual impairment, few nursing home residents receive low-vision care. For example, one study estimated only 25% of visually impaired patients at a long-term care facility who were in need of vision rehabilitation were referred by their attending ophthalmologists. Another study found that there was no difference in the referral rate for vision services for nursing home residents between those who complained about their vision and those who did not. Another study found that only 11% of all residents in 19 nursing homes had received eye examinations in the last 2 years. Providing information about vision and vision impairment to the nursing home staff is important for assisting residents in using their remaining vision effectively. Because stroke is another common medical condition requiring rehabilitation for older adults, it is important that the low-vision team work closely with those professionals who diagnose, treat, and rehabilitate older adults who have experienced cerebrovascular accident. Currently, Hadley School for the Blind provides an online curriculum in visual impairment for in-service training for people with visual impairment and their family members as well as professionals and technicians who work with them (www.Hadley.edu). The use of curricular materials by long-term care staff has proven effective in increasing staff knowledge and positive outcomes for patients.

Hospital Settings

Low-vision care is routinely provided to older veterans in the hospital system of the Veterans Health Administration (VHA). In the inpatient Blind Rehabilitation Centers, a veteran who is severely disabled is seen for up to 10 weeks of rehabilitation, including low-vision rehabilitation. Results from a national outcomes study indicate positive outcomes and veteran satisfaction from these programs that exceed the outcomes of rehabilitation in the private sector. The VHA

also provides low-vision rehabilitation for veterans who are visually impaired but have remaining vision. In 2009, the VHA expanded low-vision services at medical facilities and in patients' homes providing $40 million in funding for a continuum of care closer to veterans' homes. Outcome studies of all VA vision rehabilitation services indicate that veterans who are provided low-vision services regain their ability to perform independent activities of daily living (IADLs) independently and become active community participants. VHA is the only national medical system that completely integrates vision and blind rehabilitation into the system of care. In fiscal year 2014, VHA provided inpatient, outpatient, and home-based vision and blind rehabilitation to approximately 29,000 unique patients. Further, there are approximately 50,000 severely disabled blind veterans on the rosters of VHA case managers, who assure that this vulnerable population receive all the VA benefits that should accrue to them. Hospitals in the private sector are increasing providing services to older people as a part of outpatient services, and low-vision rehabilitation is often provided.

Community Service Agency Settings

The Older Americans Act (OAA) is a major source for the organization and delivery of social and nutrition services for older adults as well as their caregivers. The OAA authorizes many services through a national network of 56 state agencies on aging, 629 area agencies on aging, 244 tribal organizations, and 2 native Hawaiian organizations representing 400 tribes. The OAA programs include community service employment for low-income older Americans; training, research, and demonstration activities in the field of aging; and vulnerable elder rights protection activities. These programs may be contacted through the local telephone book yellow pages. For example, in Atlanta, the services are clustered in the BellSouth Yellow Pages under the heading, "Senior Services." The explanation of the local county services contracts is provided and a contact number for each county is listed. Low-vision services might be provided onsite at some community service settings because of the prevalence of visual impairment among older adults. A description and national access to these programs may be viewed on the website http://www.aoa.acl.gov/ (accessed January 2, 2015).

Private Home Settings

Pew Research Center estimates that 4 in 10 adults in the United States are caring for a sick or older family member at home. The number of caregivers increased 10% between 2010 and 2013; most caregivers surveyed were between 30 and 64 years old. Approximately 70% of the older population requiring long-term care resides in the community. Senior residential retirement centers have increased in number. Most frail older people requiring care are living at home with family members, and not in long-term care facilities. It is crucial that family members and caregivers understand the sometimes contradictory nature of visual impairment; for example, visual performance varies widely under different levels of illumination and can decline if the older person is fatigued. Comorbid conditions such as dementia, mobility impairment, and depression can affect how the older person uses vision and interprets visual images. Understanding the interaction of these factors will help family members in supporting the older adult achieve their goals for vision rehabilitation.

Functional Visual Assessment

Whenever possible, a functional assessment should take place in the older adult's daily environment. Specific goals for using vision independently stated by the older adult will guide the functional assessment to discover what visual target size, target distance, and visual skills are required to achieve that goal. For example, if the patient's goal is to read the newspaper again, the target size requires approximately 20/40 or better visual acuity with spectacles and magnification, the target distance will be determined by the magnification device, and the visual skills required are precise visual fixation and saccades while maintaining the focal distance of the magnification device. The older adult must learn not only new visual strategies, but also new cognitive strategies to aid comprehension, even with a slower rate of reading. The functional assessment can also uncover the need to address other goals, the need for environmental assessment and modification, and to provide ongoing opportunities to educate the older adult and family about vision and rehabilitation. **Table 38-5** presents the key aspects of the functional vision assessment.

TABLE 38-5 KEY ASPECTS OF THE FUNCTIONAL VISUAL ASSESSMENT

Functional visual acuities	Distance and lighting required for discriminating detail of objects in the environment

Functional visual fields	Ability to perceive objects in the environment in central and peripheral quadrants of the visual field at near and distance
Color/contrast discrimination	Ability to detect objects, their color, and contrast with the varying light/dark backgrounds at varying distances
Ocular motor skills	Ability to maintain fixation and move the eyes/head/body to fixate, scan, track, and localize targets in the environment
Visual perceptual skills	Ability to make sense of what is seen; recognize critical features, perceive part-to-whole relationships, identify figure-ground, etc
Lighting	Analysis of the usefulness of environmental lighting; need for greater/less illumination and controls such as filters, sunlenses, etc
Use of visual and nonvisual cues	Availability and use of visual and nonvisual cues in the environment that enhance task performance
Performance of activities of daily living and instrumental activities of daily living that are affected by vision	Observe for ability to perform, ease and speed of performance, comfort and stress level, safety

The functional low-vision assessment may be completed by a wide variety of rehabilitation professionals. Traditionally, the functional low-vision assessment of older people has been provided by a low-vision therapist, a rehabilitation teacher for the visually impaired, an orientation and mobility specialist, or some other professional from the field of visual impairment, such as an eye care technician or technologist. Now, as vision rehabilitation is increasingly a part of hospital services and comprehensive outpatient rehabilitation facilities, the functional assessment may be provided by a rehabilitation nurse, an occupational therapist, or some other rehabilitation professional who has received specialized training in low vision.

Regardless of the background of vision rehabilitation professionals, they should be well versed and experienced in basic optics of the eye, lenses, and low-vision devices; methods of observation and evaluation of visual skills for all daily tasks; the causes and functional implications of visual impairments; basic techniques of sighted guide and basic orientation and mobility; assessment of safety (falls, medication access, sharps, burns, etc); assessment of literacy (reading, numeracy); assessment of the visual aspects of environment; and basic techniques of assessing and using technology such as optical devices (eg, magnifiers, spectacles, monoculars) and electronic devices (eg, Braille writer, smartphones, tablets, computers, and closed-circuit television [CCTV] system). The rehabilitation professional providing the evaluation may also be the rehabilitation therapist, in which case they must be familiar with techniques of instructing visual-motor skills for all daily, vocational and avocational tasks (with and without optical devices and access technology), task analyses, organization and time management, basic orientation and mobility, basic techniques of literacy, and safety in the home. The professional must also be familiar with tools and techniques that do not require the use of vision. There are situations in which using vision is not the safest or most efficient way to complete a task. In that case, other nonvisual strategies such as voice-over, use of Braille tags, use of a long cane on a dark street, etc, are more helpful. The rehabilitation professional will work closely with the eye care specialist providing the clinical low-vision examination, and the low-vision team may also include a counseling professional and any other professionals who are providing care associated with vision impairment or comorbid disabilities. Because many older people are at risk for multiple impairments, this team may also include other physicians, such as a geriatrician or physiatrist, orthopedist, speech, physical, respiratory, and recreational therapists, nurses, and technicians.

MANAGEMENT OF LOW VISION

Developing a Vision Rehabilitation Plan

The clinical low-vision examination and functional visual assessment culminate in a vision *rehabilitation plan* that summarizes the information obtained in the evaluations into clearly stated goals and objectives. If Medicare is funding the low-vision services, the plan will follow that format and requirements. In many cases, family members also may be involved. The implementation of the vision rehabilitation plan should emphasize a process using the principles of andragogy, or adult learning, that incorporate the older person's values, beliefs, attitudes, and life experiences.

Following the clinical examination and functional assessment, the low-vision team will recommend low-vision

devices (including optical, electronic, nonoptical, and environmental modifications) that will be evaluated to assess their usefulness by the older adult. There should be additional focus on the rehabilitation program and its adaptation for older individuals. Successful use of low-vision devices is related to the intensity of the instructional program. Research shows that specialized therapy in the use of visual skills and low-vision devices improve the abilities of low-vision individuals who are older to a greater extent than do the services provided by eye care specialists alone.

Low-Vision Therapy

Low-vision therapy is a crucial aspect of providing care. Therapy is dependent on the goals of the older adult and might include the following:

- Visual skills rehabilitation training including fixation, preferred retinal locus ability for reading, and visual scanning for other visual tasks such as locating a traffic light or street sign.
- Literacy assessment and training to improve reading accuracy, speed, comprehension, and duration.
- Legible handwriting, and written expression (including being able to read one's own handwriting).
- Use of low-vision devices for daily tasks.
- Modification of the environment to enhance safety and ability to complete activities including lighting, contrast, organization, labeling, glare control, removal of hazards, and other safety measures.
- Use of access technology such as computers, smartphones, tablets, global positioning devices, etc.
- Guidance on safe functional movement within the known environment.
- ADLs such as home maintenance, meal preparation and cleanup, clothing care, grooming, etc.
- Strategies for self-management of health such as organizing and accessing medications, blood pressure check, diabetic management, ostomy care, etc.
- Assessment and modification of work stations at home or away.
- Information and education of caregivers such as understanding the functional implications of low vision and their effect on daily life, understanding the use of assistive devices.
- Visual strategies for safe driving, or managing daily routines without driving.
- Use of community resources for people who are visually impaired such as support groups, free services such as *Library for the Blind* talking books, Treasury Department's free money identifier, low or no cost transportation, etc.
- Referral to other practitioners in a broader low-vision team, for example, referrals for assessment and training in the use of long white cane for mobility, guide dog, Braille training, diabetic education, etc.

Instruction and Guided Practice Using Remaining Vision and Low-Vision Devices

Working with a low-vision therapist will provide an opportunity for the older adult to develop the appropriate visual skills; use optical devices and access technology; and learn to apply principles of color, illumination, and contrast that make the environment as conducive as possible to the use of remaining vision. It is important to assist caregivers in understanding how rehabilitation interventions aid the older adult in accomplishing visual tasks. Family members and caregivers can provide important social support in this regard, but must understand the process in order to be most helpful. In a study of visually impaired older veterans, a supportive caregiver was the most strongly correlated variable to continued use of low-vision devices 1 to 2 years after they were prescribed. If at all possible, devices should be loaned for use in the daily environment before they are prescribed to assure that they are useful.

Some aspects of instructing the use of vision, prescribed devices, and access technology are particularly important when working with older people with low vision. Because of the potentially devastating consequences of falling, the low-vision therapist must be certain to address safety issues related to using low-vision devices that will prevent falls. Nausea, dizziness, and other aspects of motion sickness can be side effects of using magnification, and reducing them is an important aspect of instruction. Monoculars and binoculars should be used as spotting devices only, and older adults must never attempt to walk while viewing through them. If the older person's goal is watching television or spectator sports, binoculars that are spectacle-mounted may be provided and the older person will use them only while seated.

Another factor to be explored in the use of low-vision devices for older adults is hand tremor. Hand tremor may be severe enough that handheld magnifiers or telescopes are not useful. The low-vision team may want to explore spectacle-mounted devices to avoid the difficulty of maintaining focus, if hand tremor is problematic.

Postural support and ergonomic considerations are important to using devices for people who are older. Because of

the prevalence of back and neck pain, as well as limited stamina, it is important that the therapist assure the older person to be as comfortable as possible. The low-vision therapist will evaluate and demonstrate the use of appropriate ergonomic devices such as the appropriate chair and table, lumbar and cervical support, footstool, lamps, and reading stands. One study demonstrated that older adults who were supported according to ergonomic standards achieved significantly better reading performance.

Cognitive decline may limit the usefulness of low-vision devices for independent functioning; however, an additional goal can be added for rehabilitation—reducing caregiver burden. Vision rehabilitation for older adults with cognitive decline may include ergonomic solutions for comfort, increasing safety by providing good lighting for ambulation and other visual tasks, judiciously adding bold color and contrast for cuing activity and movement, and using simple assistive devices for common activities (eg, watching television on a larger screen, reading large-print books, getting a bright-colored snack from the refrigerator).

Finally, illumination is an important aspect of the instruction. Most older people need more light, but some may be extremely sensitive to light. An evaluation of a variety of lamps and overhead lighting situations is necessary, with the use of illumination controls that are individually recommended such as filters, absorptive lenses, hats with brims, and pinhole glasses.

Low-Vision Devices

Low-vision devices are optical devices, electronic devices, lighting devices, ergonomic devices, access technology such as global positioning devices, accessible smartphones and tablets, and other tools that enhance the use of vision. Some devices, such as those optical devices that incorporate refractive correction, require special prescription. Others are more simple and straightforward in their assessment and recommendation, such as lamps, reading stands, or large-print books. During the clinical evaluation and functional assessment, the low-vision team will discover whether magnification, minification, voice-over, or other nonoptical devices (such as large-print books, lamps, reading stands, etc) will be useful for enhancing the vision. **Table 38-6** summarizes the types of devices available and their uses. Devices are prescribed/recommended based on the goals of the older person and most people require instruction and practice in their use.

TABLE 38-6 ■ LOW-VISION AND SPEECH-OUTPUT DEVICES

OPTICAL/ELECTRONIC DEVICES	TYPICAL USE
Stand or handheld magnifiers (both optical and electronic, eg, smartphones with universal design)	Short-term reading or writing tasks such as checking a price tag or recipe, signing a check
Spectacle-mounted magnifiers	Long-term reading such as newspaper; used for writing in low powers
Handheld monoculars or binoculars	Traffic or street signs, spectator events
Spectacle-mounted monocular or binocular telescope	Television viewing, spectator events, possible driving Short-focus telescope can be used for cards, reading music, games, woodworking, etc
Closed-circuit television system (may be free-standing or incorporated into computer)	Reading, writing, independent activities of daily living, with distance camera, can be used like a telescope with very wide field of view
Field-expansion devices: • Reverse telescope • Field-expansion prisms • Hemianopic mirrors	Field expansion for ambulating or obstacle detection, identification, and/or avoidance Best with normal or near-normal acuity
NONOPTICAL DEVICES	**TYPICAL USE**
Lamps	Provide brighter illumination, primarily used as task lighting
Illumination control devices	Control glare, may increase contrast: sun lenses, hats, visors, colored filters
Handwriting implements	Felt-tip pens, bold-line paper, check- and letter-writing stencils,

	allow user to stay on line and write legibly
Posture and focal distance support	Upright reading stand, footstool, chair with arms and high back Cervical and lumbar support: provide comfort and allow user to read or write for a longer period
Large print	Large-print books and news, large phone dials, etc, to enhance visibility
Color/contrast aids	Brightly colored tape/paint for marking dials, edge of steps, etc, to enhance visibility and safety
Speech-output (aka voice-over) devices	Software, hardware, or applications that provide salient electronic information in spoken format. Spoken format reduces reading fatigue for long-term reading tasks or mobile tasks, such as electronic global positioning systems with spoken format.

Magnification devices may be categorized as four types: relative distance, relative size, angular, and electronic. Relative distance magnification is provided by bringing the device to be viewed closer to the eyes. Often older adults who want to recognize someone will move more closely to the face they want to see, exhibiting this type of magnification. Spectacle-mounted magnifiers focus the target image, such as print for reading, at ranges closer than the older eye can accommodate, and allow very close distances to be maintained. These lenses must be prescribed by an eye care specialist experienced in low vision in order to incorporate the refractive correction of the older person when required. Typically, these devices require a close focal distance and have a short depth of focus. Depending on the power and focal distance, they can be used for near tasks such as reading, writing, and viewing photographs.

Magnification may also be provided by stand or handheld magnifiers, which are often more familiar to older adults who may have used them previously for maps or coins. These devices do not require a close eye-to-lens distance, but the closer to the eye the lens is held, the wider the field of view. Some are available with built-in illumination, which overcomes the problem of illuminating the target the older adult is viewing. Handheld magnifiers require a steady hand to maintain focus and may be fatiguing to use for long periods. Older adults who use stand magnifiers must wear their bifocal correction for visual accommodation, as the lens is set slightly inside the true focal distance of the lens in order to provide a better optical image at the periphery of the lens.

Relative size magnification is used whenever a target to be viewed is made physically larger. Examples of this are magazines and books that are printed larger than normal. Environments such as older adult high-rise apartments or condominiums and planned communities may also use enlarged signage, another example of relative size magnification.

Telescopic devices provide angular magnification by the use of a positive and negative lens in housing (galilean) or by the use of two positive lenses with an erecting prism (keplerian). Older adults may have used monoculars or binoculars in the past for sporting or other events, and may have developed basic skills in their use. Older adults may use telescopic devices for identifying targets that are further away, such as street signs, sporting events, or television. The telescope may be handheld or may be mounted into spectacles for hands-free viewing. Mounted short-focus telescopes may be used for tasks that are closer, such as reading music from a stand or identifying cards on a table. Some older adults with visual impairment who meet visual and driving requirements may use miniature mounted telescopes (called bioptics) for driving.

The CCTV system, used by people who are visually impaired, is an example of electronic magnification. The CCTV provides a camera to focus on the visual task and the older adult sees the image projected onto an enlarged screened monitor or his television set. The visual task may be reading and writing from a desktop or the camera may be positioned for visual tasks at a greater distance such as seeing the minister and choir at church. The advantages of the CCTV include more magnification than any other device, a wider field of view, and color and contrast enhancement capability. CCTV offers a mechanism for the development of new technologies such as miniaturization, head-worn devices, and contrast enhancement.

Computer configuration with the CCTV can use multiple cameras to provide split-screen images for designing a workstation that simultaneously accesses computer, print viewing, word processing, and distance viewing.

Expanded field devices are helpful to older adults who maintain normal or near-normal acuity while experiencing decreased field of view, such as that caused by glaucoma or hemianopsias. Expanded field devices provide the ability to find targets by increasing the perceived view of a scene. For example, an older adult with restricted fields wishes to find the arriving and departing flight monitors in an airport. By using a field-expansion device, these monitors can be

more easily located and the user then moves closer to them in order to read the information without the device if central vision is intact. A reverse telescope functions similar to a peephole in a door, but with better optics. Another type of field-expanding device minifies in the horizontal meridian only. The visual field may also be expanded by the use of base-out prisms incorporated into spectacles. The base-out prism shifts the image in, allowing a small eye movement to see the expanded field. Small mirrors attached to spectacles may also be used for field expansion.

Universal design in small portable electronic devices such as smartphones and tablets has revolutionized the field of vision rehabilitation. These devices are manufactured with sensory access (both vision and hearing enhancements) included in each one manufactured. The visually impaired user merely accesses the settings to turn on magnification or voice-over controls in the device, and then downloads a myriad of applications that provide the ability to ask the current location; use navigation systems; read; capture spoken commands, notes and documents; turn on a flashlight in the device; take a picture and ask what the picture depicts; use a wireless keyboard to use the device as a computer and other activities too numerous to mention. Universal design for access is becoming a marketing strategy for companies; one large cable company recently announced voice-over for navigating channels and finding desired programming. For older adults who are technologically adept, accessible smartphones and tablets are quickly learned and highly used. For older adults who have struggled with computers and other technology such as “smart” microwave ovens, these access devices may be very frustrating. However, even very older adults who are cognitively intact can master these intricate but powerful devices with good rehabilitation techniques.

If a smartphone, tablet, computer, CCTV, or other electronic device is to be used visually, the eye care specialist will assure that the older adult’s vision is best corrected for the viewing distance of the screen. A pair of reading spectacles may be prescribed.

Instruction in the Use of Devices That Enhance Remaining Vision

A sequence of instructional procedures covers several areas:

- Use of visual skills without low-vision devices
- Use of visual skills with low-vision devices
- Use of vision and low-vision devices for individualized functional tasks that lead to the accomplishment of defined goals

Instruction in the use of visual skills without devices covers fixation, spotting, localization, scanning, tracing, and tracking. Individuals with maculopathy (such as age-related macular degeneration or diabetic retinopathy) may require additional instruction in the development and maintenance of visual skills using the PRL.

Instruction in the use of visual skills with low-vision devices includes integrating unaided visual abilities with the unique demands of a low-vision device such as maintaining the focal distance or focusing the device, and adjusting eye and head movements to compensate for a restricted field of view through the lens. If the individual is using eccentric viewing (the use of a PRL other than the fovea), the instructor assures that the device selected allows the opportunity to maximize field and acuity in the eccentric position.

Reading and Writing With Low-Vision Devices

Reading is a task that is so fundamental to our society and so disrupted by age-related visual impairment that it is the primary goal for vision rehabilitation among older adults. Readers with low vision can develop visual skills that are well-adapted to reading if they receive appropriate intervention. Most readers develop a strong PRL following the onset of central scotoma. The PRL is an area that will take over the function of fixation in an eccentric, nondamaged area of the retina. The reader may require instruction and practice in using the PRL for reading, especially because of the demands of using magnification to compensate for acuity loss. A Swedish study found that 71% of older adults with low vision could read the newspaper following rehabilitation, although at a 3-year follow-up that number had dropped to 48%. However, the number of fluent readers (70 words per minute or better) had increased from 41% to 48% over the 3-year period. These results indicate that those older adults with vision loss who persevere with rehabilitation strategies are able to continue improving their skills over time. In another study, people with macular loss who had a PRL below the scotoma exhibited faster reading rates, and the size of the atrophic area in the macula was the predominant limiting factor in reading; the larger the atrophy, the lower the reading rate. Reading rate is also related to visual span (number of characters available in the field of view) and the reserves of acuity and contrast sensitivity provided by the visual system and low-vision device. Accuracy of word identification and comprehension

of reading, however, can remain near normal for readers with macular loss despite their slow rates. Readers with low vision often supplement visual reading with speech output devices such as spoken computer programs and books on audiotape.

Older adults with low vision can write effectively using a combination of magnification devices, lighting devices, stencils (templates for checks, envelopes, letters, etc that assure that writing is spatially correct), and pens that provide more visibility.

Older adults who have good computer skills can substitute desktop computer, laptop, or smart phone for most low-vision devices and use the universally designed magnification, voice-over, and/or both to achieve reading and writing goals.

ENVIRONMENTS FOR OLDER PEOPLE

The onset of visual impairment for older adults can make even the most familiar environment seem strange and hazardous. It is important that older adults be oriented to familiar and unfamiliar environments, and that the environment be as "user-friendly" as possible to increase independence and safety. There are a variety of rehabilitation techniques that assist in accomplishing this task. **Table 38-7** presents the basic strategies.

TABLE 38-7 WAYS TO MAKE AN ENVIRONMENT MORE VISUALLY ACCESSIBLE

Change the real or perceived size of objects to be viewed	For loss of detailed vision: • Increase size (large print) • Move closer (move chair closer to the television) • Use magnification For loss of peripheral fields with normal acuity: • Minify image (reverse telescope) • Move further away • Use field-enhancement devices such as mirrors
Improve lighting	Use appropriate environmental lighting to decrease glare and increase overall light level; use illumination controls such as sunlenses, hats with brims, visors, colored filters; use task lighting such as flex-arm lamps
Increase contrast between objects and background	Eliminate busy background patterns, mark down steps with contrasting color on risers; increase contrast between furniture, eating utensils, etc, and their background
Use bright, clear colors	Mark light switches, dials, etc, with colored tape; use large areas of bright color for discrimination of objects
Organize the environment for ease and safety	Doors completely open or closed, chairs under table when not in use, furniture against the wall, organize clothing for color and function, organize and mark food stuff, etc
Consider alternative strategies that do not use vision	Use of other senses for task performance, such as voice-output for reading materials, use of long white cane for safe travel, olfactory cues for doneness of food, etc

Improving the Lighting

Most older people require two to three times more light than do younger people for the same tasks, but those with cloudy media (cataract, keratoconus, vitreous floaters, etc) are more sensitive to glare. The challenge is to get enough light without creating glare, which can be disabling. For example, the glare from a sunny window onto a waxed floor, tabletops, and glass could cause objects in the dining room of a senior community to be obscured. An older person with low vision might function as if blind in that environment and be unable to find a chair, recognize his friends, serve his plate, or identify the food in a buffet line.

In an environment that is conducive for the function of older people, it is important to manage not only light, but also shadow, which can be conducive to function, for example, a triangular shadow at the end of a step indicates the

height and depth of the step as well as how many steps are there. But shadow can also be hazardous, such as the shadow of a garden wall that obscures a sidewalk curb, causing a person to trip or fall.

Lighting is best if controllable, no matter what type it is. Many older people with low vision will require task lighting that can be positioned closer to reading/writing material or craft activity. Because the intensity of light is inversely related to the square of distance from its source, adding light at ceiling height will not provide adequate task illumination for older viewers. Task lights must be used that can be positioned closely, and therefore flex-armed lamps are best in this regard.

There are a variety of different types of bulbs that are useful and recommended for older viewers with low vision.

- Fluorescent lighting spreads evenly, is inexpensive and energy efficient, but provides less contrast because of that evenness and produces less shadow. It is a harsh light and flickers and may be bothersome to some viewers, causing headache and eye strain. Covering or shading fluorescent bulbs or bouncing the light from the ceiling to the eye may be helpful.
- Incandescent light is easily directed and provides more contrast and shadow. But the light can pool, especially if provided by one bulb suspended from the ceiling, causing pinpoint glare or pools of light within relative darkness. Using multiple incandescent fixtures can eliminate this problem. Incandescent lamps are good for task lighting such as reading, sewing, or hobbies.
- Halogen light uses the glow of halogen gas, as well as the incandescent filament to create a brighter light. The light is more blue and therefore may require filtering. Ultraviolet or blue light may generate superoxide and hydroxide free radicals that may be related to damage in the eye. Although controlled clinical studies have not been done, blue light has been suggested as increasing risk of cataract and macular degeneration. Subsequent studies have not shown a correlation to visible light exposure and risk, but many rehabilitation services are cautious about “blue light hazard.” An Australian study suggests that people with less melanin (ie, light-colored iris, fair skin) are at more risk from light.
- Neodymium oxide and incandescent bulbs are currently touted as “full-spectrum lighting.” These bulbs emit fewer ultraviolet and infrared rays and provide a sharp drop in the emission of yellow light. The effect is a more vivid “true” color, similar to sunlight, so contrast is increased.

These types of lighting can be mixed to achieve effects that are most pleasing and comfortable for older people with low vision. A study exploring these types of lighting in reading lamps found strong preferences among older readers with low vision, but no differences in objective measures of reading performance based on the type of light. Thus, informed reader choice should guide the selection of the type of light for older readers.

Light/dark adaptation is another aspect of environmental lighting that must be considered. Most older people have difficulty traveling from bright areas to dim ones because their dark adaptation is not as efficient as in young adults. People with severely restricted field loss (eg, advanced glaucoma) become functionally blind in dim lighting. Avoiding light/dark areas in the environment such as a bright dining room and dim hallway is helpful. When these areas are unavoidable, the older person could use illumination controls such as sunglasses or brimmed hats to assist with light/dark adaptation. People with severely restricted visual fields who are at risk for falling when ambulating at night may use lightweight, very bright, portable lamps with long battery life that have been designed for night hunters.

Increasing Contrast

Light/dark contrast is produced by the amount of light that is reflected from different surfaces (a light object is brighter than a dark one). A greater contrast between objects and their backgrounds make them easier to see. Therefore, providing an area of dark background and an area of light background in the bathroom, kitchen, and bedroom can help a person more easily identify possessions. For example, if a comb and brush are of light color, they may be kept on a dark tray. Most TV remotes are black, so they should be placed on a very light background. Similarly, marking the edge of stairs with contrasting colored tape makes each step more visible.

Using Color

The ability to identify colors, especially darks and pastels, diminishes with age. Certain visual impairments, especially those that affect the cones, such as macular degeneration, also reduce color vision. However, bright, clear colors can be seen by most older people with low vision. For example, yellow against navy blue is very visible, because it combines both color and contrast cues.

Using Organizational Strategies

Organization can be extremely helpful for the person with low vision. For example, always making sure that doors are completely open or completely closed, and placing chairs under the table when not used increases the safety of the environment. Organizing and labeling clothing by color and function in closets and drawers and organizing the kitchen can assist an older person in continuing to live independently. Learning new ways of performing daily tasks can make the loss of vision less of a problem in independent living. For example, retrieving a pair of spectacles that have fallen onto a light carpet might be difficult for some older adults. Learning a visual scanning pattern that begins at the site where the spectacles seem to have fallen and then continues in a circular pattern outward until they are found will assist in retrieving them.

Using color coding can be helpful as well. For example, chicken soup cans could be marked with wide yellow rubber bands, and tomato soup cans could be marked with wide red rubber bands. These markers could be quickly identified, avoiding the necessity for identifying the soup with a magnifier each time a can is retrieved from the cabinet. Brightly colored and nubby stick-on "dots" may be provided that provide both contrast and tactual cues for marking dials, buttons, and controls of appliances.

Using Alternative Strategies

Even when an older adult with low vision retains useful vision for a wide variety of tasks, it is sometimes helpful to use alternative techniques that do not require the use of vision because vision may not be the most efficient or safest way of accomplishing some tasks. For example, even though an older adult may have useful vision for walking, he may find it best to use a long white mobility cane in order to detect drop-offs, so that vision can be used to seek landmarks for orientation. An older adult with low vision may use speech output (a program that speaks symbols or words) for most computer word processing so that limited stamina for reading and writing may be used for reading mail, which must be done visually. A metal plate called a "flame-tamer" may be placed on the eyes of a gas stove in order to avoid burns in the kitchen. Knowledge of a wide variety of rehabilitation strategies and tools will assist older adults with low vision in developing a repertoire of techniques and devices that allows them to complete tasks safely, efficiently, and effectively.

Orientation to a new setting requires some basic alternative techniques that can be used anywhere. Some older adults may be able to use all of the techniques; some may only need one or two. It is important to remember not to rush the older adult in orientation, whether it is a long-term care facility or physician's office. These exercises may be repeated as often as necessary. Teaching family members these techniques may be helpful when new environments come up in the future. **Table 38-8** presents an overview of these techniques.

TABLE 38-8 ■ ORIENTATION TO A NEW SETTING FOR OLDER ADULTS WITH VISION LOSS

Using a starting/ending point	Begin at one starting/ending place in the room, such as the door. While leading an older adult via human guide, have the older adult reach out and feel both sides of the doorway, then describe the contents of the room. While leading him, allow him to trail his hand against the wall and furniture to feel their features. Give simple names to the walls using some feature of the wall (eg, the wall to the right is the bed wall, the wall opposite is the window wall).
Using compass directions or clock face	Some older adults will be more familiar with compass directions. Using the same starting point of the doorway, proceed as the older adult's human guide and use north wall, south wall, east wall, and west wall to name the four sides of the room. Use compass directions as the way of finding and naming locations in the room. Use clock face numbers in a similar manner for those who can more easily understand them.
Using landmarks and cues	Use familiar landmarks for orientation to a new environment, for example, the smell of food is a landmark for the dining room. The audible hum and red glow of a soft-drink machine may be another landmark.

PSYCHOSOCIAL CONSIDERATIONS

Adaptation to Vision Loss

Anxiety and depression are common reactions to loss, and age-related visual impairment is complicated by the other losses associated with aging. There are two schools of thought on the timing of rehabilitation related to adaptation. Some rehabilitation professionals subscribe to a "loss theory" of psychological adjustment. This theory proposes that the person must "die" as a sighted person, and be "reborn" as a visually impaired person, incorporating the visual impairment into the sense of self. According to this theory, attempting rehabilitation would be fruitless until the process is complete. Others subscribe to the theory that anxiety and depression are related to a person's negative stereotypes about visual impairment and a lack of confidence and motivation to attempt rehabilitation, but that if rehabilitation is successful, depression and anxiety should be reduced.

Older adults may hold many negative stereotypes associated with visual impairment: increased helplessness, inhabiting a world of darkness, increased vulnerability to crime, the perception that use of devices mark them as different, or to be pitied. Older adults with low vision may attempt to pass as fully sighted in order to avoid having others project these negative stereotypes onto them. But attempting to pass as fully sighted may cause other difficulties. For example, older adults with low vision do not recognize faces well, and the lack of a friendly hello when passing acquaintances may be interpreted as unfriendliness. Failure to use alternative techniques for identifying targets and moving in the environment may lead to falls, burns, or other safety hazards.

Support groups and peer counseling for older adults with low vision can be extremely helpful in coping with vision loss. Support groups may be found through local multiservice agencies for people who are visually impaired or may be started by senior citizen's centers or other groups. Short-term professional counseling in conjunction with rehabilitation may be very helpful.

Family and Social Support

In a recent study of low-vision device use among veterans, most of whom were older males with macular degeneration, family support was the most powerful predictor of continued use of devices up to 2 years following their prescription. Providing information and support to family members who are experiencing the impact of an older member's vision loss can be powerful. Visual impairment is experienced by the entire family or caregiving system, not just by the older person, and both social and psychological concerns must be addressed. The loss of vision by one family member can disrupt roles in the family, create economic demands, and add stress when tasks previously performed by the older adult must be performed by someone else.

For family members who understand the functional implications of visual impairment, understanding the behavior of their older adult with low vision is easier. For example, understanding the effect of changing lighting conditions, the effects of glare, and the adaptation times when traveling from dim light to bright and vice versa, can help explain behaviors like shielding the eyes, shuffling the feet, hesitation, fear of falling, and ceasing previously enjoyed activities. The fact that an older adult with restricted visual fields may pick up a dime from the floor, then bump into a partially open door seems contradictory, but is perfectly explained by the functioning field of view.

Assisting older adults with low vision in continuing social activities, such as hobbies, crafts, games, and traveling can aid them in maintaining important contacts with family and peers. Social support and contact is associated with less depression in older adults with low vision. Support groups can assist older adults with low vision in completing and using their rehabilitation, as well as facilitating adaptation to vision loss. Peer support, or mutual aid groups who meet regularly to share their concerns may be especially beneficial for older adults who may be overprotected, abused, or treated paternalistically by those who do not understand visual impairment or aging. Facilitating assertiveness for older adults with low vision is recommended because it is linked to less depression and more social support. Social skill training in assertiveness for older adults with low vision has been shown effective in decreasing depression, and in deriving greater satisfaction in life.

FUNDING FOR LOW-VISION REHABILITATION

Rehabilitation Services Administration

Vision rehabilitation services have been funded through private pay, or through vocational rehabilitation services for individuals who were preparing for the work force. Funding for services to older adults with vision impairment has been a critical health care issue in the United States. Public funding through Rehabilitation Administration Service for

the *Independent Living Services for Older Individuals Who Are Blind* program under the Rehabilitation Act is minimal, with approximately $495 million allocated nationally in fiscal years 2014. These funds provide services in the traditional "blindness" system—state services or private agencies for the blind. State governments may also allocate funding for low-income older people to receive vision and blind rehabilitation as well.

Veterans Health Administration

Prior to 2002, only older veterans with legal blindness who served in the US military and whose disability is service-connected had full access to comprehensive blindness and services through the Department of Veterans Affairs Medical Centers. However, most visually impaired veterans have age-related vision loss and their income is such that a copayment is required from them or from their private insurance carrier. Vision rehabilitation services were developed initially to meet the needs of blinded veterans returning from World War II. Young war-blinded men had few other medical problems, so efforts to rehabilitate them for the work force spawned the professions of orientation and mobility instructors, rehabilitation teachers for the blind, and low-vision therapists in order to meet their unique needs. Services for veterans who are visually impaired but not legally blind were provided nationally beginning in 2008. This specialized "blindness and low-vision" rehabilitation was not considered part of the broader medical rehabilitation. Credentialing of vision-rehabilitation professionals developed separately from occupational or physical therapists, and their practice was autonomous, requiring neither medical referral nor physician supervision. As a result, many medical professionals are unaware of their services and do not understand the "blindness" rehabilitation system in which their practice began. The Department of Veterans Affairs model of service delivery in vision rehabilitation continues today in the same vein. Services are provided nationally by teams of professionals. Ophthalmologists or optometrists provide the medical eye care services, and the vision and blind rehabilitation professionals are orientation and mobility specialists, rehabilitation teachers, and low-vision therapists. Recently the Department of Veterans Affairs appropriated $40 million to provide vision rehabilitation services in a continuum of care for patients who have low vision as well as those who are blind, in recognition that veterans are aging in place and require services close to home. The vision/blind rehabilitation service in this milieu is also unique in that prosthetic devices are provided. Devices such as magnifiers, telescopes, binoculars, CCTV system, computer equipment, accessible smartphones and tablets, etc are dispensed according to Veterans Affairs (VA) policy at no cost to veterans as a part of the VA's commitment to vision/blind rehabilitation services.

Medicare Funding for Vision Rehabilitation

The rise in older adults with low vision has spurred Medicare to produce a national policy of reimbursement as well. In 2002, the Centers for Medicare and Medicaid Services (CMS) released a national program memorandum to alert the provider community that Medicare beneficiaries who are blind or visually impaired are eligible for physician-prescribed rehabilitation services from approved health care professionals on the same basis as beneficiaries with other medical conditions that result in reduced physical functioning. This memorandum was issued in response to the committee report accompanying the FY 2002 Labor/Health and Human Services/Education appropriations bill.

The memorandum further directed that the patient receiving services must have a potential for restoration or improvement of lost functions, and must be expected to improve significantly within a reasonable and generally predictable amount of time. The rehabilitation that is covered is to be short term and intense; maintenance therapy is not covered. Applicable Health Care Common Procedural Coding System therapeutic procedures are outlined in the memorandum, as are applicable International Classification of Diseases (ICD)-9 codes that support medical necessity.

The effect of the program memorandum has been to increase the visibility of Medicare provisions for vision rehabilitation, but it is not a national coverage decision. Medicare carriers are not compelled by the memorandum to develop a Local Medical Review Policy as a result, and are still able to deny all claims that the local carrier does not deem medically reasonable or necessary.

In 2003, Congress authorized the Secretary of Health and Human Services to carry out a nationwide outpatient vision rehabilitation services demonstration project. The purpose of the project was to examine the impact of standardized national coverage for vision rehabilitation services in the home by physicians, occupational therapists, and certified vision/blind rehabilitation professionals. The 2003 Demonstration Project did not provide coverage for adaptive equipment (low-vision and blindness devices). The project proceeded for 2 years without clear results. The outcome of the project was status quo, with no new practitioners added to Medicare for reimbursement in providing care for older people with low vision.

To date, the national funding sources for providing vision and blind rehabilitation care continue to be CMS,

Department of Veterans Affairs, and Rehabilitation Services Administration.

PALLIATIVE CARE FOR OLDER ADULTS WHO ARE VISUALLY IMPAIRED

Palliative care for older adults with visual impairment may focus on assuring that patients are able to see as well as participate in activities that mean the most to them; continue hobbies and other desired activities that relieve stress and help them to feel that life is as normal as it can be; participate in diversions that may assist in managing pain; participate in spiritual activities such as reading or listening to devotional materials that strengthen faith and may reduce anxiety and depression; and reduce caregiver burden.

In addition to the suggested strategies in the section of this chapter titled "Environments for Older People," the following considerations may assist patients with visual impairment in palliative care.

- Assure that spectacle correction in eyeglasses is up-to-date. Assure that spectacles, magnifiers, and other useful devices are within patient's reach, and are kept in the same known place, so that they may be used whenever desired.
- Assure that patient's autonomy is respected in long-term care. When entering the patient's room, knock on the door and ask to enter the room; address the patient by name and identify yourself.
- If the patient is not in home environment, ask the patient how he or she performs activities of daily living such as bathing, eating, and dressing, and how you can help. Include the patient, family, and palliative team in the plan.
- Talk in a normal, natural tone of voice, face the patient directly, and if possible, make eye contact and explain what you're going to do in detail before you do it (eg, taking blood or vital signs); ask permission or notify the patient before you touch him or her.
- Always address the patient directly, even if family members are present. Don't worry about saying the words "look," "see," or "blind."
- If the patient is in palliative care in a facility, describe the room layout including dimensions. Use compass directions to describe the location of objects in relation to the bed (eg, "you are facing north in the bed," "the door is to the west").
- Place the phone, call bell, and bedside table within the patient's reach in a known location, and let the patient know where they are. Do not move them.
- Place the item in the patient's hand, or the patient's hand on the item, if needed.
- Once you've oriented the patient to the room, alert staff to leave things in position. Notify the patient before you move, take, or add any objects (eg, furniture, trash can, grooming aids).
- If the patient is mobile, use the "Human Guide" technique to assist the patient with ambulating:
  - Ask the patient from which side he or she would prefer to be approached and guided.
  - Extend your arm so that it touches the patient's; he or she can grasp and follow your elbow.
  - While the patient is holding your arm, walk to his or her side, one step ahead, at a pace that is comfortable for him or her.
- Use clock coordinates to describe the location of food on the plate and all items on his food tray. Ask the patient what assistance is needed.
- Indicate to the patient when you are leaving the room so she will know you are leaving.
- Encourage the patient to use assistive devices (eg, talking clocks/watches, radios, speech-output reading devices, etc).
- Encourage the patient to use reading technology for pleasure reading, devotionals, etc. If the patient does not have the stamina for reading, experiment with talking books or voice-over devices. Reading to the patient with visual impairment may be a bonding experience for family members and friends.
- Craft activities and games are available that are enlarged and use bright saturated colors and good contrast.

FURTHER READING

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Chapter 39

The Auditory System

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Learning Objectives

- Learn the epidemiology, pathophysiology, diagnosis, clinical features, risk factors, and treatment of hearing impairments in older adults.
- Understand the interplay between common medical comorbidities, medications, genetics, and hearing disorders in older patients.
- Gain a clear understanding of tests used to distinguish various kinds of hearing impairments.
- Learn about recent technological advances involving hearing aids and cochlear implants, as well as emerging therapies targeting hair cell regeneration.

Key Clinical Points

1. **Aging-related hearing impairment (ARHI) is the most common sensory impairment in older adults, and its prevalence increases steadily with age.**
2. **Men develop ARHI earlier than women. Family history and specific genes increase risk for presbycusis. Over 55% of ARHI in older patients can be attributed to heritability.**
3. **Diabetes mellitus and cardiovascular disease, two of the most common comorbidities seen in older adults, promote hearing loss and cochlear pathology.**
4. **Pure tone audiometry, tympanometry, acoustic reflex measurements, and word recognition scores are the most common methods for hearing assessment.**
5. **Older patients often present with difficulties in speech recognition rather than inability to hear sound.**

INTRODUCTION

Our sense of hearing is unequalled by our other sensory modalities in terms of its sensitivity, dynamic range, and discrimination of the finest nuances in stimuli. It does serve us well through a part of our lifetime, but beginning in our forties (slightly earlier for men and later for women) our inner ears suffer the influence of aging in a very subtle yet progressive manner. Aging-related hearing impairment (ARHI) affects most people aged 65 and older and represents the predominant neurodegenerative disease of aging. Hippocrates had already noted deafness to be more prevalent among his older patients and in *The Comedy of Errors*, Shakespeare's elderly merchant, Aegeon, complains of his own "dull deaf ears." Thus, ARHI or presbycusis is not a disease of modern societies but has been accepted for centuries as one of Lord Byron's inevitable "woes that wait on age" that it still appears to be today.

It was the New York otologist St. John Roosa who first drew the attention of his colleagues to hearing loss of the older adults as a medical condition. In 1885 he proposed the name presbycusis that he had coined from the Greek *πρέσβυς*, old man, and *ακούειν*, to hear. Systematic studies of the anatomic pathology began in the late nineteenth century, leading by the 1930s to the realization that the decreased auditory acuity could be attributed to deterioration of the auditory sensory cells and the auditory nerve. These changes frequently affect the perception of the upper

frequencies first, resulting in high-frequency hearing loss as a hallmark of presbycusis. However, ARHI is not a uniform condition, but a multifactorial one combining genetic predispositions with a plethora of lifetime insults to the hearing organ because, in all its versatility and efficacy, our sense of hearing is also uniquely vulnerable to environmental influences. These may include noise, chemicals and solvents at the workplace, lifestyle (eg, smoking) and leisure activities (from iPods to rock concerts and target shooting), diseases (eg, diabetes, respiratory disorders), viral or bacterial infections, and even the adverse effects of the very medications (aminoglycosides, cisplatin) designed to cure diseases and infections. This spectrum of potential abuse to our auditory organ yields an exceedingly intricate etiology and pathology of hearing loss in older adults. Age-related pathology of the central auditory system adds to the complexity of the problem. Consequently, presbycusis has been defined as "hearing impairment associated with various types of auditory dysfunction, peripheral or central, that accompany aging and that cannot be accounted for by extraordinary ototraumatic, genetic, or pathologic conditions" but it is almost impossible in practice to separate the confounding factors from the "true" effect of aging. It has therefore often been debated whether presbycusis indeed exists in populations that are isolated from adverse environmental influences.

Animal models provide hope to resolve some of the basic mechanisms that underlie the deterioration of hearing and point to ways and means to delay or prevent presbycusis. By virtue of the availability of molecular and genetic information and of transgenic and knock-out animals, mice have become one of the preferred model animals although, as we shall point out later, caveats do apply here too. This review will illustrate the features of human presbycusis and draw on animal models to discuss its potential molecular basis.

EPIDEMIOLOGY OF AGE-RELATED HEARING IMPAIRMENT

ARHI is the most frequent sensory impairment in older adults and the prevalence of the disorder increases with age. In humans, as in most other species, ARHI begins at the high frequencies and progresses gradually into the lower speech range. Males experience ARHI earlier than females, beginning in the late thirties to early forties while women will match men's deficits in the later decades of their lives. Approximately 44% of people suffer from a significant hearing loss in their sixties; this number rises to 66% between the ages of 70 and 79 years, and skyrockets to 90% after age 80. With an increased lifespan of the population worldwide, especially in developed countries, the impact of ARHI will continue to increase in the future.

The individual rate of decline in hearing, however, is exceptionally variable and some people may maintain excellent hearing with "golden ears" late into life as a result of genetic traits that have yet to be elucidated. Superimposed on the gender differences, race apparently also plays a role, although whether this role is causative or correlative is unknown. One study of over 2000 older Americans aged 73 to 84 found the incidence of high-frequency hearing loss that met their criteria to be 91.8% in Caucasian American men, 76.1% in African-American men, 74.2% in Caucasian American women, and 59.2% in African-American women.

RISK FACTORS MODULATING AGE-RELATED HEARING IMPAIRMENT

The large variability in the age of onset, rate of progression, and the nature and severity of the hearing impairment suggests that ARHI is a complex genetic disorder with superimposed environmental and health-related risk factors.

Genetics

Family history plays a role in predisposition to presbycusis. An analysis of hearing thresholds in sibling or parent/child pairs versus spousal pairs (controls) in Framingham Heart Study patients found that the inherited genetic effects were significant. The predictive power of family history appeared stronger for females than males and stronger for "metabolic" type rather than sensory type hearing loss (see Schuknecht's classification of age-related hearing loss in the section on "Peripheral Pathology of Age-Related Hearing Impairment in Humans"). Overall, the study suggested that about 55% of ARHI in older adults can be ascribed to heritability.

Further studies detailing genes that contribute to ARHI in humans have pointed largely to those involved in detoxification of reactive oxygen species and include glutathione S-transferase polymorphisms (in the *GSTM1* and *GSTT1* genes), an *N*-acetyltransferase 2 gene polymorphism, and superoxide dismutase 2 promoter variants. Recently, a genome-wide association study (GWAS) of presbycusic subjects at the Audiological Center of the Antwerp University Hospital found no variants with genome-wide significance. Previously reported genes for ARHI could not

be confirmed, indicating that ARHI is highly polygenic in nature with probably no major genes involved.

Gender and Hormonal Factors

ARHI sets in earlier in males than in females, both in the human population and experimental animals, but in the later decades of life these differences diminish, suggesting a modulation of ARHI by the hormonal status of an individual. In support of this notion, receptors for steroid hormones are indeed present in the cochlea. In further support of a link between ARHI and hormonal levels, fluctuations in hearing thresholds have been observed during the menstrual cycle, and estrogen therapy slowed the development of ARHI in postmenopausal women. Furthermore, in patients (and mouse models) with Turner syndrome who synthesize inadequate levels of estrogen, ARHI sets in early. While estrogen seems to be protective of hearing, progesterone replacement is detrimental in postmenopausal women, negatively affecting the auditory nerve pathway and neurotransmitters, underscoring the complexity of hormonal regulation of ARHI.

Another class of steroid hormones, mineralocorticoids, may also influence ARHI. A correlative study in human subjects showed a protective effect of elevated serum levels of aldosterone on auditory thresholds and an improvement of speech perception ("hearing-in-noise") in older individuals. Although aldosterone primarily acts on water and ion resorption in the kidney, aldosterone receptors have also been localized to the inner ear. They are hypothesized to influence the ionic composition of inner ear fluids, which is essential for cochlear homeostasis and the transduction of sound (see section on "Anatomy of the Auditory Periphery").

Diseases

A contribution of specific diseases to the rate and severity of hearing loss has long been speculated, but is difficult to ascertain. The complex etiology of ARHI renders it difficult to eliminate all potentially confounding factors in human population studies. However, good evidence exists for diabetes and cardiovascular disease as risk factors in age-related hearing impairment.

Diabetes mellitus Both types 1 and 2 diabetes promote hearing loss and cochlear pathology in humans and in animals. Deficits in several aspects of auditory function were significantly more pronounced in a group of people with type 2 diabetes aged 60 or older compared with a group of age- and sex-matched controls and excluding those with other significant health issues or a history of hearing problems. Plasma concentrations of glycosylated hemoglobin (HbA_{1c}), an indicator of potentially elevated glucose levels, have been found to correlate with ARHI in a cohort aged 65 or older, even in those without levels high enough to be diagnosed with diabetes.

Diabetes mellitus and associated deregulated blood glucose levels exact a multitude of stresses on a cellular level, which could lead to loss of function in the delicately balanced hearing organ with time and age. Fundamentally, increased blood glucose levels lead to cellular hypoxia and build up of reactive oxygen species and other metabolic by-products, as well as changes in the collagen and microtubule structure of the cells. Also, the effects of diabetes on vasculature are profound, including atherosclerosis and vessel wall dystrophy. In the inner ear, which depends on the stria vascularis to carefully maintain the endocochlear potential, this could result in apoptosis of cells and impaired sensory function.

Cardiovascular disease All conditions that affect the function of blood vessels such as hyperlipidemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, and cardiovascular disease have been implicated in ARHI. Specifically, strial metabolic ARHI (see next section) appears to be associated with those conditions because the stria vascularis is most vulnerable to any restriction of blood flow. Just as in diabetes, any disease leading to vascular compromise will impair the function of this tissue and, by way of decreased endolymphatic potential and driving force for the transduction process, diminish the sensitivity of the cochlear organ to sound.

Lifestyle and Environmental Factors

Poor health habits with regard to exercise, smoking, and diet are also considered risk factors for ARHI based on data from population studies. Since some of these habits influence cardiovascular function and other potential risk factors for ARHI, it remains open to what extent lifestyle directly influences the auditory organ or whether the effects are secondary to general health.

Major environmental risk factors that may contribute to the manifestations of ARHI, briefly mentioned above, include exposure to excessive noise, ototoxic medications (primarily aminoglycoside antibiotics and anticancer agents

of the cisplatin class), and industrial solvents. At levels that do not necessarily inflict acute damage by themselves, these environmental factors appear to sensitize the auditory system to subsequent impairment and aggravate any age-related changes. This notion was borne out in recent experiments in which mice at a young age (1–3 months) received a moderate noise exposure that resulted in temporary hearing loss only. Although their hearing recovered to normal baseline levels within a few days or 1 week after the noise exposure, these mice developed a significantly greater hearing loss with progressing age than control animals. The implication of this finding is that occupational or recreational (target shooting, rock concerts) noise exposure, even if no deficit is noted at the time, will take its toll in later years.

Psychology

Interestingly, adherence to negative stereotypes regarding older adults, the concept in many societies that aging is met with an inevitable decline in function of all faculties, demonstrates as a predicting risk factor for ARHI. External stereotyping (the prevalence of stigmata with aging in the subject's culture) and negative internal perception (extent of internalization of these stigmata) acted as independent risk factors on hearing loss with age, and had a stronger impact than gender or race. This predicts an observable phenomenon wherein cultures with positive concepts of aging do not expect their elders' hearing to become enfeebled and, in fact, the incidence of ARHI is then lower. Here again, an influence on the auditory system maybe secondary to the effect of stigmata on general well-being and levels of stress hormones in particular.

BASICS OF HEARING AND HEARING LOSS

In order to understand different forms of presbycusis and their underlying mechanisms, some knowledge of auditory anatomy and physiology is required. The following sections briefly summarize the essentials.

Anatomy of the Auditory Periphery

Not only is ARHI shaped by many influences, it also shows a variety of morphologic manifestations. The present framework for classifying age-related hearing loss was proposed by Schuknecht in 1964 based on the histopathology of human temporal bones. In order to understand its age-related changes, we should first sketch the structure of the mammalian auditory organ, the cochlea (**Figure 39-1**). Encased in bone, the tissues and fluids of the cochleae of different species coil "snail-like" for 2½ to 4½ turns and a total length of a few centimeters without any relationship to body size. A human cochlea, for example, on average extends for 33 mm in 2½ turns while the dimensions in the guinea pig are 20 mm and 4½ turns. In all species, however, the cochlea is tonotopically organized, meaning that high frequencies are processed in its basal part, low frequencies in the apex.

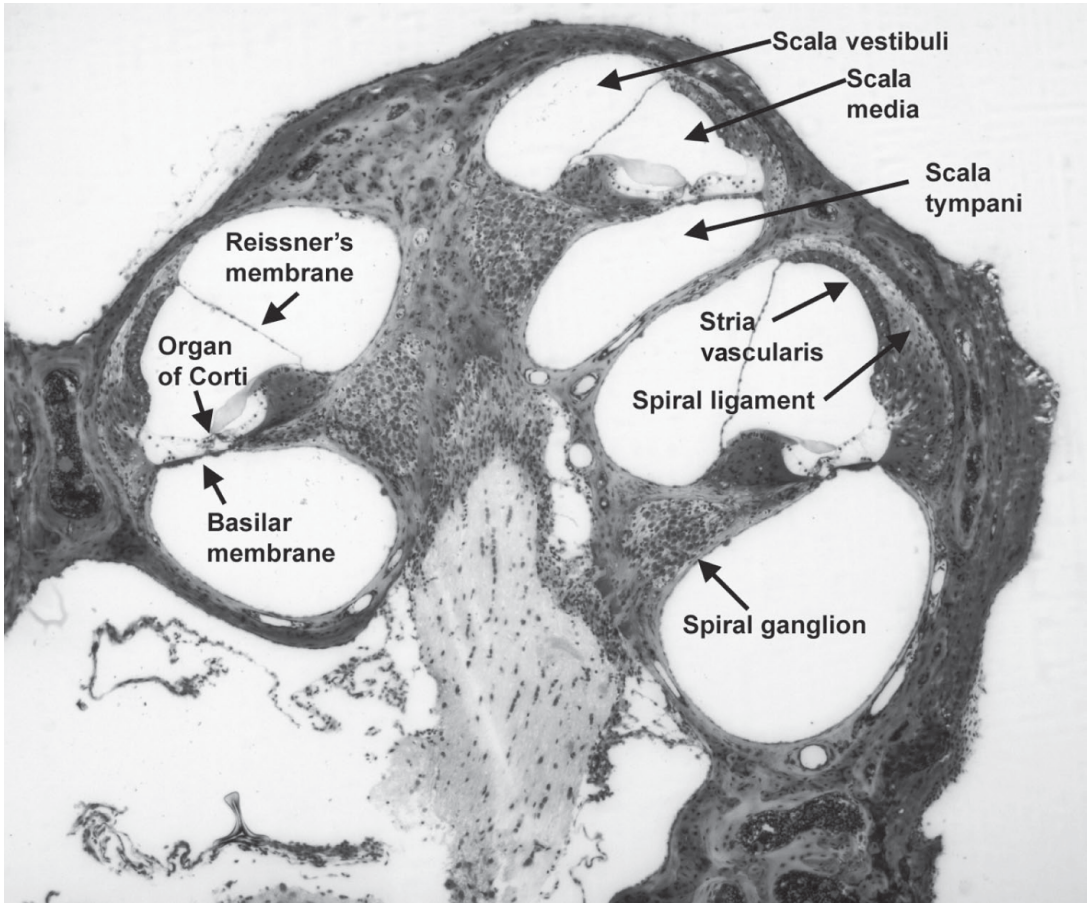


FIGURE 39-1. Anatomy of the cochlea. A low magnification light micrograph of a near midmodiolar cross-section illustrates the tissues and fluid-filled spaces of the 2½ turns of the mouse cochlea. As indicated in the upper turn, the fluid spaces are the scala tympani and scala vestibuli filled with perilymph, and scala media filled with endolymph. They are separated by the thin Reissner membrane and by the basilar membrane on which the organ of Corti is located. When sound reaches the ear, the vibrations of the tympanic membrane (ear drum) are passed along the middle ear ossicles to the cochlea where they initiate a traveling wave in the fluids, which, in turn, moves the basilar membrane. The tectorial membrane, an acellular structure, rests on the stereocilia of the hair cells. Spiral ganglion neurons run from the organ of Corti where they contact the hair cells through the modiolus to the central auditory system. The stria vascularis and spiral ligament, tissues involved in setting up the ionic composition and high (+70 to +100 mV) potential of the endolymph, lie along the lateral wall of the cochlea.

Several structures with distinctly different functions and susceptibility to environmental and age-related insults can be discerned within this membranous labyrinth and are best seen in a midmodiolar section that transverses the length of the cochlea. The lumen of the cochlea is separated into three fluid-filled compartments by the basilar membrane and Reissner membrane. Scala vestibuli and scala tympani contain perilymph, similar in composition to extracellular fluids. Scala media contains endolymph, unique among body fluids by its high concentration of K^+ and low Na^+, creating a large positive endolymphatic potential (also referred to as endocochlear potential) as a driving force for the transduction current, which is used by the sensory cells. Scala media is bounded laterally by spiral ligament and stria vascularis, the tissues that are responsible for maintaining the ionic composition and hence the potential of endolymph. These tissues are also highly vascularized and provide most of the oxygen and nutrient supply to the cochlea.

The organ of Corti (**Figure 39-2**), located on the basilar membrane, is the auditory end organ containing sensory cells and supporting cells. Sensory cells include one row of inner hair cells and three rows of outer hair cells, numbering several thousand in all species. The name "hair cell" is derived from the stereocilia that protrude from the apical end of the cells (**Figure 39-3**) and contain the mechanotransduction channels. Inner hair cells are the primary sensory cells that convert the mechanical acoustic input into receptor potential and release of neurotransmitter, triggering action potentials that are carried to the brain by the spiral ganglion neurons. Most of the afferent innervation by this auditory nerve converges on the inner hair cells. The major function of outer hair cells is to enhance the performance of the cochlea, particularly at low intensities of sound. They receive mostly efferent innervation from auditory centers in the brain. Supporting cells include the inner pillar, outer pillar, Deiters, Hensen, and Claudius cells, about whose function we know relatively little.

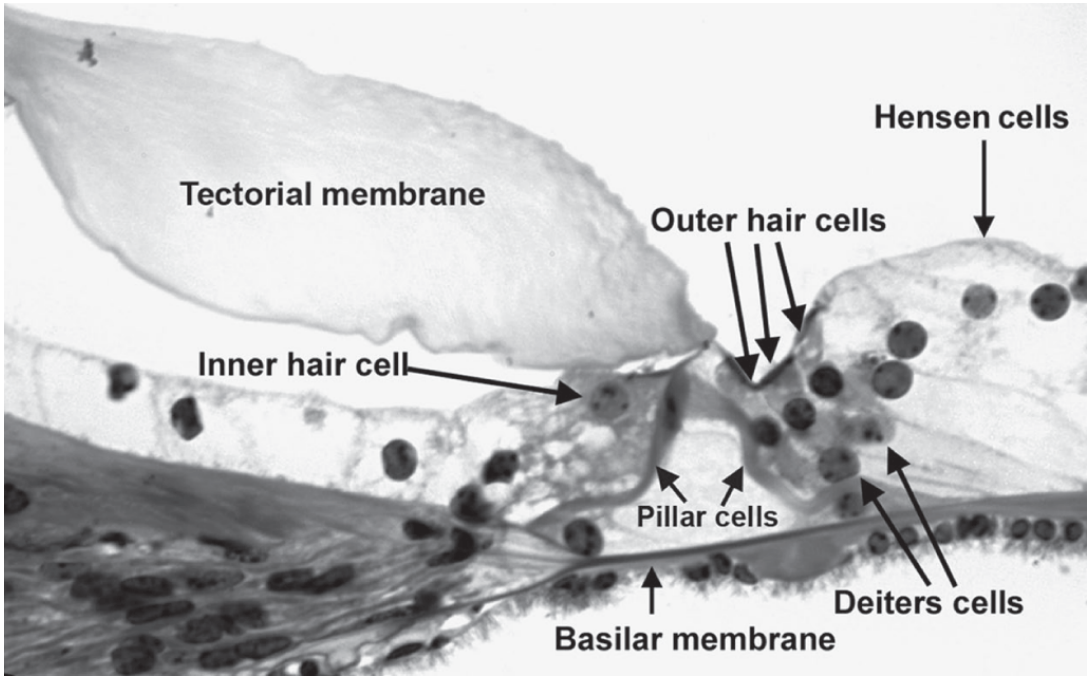


FIGURE 39-2. The organ of Corti. A cross-section shows details of the mouse organ of Corti located on the basilar membrane. The sensory cells are arranged in one row of inner hair cells and three rows of outer hair cells. Inner hair cells are the primary transducers of sound and receive most of the afferent innervation of the spiral ganglion nerve. Outer hair cells amplify transduction and receive most of the efferent innervation. Supporting cells include Deiters, Hensen, and pillar cells. The tectorial membrane does not extend to its full length because of preparation artifacts.

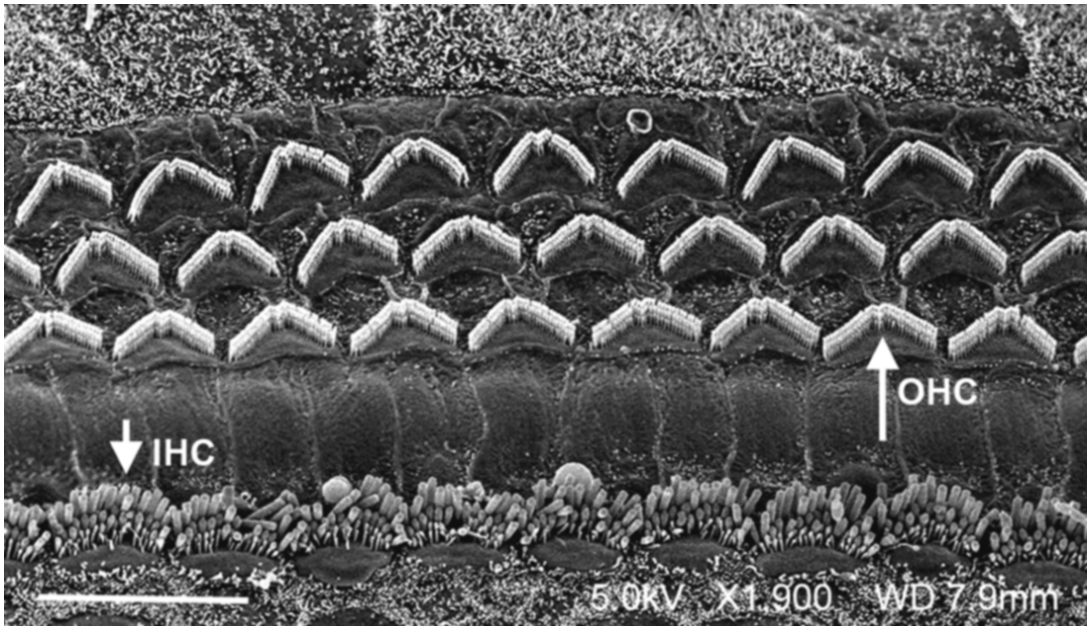


FIGURE 39-3. Hair cells and their stereocilia. A scanning electron micrograph of a "surface preparation" gives a top view of the organ of Corti, presenting the apical aspects of hair cells and supporting cells. The hair cells are distinguished by their stereocilia, the white tufts arranged in linear (inner hair cells, IHC) and W-like (outer hair cells, OHC) form. During sound transduction, the stereocilia are deflected by a shearing motion generated between the basilar membrane and the tectorial membrane, causing transduction channels to open for influx of potassium from the endolymph. This influx triggers a receptor potential and release of neurotransmitter (glutamate) at the synapse between the inner hair cell and the spiral ganglion nerve. Scale bar: 20 μm. (Scanning electron micrograph from mouse cochlea kindly provided by Dr. Andrew Forge, Institute of Laryngology and Otology, University College London, UK.)

The cells in the sensory epithelium are highly differentiated. Hair cells, once lost, are not regenerated by other cell types in the mammal but are replaced by permanent "scars" (**Figure 39-4**). Consequently, any damage to these cells leads to irreversible hearing loss. Considerable research effort is currently expended on determining any factors that might regenerate hair cells from supporting cells or enable the differentiation of stem cells into hair cells.

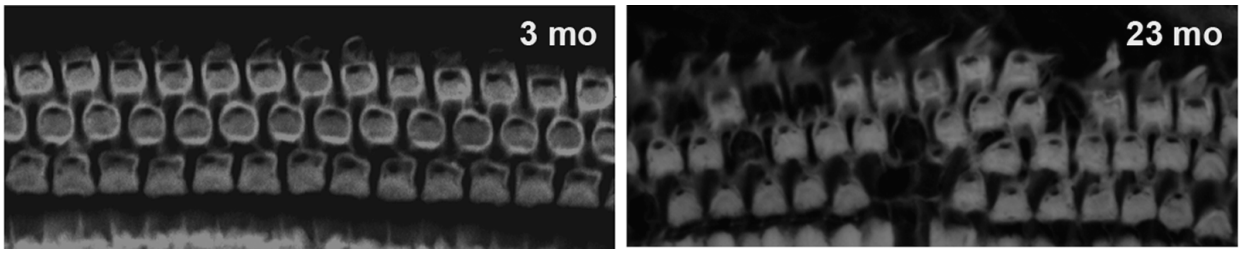


FIGURE 39-4. Loss of hair cells with age. Surface preparations of the mouse cochlea are stained with phalloidin to visualize F-actin, a major component of stereocilia and hair cells. Three rows of outer hair cells are complete and arranged in an orderly fashion in an animal of 3 months. At 23 months, the structure is disturbed and some cells are missing.

Functional Assessment of Hearing

From a clinical functional aspect, pure tone audiometry, tympanometry, acoustic reflex measurements, and word recognition scores with behavioral tests are the most common and important methods for hearing assessment. Tympanometry and acoustic reflex (stapedius reflex) test the integrity of the middle ear while audiometry yields information about acoustic thresholds at distinct frequencies. Word recognition and behavioral tests explore more complex tasks that involve both the auditory periphery and central processing of the information. Auditory brainstem response (ABR) and otoacoustic emission measurements provide information on the integrity of the auditory pathway and outer hair cells, respectively. They are passive sound-evoked responses and therefore suitable for infants or incapacitated individuals as well as most easily adapted to routine testing in animals. Some invasive methods, essentially limited to animal experimentation, such as recordings of cochlear microphonic potential (largely derived from outer hair cells), cochlear whole nerve action potential, and single unit recordings can be used to asses hair cell transduction and synaptic activity, the function of auditory afferent nerves, and individual neurons of the cochlear and vestibular nerves.

Frequencies and Sound Intensity: What Constitutes Hearing Loss?

A significant hearing loss of any origin will eventually lead to difficulties in communication and a decreased awareness of the environment. In addition to the social isolation at all ages, subjects with early-onset presbycusis may suffer economic consequences from difficulties in employment or professional advancement. The question of what constitutes a significant hearing impairment is complex as it involves consideration of both the magnitude of sensitivity loss and the frequencies at which the loss occurs. Although the most convenient assessment criterion for age-related hearing loss is a subjective one—that is, posing the question, “do you have a hearing problem?” or answering a more elaborate questionnaire like the Hearing Handicap Inventory for the Elderly-Short (HHIE-S)—a more quantitative evaluation can be obtained by an audiogram. While there is not one set paradigm for classification of audiograms into handicapping and nonhandicapping hearing thresholds, the American Medical Association/American Academy of Otolaryngology–Head and Neck Surgery sets the bar at an average threshold shift (hearing loss) of 25 dB or above at frequencies between 500 and 3000 Hz.

What does a loss of 25-dB hearing acuity mean in practical terms? The bel or decibel (dB) scale of sound pressure (“intensity”) is logarithmic, such that an increase in 3 dB confers approximately a doubling of the sound intensity. Therefore, a reduction of sensitivity of 25 dB, as is required for some definitions of occupational hearing impairment, is considerable. In rough terms, a difference of 25 dB in threshold makes normal conversation equivalent to a whisper, and a whisper equivalent to silence (**Table 39-1**). The crying baby would still be noticed—albeit subdued—but the leaves rustling in the forest or the crickets in summer would not be heard.

TABLE 39-1 TYPICAL SOUND LEVELS

DB	SOUND
15	Pin drop at close range
15–20	Rustling leaves, dripping faucet
35	Whisper

50–60	Normal conversation
60–70	Vacuum cleaner
70–90	Screaming child
85	*Safety limit for an 8-h workday*
100	*Safe for 15 min or less*
105–110	Gas engine mower, chain saw
110	Car stereo at maximum volume
110	*Safe for 1 min 29 s*
115	Maximum volume from an iPod
116	*Human body perceives low frequency*
120	Front row at a rock concert
120–130	Jet plane taking off
127	*High risk of tinnitus*
130–140	Gun shot from a hunting rifle
140	*Hearing deficit at exposures < 1 s*

Intensity levels of some familiar sounds can provide a guide to understanding the impact of hearing loss as discussed in the text. The comparison of these levels to safety standards also illustrates the potential impact of environmental noise exposure on the complex manifestations of presbycusis.
Safety levels are taken from DHHS (NIOSH) Publication No. 98–126 on Occupational Noise Exposure.

ARHI poses a specific problem as the hearing loss progresses slowly and mostly sets in at the high frequencies. The frequency spectrum of human hearing, at its best, ranges from about 60 Hz to 16 kHz. A hearing loss at the very high frequencies may not produce any communicative disadvantages since frequencies over 4 kHz contribute little to speech (**Table 39-2**). As a result, many with age-related hearing loss do not recognize their condition for a long time. Even musical instruments have a limited range in their fundamental frequencies. Since the progression of ARHI is also gradual, the subject maybe unaware of the gradual loss of overtones in speech or instrumental music, which can extend two or three octaves higher than the fundamentals, that is, to two or three times the frequencies.

TABLE 39-2 FREQUENCY RANGES OF COMMON SOUNDS

SOUND	APPROXIMATE FUNDAMENTAL FREQUENCY RANGE (HZ)
Guitar	82–1175
Truck engine	125–250
Dog’s bark	200–300
Violin	196–4400
Soprano singer	200–1400
Most spoken consonants	250–500
Middle C of the musical scale	264
Spoken vowels	500–750
Crying baby	750–1000
Consonants: c, p, ch, g, h, sh	1000–2000
Telephone ring	3000–4000
Consonants: f, k, s, t, th	3000–8000
Birds chirping	4000–8000

In addition to these fundamental frequencies, most sources of sounds and musical instruments, in particular, produce overtones that add to the richness of the sound. These overtones reach two to three times the fundamental frequencies. Comparison of the frequencies to the classical pattern of high-frequency age-related hearing impairment illustrates the early impact on specific speech features and the quality of music appreciation.

Although speech frequencies and hence, basic hearing needs, center on the 1000- to 2000-Hz range, losses at higher frequencies like those in ARHI cost the ability to discriminate between many words with f, p, k, s, t and th sounds (see **Table 39-2**). For example, to a person with high-frequency hearing loss, "sick" and "thick" maybe difficult to differentiate, and "three socks" may sound like "free fox" unless the listener has developed the ability to read the speakers lips for supplementary information. Such communication errors may seem trivial, but can cause enormous social disability when they happen in work situations or become cumulative.

Audiologic examinations routinely include frequencies up to 8000 Hz and could reveal the presbycusic changes, although the individual may still be told by the audiologist that their hearing is "normal for the age." Such a statement should not be taken to mean that a hearing aid is not necessary or not useful. Quite frequently, an individual with a reasonably reliable pure tone audiogram and good one-on-one communication skills may experience difficulties in speech perception in a noisy environment such as a restaurant, a party, or a conference. This "party effect" is often the first signal indicative of presbycusis. Although not necessarily due to a single cause, the age-related loss of high frequencies is an important contributing factor because high frequencies are important for auditory discrimination in the presence of background noise. Such individuals may greatly benefit in their enjoyment of conversation and music by modern hearing aids fitted to their particular deficits.

PERIPHERAL PATHOLOGY OF AGE-RELATED HEARING IMPAIRMENT IN HUMANS

Schuknecht's classification of 1964 is still a valuable guideline today for the various forms of presbycusis, although the framework has limitations. The broad categories of ARHI are as follows: (1) *Sensory* ARHI refers to a primary degeneration of hair cells of the organ of Corti that begins in the base, yielding an audiogram that is abnormal only at the high frequencies (**Figure 39-5A**). Current data suggest that ARHI in humans largely follows such a pattern of a high-frequency hearing loss. (2) *Neural* ARHI mainly reflects loss of afferent neurons while cochlear structures remain relatively normal, leading to a loss of word discrimination ability. In general, aging people lose afferent neurons only slowly and significant changes in the audiogram may require a loss of up to 90% of neurons. The incidence of neural ARHI is low and the existence of a purely neural ARHI is even controversial. As hair cells degenerate, secondary neuronal degeneration follows, so that the term "sensorineural" ARHI is favored over a separation of sensory and neural ARHI. (3) *Strial*, or *metabolic*, ARHI is caused by a degeneration of the stria vascularis (primarily a "flattening," reduction of volume, concomitant with dysfunction) resulting in a decrease of the endocochlear potential. This decrease of the driving force for transduction affects the entire cochlea and therefore all frequencies. The audiogram shows a flat hearing loss (**Figure 39-5B**). Strial ARHI may account for 20% to 35% of ARHI according to Schuknecht, who also noted that strial ARHI tends to occur earlier in life than other forms. Others peg the incidence of this form of hearing loss much lower. Although Schuknecht did not include the spiral ligament in the hallmarks of strial ARHI, human and animal studies have tied strial pathology to that of the adjacent spiral ligament. (4) *Cochlear conductive* ARHI *or mechanical* ARHI is caused by changes in the stiffness of the basilar membrane. An audiogram of this type shows a linear decline of over 50 dB at all frequencies without degeneration of any cochlear cells or structures. Only a small portion of ARHI is estimated to fall into this category. (5) Mixed ARHI is the overlap of multiple pathologies. About 25% of cases may be of mixed pathology.

In evaluating ARHI, it is often difficult to determine the contributions of environmental influences that also damage the hair cells in the organ of Corti, such as exposure to noise, industrial solvents, or ototoxic medications. Aminoglycoside antibiotics (exemplified by streptomycin, gentamicin, kanamycin, and related drugs), in particular, destroy hair cells in a base-to-apex progression, causing an initial high-frequency hearing loss reminiscent of sensorineural presbycusis. Noise-induced hearing loss usually differs in its pattern as the site of cochlear damage relates to the frequency of the exposure. Furthermore, a fingerprint of noise trauma in hunters and shooters is a unilateral hearing deficit in the 4-kHz region (**Figure 39-5C**). Damage from industrial noise would be expected to be bilateral and show a broader area of hearing loss.

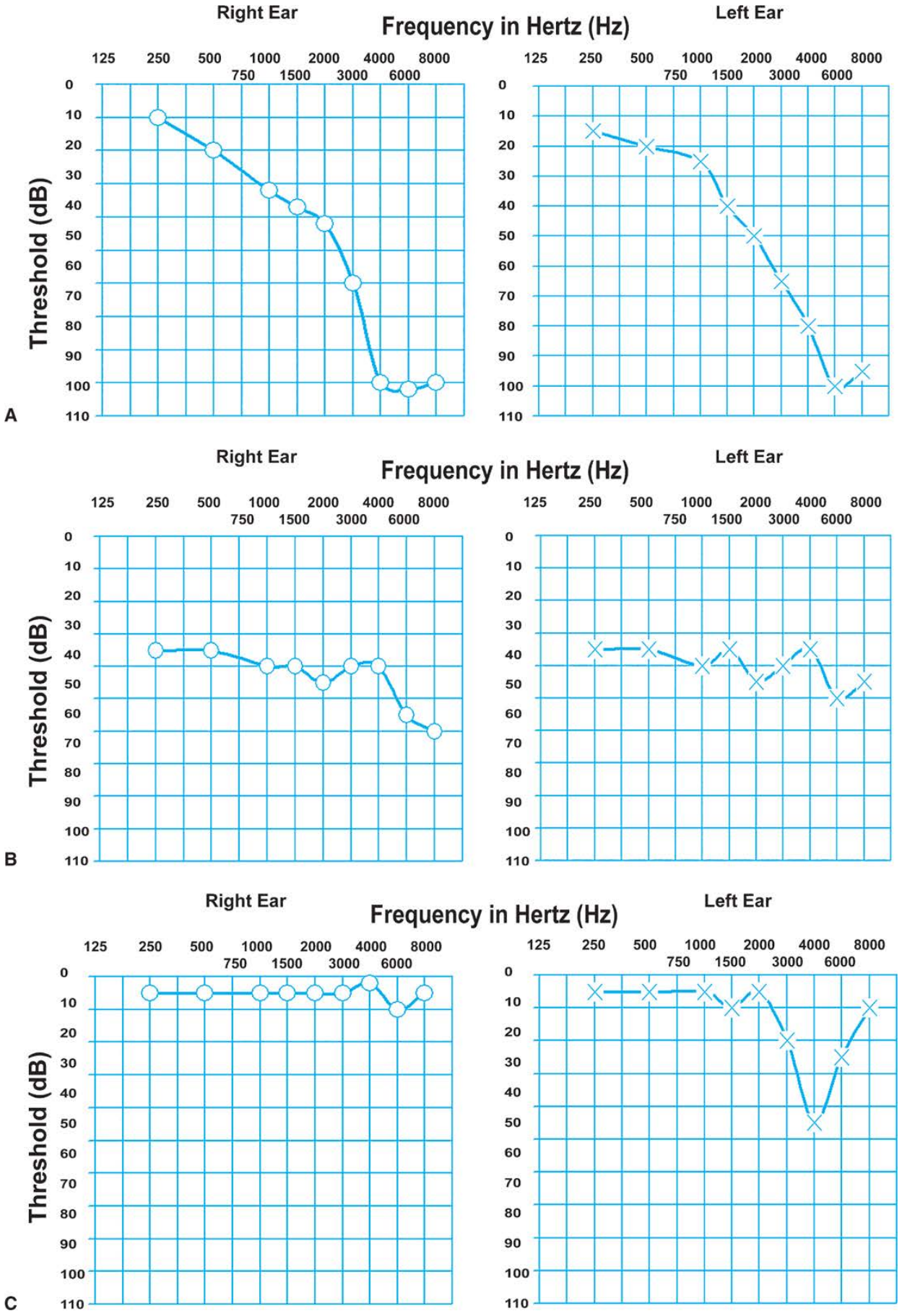


FIGURE 39-5. Audiograms of different forms of hearing loss. Pure tone audiograms record the auditory thresholds, that is, the minimal sound level necessary to elicit a response in the listener at specific frequencies. Typical audiograms cover the range from 250 to 8000 Hz, and the increasing intensity of the sound is plotted downward on the y-axis. A normal ear (**Figure 39-5C**, right ear) would yield an audiogram

with flat responses around 0 to 10 dB; if the threshold is increased in a subject, the curve drops lower. Thresholds of 25 to 30 dB constitute a subjectively noticeable impairment, whereas 70 dB and above would make perception at this frequency difficult to impossible. **A.** The sloping audiogram from a 62-year-old man shows progressive high-frequency hearing loss in both ears. Fundamental speech frequencies are moderately affected but the threshold of 65 dB at 3000 Hz renders speech discrimination in noise difficult. **B.** The flat audiogram from a 64-year-old man shifted to higher thresholds is indicative of a "metabolic" presbycusis. **C.** The audiogram from a 32-year-old man shows a sharply defined hearing loss of 45 dB only at 4 kHz in the left ear. Such a "notch" in the audiogram is typical for noise damage, here from target shooting or hunting.

CENTRAL AUDITORY ASPECT OF AGE-RELATED HEARING IMPAIRMENT

In addition to deficiencies in peripheral auditory processing, advanced age can lead to changes in the central auditory system, which can essentially be classified into two major types. The first is referred to as "peripherally induced central effects," which presents with changes in the cochlear nucleus driven by the decline of peripheral cochlear inputs that occur with age, typically starting with hearing loss at high frequencies. The other is referred to as "true aging" neurodegenerative changes in the brain. In this case, ARHI shares similarities or common mechanisms with other central nervous system conditions of the aged such as Alzheimer and Parkinson diseases. Age-dependent changes in auditory structures include declines in the number of ventral cochlear nucleus and lemniscal nerve fibers.

The olders often present with difficulties in speech recognition, rather than an inability to hear sound. Despite audiograms within the normal range, the subjects still require a stronger speech signal, particularly in a noisy environment, or might experience better comprehension when speech is slowed down. These subjects may have deficits in processing sound in the higher auditory centers. Specific comprehension tests (eg, a speech perception in noise [SPIN] test) can be used to diagnose such a condition.

Animal models have helped to illuminate some central consequences of degeneration of the auditory periphery. Neurons with low thresholds for high-frequency tones (eg, in the ventral inferior colliculus) cease to respond and the anatomic locations of frequency representation change. Synaptic connections may also change in number, spontaneous activity, or their inhibitory or excitatory properties. In addition to their direct effect on speech processing, such changes do not bode well for rehabilitation of the hearing impaired with, for example, cochlear implantation (see section on "Management of Age-Related Hearing Impairment") which aims at compensating for peripheral deficits. The adult auditory system, however, shows surprising plasticity, and electrical stimulation by implants can reverse some of the central changes.

LESSONS FROM ANIMAL MODELS

Suitability of Different Species as Models

A large variety of species has been studied for age-related auditory pathology, including chinchillas, guinea pigs, primates, dogs, and rodents. These species cover the range of cochlear pathologies, including organ of Corti, neural, and strial degeneration, and the majority of animals show a complex mix. Mongolian gerbils are considered a model for strial presbycusis, presenting with strial atrophy, decreased endocochlear potential, and decreased cochlear blood flow. Degeneration of spiral ganglion cells and fibrocyte vacuolization and interstitial edema in the spiral ligament are also observed. In cats and rats, the underlying pathology has been linked to a combination of hair cell and spiral ganglion cell loss. Recently, a strial type of hearing loss was also observed in the rat underscoring the fact that a singular "pure" type of hearing loss maybe rare in any species.

Mice have become favored for study of ARHI, because of availability of molecular and genetic information and transgenic and knock-out animals. A caveat, however, is that each mouse strain differs significantly in its rate of hearing loss, ranging from those such as CBA and CAST, which exhibit minimal hearing loss by 18 months, to those such as C57BL/6 and DBA, which exhibit significantly accelerated hearing loss by approximately 8 and 3 months, respectively. The accelerated loss of hair cells and hearing found in C57BL/6 and BALB/cJ mice correlates with the presence of a recessive locus on proximal mouse Chr 10, the age-related hearing loss (*Ahl*) gene. The $Cdh23^{ahl}$ allele (cadherin 23 or otocadherin) promotes degeneration of the organ of Corti in the cochlear base and high-frequency hearing loss beginning after 1 year of age as shown in congenic B-6.CAST-$Cdh23^{ahl}$. Furthermore, $Cdh23^{ahl}$ also promotes noise-induced hearing loss, suggesting a connection between noise and ARHI. Since BALB/cJ and C57/BL mice are genetic mutations, they may not reflect a normal biological aging process. In fact, a genetic analysis of

human presbycusis found no evidence for the presence of a mutation in cadherin 23.

The CBA/J mouse is among the strains in which the progression of ARHI more closely approximates human presbycusis. CBA/J mice lose hearing sensitivity late in their lifespan, advancing from high to low frequencies. ARHI begins around 12 months—here again the onset is earlier in males than in females—and progresses slowly until 18 months, after which point a more rapid rate of hearing loss is seen. The hearing loss at high frequencies is accompanied by loss of outer hair cells and a moderate degeneration of spiral ganglion cells. Since the CBA/J strain maintains normal morphology of the stria vascularis and normal endocochlear potential in aging, a sensorineural origin of the observed auditory deficits can be inferred.

Molecular Mechanisms

Significant progress has been made in our understanding of the pathologic and functional changes that occur in the inner ear with age using animal models. However, less is known about the specific molecular and genetic mechanisms contributing to ARHI. Recent work suggests to place "auditory aging" in animals—at least for sensorineural presbycusis—into the category of oxidant-stress related events. Oxidant stress is caused by the metabolic overproduction of reactive oxygen species (ROS) or reactive nitrogen species (RNS), including singlet oxygen, superoxides, peroxides, hydroxyl radicals, and hypochlorous acid or nitric oxide–derived compounds such as nitroxyl anions, nitrosonium cations, higher oxides of nitrogen, *S*-nitrosothiols, and dinitrosyl iron complexes. Maintaining cellular redox homeostasis depends on the rate of production of ROS and their removal by cellular antioxidants. If such homeostasis is disrupted, cell death is a potential consequence. Markers of oxidative stress are indeed elevated in the cochlea of the aging CBA/J mouse while antioxidant defense systems decrease. Other suggestive evidence for an involvement of oxidative stress comes from heterozygous mice lacking superoxide dismutase; ARHI developed earlier and with greater severity, as evidenced by an increased hair cell loss following the canonical base-to-apex progression. Consistent with oxidative stress is also the observation that the severity of ARHI in humans correlates with plasma levels of hydroxyl radicals and hydrogen peroxide, although a causal relationship cannot be inferred. While oxidative stress may be a contributing factor, failed attempts to slow the progression of cochlear degeneration and hearing loss with antioxidants point to a more complex picture (see section on "Prevention of Age-Related Hearing Impairment"). Recent studies in lower organisms suggest that low levels of mitochondrial ROS (mROS) regulate immunity and autophagy, which positively affect aging. The dual function of ROS to both promote cell damage and cell adaptation to stress responses makes them challenging as potentially therapeutic targets.

Deletions in mitochondrial DNA are also an established indicator of cumulative oxidative damage to a tissue and have been observed in the aging—including human—cochlea. DNA in mitochondria, in contrast to nuclear DNA, is particularly vulnerable because these organelles possess less efficient machinery to repair DNA damage, leaving mutations uncorrected and prone to adversely affecting mitochondrial function. A $mtDNA^{4977}$ deletion is the most common mutation found in human temporal bones and significantly correlated with individual audiometric thresholds and the severity of presbycusis.

Vascular abnormalities are another pathologic change with aging potentially affecting supply of nutrients and oxygen as well as mitochondrial respiration, thus adding to oxidant stress in the inner ear. As a case in point, suppression of cochlear blood flow promotes mitochondrial DNA mutations and may impact hearing loss. In addition, reduction of cochlear blood flow from age-related degeneration could lead to a compromised function of the stria vascularis and an inability to maintain cochlear homeostasis for the maintenance of transduction currents and tissue integrity. The sum of these considerations supports the general concept that ARHI is a consequence of accumulated environmental injuries to the cochlea along with the intrinsic genetically controlled aging process.

Genetic Contributions

The vast majority of so-called mouse models of genetic hearing loss exhibit sensory dysfunction soon after birth; in other words, these are models of accelerated hearing loss not necessarily reflecting human pathology. Hence, the utility of these models for understanding presbycusis-type later-onset hearing loss is unclear. As already noted, C57 mouse strains, frequently used as an ARHI model, carry a mutation in cadherin 23. In humans, Cdh23 mutations are present in type I Usher syndrome, but a relation of this mutation to presbycusis is probably nonexistent; a recent population study found no association between Cdh23 mutations and ARHI.

In contrast, a genetically heterogeneous population of mice at the ages of 8, 18, and 22 months was tested for auditory hearing function by auditory brainstem response (ABR), and genotyped at 128 markers to identify loci that modulate late-life hearing loss. Polymorphisms significantly affecting hearing at 18 or 22 months were noted on

several chromosomes. Such phenotypic variability strongly suggests that ARHI is a complex polygenetic disorder possibly involving numerous alleles on multiple genes. These conclusions from an animal model fit well with the previously mentioned genome-wide association study in humans.

PREVENTION OF AGE-RELATED HEARING IMPAIRMENT

As discussed earlier, several environmental and personal behavioral factors are associated with the overall manifestations of ARHI. Therefore, avoiding noise, ototoxins, and smoking, regular exercising, and maintaining a healthy diet will aid in slowing progressive hearing loss as it will contribute to general health. The question as to what extent interventional strategies can specifically delay ARHI cannot yet be conclusively answered but some data point to the general concept that the rate of ARHI can be influenced.

"Augmented acoustic environment" is a concept to influence the progression of presbycusis by exposure to controlled stimuli. This environment could be created by an enhanced ambient acoustic background or by delivery of specific stimuli through hearing aids. Studies in mice, although mostly on inbred strains with accelerated hearing loss, confirm that the auditory system responds to such treatment but not necessarily in predictable ways. While amelioration of some forms of age-related changes was found, other effects were detrimental, leaving final judgment to future experimentation.

Dietary restriction has been widely used in aging studies and can slow certain age-related physiologic declines and extend longevity. For the auditory system, results of such studies are inconclusive and emphasize the point that organ-specific effects of a generalized treatment are impossible to predict. Caloric restriction had positive effects on the progression and magnitude of ARHI in rats but was ineffective in rhesus monkeys. A comprehensive study of 15 mouse strains brought every conceivable result from an apparent amelioration of the rate or severity of presbycusis to no effects and to an acceleration of hearing loss. Such results indicate a major influence of genotype on the outcome, cautioning that similar problems might be encountered in presbycusis therapy in humans.

Antioxidant therapy in animal models, based on the premise that oxidant stress is a contributor to ARHI, has shown inconsistent results. Rats that were placed on vitamin supplementation (vitamins C and E) shortly after birth outperformed their placebo controls in hearing tests at old age but the number of animals in this study was exceedingly low and the results might have been skewed by a more robust health of the surviving small cohort. When the supplementation with antioxidants (acetyl carnitine and lipoic acid) in rats was started later in life and upheld for 6 weeks, results were less convincing. Dogs, on the other hand, fed an antioxidant diet for the final 3 years of their life had better preserved auditory neurons; a confounding factor, however, might have been the high noise level in the kennels, which can contribute to noise-induced hearing loss that may be attenuated by antioxidants. In a long-term longitudinal study, 10-month-old female CBA/J mice were maintained on either a control or antioxidant-enriched diet and monitored through 24 months of age; ARHI showed no difference between the two groups. The simple approach to attenuate ROS generation may therefore be an inadequate therapy, perhaps due to the dual role of ROS in adaptation to stress and promotion of cell damage.

Nevertheless, human studies suggest the hypothesis that ARHI can, to some extent, be influenced by dietary or therapeutic intervention. Daily supplementation of folic acid for 3 years positively affected the hearing of older participants in a study in the Netherlands. The effect was significant but very small on low-frequency hearing while age-related changes in high-frequency hearing, the area normally most afflicted by presbycusis, proceeded unaffected. Since low-frequency hearing is important for speech, the result can be considered encouraging. The underlying mechanism of this protection has yet to be established but the effect goes hand-in-hand with controversial observations that patients with higher erythrocyte and serum concentrations of folate maintain lower hearing thresholds. It should be noted however that routine folic acid supplementation of foods is not permitted in the Netherlands but common in other industrialized countries. Results therefore may differ in countries where basic folate levels in the population can be expected to be higher. Finally and quite intriguingly, several surveys indicate alcohol consumption as a possible modulator of ARHI. Moderate use of alcohol was associated with better hearing in the older adults in three independent studies, an effect in line with observations that low alcohol intake can be beneficial for general health. Heavy drinkers, in contrast, had a tendency toward more pronounced high-frequency hearing loss.

MANAGEMENT OF AGE-RELATED HEARING IMPAIRMENT

The major cause of ARHI is the loss of hair cells and cochlear neurons. Since hair cells, as mentioned earlier, cannot regenerate, restoration of normal hearing is not possible. The current choice for rehabilitation of ARHI is hearing aids. Digital hearing aids present a wide range of user options and have advanced technologically in all aspects including the tolerance of a noisy environment and improved cosmetology. Hearing aids, individually tailored to a subject's audiogram, provide clearly increased hearing ability and speech discrimination (**Figure 39-6**). However, knowledge about the benefits and acceptance of hearing aids is low. About one-half of older people who could benefit from a hearing aid never try; others are dissatisfied after short use and only 10% to 30% continue to wear hearing aids. Rejection to a large extent depends on personal idiosyncrasies, education, and cultural aspects. Health care costs do not appear to be a decisive factor. The compliance rate is the same in the United States (where patients pay or copay for the hearing aid) and the United Kingdom (where they are free), around 15%. As mentioned earlier, in some instances the pathophysiologic basis may lie beyond the cochlea. "I can hear but I can't understand" may point to a central auditory deficit that cannot be easily corrected by enhancing the peripheral stimulus.

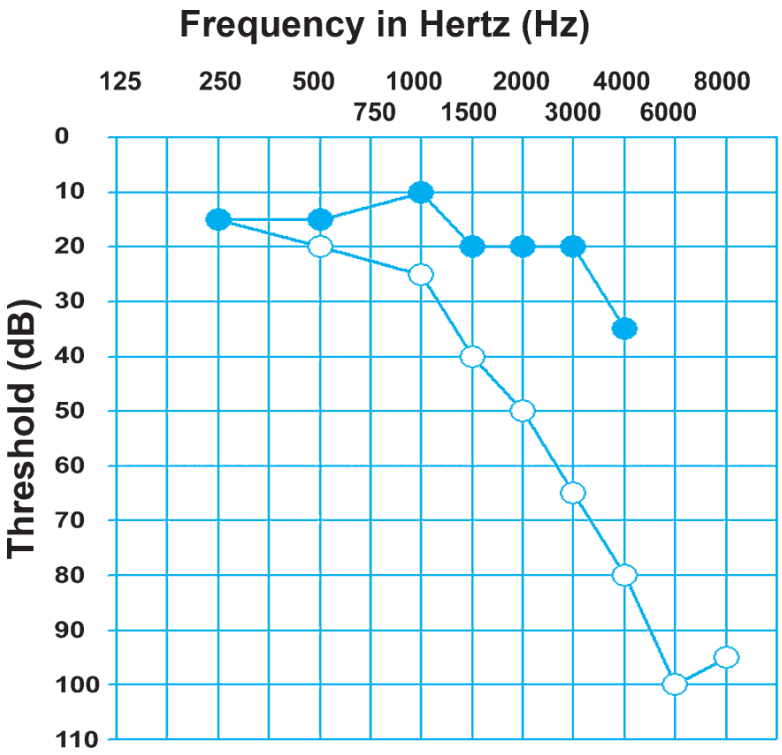


FIGURE 39-6. Typical effects of a hearing aid. The unaided audiogram (open circles) shows presbycusic high-frequency hearing loss. With hearing aids in place (closed circles), acuity is improved to near-normal levels for frequencies up to 3000 Hz. Note that low frequencies deliberately are not boosted and that rescue of the elevated thresholds at high frequencies is not possible.

If the magnitude of the hearing loss exceeds the corrective capability of hearing aids, cochlear implants are recommended with increasing frequency to older subjects. Such "bionic ears" are indicated for persons with bilateral hearing loss and 50% or poorer word recognition. While a hearing aid essentially amplifies sound to the cochlea and therefore depends on remaining sensory cells, the cochlear implant bypasses the sensory cells and directly stimulates the auditory nerve electrically. To achieve an effective transformation to an electrical stimulus, the acoustic information needs to be preprocessed and delivered to the nerve via an electrode implanted into the cochlea. The success depends on appropriate coding paradigms and a healthy complement of cochlear nerve innervation. Since the degeneration of the cochlear nerve is slow in humans, much of the aging population presenting with presbycusis would be good candidates. The outcome of implantation is variable but almost all of the patients greatly improve speech perception and most even acquire the ability to carry on telephone conversations. Challenges that remain are speech recognition in unfamiliar contexts and the enjoyment of music.

OUTLOOK

ARHI is an exceedingly complex disease besetting an organ of even greater complexity. It appears to be a sequel to

numerous morphologic and molecular changes that befall the auditory system as we age, and which are being characterized with increasing acuity by basic and clinical research. One of the major reasons for the lack of treatment of ARHI is the extensive phenotypic variability in hearing loss among human subjects. Our understanding and ability to design interventional and curative therapies will much depend on advances into the molecular and cellular mechanisms of auditory pathologies and identification of genetic variants associated with ARHI. Recent new technologies such as next-generation sequencing including DNA-Seq, RNA-Seq, ChIP-Seq, Methyl-Seq, targeted sequencing utilizing Illumina HiScanSQ, and Ion Torrent instrumentation will provide the platform to perform large-scale genome-wide phenotype association studies with ARHI.

Given the partial success of pharmacologic protection, this approach should yield the first practical results. Appropriate agents for and timing of interventions will be explored in animal models, both independent of and tied into interventions in extending lifespan and general health. Gene therapy also shows promise as a possible strategy to protect hair cells. To date, research has successfully focused on prevention of hearing loss caused by acute traumata like drugs and noise. Such model systems can easily be applied to hearing loss from aging as the etiology of these insults can be strikingly similar to age-related sensorineural hearing loss. As the caveats in the preceding sections point out, we have to be careful in translating results from models to humans, and the necessity for lengthy trials may prevent the immediate implementation of prospective solutions.

In the area of rehabilitation, technological advances of hearing aids and cochlear implants will improve not only speech recognition but also music appreciation, an area currently of difficult rehabilitation. A direct nerve implant, already successfully tested in an animal model, may replace the cochlear implant for better efficacy of stimulation and a wider range of frequency and intensity perception. The following generation of prostheses will bypass the cochlea and its nerve and stimulate higher auditory centers. Although clinical application of auditory midbrain implants is in its infancy, a handful of patients have already been treated. Such prosthetic therapy could prove advantageous for patients with massive degeneration of the auditory periphery and/or the auditory nerve as in a severe neural type of ARHI.

Lastly, functional hair cell regeneration is the final frontier in the field. Recent studies have shown that cells in the organ of Corti, such as supporting cells, may mitose or transdifferentiate into hair cells if appropriately stimulated. The challenges, however, are highly complex: not only do hair cells need to be (re)generated, they also have to be incorporated into the intricate cytoarchitecture of the cochlea and find their appropriate connections to the central auditory structures. Stem cell research may likewise provide new insights for replacement of hair cells and the regeneration of the auditory nerve.

Although presbycusis is not yet preventable or treatable, progress in basic and clinical research promises hope for the future. Most realistic in the near term seem protective pharmacologic strategies to delay or attenuate age-related hearing impairment and improved rehabilitation through next-generation hearing aids and implants. A plausible clinical therapy for the regeneration of new and functional hair cells may, despite recent encouraging advancements, still be decades away.

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Chapter 40

Menopause and Midlife Health Changes

Carrie Karvonen-Gutierrez, Sioban D. Harlow

Learning Objectives

- Define the clinical diagnosis of menopause.
- Describe the key changes in sex steroid hormones that occur during the menopausal transition.
- List common menopausal symptoms and describe their relationship to chronic disease risk.
- Describe the significant changes in bone health, obesity, and body composition and the cardiovascular risks that are associated with the menopausal transition.
- List physiologic changes during the menopausal transition that may link menopause to physical functioning decline and osteoarthritis (OA).

Key Clinical Points

1. **Between 60% and 80% of menopausal women experience vasomotor symptoms (VMS) at some point during the menopausal transition; VMS are associated with sleep difficulties and changes in cardiovascular risk.**
2. **Physiologic changes associated with cardiovascular disease (CVD) risk begin in the midlife, including an accelerated increase in total cholesterol, low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B, and adverse changes in intima-media thickness and adventitial diameter of the carotid artery.**
3. **Sleep difficulties increase as women transition through menopause, and women with surgical menopause report the highest prevalence of problems.**
4. **The increase in weight during the midlife is related to both aging and ovarian aging. This midlife increase in body weight is associated with both increased fat mass and decreased lean mass.**
5. **In women, half of the lifetime loss in bone mineral density (BMD) occurs during the menopausal transition and early postmenopausal period.**
6. **Up to 25% of newly postmenopausal women have substantial functional limitations.**
7. **The incidence of OA among women increases fivefold between the ages of 40 to 49 and doubles again between the ages of 50 and 59, with up to 66% of women having radiographic evidence of knee OA in early postmenopause.**
8. **Women are twice as likely to suffer from depression as compared to men, and the menopausal transition and postmenopausal period are associated with increased risk of depression as compared to the premenopausal period.**

INTRODUCTION

The profile of female geriatric patients will be changing considerably over the next decade. A substantial number of women born during the baby boom following World War II are at or beyond midlife, resulting in an increasing number of women who will be seeking treatment for symptoms associated with menopause and for chronic conditions that have their origin in midlife (see Chapter 5 for details on demographics). Further, the cohort of US women who are now at midlife is unique. More than three-quarters are in the workforce; more than one-third have college degrees; and family composition has changed remarkably as evidenced by the number of live births that have declined by almost half.

The midlife encompasses approximately the ages of 40 to 65 and, for women, the menopausal transition. For many women, this life stage will be a significant milestone and a harbinger of their health status and their interaction with health care systems for the ensuing decades. Thus, it is important to understand the events of the menopausal transition and how these events are likely to affect health, the perception of health, and the perception of the contribution of the health care provider to health maintenance.

The initiation of the menopausal transition (that 5–10-year period following the waning of reproductive potential to the cessation of significant estrogen secretion because of the depletion of functional ovarian follicles) is an ill-defined period that typically commences with the onset of menstrual irregularity defined by increased variation in the length of a woman's menstrual cycles. The transition progresses through the experience of skipped cycles or cycles longer than 60 days, with menopause defined by the permanent cessation of menses. Menopause is clinically diagnosed by the final menstrual period (FMP), which is retrospectively identified following 12 continuous months of amenorrhea. The 8- to 10-year period following the FMP constitutes the postmenopause. The median age at FMP is currently estimated to be 51.4 years. Cigarette smokers have an estimated 0.5 to 1.0 year earlier median age at menopause, while higher parity and use of oral contraceptives have been associated with a later age at menopause.

This geriatrics textbook includes a chapter on menopause because exposure to declining levels of ovarian hormones appears to modify risk factors associated with the development of debilitating diseases and health concerns of the geriatric patient. Furthermore, the menopausal transition may represent an optimal time for clinical intervention. These clinical interventions can address two potential patient groups: (1) the 12% to 25% of women who already have some evidence of disability (see the Physical Limitations section) and for whom active interventions are critical and (2) the majority of women who are not disabled and are open to information about preventive care, risk factor screening, and may be seeking care for menopausal symptoms.

PHYSIOLOGIC BASIS OF REPRODUCTIVE AGING

Aging of the female reproductive system is unique because the time frame for the permanent cessation of menses has changed little over time, while the average life expectancy of women now extends more than 30 years after the FMP. Further, women have a finite period of reproductive capacity. Unlike men, who usually retain reproductive capacity throughout their lifetime, women are born with a set number of primordial follicles, whose depletion begins prior to birth (**Figure 40-1**). The marked decline in follicle number in late reproductive life is associated with declining anti-müllerian hormone (AMH) levels which become undetectable approximately 3 to 5 years before the FMP, although increasingly sensitive assays for AMH are being developed. Declining AMH levels are associated with a loss of fecundability in late reproductive life and are predictive of the timing of menopause. At menopause, when a woman's ovarian reserve is depleted, the number of available follicles recruited to form preovulatory follicles has dwindled to a point where ovarian-based hormones, including AMH, estrogens, and progesterone, are no longer predictably produced. A progressively greater rise in gonadotropin levels, that is follicle-stimulating hormone (FSH), is observed with the diminution of the follicular pool and their increasing nonresponsiveness in regulation of hormone secretion.

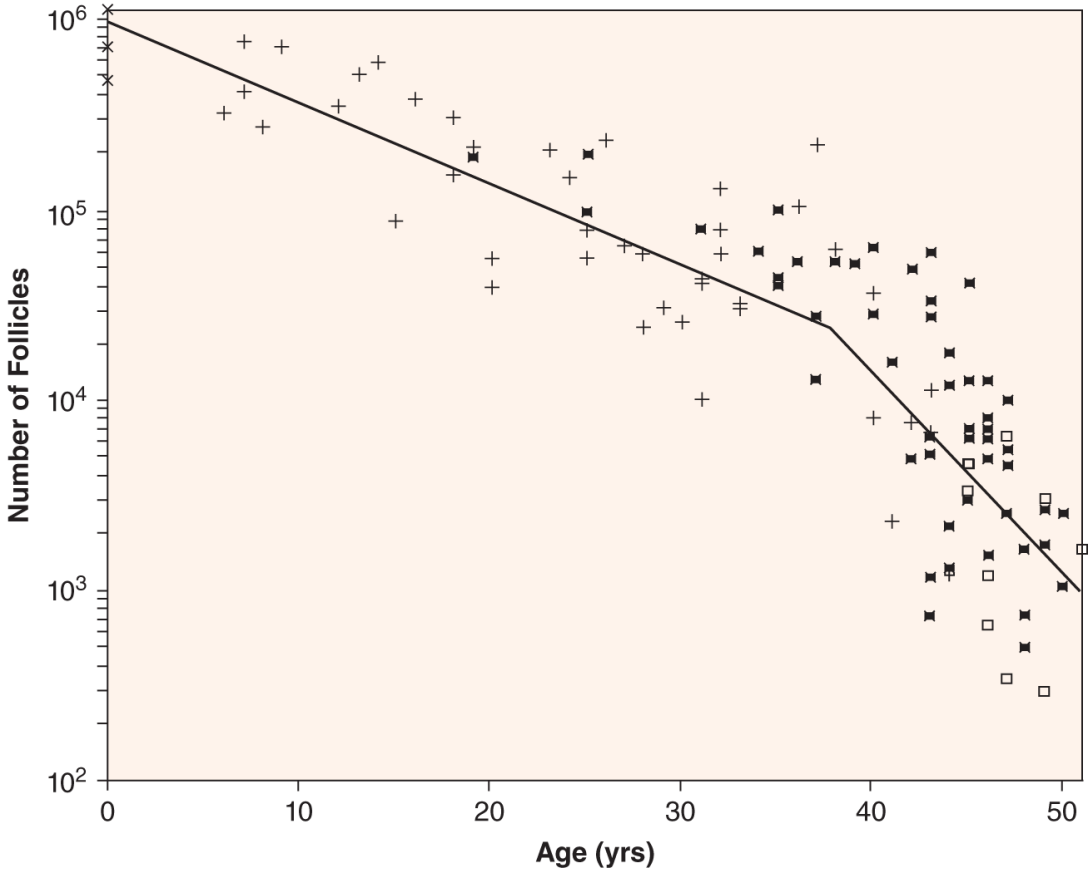


FIGURE 40-1. Biexponential model of declining follicle numbers in pairs of human ovaries from neonatal age to 51 years. Data were obtained from the studies of Block [1952 (x), 1953 (+)], Richardson et al. (1987) (□), and Gougeon (1987) (■). (From Faddy MJ, Gosden RG, Gougeon A, et al. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. *Human Reprod*. 1992;7:1342–1346. With permission from Oxford University Press.)

Several studies, including the Michigan Bone Health and Metabolism Study (MBHMS), the Penn Ovarian Aging Study (POAS), the Seattle Midlife Women's Health Study (SMWHS), and the Study of Women's Health Across the Nation (SWAN) have documented the change in FSH and estrogen values in relation to time of the FMP. An accelerated rise in FSH levels begins between approximately 5 to 8 years prior to the FMP with the rise in FSH levels further accelerated from approximately 2 years prior to 1 to 2 years after the FMP; thereafter, the FSH levels tend to plateau reflecting the high FSH levels characteristic of the postmenopausal period. In contrast, estradiol levels remain elevated until approximately 2 years before the FMP at which point estradiol levels decline sharply until about 2 years after the FMP, and then stabilize. This pattern of hormonal change in relation to the FMP is independent of age at menopause, race/ethnicity, and smoking status, although absolute hormone levels do differ by race/ethnicity and smoking status. Obese women have lower levels of estradiol before the FMP with higher levels after the FMP (**Figure 40-2**). Evidence is increasing that changes in lipids and bone, and potentially immunologic functioning, among others, are related to the marked changes in estradiol and FSH concentrations that occur during the menopausal transition, particularly in close proximity to the FMP when hormone changes are most pronounced.

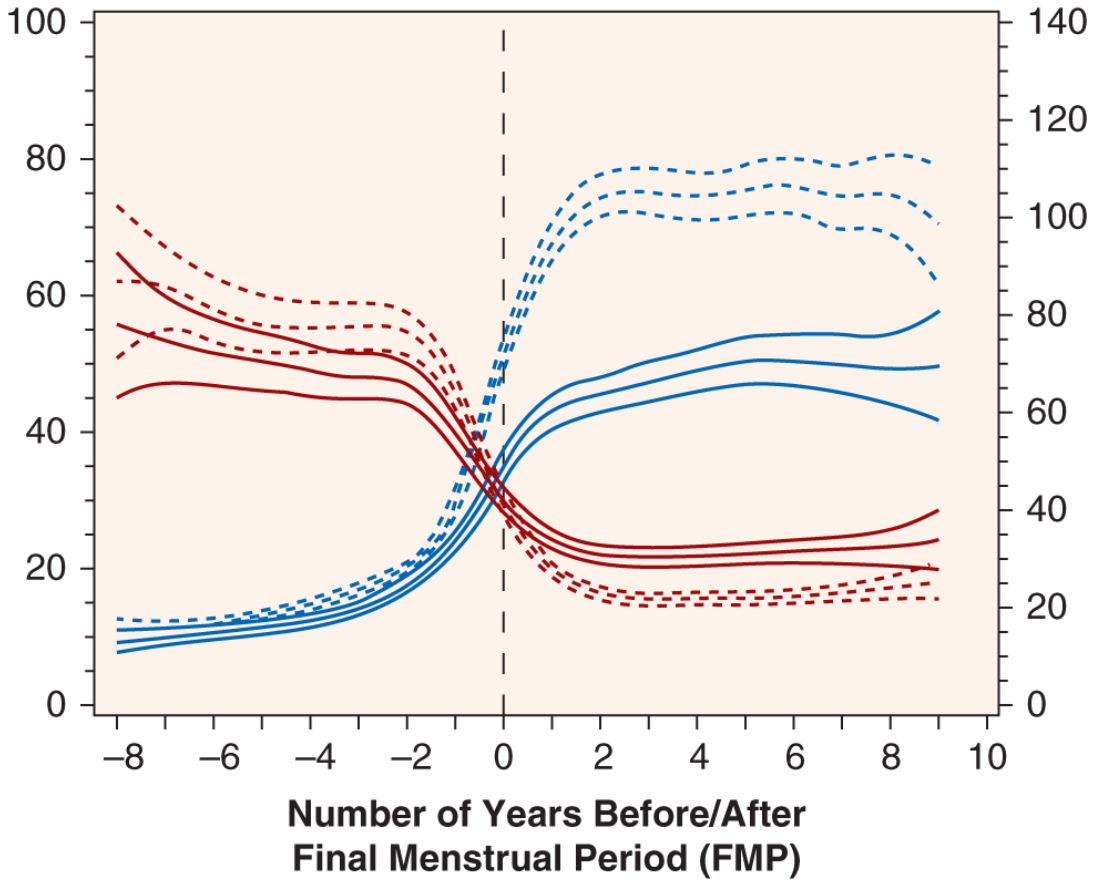


FIGURE 40-2. Population mean (95% confidence interval [CI]) follicle-stimulating hormone (FSH) (in blue, right y-axis, IU/L) and estradiol (E2) (in red, left y-axis, pg/mL) concentrations for obese (solid line) and nonobese (dashed line) women in relation to time to the final menstrual period (FMP), Study of Women's Health Across the Nation (n = 1215 women).

Given the complexity and the cost of measuring these hormone-driven menopausal transition events in the clinical setting, progress through the transition is frequently estimated with menstrual cycle characteristics. In 1996, the World Health Organization suggested definitions of the stages describing the transition to natural menopause. A more comprehensive staging system, including earlier stages of reproductive aging and later stages of postmenopause, has now been proposed and accepted by the 2001 and 2011 International Stages of Reproductive Aging Workshops (STRAW, STRAW+10). STRAW characterized reproductive life in seven stages, with five stages of reproductive life prior to the FMP. Reproductive life is divided into the *reproductive* years (three stages: early, peak, and late) and the *menopausal transition* years (two stages: early and late). The *postmenopause* (two stages: early and late) follows the FMP. STRAW+10 staging definitions are based primarily on bleeding changes with the acknowledgment that discriminating hormone levels, specifically AMH and FSH, now add precision as scientific understanding of their longitudinal patterns and their relationship to fertility and ovarian reserve advances (**Table 40-1**).

TABLE 40-1 ■ DEFINITIONS OF THE STAGES OF REPRODUCTIVE AGING AND MENOPAUSE

Natural Menopause
The permanent cessation of menstruation resulting from the loss of ovarian follicular activity. It is recognized after 12 consecutive months of amenorrhea, for which there is no other pathologic or physiologic cause. An adequate independent biological marker for the event does not exist.
Menopausal Transition
The 3–10 y period of time before the final menstrual period (FMP) following late reproductive life when variability in the menstrual cycle increases and anti-müllerian (AMH) hormone levels are very low or undetectable.
The menopausal transition consists of two stages, early and late transition. Early transition is generally characterized by increased variability in menstrual cycle length and increases in follicle-stimulating hormone (FSH). Late transition is characterized by long cycles of 60 days or more, elevated FSH, and low estradiol.
Postmenopause

The period dating from the FMP, regardless of whether the menopause was induced or spontaneous. The postmenopause also has two stages, early and late with the early postmenopause lasting from about 3 to 5 y.
Reproductive Life and Reproductive Stage Reproductive life includes the period from menarche to menopause. The reproductive stage includes the period from menarche to the menopausal transition and includes three substages: early, peak, and late.
Perimenopause Older terminology referring to the period when the endocrinologic, biological, and clinical features of menopause begin through the first year after the menopause.
Premenopause An older ambiguous term that may refer to the period prior to the onset of the menopausal transition or to the whole of the reproductive period prior to the menopause.
Induced Menopause The cessation of menstruation following either surgical removal of both ovaries or iatrogenic ablation of ovarian function.
Simple Hysterectomy At least one ovary is conserved. It is used to define a distinct group of women in whom ovarian function may persist for a variable period after surgery.
Premature Menopause Menopause that occurs at an age less than two standard deviations below the mean estimated for the reference population. In the absence of reliable population estimates, 40 y is frequently used as an arbitrary cutoff point.

Sources: World Health Organization. Research on the Menopause in the 1990s: Report of a WHO Scientific Group. Geneva: World Health Organization; 1996:12–14. WHO Technical Report Series No. 866; Harlow SD, Gass M, Hall JE, et al; for the STRAW + 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012;97(4):1159–1168; Menopause. 2012;19(4):387–395; Fertil Steril. 2012;97(4):843–851;. Climacteric. 2012;15(2):105–114.

Based on menstrual calendar diary data recorded by women undergoing the menopausal transition, cycle lengths in excess of 60 days are a sensitive indicator of onset of the late menopausal transition and an impending FMP. This represents a pragmatic marker for use by patients and clinicians alike in characterizing a woman's menopausal status. Further, these time frames are consistent with the presence of two follicle pools: one recruitable pool in which follicles, when stimulated, are immediately available for growth; and a second pool of follicles insensitive to gonadotropin signals. The growable pool is refreshed approximately every 60 to 90 days. As the follicle supply decreases, the growable pool of follicles can no longer replenish itself to those numbers seen in the peak reproductive life stage. As the follicle reserve becomes critically diminished and few remaining responsive follicles are present, menstrual cycles become more infrequent and are more likely to be anovulatory.

Aging of the reproductive system involves all three levels of the reproductive axis—the brain, pituitary, and the ovary. While the hypothalamus and pituitary play extensive roles in all aging processes, the exact mechanisms by which gonadotropin-releasing hormones (GnRH) change with age with respect to biosynthesis, transport, release, and receipt of feedback from neurotransmitters or steroids is incompletely understood. The total numbers of GnRH neurons do not appear to be the critical factor in determining reproductive senescence. Rather, changes in intermittent hormone secretion (ie, luteinizing hormone [LH] or FSH) or glycoprotein free α-subunit (FAS) in pre- versus postmenopausal women result in a change in gonadotropin levels, characterized as a change in their pulse amplitude and, possibly, their pulse frequency. These changes in pulsatile release may reflect an unappreciated aging process or a greater insensitivity to feedback during the menopausal transition.

In the aging hypothalamus, dopamine secretion into the portal vasculature declines and, with aging, the stimulatory action of estrogen is absent. In addition to dopamine, it is thought that norepinephrine, acting primarily through the α-adrenergic receptor, stimulates GnRH release, a process that declines with aging. This aging phenomenon may explain why some of the symptoms commonly associated with the menopausal transition (including potential cognitive changes) are more likely to reflect chronological change while other symptoms, such as VMS, appear to be more reflective of the events of change in ovarian hormone concentrations.

Disaggregating Menopause Symptoms and Chronological Aging

The onset or exacerbation of a constellation of symptoms, including vasomotor problems, vaginal dryness and other

sexual symptoms, urine leakage, changes in skin, fatigue, and problems with sleeping, negative mood, and decline in cognitive acuity, is frequently attributed to the menopause. Many women may choose to begin short-term hormone therapy in an effort to combat these menopausal symptoms. Below we describe these symptoms in relation to their development, frequency, and degree of bother during the menopausal transition and, when relevant, the effect of hormone therapy (HT).

MENOPAUSAL SYMPTOMS

Vasomotor Symptoms

VMS, such as night sweats and hot flushes, are a very common occurrence in women undergoing the menopausal transition. In SWAN between 60% and 80% of menopausal women experienced VMS at some point during the transition. The occurrence and frequency of VMS peak in the late menopausal transition with the approach of the FMP and in the early postmenopause. Although symptoms generally peak during this time frame, many women experience symptoms much earlier and/or much later. In SWAN the median duration of VMS postmenopause was over 6 years. In fact, a significant proportion of women report VMS well into their sixties.

Although the physiologic causes of VMS are not fully understood, their common occurrence during the menopausal transition suggests a role of reproductive hormones. In SWAN, higher FSH and lower estradiol levels are associated with greater likelihood of reporting VMS. Women with high body mass index (BMI) or who are current smokers are more likely to report VMS.

In SWAN there are race/ethnic differences in VMS prevalence whereby African-American women report more VMS and Chinese and Japanese women report less VMS than white women. African-American women also report a longer median duration postmenopause (8.6 years). Associations of VMS with poorer adipokine profiles, higher levels of anxiety, depression and perceived stress, and low socioeconomic status may, in part, explain these race/ethnic differences in VMS.

Sleep Disturbances

Sleep disturbance is observed in 30% to 60% of midlife women. While decrements in sleep quality are associated with aging, gender differences in sleep disturbances that emerge at midlife suggest that the increase in sleep difficulties may not simply be an aging effect. In SWAN, nearly 37% of midlife women reported having sleep disturbances. Overall sleep complaints are associated with menopausal status. In SWAN, difficulty falling asleep and staying asleep increased through the menopausal transition and women with surgical menopause had the highest prevalence of trouble falling asleep, waking several times, and waking up early (**Table 40-2**). Accordingly, low estradiol levels and high FSH levels were also associated with higher report of sleep problems. Polysomnography studies, however, have not found any association between menopausal status and diminished sleep quality.

TABLE 40-2 MENOPAUSAL STATUS AND ODDS OF SLEEP DISTURBANCES

	TROUBLE FALLING ASLEEP		WAKE UP SEVERAL TIMES		WAKE UP EARLY	
MENOPAUSAL STATUS	ODDS RATIO	95% CONFIDENCE INTERVAL	ODDS RATIO	95% CONFIDENCE INTERVAL	ODDS RATIO	95% CONFIDENCE INTERVAL
Premenopausal	1		1		1	
Early perimenopausal	1.36	(1.11, 1.67)	1.41	(1.21, 1.63)	1.20	(1.00, 1.44)
Late perimenopausal	1.95	(1.45, 2.63)	2.39	(1.92, 2.97)	1.93	(1.48, 2.50)
Postmenopausal	2.35	(1.75, 3.17)	2.24	(1.79, 2.80)	1.54	(1.18, 2.01)
Surgically menopausal	3.34	(2.13, 5.23)	2.52	(1.73, 3.67)	2.05	(1.34, 3.12)
Postmenopausal on hormone therapy	1.24	(0.78, 1.97)	1.44	(1.05, 1.98)	1.17	(0.79, 1.72)
Surgically menopausal on hormone therapy	1.44	(0.81, 2.54)	1.90	(1.23, 2.92)	1.93	(1.19, 3.13)

Adapted from Table 2 in Kravitz HM, Zhao X, Bromberger JT, et al. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. Sleep. 2008;31(7):979–990.

Concomitant with the menopausal transition are many physiologic and psychosocial changes that may impact sleep including VMS, sexual dysfunction, stress, and psychological symptoms. Women with frequent VMS report nearly three times higher odds of trouble falling asleep, regular waking, and waking too early as compared to women without VMS. In the SWAN Sleep Ancillary Study, VMS report after waking was negatively associated with sleep efficiency, but there was no association with measured VMS or VMS reported during the night.

Worsening sleep during the menopausal transition is important because data from midlife women demonstrate that poor sleep is associated with greater risk of hypertension and aortic calcification as well as increased incidence of mood and anxiety disorders. There are also associations of poor sleep with other health problems including increased risk of diabetes, metabolic syndrome, and cardiovascular mortality.

Sexuality Dysfunction

Although midlife women report a high importance of sexual activity in their lives, sexual dysfunction is a highly prevalent issue. In SWAN, among more than 1700 mid-aged women (mean age 50), 42% reported having a sexual problem. Menopausal status was associated with many domains of sexual function including desire, frequency, arousal, and pain. The impact of social and medical factors including availability of a partner, relationship quality, psychological function, and overall health may have important effects on sexual function during the menopausal transition. However, after consideration of such factors, there were no differences in arousal, frequency of sexual activity, physical pleasure, or satisfaction by menopausal status.

Common symptoms associated with sexual dysfunction among midlife women include vaginal pain and vaginal dryness. These conditions are thought to be influenced by reproductive hormone changes during the menopausal transition, but may also reflect presence of the often overlooked chronic pain syndrome, vulvodynia. Hormonal changes may affect sexual function directly via their involvement in pain processing or indirectly through their effect on the anatomy and physiology of the vaginal environment. Among more than 3300 multiethnic mid-life women in SWAN over a 10-year period aged 42 to 52 at baseline, testosterone levels were positively associated and FSH levels were negatively associated with masturbation and arousal but there was no association with estradiol levels. These findings are consistent with other epidemiologic studies of midlife women including the Melbourne Women's Midlife Health Program (MWMHP) and the Massachusetts Women's Health Study.

Depressed Mood

Depression is the leading cause of health-related disability in women, who are twice as likely to suffer from depression as compared to men. Several factors, including hormones, reproductive factors, gender-based violence and other cultural norms, as well as genetics and biology have been associated with this increased risk among women. Many of these factors are especially salient during the menopausal transition. First-onset incidence or recurrent episodes of clinical depression occur in 20% to 30% of midlife women. The menopausal transition and postmenopause periods are associated with greater risk of major depressive episodes as compared to the premenopause. Notably, this increased risk is similar across all women, regardless of preexisting symptoms.

Changes in reproductive hormones including fluctuations in estradiol and FSH during the midlife are implicated as one factor associated with depressed mood. However, other menopause-associated attributes including anxiety symptoms, BMI, smoking behavior, vasomotor symptoms, low social support, and stress may be highly relevant with respect to depressed mood occurring during the midlife period.

Cognition and Memory

Self-reported memory and concentration difficulties are commonly reported among women during the menopausal transition, and recent data suggest that changes in cognitive function may be occurring during this time. In SMWHS (mean age 46.7), 62% of women reported memory changes "over the past few years." The most common types of memory complaints included difficulty recalling words or numbers, forgetfulness, and needing memory aids. In the SWAN cross-sectional study among more than 12,000 women (age 40–55), menopausal status was associated with self-reported forgetfulness. The prevalence of forgetfulness was 44% among women in the menopausal transition and 42% among naturally postmenopausal women but only 31% among premenopausal women.

Three longitudinal studies have examined objective measures of cognitive performance in women traversing the

menopausal transition. Two of these studies found some learning deficits, especially in late menopausal transition women (**Table 40-3**). The learning deficits were independent of depressive, anxiety, sleep disturbance, and vasomotor symptoms. One of these studies observed actual declines in verbal memory during the menopausal transition among 400 white and black women.

TABLE 40-3 MENOPAUSAL STATUS AND COGNITIVE PERFORMANCE IN MIDLIFE WOMEN

COGNITIVE TEST	MENOPAUSAL STATUS	RATE OF CHANGE PER YEAR	STANDARD ERROR
Symbol Digit Modalities	Premenopausal	+0.94	0.28
	Early perimenopausal	+0.54	0.11
	Late perimenopausal	+0.26	0.22
	Postmenopausal	+0.63	0.13
	Postmenopausal with current hormone use	–0.02	0.31
East Boston Memory Delayed Recall	Premenopausal	+0.14	0.06
	Early perimenopausal	+0.04	0.02
	Late perimenopausal	+0.01	0.04
	Postmenopausal	+0.13	0.03
	Postmenopausal with current hormone use	–0.09	0.07

Adapted from Table 2 in Greendale GA, Huang MH, Wight RG, et al. Effects of the menopausal transition and hormone use on cognitive performance in midlife women. Neurology. 2009;72(21):1850–1857.

Declines in estrogen have been hypothesized as the mechanism underlying changes in cognitive function during this life stage. Estrogen receptors are found in the hippocampus and prefrontal cortex and in animal models, estrogen has a positive impact on the secretion of neurotransmitters and growth of neurons. While data from observational studies suggest that exogenous estrogen may be beneficial for memory and cognitive function early in the menopausal transition, clinical trials of hormone therapy have not been successful in reducing late-life memory complaints or dementia risk. In fact, the Women's Health Initiative Memory Study (WHIMS) found an increased risk of dementia associated with hormone therapy treatment as compared to placebo.

In older adults, vascular pathology has been identified as a contributing factor to cognitive decline, dementia, and Alzheimer disease, and changes in cardiovascular risk factors during the midlife may be related to risk of future cognitive decline. The presence of diabetes, hypertension, high cholesterol, and smoking during midlife predicts late-life cognitive impairment and dementia. Notably, the association of midlife cardiovascular risk factors and cognitive decline and dementia is greater than the association of concurrently measured cardiovascular risk factors. This suggests that the midlife is a critical window for pathologic changes leading to cognitive decline.

In summary, while the evidence shows small differences in objective cognitive performance associated with menopausal stage, the high prevalence of self-reported memory complaints among menopausal women suggests that the level of bother reported by individuals is high, and thus, these changes may be clinically significant.

CLINICAL CHANGES AND CHRONIC DISEASE RISK

Cardiovascular Disease Risk

In the United States, one in four women die from heart disease. It has long been hypothesized that the menopausal transition increases the risk of coronary heart disease, although the relationship is not fully understood. The incidence of CVD increases in women after the age of 50; however, differentiating between the normal aging process and changes unique to the menopausal transition is difficult. Earlier age at menopause, premature menopause, and surgically induced menopause have been associated with CVD in some studies, thereby prompting hypotheses regarding the importance of estradiol loss in cardiovascular risk. However, the WHI trial found that hormone therapy was associated with greater risk of heart disease, highlighting the complexities of understanding the underlying causes

of CVD risk among women and suggesting that a uniquely estrogen hypothesis is too simplistic.

Many physiologic changes occur during the transition: cessation of ovarian estrogen secretion, changes in body fat distribution, adverse changes in lipid profiles, insulin resistance, and adiponectin levels with an increasing proportion of women developing metabolic syndrome and diabetes. Many of these occurrences have been hypothesized to mediate the development of adverse cardiovascular outcomes yet few have actually shown an independent association with the menopausal transition including changes in blood pressure, blood glucose, body weight, C-reactive protein, or fibrinogen.

SWAN has demonstrated that changes in lipid profiles among midlife women, specifically significant elevations in total cholesterol, LDL-C, and apolipoprotein B, occur during the 2-year window on either side of the FMP, but not other characteristics such as insulin and plasminogen activator indicator-1 (PAI-1), whose trajectories are more consistent with an aging model (**Figure 40-3**). Given that most cardiovascular events occur in the seventh or eighth decade, understanding the impact of menopause-associated lipid changes on risk of heart attack or stroke is difficult. Measures of subclinical CVD in SWAN show progression of intima-media thickness and adventitial diameter during the late menopausal transition, providing further evidence that important physiologic changes associated with cardiovascular risk begin in the midlife, 10 to 15 years prior to major cardiovascular events.

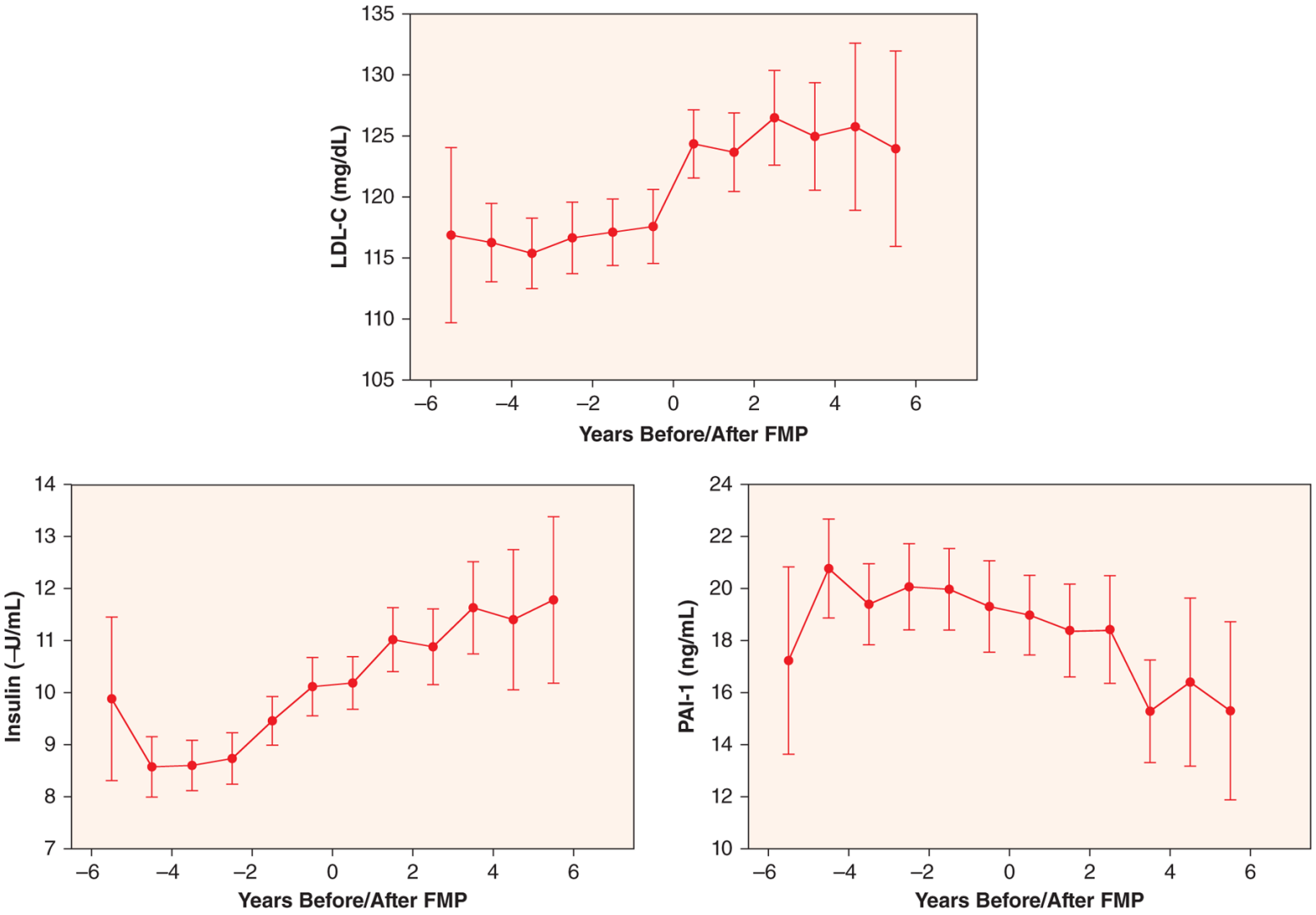


FIGURE 40-3. Change in mean low-density lipoprotein cholesterol (LDL-C) (top), mean insulin (bottom left), and mean plasminogen activator inhibitor-1 (PAI-1) (bottom right)—measures of three axes of cardiovascular disease risk—across the menopause transition, Study of Women's Health Across the Nation. Data represent measures taken approximately 6 years before through 6 years after the final menstrual period (FMP) for a total of 2336 observations in 722 women.

Vasomotor symptoms, the hallmark symptom of menopause, are also associated with cardiovascular risk. Vasomotor symptoms are related to reduced endothelial function, carotid intima-media thickness and adventitial diameter, and aortic calcification in midlife women. The WHI reported that risk for a CVD event among

postmenopausal women on hormone therapy was highest in the subset of those women reporting moderate to severe vasomotor symptoms at enrollment.

The role of menopause as a risk factor for CVD remains controversial and, given the time lag between menopause and cardiovascular endpoints, is difficult to assess. Multiple avenues of inquiry are being pursued including the impact of lifestyle modification, pharmacologic management of risk factors, and hormonal changes during the midlife.

Diabetes Risk

The relationship between menopause and risk for diabetes is not completely understood. Diabetes is a significant health issue for middle-aged and older women, and accounts for over 2% of deaths and over 3% of the disability in women aged 50 and older. Although there is a marked increase in diabetes prevalence among postmenopausal women, its cause and relation to menopause have not yet been well established. Different factors possibly playing a role in diabetes risk in postmenopausal women include changing sex hormone profiles, changing iron stores, changes in body composition, and age at menopause onset.

The sex hormone profile of a postmenopausal woman is a relatively androgenic state compared with premenopause, as the ovaries cease to produce estrogen while production of adrenal androgens remains stable. This is significant because greater levels of androgens are associated with glucose intolerance. Increased iron stores may be associated with increased insulin resistance and iron may play a significant role in the development of diabetes. Measures of iron stores increase from premenopause to postmenopause. Body composition changes have been independently associated with menopausal status, and insulin sensitivity and glucose metabolism in postmenopausal women are altered as a result. Obesity also increases during this life stage, although longitudinal studies such as SWAN have shown weight gain in midlife women is due to chronological aging rather than menopause. However, all of these factors increase risk of diabetes. Earlier age at menopause is also associated with a greater risk of type 2 diabetes. In addition, the incidence of metabolic syndrome increases during the menopausal transition. In SWAN, 13.7% of premenopausal women had developed new-onset metabolic syndrome by the time they reached menopause. Metabolic syndrome is linked to risk of both diabetes and CVD. While the relationship between menopause and diabetes is not yet known to be one of causal or indirect correlation, the associations continue to be an area of active investigation.

Obesity and Body Composition

More than one-third of adults in the United States are obese (BMI $\geq$ 30 kg/m^2), and the prevalence of obesity is higher among women as compared to men. Several factors associated with the menopausal transition, including menstrual cycle characteristics, timing of the menopausal transition, and vasomotor symptoms, are thought to be associated with midlife changes in obesity. Obese women have longer menstrual cycle lengths, and some, but not all, studies have found that obese women have a later age at menopause compared to nonobese women.

Of particular relevance, the level and change of estradiol levels during the menopausal transition differ by obesity status. Obese women have lower estradiol levels prior to the FMP but higher levels after the FMP due to less rapid estradiol declines during the menopausal transition as compared to nonobese women. Similarly, rises in FSH around the final menstrual period are less dramatic among obese women.

Longitudinal changes of body composition during the menopausal transition (**Table 40-4**) include annual increases of 0.6% (~ 0.5 kg) in weight, 0.7% (~ 0.2 kg/m^2) in BMI, 1.6% (~ 0.57 kg) in fat mass, and 1% (~ 0.9 cm) in waist circumference. Annual measurements of lean mass do not change across the 6-year time period. Increasing levels of FSH are associated with increasing fat mass and waist circumference, and decreasing lean mass and skeletal muscle mass across the 6-year time frame. While waist circumference continues to increase during the transition, the rate of increase slows approximately 1 year after FMP. Women continue to gain fat mass, with no similar slowing observed. These body size changes have potentially important implications, as adipose tissue functions as an endocrine organ, secreting a variety of cytokines including leptin, adiponectin, resistin, PAI-1, tumor necrosis factor (TNF)-α, and interleukin (IL)-6 with immunologic, vascular, and metabolic actions.

TABLE 40-4 BODY COMPOSITION MEASURES AND 6-YEAR CHANGE

BODY COMPOSITION MEASURES	6-YEAR CUMULATIVE PERCENT CHANGE	6-YEAR ABSOLUTE CUMULATIVE CHANGE
BMI (kg/m^2)	4%	1.2 kg/m^2

Fat mass (kg)	10.1%	3.4 kg
Height (cm)	0.24%	–0.38 cm
Skeletal muscle mass (kg)	–1.06%	–0.23 kg
Waist (cm)	6.2%	5.7 cm
Weight (kg)	3.4%	2.9 kg

While changes in body weight occurring during the midlife are more likely to be due to chronological aging than due to the menopausal transition, changes in body composition or body typology may be due to loss of ovarian function. Body weight increases during the midlife are associated with increased fat mass but decreased lean mass. Adipose tissue, once considered a passive storage portal of energy, is now recognized as a highly metabolic endocrine organ that is the site of sex steroid metabolism and has the capacity to secrete active agents including adipokines. Changes in adipokine levels including lower adiponectin and higher ghrelin levels during the perimenopause are associated with FSH levels. However, adiponectin levels were not different by menopause status in a study of Japanese women.

While different hormone patterns occur across the menopausal transition for obese as compared to nonobese women, more work is needed to understand the impact of these hormonal differences on changes in body composition and adipokine levels during the midlife. Understanding these relationships will provide important and relevant information about the risks of chronic diseases, many of which are associated with obesity and often are initiated during the midlife.

Bone Loss

Women have a nearly twofold greater lifetime fracture risk compared to men. Early postmenopause is a time of accelerated bone loss, with radial bone loss in the first 5 years postmenopause reported to be 2.4% to 2.6% per year compared to 0.4% to 1.9% per year in the 5th to 11th year postmenopause. However, it is now clear that bone loss commences prior to menopause and that the acceleration in remodeling deficit is related to rise in FSH and sharp drop in estrogen prior to the final menstrual period. The menopausal transition is also a critical period of decline in bone strength, with about half the lifetime loss in BMD occurring over a relatively short time frame.

Accelerated loss in BMD and bone strength begins 1 to 2 years prior to the final menstrual period, continues until 2 to 5 years after the final menstrual period, and then slows thereafter (**Figure 40-4**). In MBHMS, annualized rates of spine bone loss in the 2 years prior to the FMP were 1.7% per year and were 3.3% per year in the 2 years after the FMP. The timing of these changes in bone with respect to the FMP have been corroborated by studies of bone resorption biomarkers, which show similar changes with respect to the timing of the menopause.

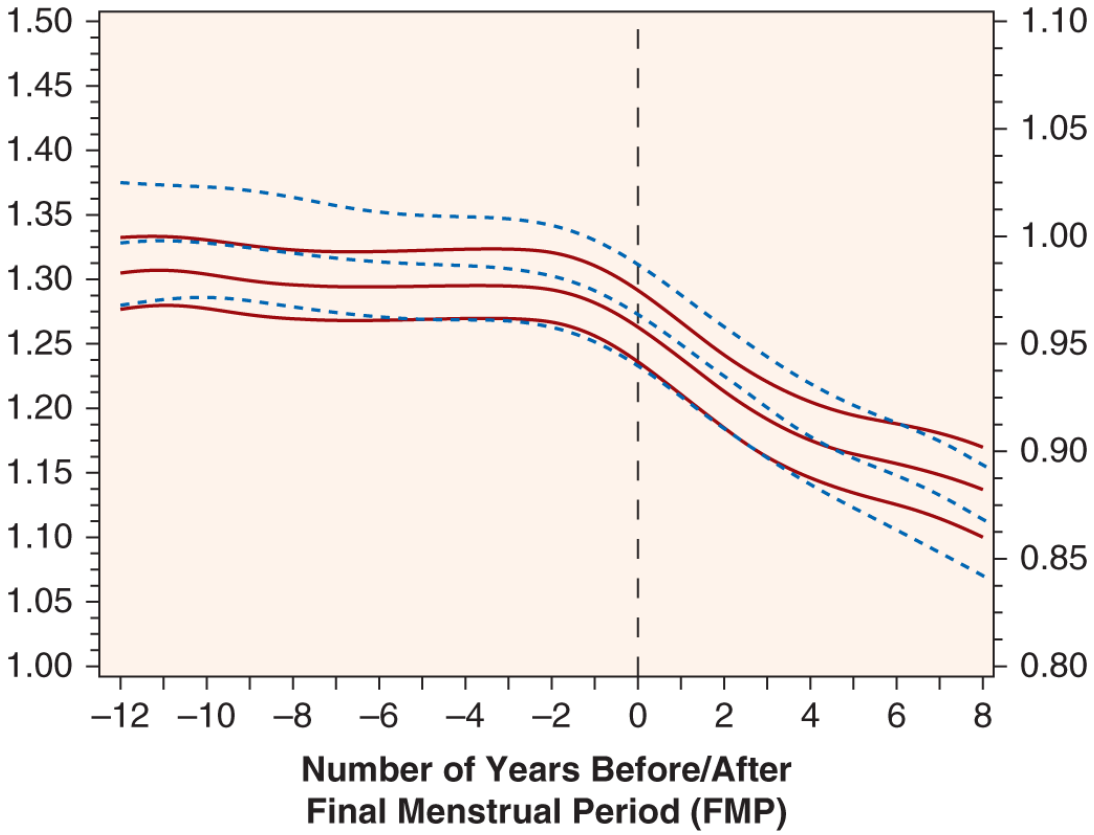


FIGURE 40-4. Population mean (95% confidence interval [CI]) spine (red solid line, left y-axis) and femoral neck (blue dashed line, right y-axis) bone mineral density (BMD) values (g/cm^2) in relation to time to the final menstrual period (FMP), Michigan Bone Health and Metabolism Study. (Adapted from Sowers M, Zheng H, Jannausch ML, et al. Amount of bone loss in relation to time around the final menstrual period and follicle-stimulating hormone staging of the rransmenopause. *J Clin Endocrinol Metab*. 2010;95(5):2155–2162).

While it has traditionally been thought that postmenopausal osteoporosis is due to estrogen deficiency, faster rates of lumbar spine bone loss in SWAN were associated with higher levels of FSH prior to the FMP, higher levels of FSH and sex hormone–binding globulin (SHBG) in the transmenopause phase, and lower levels of estradiol and SHBG in later postmenopause. However, menopausal FSH may simply be a better marker of estrogen profiles than a single estradiol measure given the variability of estradiol across a menstrual cycle. Also BMD does not capture important aspects of bone quality including the microarchitecture and geometry of bone. Transmenopausal changes in trabecular bone structure also occur. Bone strength is also associated with bone size, and increases in the medullary bone diameter and periosteal diameter are correlated with estradiol levels. Several mechanisms likely underlie bone loss at menopause in addition to direct hormonal influences on bone. For example, the responsiveness of the vitamin D system to estrogen may also contribute to the bone loss observed with menopause.

Thus, bone loss begins earlier than thought, accelerates in the late perimenopausal period, and continues into the early postmenopausal period. The rate of loss appears to decelerate approximately 10 years after the FMP. There are marked individual differences in the rate of bone loss, but risk factors contributing to this wide variation are yet to be fully characterized. More research is needed to evaluate the predictive value of measures of bone microarchitecture and to consider the predictive value of biochemical markers of bone turnover in relation to perimenopausal bone loss, and to address rates of bone loss in determining subsequent fracture risk.

Physical Function and Disability

Geriatricians are familiar with the role of physical function assessment in older people, but increasing information suggests that 12% to 25% of newly menopausal women already have substantial functional limitations. The long-term implications for physical limitations presenting in women in their forties to sixties have not been well evaluated. Women are more likely than men to report a physical limitation, for reasons that are poorly understood, although there is evidence that these are probably true reflections of increasing disability.

The midlife is a critical window for the onset of functional limitations and transition to disability. Temporal increases in disability rates among midlife populations despite stable rates among older adult populations highlight the importance of assessing functioning and intervening during this life stage. Changes in functioning during this life stage

may be related to the increasing prevalence of diabetes, less favorable lipid profile, decline in sensory function including hearing and vision, and greater propensity to obesity.

Based on the 10-item SF-36 physical function questionnaire (MOS SF-36), which assesses limitation in bathing, dressing, carrying groceries, bending, moderate and vigorous activities, walking, and climbing stairs, nearly one-third of women (age 45–57) in the SWAN cohort reported moderate functional limitations and 11% reported severe limitations. Mobility-based disabilities are most commonly reported by mid-aged populations; in the Michigan SWAN cohort, 39% of midlife women reported moderate-extreme difficulty in "getting around" based on the World Health Organization Disability Assessment Schedule.

Issues of functioning and disability are particularly relevant for midlife women as they have lower levels of physical functioning and more rapid declines in functioning as compared to age-matched men. The reasons for these sex differences are poorly understood but may include biological, sociological, psychosocial, and economic factors. Poorer physical functioning among postmenopausal women as compared to premenopausal women as well as the association of surgical menopause with functional limitations has fostered speculation regarding the role of menopause in the initiation of poor functioning.

The odds of physical functioning limitations were 60% to 70% higher among postmenopausal women as compared to premenopausal women, after adjustment for age, demographics, health status, and chronic conditions (**Table 40-5**). In both the Michigan SWAN study and the Michigan Bone Health and Metabolism Study, postmenopausal women and women with surgical menopause had poorer performance-based physical functioning including taking longer to walk a short distance, ascend and descend stairs, and slower walking velocity. With respect to hormones, greater declines in estradiol and testosterone are associated with higher odds of self-reported functional limitations.

TABLE 40-5 LONGITUDINAL MENOPAUSAL STATUS AND ODDS OF PERCEIVED LIMITATIONS IN PHYSICAL FUNCTIONING

MENOPAUSAL STATUS	ODDS RATIO	95% CONFIDENCE INTERVAL
Premenopause	1	Reference
Early perimenopause	1.42	0.96, 2.10
Late perimenopause	1.51	1.00, 2.27
Natural postmenopause	1.61	1.07, 2.41
Surgical postmenopause	1.73	1.06, 2.83
Hormone users/unknown	1.46	0.97, 2.22

Adapted from Table 2 in El Khoudary SR, McClure CK, VoPham T, et al. Longitudinal assessment of the menopausal transition, endogenous sex hormones, and perception of physical functioning: the Study of Women's Health Across the Nation. J Gerontol A Biol Sci Med Sci. 2014;69(8):1011–1017.

The menopausal transition encompasses complex physiologic processes beyond changes in hormone levels including rapid bone loss, changes in body composition, and onset of many chronic diseases, as shown in **Figure 40-5**. Similar to findings among older adult cohorts, higher levels of proinflammatory cytokines and hemostatic markers are prospectively associated with greater limitations in physical functioning among SWAN women. Poorer inflammatory and hemostatic profiles are characteristic changes during the menopausal transition and may represent one mechanistic pathway relating the menopause to physical functioning decline.

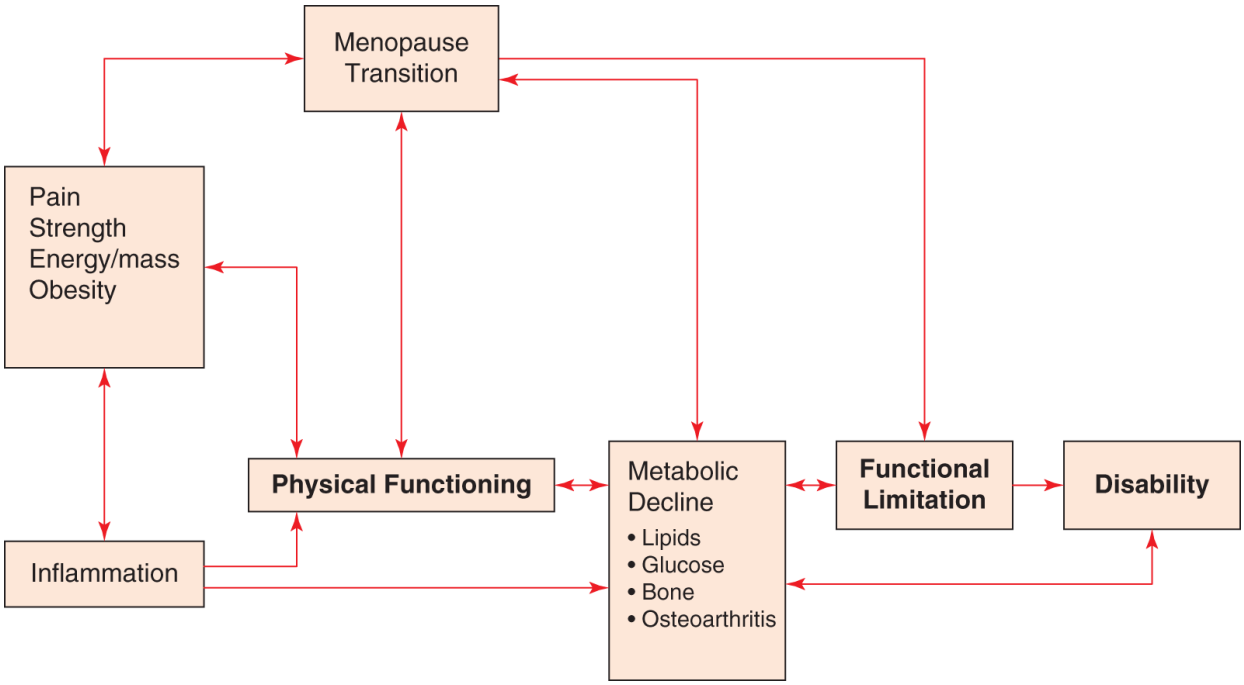


FIGURE 40-5. Conceptualization of the development of functional limitations at midlife. (Adapted from **Figure 1** of Sowers M, Pope S, Welch G, et al. The association of menopause and physical functioning in women at midlife. *J Am Geriatr Soc*. 2001;49:I485–I492.)

While there is a high prevalence of functional limitations among mid-aged women, physical functioning is a highly dynamic process. Longitudinal data from SWAN have demonstrated that the probability of improvements in physical functioning is as likely as worsening and that potentially afflicted groups including obese women and women with osteoarthritis (OA) have a high propensity for recovery. Also, while risk of functional limitations increased during the menopause transition, these risks are dwarfed by those observed in women who report difficulty in paying for basics such as food, housing, and medical care. Thus, clinical and policy interventions to forestall functional limitations or improve current functioning may be most relevant and effective among midlife populations.

Osteoarthritis

OA is a leading cause of pain and disability for adults in the United States. OA, the most common form of arthritis, is characterized by a loss of articular cartilage, subchondral bone remodeling, soft tissue damage, and inflammation. The pattern of OA prevalence and severity exhibits a sex dimorphism whereby hand and knee OA are more common among women after age 50, and postmenopausal women have more progressive and symptomatic disease as compared to age-matched men.

Increased age is a major risk factor for OA; the incidence of OA among women increases fivefold between the ages of 40 and 49 and doubles again between the ages of 50 and 59. In the Michigan SWAN study, when women were premenopausal or in the early menopausal transition (mean age 46), the baseline prevalence of radiographic knee OA was 18%; 10 years later when nearly all women were postmenopausal (mean age 57), the prevalence was 66%.

The dramatic increase in OA incidence and prevalence in this life stage which spans the menopausal transition has stimulated hypotheses regarding the importance of the menopausal transition for OA onset. While age at menopause has not been associated with OA, animal models suggest that loss of ovarian function may be deleterious to joint integrity. In animal models, ovariectomy is associated with cartilage turnover, and exogenous estrogen treatment is beneficial. In observational studies among humans, exogenous hormone therapy appears to have a modest benefit protecting against osteoarthritic structural changes but no benefit for osteoarthritic symptomatology or on pain reports. However, hormone therapy prescribing practices differ based on smoking status and body size—risk factors for OA onset and progression. With respect to endogenous levels of estradiol, the evidence is mixed; some studies have reported lower levels of estradiol among women with OA whereas other studies report no association.

The midlife period is characterized by a complex set of biological and psychosocial changes coincident with the menopausal transition including changes in body size and composition, cardiometabolic risk, physical activity, and symptom report. Understanding whether the increase in OA prevalence during the midlife is due to perturbations in endogenous hormones or other factors is critical so that effective and relevant intervention strategies may be developed to prevent or forestall the onset and progression of OA.

Skin and Collagen

Skin quality declines with age, which often coincides with the menopausal transition. Notable esthetic and health-related changes occur in skin such as change in collagen, elastin, and water content, atrophy, and change in wound-healing responsiveness. As much of this deterioration may be due to hormonal deficiency, the wrinkling, sagging, thinness, and discoloration may be due to a combination of aging and menopause. The lack of estrogen in the postmenopausal period is thought to cause decreased collagen and water content, decreased sebaceous secretions, lower elastin levels, loss of elasticity, and manifestations of hyperandrogenism. Women with premature menopause have accelerated degenerative changes in dermal elastic fibers.

In the first 5 years after menopause, up to 30% of skin collagen can be lost, and total collagen content decreases 2.1% per postmenopausal year over a 15-year period. Much of this collagen loss is preventable in women on estrogen therapy after menopause. Hormone replacement, including topical application of estradiol cream, has been used therapeutically to treat conditions of the aging skin. Additionally, transdermal estrogen delivery systems have been used to avoid the first-pass hepatic metabolism of oral exogenous estrogen replacements. While effective, these methods may have their own adverse effects including allergic/inflammatory reactions.

Wound healing can be difficult for aging women, as there are low levels of transforming growth factor. The lack of skin regeneration and healing is exacerbated by fragile skin being more susceptible to trauma causing more lacerations and bruising. Notably, skins that are richly colored with melanin are intrinsically protected from the impact of photoaging. This may explain the lower prevalence of atrophy, dry skin, and wrinkling observed in women of African descent.

CONCLUSION

The endocrine, sociological, and physiologic changes that accompany menopause occur over a 10- to 15-year period, although the actual duration of the menopausal transition period is highly variable across individual women. At least in some women changes are more pronounced as indicated by variation in levels of FSH, amount of bone loss, and changes in lipid levels for a period of time spanning 2 to 4 years around the FMP. Understanding of the reasons underlying and implications for this interwoman variation in the menopausal experience and change in health profiles is an area of active research.

Vasomotor symptoms are a hallmark of the menopausal transition, experienced by more than two-thirds of women. Emerging studies suggest that possible risk factors include greater body size and smoking behavior. Studies from community samples suggest that vasomotor symptoms have a substantial effect on the quality of life of approximately 10% of women. Further, the impact of the vasomotor symptoms may not be restricted to the actual events; their contribution to other conditions, such as disrupted sleep or exacerbation of mood disorders, may have substantial effect on the quality of life. Furthermore, they are emerging as a potentially important risk factor for CVD.

Ovarian aging appears to be associated with alterations in lipids, bone, and body composition. Thus, the midlife is a time of small but significant changes in a number of systems, including glucose, insulin, lipids, sleep patterns, bone, and joints. Weight gain in midlife is small on an annual basis, but cumulative changes over midlife can be quite substantial and have important effects on other systems. Collectively, these changes are associated with decrements in physical functioning.

It is likely that the coming generations will have higher expectations about quality of life, including those that ensue from the menopausal transition, because they are better educated, more often in the labor force, and have smaller families relative to previous generations. Midlife is an optimal time to consider a reorientation to disease prevention and health promotion by the geriatric health care team.

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Chapter 41

Sexuality, Sexual Function, and the Aging Woman

Stacy Tessler Lindau, Kaitlyn Fruin

Learning Objectives

- Apply a biopsychosocial model to research, diagnosis, and care of female sexual concerns among aging women.
- Integrate into practice knowledge of population norms of sexual activity, behaviors, and problems among aging women.
- Use knowledge of sexual physiology in aging to inform sexual history-taking, diagnosis, and treatment of sexual problems in older women.

Key Clinical Points

1. **Older women, even those without a partner, value their sexual function and expect physicians to counsel them about sexual side effects or expected outcomes of medical conditions and treatments.**
2. **An older woman with sexual dysfunction is likely to be bothered or distressed by the sexual problems, and this distress can have deleterious effects on her overall physical and mental health and intimate relationships.**
3. **Older women who identify as members of a sexual minority group are marginalized and stigmatized in medical care generally, and they are particularly vulnerable with respect to receiving appropriate medical attention for their sexual concerns.**

INTRODUCTION

Sociological evidence about sexuality of women in middle and later life has increased substantially over the last decade, but sexual function and outcomes among middle age and older women are still largely overlooked in the context of medical care. Negative societal attitudes about aging, sexuality among older people, and women's sexuality in particular, present a significant barrier to scientific inquiry and medical attention to older women's health concerns. Proven interventions for promoting female sexual well-being or treating women's sexual problems are limited. Although older women experience high rates of sexual problems and the majority of partnered older women are sexually active, physicians infrequently discuss sexual health with older women. Public health attention to older women's sexuality remains sparse.

The 2005–2006 National Social Life, Health and Aging Project (NSHAP), funded by the National Institutes of Health, provided the first comprehensive, population-representative biosocial data on sexuality among middle age and older women and men in the United States, and it informs many of the insights presented in this chapter. The study enrolled a national probability sample of 3005 community-residing men and women aged 57 to 85 (75.5% weighted response rate), with oversampling of African-American and Hispanic people, and men in the 75- to 85-year-old age group. About half the respondents were male, half were female, and they were divided approximately equally across three age strata: 57 to 64, 65 to 74, and 75 to 85 years. Respondents participated in a face-to-face questionnaire covering social, psychological, and health domains, including detailed information on sexual relationships and

functioning. In 2010 and 2011, 75% of participants in the baseline NSHAP study (Wave I) participated in follow-up interviews as part of NSHAP Wave II, providing data to understand within-individual change over time.

This chapter first locates older women's sexuality in a sociodemographic context, then describes sexual activity, behaviors, and problems experienced by women in later life; reviews physiologic changes that affect sexual functioning as women age; and recommends a clinical approach to evaluation, prevention, and treatment of sexual problems common among older women. Older women, and their sexual relationships, are very heterogeneous. Generalizations made in this chapter, based on population data from the NSHAP study and findings from other sources, are rooted in statistical norms but should not be interpreted as a normative prescription for older women's sexuality.

Interactive Biopsychosocial Model

The interactive biopsychosocial model (IBM) provides a conceptual framework for understanding the relationship between sexuality and health throughout the life course (**Figure 41-1**). To the degree that medicine attends to matters of sexuality, the orientation is largely negative. The medical model approach to understanding sexuality focuses on sexual dysfunction as a problematic consequence of aging, disease, or treatment. Occasionally, medical texts suggest that older patients' complaints about sexual problems, particularly male erectile difficulties, may herald serious underlying disease and ought not be ignored. Growing attention to older adult sexuality has been prompted by the greater longevity of individuals living with HIV and concerns of an increase in sexually transmitted infections (STIs) among older adults. While clinically valid, this narrow conceptualization of sexuality defies its multidimensional nature and limits understanding of the meaning of sexuality for health and the iatrogenic causes of sexual problems or dysfunction.

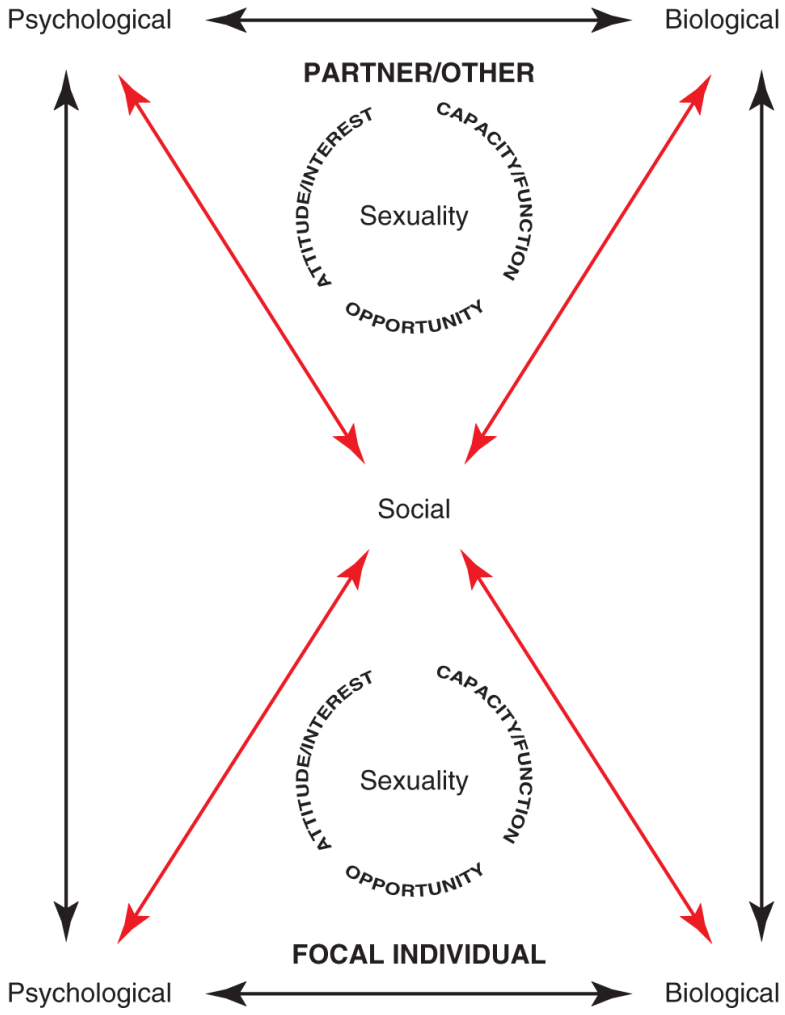


FIGURE 41-1. The interactive biopsychosocial model. (From Lindau ST, Laumann EO, Levinson W, Waite LJ. Synthesis of scientific disciplines in pursuit of health: the Interactive Biopsychosocial Model. *Perspect Biol Med*. 2003;46(suppl 3):S74–S86.)

A broader framework, as defined by the IBM, conceptualizes a bidirectional relationship between sexuality and health. Sexual behavior can result in health problems, such as sexually transmitted infection, victimization, and, in younger women, unwanted pregnancy. Aging, physical and mental health problems, surgeries, medications, and other medical treatments can cause sexual dysfunction. The IBM acknowledges this reciprocal relationship between sexuality and health but incorporates the possibilities that sexuality may also be health-promoting and that aging, or even illness, may confer advantages for sexual life.

In this model, health comprises biological, psychological, and social components and is conceptualized as jointly produced by a woman in conjunction with her spouse or other intimate partner(s). Joint production of health means that partners contribute assets (or liabilities) to the "health endowment," and these assets and liabilities impact the health of the other(s). The hourglass shape symbolizes the dynamic nature of both health and intimate relationships over time. Clinically, this model can be used as a mnemonic for the broad domains of inquiry pertinent to assessing a patient's sexual history and reminds the clinician of the importance of ascertaining the presence, and health, of the patient's intimate partner(s).

SOCIODEMOGRAPHIC CONTEXT OF OLDER WOMEN'S SEXUALITY

Sexuality in later life for most, but not all, people occurs in the context of a long-term marital relationship. For men, aging is largely a partnered experience. Men are significantly more likely than women to have a spouse or other romantic partner in later life and to be engaging in a satisfying sexual relationship, despite a high prevalence of erectile difficulties. As a result of greater longevity, women, in contrast, are much more likely to experience aging, illness, and death without their life partner (**Figure 41-2**).

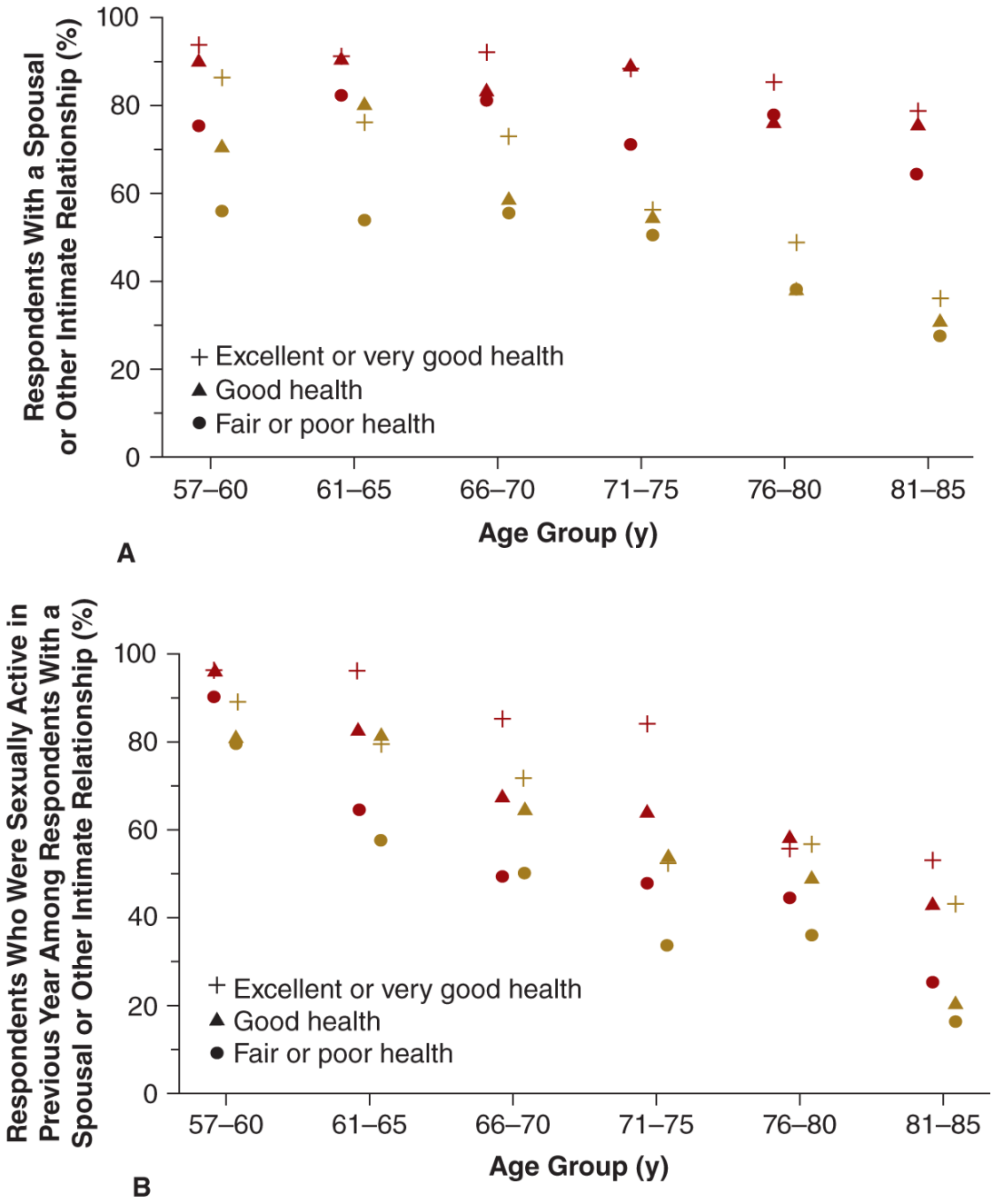


FIGURE 41-2. Prevalence of relationships and sexual activity by age and health status. *Note: Red symbols denote men; yellow symbols denote women*. (From Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med*. 2007;357(8):762–774.)

Still, many older women regard sexuality as important for health and relationships and, among those with a spousal or other intimate relationship, many engage in regular sexual activity. Women tend to be less satisfied with sex in later life than men, and they also report a high frequency of sexual problems including low desire, vaginal dryness, and difficulty experiencing orgasm. An older married woman is often healthier and more vital than her spouse and commonly assumes a caregiver role, which can interfere with the romantic dynamic of the relationship. Physical health problems, medications, and medical treatments affect the sexual lives of older couples; older heterosexual adults with a spouse or other intimate partner who are not sexually active most commonly attribute this to the male partner's health problems.

Sexuality is widely valued by older adults, even those without a partner, as an important aspect of health and life. In his 2001 report, the US Surgeon General David Satcher acknowledged that "sexuality is an integral part of human life. . . . Sexual health is inextricably bound to physical and mental health. . . . [It] is not limited to the absence of disease or dysfunction, nor is its importance confined to just the reproductive years."

Although some aspects of aging are regarded as detrimental to sexual life, older women also identify ways in which aging is beneficial for sexuality (**Table 41-1**).

TABLE 41-1 ■ OLDER WOMEN'S VIEWS ON SEXUALITY AND AGING

	EFFECTS OF AGING ON SEXUALITY	EFFECTS OF SEXUALITY ON AGING
Beneficial	• Partners know each other better • Decreased sexual inhibition • More time • Fewer distractions • Know own body	• Better circulation • Form of exercise • Feeling of youthfulness or completeness • Security of not being alone • Pride in body • Optimistic outlook on life • Indicative of general good health • Happiness/endorphins • Physical release, outlet • Alleviates arthritic pain
Detrimental	• Less intense physical sexual response • Increased inhibition due to poor body image • Societal prejudice • Need for secrecy	• Worry about transmitting or contracting infection • Loss of status as respected elder

Based in part on qualitative work by ST Lindau funded by the John A. Hartford Foundation, 1993.

Lack of formal sexuality education combined with widely restrictive social, religious, and cultural practices around female sexuality during much of the twentieth century have influenced the current generation of older women's sexual expectations throughout their lives. As a result, many report that they have never discussed nor would they initiate discussion of sexual matters with anyone, including their spouses. Most older women report that they have never spoken of sexual matters with a physician, yet feel that sexuality is an appropriate issue for physicians to address and that the physician, rather than the patient, should initiate the discussion (**Table 41-2**). Gender and age differences between women and their physicians can also present barriers to communication about sexual matters. In addition, older women perceive physicians to be poorly trained to deal with patients' sexual concerns and that physicians presume older women to be asexual or disinterested (see **Table 41-2**).

TABLE 41-2 ■ OLDER WOMEN'S PERCEPTIONS ABOUT BARRIERS TO DISCUSSING SEX WITH A PHYSICIAN

WHY PATIENTS DON'T DISCUSS SEX	WHY DOCTORS DON'T DISCUSS SEX
• Patients "don't know what we don't know" • Feel intimidated • Feel it might be disrespectful to physician • Feel uncomfortable discussing sex with male physician • Feel uncomfortable discussing sex with younger physician • Fear that a physical examination may be embarrassing, uncomfortable, or painful • Worry that difference in sexual orientation between patient and physician will threaten relationship • Think physicians not capable of or interested in discussing sex, so no value in raising the issue • Feel the physician would raise the topic if relevant	• Doctors assume older people are not interested in talking about sex or having sex • "Look upon us as their parents" • Don't know enough to feel qualified to talk about sex • Assume someone else is dealing with these issues • Focused on treating older people for illness rather than maintaining health and quality of life • Don't have time • Have their own hang-ups about sex • Embarrassed to talk about sex with older female patients • Religious beliefs interfere

Based in part on qualitative work by ST Lindau funded by the John A. Hartford Foundation, 1993, and data from the University of Chicago Program in Integrative Sexual Medicine Registry (2008–2014).

Aging of the baby boomers, the generation of the sexual revolution, is expected to increase demand for medical attention to sexual matters over the next several decades. Although male longevity is expected to increase, older women will continue to outnumber older men through 2050; this presents a significant gender disparity in the opportunity for formation of new sexual relationships in later life and, in some cases, results in multiple women sharing a single male partner. Little is known about the health implications of emerging trends among older adults including nonmonogamy, rising rates of divorce, unmarried cohabitation, same-sex marriages and later life dating.

Sexuality in Long-Term Care Institutions and Palliative Care

The early literature on sexuality and aging was prompted by the "problem" of sexual activity and behavior in the nursing home or long-term care setting and contemplated strategies for staff to manage—mainly to eliminate—this behavior. Over time, sexual behavior in the context of dementia, specifically, has become understood as a normal behavior that in some cases is intended to be sexual and in other cases is a manner of communicating other needs. Residents of long-term care institutions are less likely to be sexually active than community-residing older adults, and they cite lack of partners, lack of privacy, lack of interest, sexual dysfunction, and negative attitudes of staff as limiting sexual expression. Older lesbian, bisexual, and transgender individuals are at increased risk of stigma and discrimination, especially in settings where the right to privacy is not permitted.

Increasingly, as a human rights matter, long-term care institutions provide private rooms for residents and have trained their providers to understand and accept elder sexuality in a respectful manner. Sometimes, sexual relationships form among people with dementia who have, but may not remember, a community-residing spouse. Likewise, community-residing spouses may initiate new intimate relationships while maintaining involvement with and commitment to their institutionalized spouse. The implications of these relationships for health and integrity in later life are a growing reality, but poorly understood and often a cause of distress for families. Sexual exploitation and abuse of older women living in residential facilities (and in the community) are poorly documented, but vulnerability is heightened by cognitive impairment, which can interfere with a woman's ability to consent to sexual relations.

Palliative care, whether provided in an institutional or community setting, does provide opportunity for attention to ensuring a patient's capacity for sexual function and fulfillment of sexual needs. Palliation for sexual function could entail providing estrogen and/or testosterone therapy to a patient even if she has a history of an estrogen-sensitive cancer. It could also involve treatment aimed specifically at alleviating nonhormonal causes of dyspareunia. While many patients bring closure to their sexual lives before entering palliative care, it is not uncommon for a patient and her partner to wish to remain intimate as long as possible. Optimization of sexual function for middle age and older women in palliative care is understudied and often overlooked in clinical care, but is an area of increasing attention.

SEXUAL ACTIVITY, BEHAVIOR, AND PROBLEMS

Sexual Partnership

Population-based normative data for older women show that sexual activity is largely determined by availability of a sexual partner. Among women aged 57 to 64 in the 2005–2006 NSHAP study, about 85% had a current spouse or other romantic or intimate partner. Nearly all of these relationships were reported as heterosexual, monogamous, and involving sexual activity. The proportion of women with a partner declined with age, because of earlier male mortality. By age 85, only about 40% of women had a partner, and fewer than 20% of all women engaged in sexual activity.

As compared with findings for younger women, women 57 years and older reported fewer total sexual partners over the lifetime. Most sexually active older women reported that their current relationship was monogamous. Nonmarried women with a partner were significantly more likely to report that their partner had other sexual partners during the relationship. In the NSHAP baseline study, nearly 1 in 10 married women and twice as many nonmarried women with a sexual partner believed that their current partner had other sexual partners during the relationship.

In the NSHAP baseline study, 5% of women reported ever having a female sexual partner and only five women (0.3%) reported currently being in a relationship with another woman. Although population data on lesbian relationships at older ages are only just beginning to emerge, estimates from the younger population suggest that women in this study may have underreported same-sex relationships. Qualitative research and clinical experience reveals cases of older women choosing or demonstrating receptivity to intimacy with female partners for the first time in later life. Some women explain this as a choice caused by the scarcity of males in later life, while others are fulfilling, for the first time, a lifelong interest. The Caring and Aging with Pride study, a national community-based

study (2010) of lesbian, gay, bisexual, transsexual (LGBT) aging, found that among individuals older than 50 years, lesbian and bisexual adults were less likely to have a partner or be married than people identifying as heterosexual.

The low representation of sexual minorities in studies of older adults, the frequent exclusion of older adults in studies of sexual minorities, and the lack of inclusion of questions ascertaining sexual orientation in routine research practice render older LGBT adults largely invisible in most research. This invisibility is perpetuated in clinical settings when providers do not ask about sexual orientation and when patients feel unsafe disclosing their sexual orientation. Further research is necessary to understand the barriers to accessing care and the health needs of aging sexual minorities so that culturally competent care and targeted interventions can be delivered. With marriage equality declared a constitutional right, we expect that older adults who identify as members of a sexual minority group will be more likely to disclose their status in research, clinical, and institutional living settings.

Sexual Activity

Among those who are sexually active (defined in the NSHAP study as engaging in "any mutually voluntary activity with another person that involves sexual contact, whether or not intercourse or orgasm occurs" during the prior 12 months), the kinds and frequency of sexual activity in which women engage are similar to those observed among younger women. Most commonly, sexual activity involves vaginal intercourse, hugging, kissing, or other forms of sexual touching, and about 45% of sexually active women engaged in oral sex. On average, the frequency of sexual activity for those with a sexual partner ranges from one to three times per month. This frequency is similar to that observed among younger sexually active adults. About a quarter of women aged 57 to 85 reported masturbating in the previous year. The prevalence of masturbation among women without a partner is the same as among women with a partner. This is also true for older men (50% report masturbating) and suggests that older adults maintain an individual desire for sexual activity, even in the absence of a sexual partner.

Sexually Active Life Expectancy

Sexually active life expectancy projects population patterns of sexual activity to estimate the number of years, for any given age, of expected future sexual activity. As calculated based on 1995–1996 and 2005–2006 data, at age 55, sexually active life expectancy is about 16 years for women with a spouse or other intimate partner (**Figure 41-3**). Among sexually active women, good health was associated with a gain of 3 to 6 years of expected future sexually active life. Communication of normative expectations to patients about the longevity and quality of their sexually active lives assuming good health could motivate patients to stop smoking, adhere to medication regimens, exercise regularly, or engage in other health-promoting behaviors. Further research is needed to evaluate the potential impact of sexually active life expectancy projections on individual health behavior. The sexually active life expectancy measure also quantifies years of sexually active life lost in the absence of knowledge and treatments to preserve sexual function as people age.

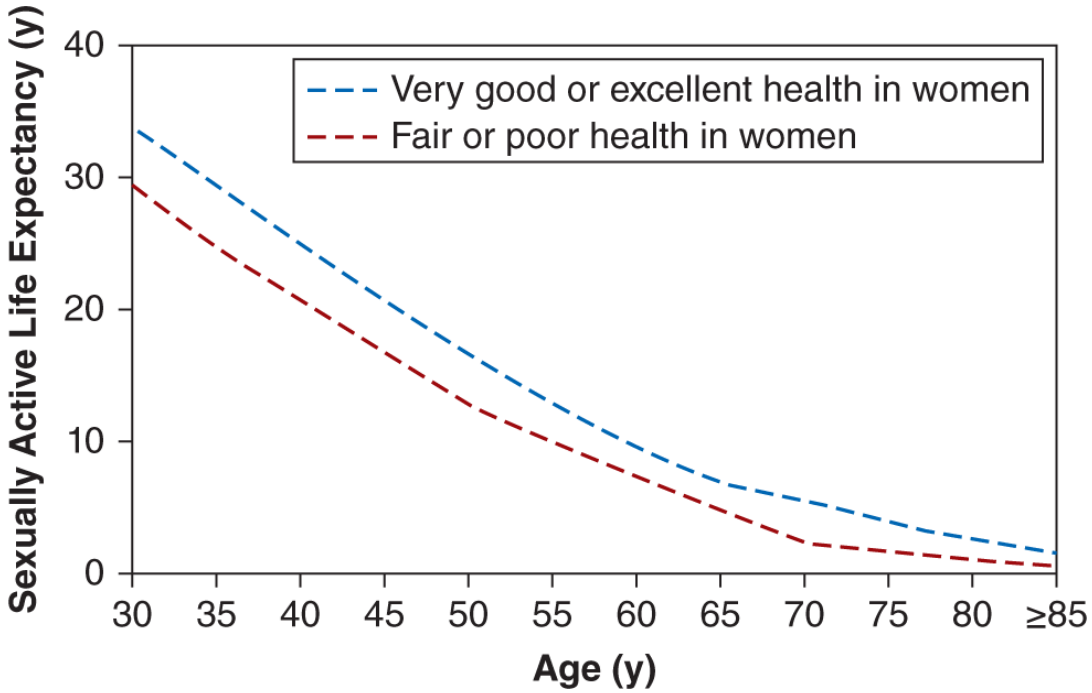


FIGURE 41-3. Sexually active life expectancy. (Adapted from Lindau ST, Gavrilova N. Sex, health, and years of sexually active life gained due to good health: evidence from two US population based cross sectional surveys of ageing. *BMJ*. 2010;340:c810.)

Sexual Problems

Among sexually active women, approximately half reported having one bothersome sexual problem; almost one-third reported having two. The most common sexual problems experienced by older women are summarized in **Table 41-3**. Lack of interest in sex, pain with intercourse, unpleasurable sex, and inability to experience orgasm are much more common among older women as compared to men and somewhat more common compared to younger women. Of course, some proportion of sexually inactive women discontinued sexual activity as a result of bothersome sexual problems and, therefore, the NSHAP baseline study underestimates the prevalence of problems in the whole population. On the other hand, many women engaged in sex despite bothersome problems. The rewards or gains of sexual engagement may outweigh the experience of sexual pain or lack of physical pleasure; some women may obligatorily participate in sex to satisfy their partner while others may lack agency to refuse.

TABLE 41-3 MOST COMMON SEXUAL PROBLEMS AMONG A POPULATION-BASED SAMPLE OF OLDER WOMEN IN THE UNITED STATES (*N* = 1550)

	PERCENTAGE BY AGE GROUP (95% CONFIDENCE INTERVAL)		
	57–64	65–74	75–85
Lack of interest in sex (*n* = 504)	44.2 (36.8–51.6)	38.4 (29.5–47.4)	49.3 (36.8–61.9)
Difficulty with lubrication (*n* = 495)	35.9 (29.6–42.2)	43.2 (34.8–51.5)	43.6 (27.0–60.2)
Inability to climax (*n* = 479)	34.0 (28.0–40.1)	32.8 (24.9–40.6)	38.2 (23.7–52.8)
Pain during intercourse (*n* = 506)	17.8 (13.3–22.2)	18.6 (10.8–26.3)	11.8 (4.3–19.4)
Sex not pleasurable (*n* = 498)	24.0 (18.0–30.1)	22.0 (15.0–29.0)	24.9 (14.8–35.0)
Anxiety with performance	10.4	12.5	9.9

(*n* = 500)	(6.3–14.5)	(6.1–18.9)	(1.7–18.2)
Avoided sex because of problems	34.3	30.5	22.7
(*n* = 357)	(25.0–43.7)	(21.5–39.4)	(9.4–35.9)

Note: Estimates are weighted to account for differential probabilities of selection and differential nonresponse. Data in this table reflect prevalence among those of 1550 women surveyed in the National Social Life, Health and Aging Project who reported having sex in the last 12 months and having at least one sexual problem.

Data from Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. N Engl J Med. 2007;357(8):762–774.

In a 2006 mail-based survey (*N* = 31,581; 63% cooperation rate) referenced in the 2011 American College of Obstetrics and Gynecology Practice Bulletin on Female Sexual Dysfunction, Shifren and colleagues ascertained sexual problems and distress among sexually active and inactive women, including more than 6000 women aged 65 and older. The overall prevalence of sexual problems among all women 65 years and older was higher than reported by NSHAP (NSHAP estimated the prevalence of problems only for women who were sexually active) and the proportion of women who were distressed by these problems was substantially lower.

Problems related to sexuality in later life, including female sexual dysfunction, can result from sexually transmitted infection, trauma, and sexual violence or abuse. These topics are discussed below. Sexual dysfunction, including clinical diagnosis and treatment, is discussed in more detail later in this chapter.

Sexually Transmitted Infections

Data from the NHANES and the baseline NSHAP study provide the population prevalence of STIs among older women. Overall, the prevalence of most STIs in the general older adult population is very low (<1% for *Chlamydia trachomatis*, *Neisseria gonorrhea*, and syphilis), although rates of some infections may be higher in residential communities or geographic regions with high concentrations of sexually active older adults (eg, Florida and Hawaii in the United States), or in other subpopulations. A prevalence estimate for *Trichomonas vaginalis* among older US women is not available; late twentieth-century data from Danish and Chinese epidemiologic studies indicate that very few cases occur among women older than 60 years. Changes in the cervical epithelium caused by loss of estrogen in older women may account for reduced susceptibility to these infections. Although there is no evidence for an epidemic, STI prevalence among older adults is likely underestimated because of lack of uniform tracking systems and underidentification in the clinical setting. One study showed that physicians were more likely to counsel older African-American and married women about human immunodeficiency virus (HIV) and other STIs, but the majority of older women reported that a physician has never initiated such discussion.

Viral infections, including genital herpes simplex virus (HSV) and human papillomavirus (HPV), are among the more prevalent STIs among older women. HSV-2 seroprevalence among men and women 70 years and older based on NHANES III data (1988–1994) was 28%, but women had a higher overall prevalence than men and rates were much higher among African Americans (74%) and Mexican Americans (45%). High-risk, or oncogenic, HPV (HR-HPV) prevalence among women aged 57 to 85, based on 2005–2006 NSHAP data, was 6% and did not vary significantly across age or racial/ethnic groups. The prevalence of HR-HPV among older women is similar to that documented by NHANES for women aged 50 to 59. HR-HPV is an important factor in both cervical dysplasia and cervical cancer, a leading cause of female cancer death in the world. In the United States, about 20% of cervical cancer cases, but more than a third of cervical cancer deaths, occur in women aged 65 and older. Most screening and prevention strategies, including HPV vaccine, use age-based eligibility criteria that exclude older women.

The rate of new HIV infection among older women in the United States, particularly those of minority racial and ethnic groups, has been increasing over the last several years, due mostly to transmission by heterosexual sex. Mucosal atrophy (vaginal, rectal) related to menopausal estrogen depletion increases an older woman's susceptibility to mucosal tears and abrasions that can facilitate HIV transmission. In 2010, 27% of Americans diagnosed with HIV/AIDS after the age of 50 were women. Public health messages regarding HIV/AIDS prevention and detection do not target older women, and physicians rarely offer HIV counseling or testing to this group. The effects of HIV/AIDS and treatments on sexual function among older women have been minimally investigated. Please see Chapter 128 for further discussion of HIV in later life.

STI prevention strategies have not been well-tested for older adults. Few older adults, including those in nonmarital sexual relationships, report using condoms. Condom use by older couples to prevent STIs may be compromised by similar knowledge, communication, behavioral, and cultural barriers experienced by younger couples;

by the belief that condoms are not necessary if there is no risk of pregnancy; and by changes in male and female physiology that occur with age. A male condom is best applied when the penis is fully erect, but for some older men, full erection may not occur until after coitus is initiated. Female condom use does not require a fully erect penis and may be preferable for some couples. For women, increased susceptibility to condom-induced vaginal irritation or abrasion may result from vaginal dryness and/or atrophy caused by estrogen depletion.

Counseling women with new or multiple sexual partners warrants attention to prevention of STIs, including discussion of barrier methods such as male and female condoms and dental dams (for oral sex) (**Figure 41-4**). Couples receptive to using condoms should be taught proper application, encouraged to use foreplay to encourage full penile erection and maximal female arousal before penetration, and counseled to consider water-based lubricants (oil-based lubricants can reduce condom effectiveness; to reduce vaginal and vulvar friction. Condoms with spermicide are not necessary for postreproductive age women and should be avoided because they have a shorter shelf-life and have been associated with urinary tract infection in younger women. Nonlatex male and female condoms and dental dams are available for individuals with latex sensitivities and allergies, and they have physical and performance properties that some individuals may prefer. Male and female condoms and dental dams are for one-time use only.



FIGURE 41-4. Barrier methods of sexual protection. Latex male condom *(left)*, nitrile female condom *(middle)*, dental dam *(right)*.

The 2010 US Patient Protection and Affordable Care Act covers annual wellness visits that include a physical examination and health risk assessment for Medicare beneficiaries. While these visits are an ideal opportunity for physicians to assess their patients' sexual history, sexual history-taking is neither included in the CMS quick reference document for the annual wellness visit nor the Centers for Disease Control and Prevention's (CDC's) more comprehensive framework for patient-centered health risk assessments. Medicare does cover HIV testing, and, for at-risk individuals, chlamydia, gonorrhea, syphilis, and hepatitis B tests. People at increased risk of STIs can receive up to two individual 20- to 30-minute, intensive in-person behavioral counseling sessions each year. These counseling sessions can include education, skills training, and guidance on safe sexual behavior and may help mitigate the competing clinical issues that prevent discussion of safer-sex practices during routine visits.

Sexual Trauma, Violence, and Abuse

Early life events, including sexual trauma in the form of abuse, exploitation, genital injury, and rape, can have lasting effects on sexuality and health that persist into later life. Lifetime estimates among older women indicate that 20% to 26% of women experience intimate partner violence; nearly 40% in one study reported that this was severe, including forced sex or sexual contact. In the NSHAP baseline study, 9% of women aged 57 to 85 reported a lifetime history of forced sex (which may or may not have been with an intimate partner); of these, nearly 40% reported that the most recent event occurred at or younger than age 19 and 16% reported that the most recent event occurred after age 40. Sexual dysfunction, particularly conditions such as vaginismus, dyspareunia, inability to experience orgasm, lack of pleasure with sex, and disturbing fantasies are more common among women with a history of sexual trauma, violence, or abuse. In conjunction with medical treatment and/or physical therapy, psychotherapy including cognitive-behavioral techniques and strategies used for treatment of posttraumatic stress can be effective in helping women at any age cope with sexual violence and experience positive sexual relationships.

Elder mistreatment, or abuse, discussed in Chapter 54, is defined by the US CDC to include sexual abuse or abusive sexual contact but is not limited to an intimate partner. In fact, lack of a spouse or other partner, cognitive impairment, and institutionalization are risk factors for female sexual abuse and rape in later life. Very little is known about how commonly older women experience sexual violence or abuse; 3% of women aged 60 and older in one study reported having been pressured to have sex in a way they did not like or want since age 55. Few older women report that a physician has ever asked questions to ascertain sexual victimization. There is not sufficient evidence to support

the accuracy of existing screening tools to identify abuse in older adults, and studies of interventions to address sexual trauma focus almost exclusively on younger women, perhaps explaining why physicians may feel ill-prepared to screen for victimization among older women. Screening questions for identifying intimate partner violence in the clinical setting are summarized in **Table 41-4** and should be part of routine assessment of the older woman.

TABLE 41-4 SAMPLE INTIMATE PARTNER VIOLENCE SCREENING QUESTIONS

When to ask	**In private settings** **During new patient visits and annual examinations**
How to frame	**Normalize topic** For example, "We've started talking to all of our patients about safe and healthy relationships because it can have such a large impact on your health."
How to ensure confidentiality	**Explain confidentiality** For example, "Before we get started, I want you to know that everything here is confidential, meaning that I won't talk to anyone else about what is said…" **Note disclosure laws** For example, "…unless you tell me that [insert the laws in your state about what is necessary to disclose]"[a]
Sample questions	**"Does your partner threaten you or make you feel afraid?"** For example, threatened to hurt you if you did not do something, controlled who you talked to or where you went, went into rages **"Has your partner ever hit, choked, or physically hurt you?"** For example, hit, slapped, licked, bitten, pushed, shoved you **"Has your partner forced you to do something sexual that you did not want to do?"**
For women with disabilities:	**"Has your partner prevented you from using a wheelchair, cane, respirator, or other assistive device?"** **"Has your partner refused to help you with an important personal need, or threatened not to help you with these personal needs?"** For example, taking your medicine, getting to the bathroom, getting out of bed, bathing, getting dressed, or getting food or drink
For older women*[b]*:	**"Has anyone prevented you from getting food, clothes, medication, glasses, hearing aids, or medical care, or from being with people you wanted to be with?"**[b] **"Has anyone made you afraid, touched you in ways that you did not want, or hurt you physically?"**[b]

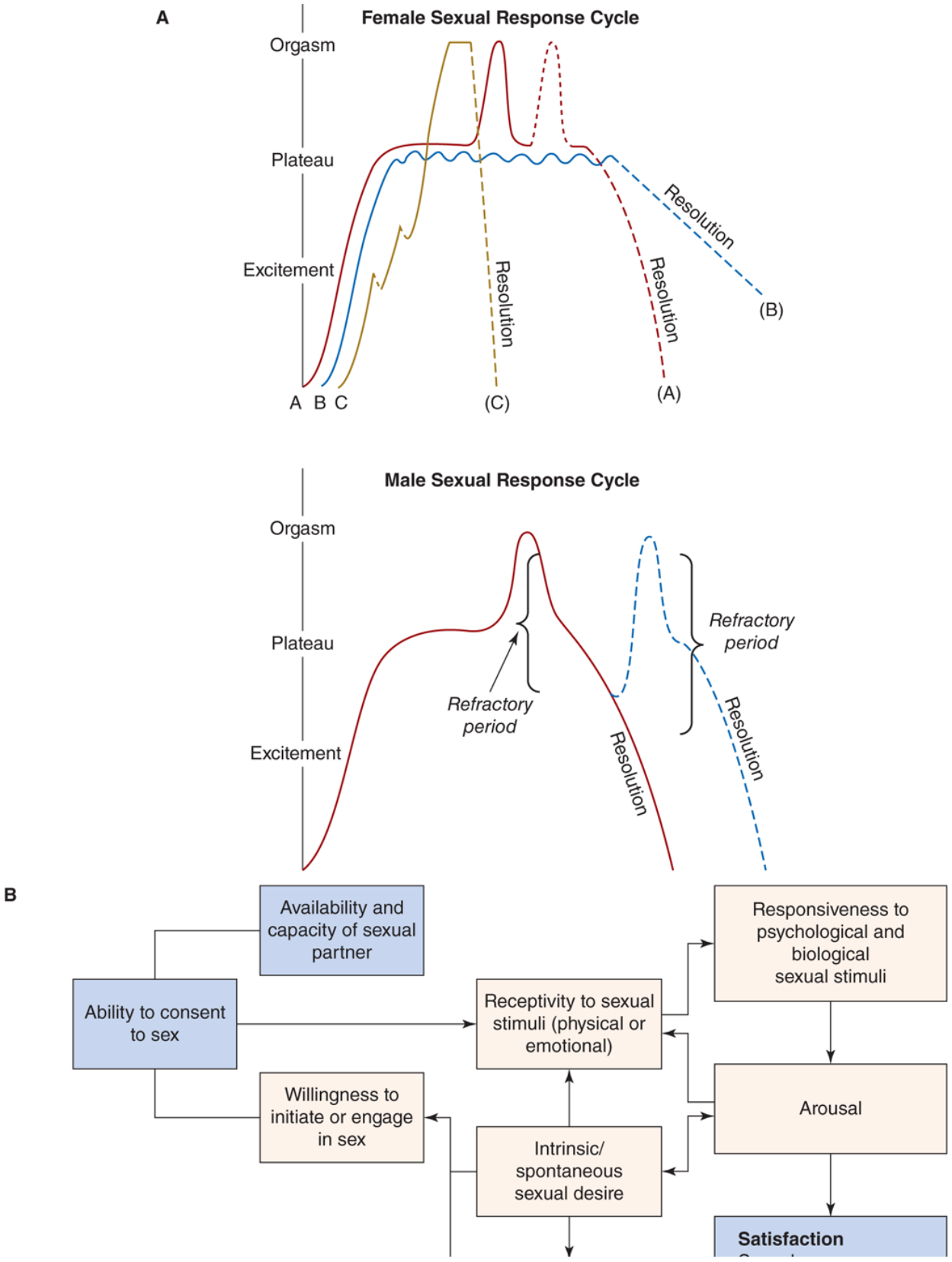
[a]For more information on mandatory reporting policies in your state, refer to Mandatory Reporting of Domestic Violence by Health Care Providers, available for free download from Futures without Violence http://www.futureswithoutviolence.org/mandatory-reporting-of-domestic-violence-by-healthcare-providers/.
[b]Items are from the Elder Abuse Suspicion Index (Yaffe MJ, Tazkarji B. Understanding elder abuse in family practice. Can Fam Physician. 2012;58:1336–1340.) Please see Chapter 54 for complete screening tool for elder abuse.
Adapted from the American College of Obstetrician and Gynecologists' Intimate Partner Violence Committee Opinion, Screening Tools—Domestic Violence, http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Health-Care-for-Underserved-Women/Intimate-Partner-Violence. Accessed March 24, 2016.

Consideration of intimate partner violence and sexual abuse in the acute or emergency care settings should be given, particularly when a woman presents with physical injury, vague symptoms (especially in recurrent visits), acute mental status changes, and/or is accompanied by a partner or other individual who interferes with the patient's interaction with health care providers.

FEMALE SEXUAL RESPONSE CYCLE

The female sexual response cycle provides one simplified framework for understanding and remembering domains of sexual problems experienced by women. The Masters and Johnson model of the female sexual response cycle (**Figure**

41-5A), based on physiologic research initiated in the 1960s with a convenience sample of local sex workers, other volunteers, and patients presenting for treatment of sexual problems or contraception, remains the most widely represented model in medical textbooks and until recently was the foundation for the Diagnostic and Statistical Manual definitions for sexual dysfunction. This traditional, linear model describes four phases of human sexual response: excitement, plateau, orgasm, and resolution (sex therapist Helen Singer Kaplan modified this in 1979 to include orgasm, excitement, and desire) and illustrates notable differences in female as compared with male sexual physiology.



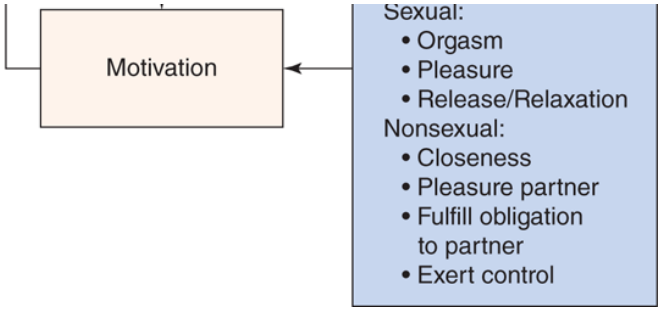


FIGURE 41-5 **A.** Masters' and Johnson's models of sexual response cycles for females and males. *Note: In female sexual response cycle*, A, B, *and* C *refer to three different sexual response patterns found in females*. (From Masters W, Johnson V. *Human Sexual Response.* Boston, MA: Little, Brown and Company; 1966.) **B.** Adaptation (blue) of Basson's model (pink) of the partnered female sexual response cycle highlighting features pertinent to older women (blue). (Adapted from Basson R. The female sexual response: a different model. *J Sex Marital Ther*. 2000;26(1):51–65.)

According to Masters' and Johnson's work, the female sexual response is more variable than that of males, and female orgasm may be single and peak-like similar to male orgasm, more gradual or undulating, and/or repetitive during a single sexual encounter. The typical male sexual response is described as much more uniform, peaking in a single orgasm, and includes a latency period during which a subsequent orgasm cannot occur. Arousal for women tends to require tactile stimulation, otherwise known as foreplay. Many women require direct clitoral or periclitoral stimulation before, during, and/or after intercourse (which may involve penile-vaginal, penile-anal, oral, or manual penetration) in order to experience orgasm. This may be particularly important for older women engaging in vaginal intercourse with male sex partners because of reduction in the firmness and fullness of the male erection in later life.

The pattern of female sexual response may vary across time within a single relationship or with different sexual partners, although little is known empirically about the physiology of the female sexual response cycle in later life or in the context of very long-term (several decades or more) relationships. Psychoemotional changes, and changes in physical appearance with age including appearance of the vulva and breasts, can negatively or positively affect an older woman's feeling of attractiveness, and can influence her interest in sex. Some women indicate decreased psychological inhibition about physical appearance or improved self-image with age, both of which can be sexually liberating.

Changes in men's sexual response that occur with age can affect female partners both physically and psychologically. As men age, the sexual response becomes more similar to that of women (a phenomenon some refer to as "feminization of the male sexual response cycle"). Tactile stimulation and foreplay are increasingly important for older male arousal, the time to erection and orgasm is longer, and latency between orgasms (the refractory period) is increased. Because few older men or women are aware of these phenomena, these changes are often perceived as abnormal, cause unnecessary anxiety and shame, and can strain both members of a couple. Some couples cease sexual activity as a consequence and most do not seek medical help. Some couples find benefit in the changes to sexual physiology that occur with age. For example, the mutual need for foreplay and the longer arousal phase in men allows, for some couples, the more frequent pleasure of simultaneous orgasm. Older women and their partners should be provided basic information about the normative changes to sexual function that can occur with aging. The National Institute on Aging offers an "AgePage" on this topic (http://www.nia.nih.gov/health/publication/sexuality-later-life); the American Association of Retired Persons (AARP) also offers accessible, consumer-focused information about sexuality and intimacy in its publications.

Building on the pioneering work of Masters and Johnson, Basson proposed a widely referenced intimacy-based, cyclical model of the female sexual response that incorporates the quality and duration of the relationship as well as the psychoemotional component of female sexuality (**Figure 41-5B**). In older and younger women, sexual desire may occur before or following sexual arousal. This model emphasizes the role of intimacy in generating female sexual desire and suggests that lack of intimacy and unsatisfying sexual encounters can raise the threshold for interest and arousal in a subsequent sexual encounter. Rather than linear and discrete, the phases of the female sexual response are described by Basson as variably overlapping in a way that "blends mind and body."

Further empirical characterization of the physiology and psychosocial aspects of the female sexual response cycle in later life, including how it might fluctuate within relationships over long durations of time, across relationships, and with aging, is needed both to inform women's expectations and the clinical approach to older women's sexuality.

FEMALE SEXUAL PHYSIOLOGY IN LATER LIFE

Effects of senescence on the endocrine, neurovascular, musculoskeletal, genitourinary, and gastrointestinal systems are particularly salient to sexual function in later life. More global changes in physical appearance, sensory function (hearing, vision, olfaction, taste, and tactile sensation), cognitive function and memory, and body aromas such as scent, breath, and genital odor can also affect sexual engagement and enjoyment. The female sexual response involves a complex and highly interconnected series of physiologic events connecting mind and body. Disruptions or changes in any of these physiologic systems caused by age-related changes, physical or mental illness, or medical procedures and medication use can alter the sexual response and the ability of a woman to derive pleasure and satisfaction from her sexual encounters.

Endocrine System

Loss of estrogen as a result of menopause is a dominant physiologic event that can affect many aspects of older women's sexual function. Despite extension of the human lifespan, the age of menopause has not changed. Women can live a third or more of life in menopause: the median age of natural menopause in the United States is 51.3 and average female lifespan is 81.1 years. Surgical menopause occurs when a woman undergoes bilateral oophorectomy (or loses ovarian function as a result of other interventions such as chemotherapy or radiation) prior to natural menopause. In the NSHAP study, about one in five US women aged 57 to 85 reported a history of surgical menopause. Women who have undergone bilateral oophorectomy, pre- or postmenopause, also experience an abrupt and irreversible loss of androgen production.

Estrogen is important for maintaining skin, subcutaneous, mucosal (vaginal, bladder, and rectal) and musculoskeletal integrity, the vaginal microenvironment (pH balance and microflora), vascular flow to the vagina and clitoris via regulation of nitric oxide synthase expression, and sensory perception. Over time, in the genital tract, low estrogen results in vaginal dryness, loss of epithelial cell glycogen, shortening of the vagina, narrowing of the introitus, thinning of the labia, and diminution of the fat pad underlying the mons pubis (**Table 41-5**). Loss of vaginal acidity results from glycogen depletion and can increase propensity for bacterial vaginitis. Urinary and fecal incontinence can be exacerbated by estrogen depletion and inhibit social and sexual relationships as well as sexual function. Maintenance of sexual activity in later life appears to offset some of these local genital changes, in part by maintaining elasticity of the vulvovaginal tissues, pelvic floor musculature, and pelvic joints. Additionally, sexual activity and other forms of physical contact may mitigate estrogen-related decline in sensory perception and function with age and may play a role in female attractiveness. Exogenous estrogen is approved by the US Food and Drug Administration (FDA) for treatment of moderate to severe dyspareunia in women. Ospemifene, a selective estrogen reuptake modulator (SERM), has also been approved for the same indication but is not yet widely used in the United States. Largely owing to highly publicized findings from the randomized, controlled hormone therapy trials of the US Women's Health Initiative Study (comparing use of combination equine estrogen alone or in combination with progesterone to placebo among postmenopausal women aged 50–79 at baseline), a minority of women currently use prolonged estrogen therapy for treatment of menopausal symptoms or preservation of sexual function.

TABLE 41-5 AGE-ASSOCIATED ANATOMIC AND PHYSIOLOGIC CHANGES IN THE VAGINA

Narrowing of vaginal barrel
Epithelium loses glycogen content and normal bacterial flora
Pathogenic bacteria often replace lactobacillus, resulting in atrophic vaginitis
Decreased lubrication results in dryness
Reduced vaginal blood flow
Vaginal pH increases
Atrophy of vaginal mucosa
Pale color
Loss of vaginal folds

Testosterone, along with dehydroepiandrosterone (DHEA), plays an important role in female libido, arousal, genital sensation, and orgasm. Loss of testosterone can exacerbate vaginal mucosal atrophy, thinning of pubic hair,

and may compromise an older woman's sense of general well-being. Female androgen insufficiency as a treatable condition or syndrome is controversial. While levels of endogenous androgens have not been found to be predictive of sexual function, testosterone therapy for low libido has been shown to be effective in clinical trials involving women with bilateral oophorectomy or total loss of ovarian function, as well as postmenopausal women on estrogen therapy (estrogen reduces bioavailable testosterone by increasing sex hormone–binding globulin production). However, the FDA has not approved testosterone for this indication. Use of testosterone or DHEA to treat female sexual dysfunction is currently off-label in the United States and most countries, and requires close monitoring for side effects. Although rare, irreversible deepening of the voice and growth of facial hair may occur with testosterone use.

Figure 41-6 summarizes central and peripheral hormonal mediators of sexual function (see also Chapter 108). Understanding centrally mediated neuroendocrine changes that occur with senescence is an active area of discovery, focused heavily on understanding cognitive pathophysiology. In women and female animal studies, interest in the cascade of neuroendocrine events resulting in menopause has been similarly driven by an effort to understand the role of sex hormones and hormone therapy in neuroplasticity and degeneration, as well as by efforts to treat female infertility. Application of this knowledge to female sexual function in later life, particularly sex differences in endocrine regulation of the sexual response cycle, is nascent.

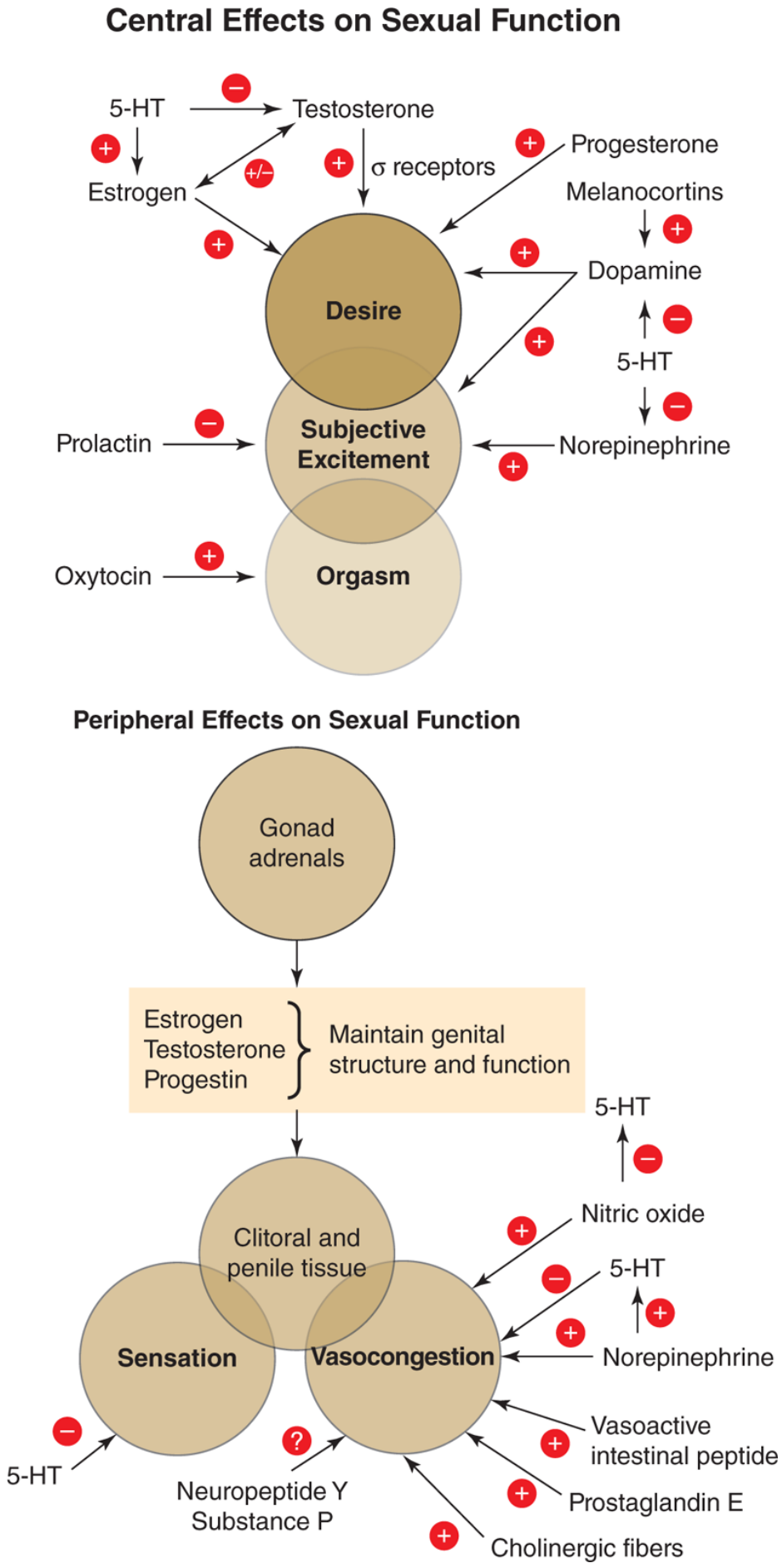


FIGURE 41-6. Central and peripheral effects on sexual function. *Note: + indicates a positive effect, – indicates a negative effect, ? indicates*

the effect is unknown; 5-HT: 5-hydroxytryptamine (serotonin). (Adapted from Clayton AH. Sexual function and dysfunction in women. *Psychiatr Clin North Am*. 2003;26:673–682.)

Aside from its peripheral effects, estrogen plays an important central role via direct membrane receptor activity and modulation of neurotransmitters. Estrogen appears to exert neurotrophic and neuroprotective activity in the brain that mitigates hypothalamic damage that occurs with age. Estrogen also interacts with serotonin and norepinephrine metabolism, which may explain the role of estrogen depletion in sleep, mood, memory, and, through these and no doubt other mechanisms, the female sexual response cycle in later life.

The hypothalamic-pituitary-adrenal (HPA) axis mediates the human physiologic stress response and, of course, is the pathway or pacemaker through which sex hormonal regulation occurs. The loss of temporality and pulsatility in HPA neural signaling is a key event in menopause; the dynamics of HPA function over the portion of the lifespan following menopause and the implications for female sexual functioning in later life are much less well-defined. Vasoactive intestinal peptide (VIP), now recognized to play a role in female sexual arousal via vasocongestion of the clitoral tissue, also signals time of day information for central gonadotropin-releasing hormone (GnRH) regulation. Rhythmic synthesis of VIP in the brain appears to wane by middle age in women and may be an important triggering event in the loss of hypothalamic-pituitary-ovarian access coordination required for ovulation and menstruation. The peripheral effects of changes in central VIP metabolism for later life sexual arousal in women are unknown.

Neurovascular System

Neurovascular physiology, mediated by the sympathetic and parasympathetic nervous systems and a growing list of nonadrenergic/noncholinergic neurotransmitters (eg, nitric oxide and VIP), is particularly important for the arousal and orgasm phases of the female sexual response cycle. Arousal involves vascular engorgement of the genitopelvic organs, including the labia, vagina, and clitoris; lengthening, dilation, and lubrication of the vagina; retraction of the clitoral hood; and tumescence of the clitoris. Microvascular integrity is important for genital sensation and orgasm. Clitoral sensation, in particular, can be compromised by microvascular disease as seen in chronic smokers and women with hypercholesterolemia or diabetes. Although clinical guidelines for diabetes care in men advise assessment and treatment of erectile problems, clinical guidelines for women do not go beyond screening for sexual dysfunction. Research on effective treatment options for sexual dysfunction among older women with diabetes is needed to inform clinical guidelines. Women with diagnosed diabetes are less likely than men to have discussed sexual problems with a physician and more likely to cease all sexual activity.

Cardiovascular disease can impair women’s sexual function in later life both through psychological and physiologic mechanisms. Although practice guidelines recommend that physicians communicate with patients about the sexual implications of heart disease and potential sexual side effects of treatment, these issues are commonly omitted from counseling, and men are significantly more likely than women to receive such counsel.

Treated and untreated hypertension are both associated with lower rates of sexual activity among older women. However, among sexually active older women, the rate of sexual problems is similar among women with treated hypertension, untreated hypertension, and no hypertension. No one class of antihypertensives has been consistently associated with female sexual dysfunction, particularly in older women. Based on expert opinion, older women with hypertension should be counseled that treatment of hypertension is likely to improve overall sexual function and longevity.

Acute myocardial infarction (AMI) is the leading cause of death among middle age and older women; approximately 40% of all AMIs in the United States occur in women. US and European practice guidelines state that patients with uncomplicated AMI can resume sexual activity within a week of AMI. Based on the largest study to date of sexual outcomes in AMI among older women, the majority of those who were sexually active before their AMI resume sexual activity within 1 year following AMI. Receipt of counseling by a physician about resuming sex is the single most important predictor of whether a woman resumes sexual activity after AMI.

Phosphodiesterase inhibitors are used in men to treat neurovascular causes of erectile dysfunction; similar effectiveness has not been found in women. The only FDA-approved device for treatment of female sexual dysfunction, the Eros Therapy (UroMetrics) clitoral pump, may assist some women with microvascular disease in experiencing improved clitoral sensation, vaginal lubrication, and orgasm.

Musculoskeletal System and Body Fat

Parity, childbirth-related injury, pelvic or lower extremity trauma, obesity, and sedentariness can compromise the integrity of the vulvar, pelvic floor, and lower extremity musculature, contributing to incontinence and pelvic organ

prolapse. Effective contraction and relaxation of the peri-introital, perineal, and pelvic floor muscles are important for penetration, arousal, orgasm, and the relaxation phase following orgasm. Loss of flexibility of hip muscles and compromised stability and mobility of hip joints, commonly experienced by women with arthritis or hip fracture, can interfere with sexual functioning in later life. Skeletal changes in the hips and vertebrae caused by loss of bone density, osteoporosis, vertebral compression and fracture, and arthritis can make vaginal penetration, particularly using "missionary" (female supine with hips and knees flexed) position, difficult and may be accommodated by use of alternative sexual positioning such as side-lying or sex without vaginal penetration. Prevention and treatment of these conditions with attention to maximizing musculoskeletal strength and flexibility can improve overall physical functioning and help preserve sexual capacity for aging women. Endorphin release associated with pleasurable sexual activity may help alleviate musculoskeletal pain.

Although more than a third of women older than age 65 are obese, little is known about the effect of obesity on older women's sexual function and satisfaction. Research is further complicated by women's varying self-appraisals of their body size and attractiveness, the frequent co-occurrence of obesity and chronic disease among older women, and the potentially different contributions of abdominal adiposity, generalized obesity, and relative weight gain post-menopause.

Genitourinary System

Changes in the genitourinary system are heavily influenced by postmenopausal loss of estrogen. The urethral orifice can become everted and sensitive to friction, which may cause pain during penetration. Laxity in the pelvic tissues can result in prolapse of the uterus and vaginal walls (ie, cystocoele, rectocoele, enterocoele). Cervical contact with sexual penetration can cause an "electric shock" or otherwise painful sensation during vaginal intercourse and limits the depth and force of penetration. Cervical prolapse that is visible at the introitus or procidentia (prolapse through the vagina) can make vaginal intercourse very difficult or impossible. Urinary incontinence and/or the fear of losing urine during intercourse or orgasm can cause avoidance of intercourse and difficulty with orgasm. Pessaries may be used to reduce prolapse and treat urinary incontinence; some, such as ring pessaries, are designed for compatibility with intercourse but should be removed and cleaned following intercourse. Procedures to treat pelvic organ prolapse and urinary incontinence may improve sexual functioning for some women, but colpocleisis (partial or total surgical closure of the vagina to treat prolapse) is largely prohibitive for penetrative vaginal sex.

Gastrointestinal System

Gastrointestinal changes with aging that are most relevant to female sexual function include incontinence of stool and flatus, hemorrhoids, and borborygmi. Anal or stool incontinence, commonly overlooked, typically results in cessation of sexual activity and can be very socially isolating. Hemorrhoids can be exacerbated by sexual activity, particularly anal intercourse, and may result in bleeding during or following sex. Borborygmi can be controlled to some degree by timing of meals in relation to symptoms. Older women who have ceased and/or who wish to resume sexual activity after a hiatus should be screened and evaluated for both urinary and anal incontinence and treated in order to prevent embarrassing or painful sexual experiences that can be very detrimental to sexual self-image and function. Constipation can be a cause of dyspareunia; this can be overcome by treating the primary cause of constipation and educating the patient to time sexual activity after moving her bowels.

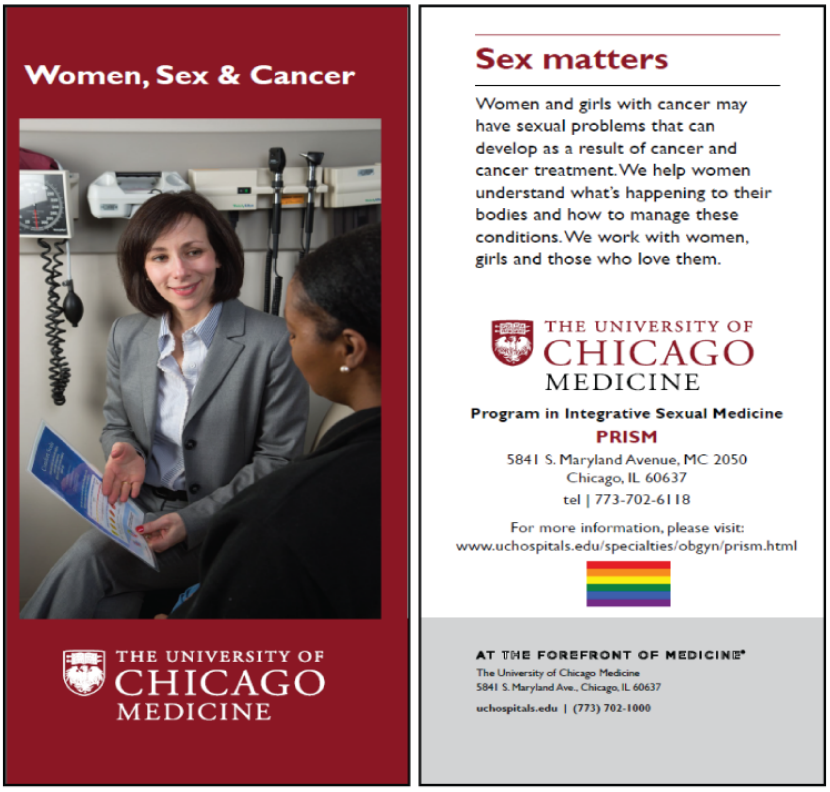
Cancer and Female Sexual Function

The vast majority of cancers affecting older women involve treatment with local or systemic therapies that impair or surgically remove the sexual organs. The majority of women, at all ages, who develop cancer value their sexual function and wish to preserve the possibility of future sexual activity. All women, regardless of age or current partner status, undergoing treatment for cancer should be counseled about the potential effects of cancer or its treatment on future sexual function, and baseline sexual activity and function (prior to cancer treatment) should be documented. Women undergoing pelvic radiation should be offered vaginal dilation therapy to preserve vaginal capacity for sexual activity and future gynecologic examinations. The most common sexual function problems in this patient population include dyspareunia, commonly resulting from or exacerbated by severe vulvovaginal atrophy, and diminished or no libido. Compromised sexual function and painful or unsatisfying sexual activity may strain intimate partnerships and provoke anxiety about cancer recurrence. Repeated studies show that women with cancer, including older women, believe that physicians should discuss sexual outcomes and side effects of treatment. As in cardiovascular disease,

women who report discussing sex with a physician are significantly less likely to avoid sex because of a sexual problem or to exhibit complex sexual morbidity.

SEXUAL HISTORY-TAKING

There is ample evidence that older women, including those who are not currently sexually active, regard sexual function as an important aspect of health, believe it is appropriate for physicians to discuss sexual issues in the context of medical care, and want physicians to be proactive in counseling about sexual outcomes or side effects of treatment. There is simply no evidence to suggest that appropriate attention to female sexual function in the context of medical care, including geriatric care, causes patient harm or other negative outcomes. To the contrary, avoidance of these matters can be deleterious, particularly for women who identify as a member of a sexual minority group. Geriatricians can signal their openness to all patients by posting commonly recognized symbols such as a rainbow flag or an explicit statement of respect for all human rights (**Figure 41-7**).



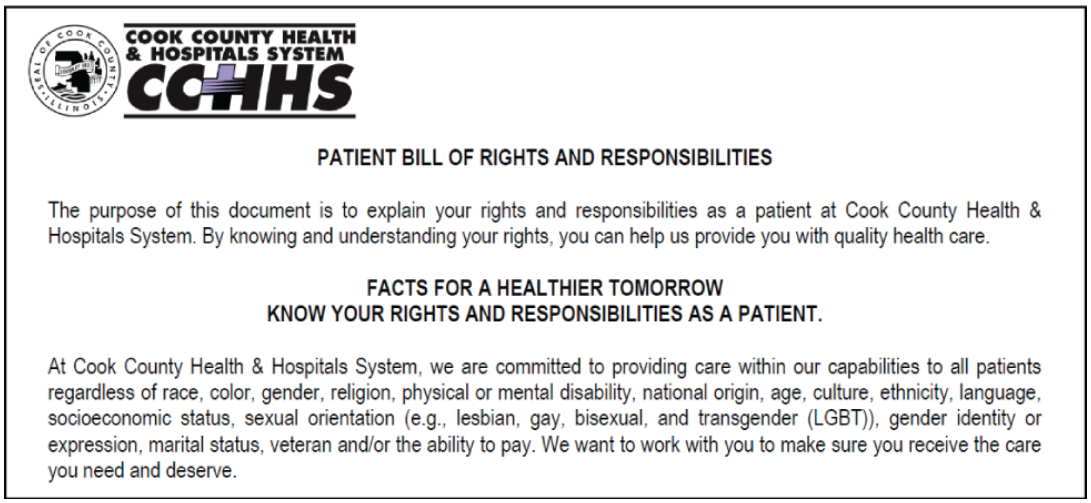


FIGURE 41-7. Examples of image and text indicating freedom from discrimination for lesbian, gay, bisexual, transsexual (LGBT) patients. Front (top left) and back (top right) of brochure for the Program in Integrative Sexual Medicine at the University of Chicago (© ST Lindau

2014, used with permission from anneryanphoto.com), showing rainbow flag icon indicating that LGBT patients are welcome; bottom: excerpt from patient bill of rights and responsibilities for the Cook County Health and Hospitals System indicating nondiscrimination policy. http://cchhs.carminaticonsulting.com/patient-services/patient-rights-responsibilities/. Accessed January 6, 2015.

Table 41-6 lists basic sexual history questions that can be incorporated into a routine geriatrics encounter and should be tailored to the individual's needs.

TABLE 41-6 SEXUAL HISTORY-TAKING AND SEXUAL EDUCATION IN THE ROUTINE GERIATRICS ENCOUNTER

Context	Ensure privacy Communicate comfort and matter-of-fact attitude If proxy required or requested, educate and engage that person	Educate patient about typical changes in sexuality that can occur with age and specific health conditions/treatments Educate about safety in sexual relationships
Transition	"To round out my understanding of your health/your health concerns today, may I ask you a couple of questions about your sexual life?"	Not always necessary, but can be useful if no other obvious transition Screening sexual history can easily come after questions ascertaining home setting, eg, "Who lives at home with you?" and "Are you safe in your home?"
Questions	"Do you currently have a spouse or other romantic, intimate, or sexual partner?"	Opportunity to communicate awareness to the possibility of nonmonogamy
	"How many partners have you had in the last year?"	
	"Does your partner have other sexual partners?"	
	"Is your partner male or female?"	Opportunity to communicate nonjudgment about same-sex relationships
	"Have your partners been male or female or have you had both male and female partners?"	
	"When is the last time you had sex?"	
	If no longer having sex: "What are the reasons you stopped having sex?"	
	"Are you satisfied with your sexual life?"	If patient responds yes, pursue questions summarized in **Table 41-10** or defer to a subsequent visit (see Conclusion)
	"Do you have any worries or difficulties with regard to your sexual life?"	
	"How's your partner's health?"	
	"Is your partner having any sexual problems?"	
	"Has anyone ever forced you to have sex or sexual contact?"	If patient responds yes or reveals risk factors, pursue questions summarized in **Table 41-4**
	If new partner or concern about risk factors: "Have you and your partner been tested for sexually transmitted infections, including HIV/AIDS?"	Educate about testing, inform about confidential versus anonymous testing and meaning of test results Plan follow-up visit to provide posttest counseling
	"Do you use condoms or other barrier methods to prevent sexually transmitted infection?"	Educate about barrier methods for sexually transmitted infection (STI) prevention
Conclusion	*If no problems identified or patient not sexually active:* "I want to encourage you to feel comfortable talking with me about any sexual concerns should they arise." *If problem(s) identified:* "I'm concerned about the problem you're having. Would you (and your partner) be willing to return (or be referred) to discuss this further?"	

The geriatrician is also encouraged to include on patient self-report or review of system checklists a simple item such as, "Do you have any sexual problems or concerns?" The widely used PLISSIT model or the "therapeutic moment" approach described in **Tables 41-7A and B** can help guide a preliminary conversation about sexual concerns. When a patient presents with multiple concerns in addition to a sexual concern, the geriatrician should work with the patient to prioritize issues for the current visit, acknowledge the sexual concern, and suggest, if necessary, that the patient return for a visit focused specifically on that issue. The IBM (see **Figure 41-1**) provides a useful framework for more in-depth assessment of a patient's sexual concern. The geriatrician should inquire about the patient's biological or medical problems, psychological or emotional problems, and relational or social problems. If the patient is in a current relationship, the history should also inquire about the partner's health in these domains, whether there has been communication with the partner about the patient's sexual concerns, and whether the partner also has any sexual function difficulties.

TABLE 41-7A THE PLISSIT MODEL FOR ADDRESSING SEXUAL HEALTH NEEDS

P	**Permission**	Give the patient ***permission*** to raise concerns about her sexual health, legitimizing her concerns and acknowledging her sexuality	Ask, "Do you have any sexual problems or concerns?"
LI	**Limited information**	Give the patient ***limited information*** about the sexuality changes common to the patient's condition	General educational resources; eg, National Institute on Aging's "AgePage" on sexuality in later life Condition-specific resources; eg, American Cancer Society's patient information booklet on cancer
SS	**Specific suggestions**	Give the patient ***specific suggestions*** about sexual dysfunction and resumption of sexual activity	
IT	**Intensive therapy**	Give the patient more ***intensive therapy*** by connecting them with other professionals that can help with sexual concerns	The International Society for the Study of Women's Sexual Health (www.isswsh.org) Society for Sex Therapy and Research (www.sstarnet.org/) American Physical Therapy Association Section on Women's Health (www.womenshealthapta.org) International Organization of Physical Therapists in Women's Health (www.ioptwh.org)

Note: An extended version of the PLISSIT model (Ex-PLISSIT) was published by Davis and Taylor in 2006. The "extended" version includes permission-giving at each stage of interaction.

Adapted from Annon J. The PLISSIT model: a proposed conceptual scheme for the behavioral treatment of sexual problems. J Sex Educ Ther. 1976;2:1–15.

TABLE 41-7B THERAPEUTIC MOMENT MODEL FOR ADDRESSING SEXUAL HEALTH NEEDS AS FOLLOWS:

	PROVIDER BEHAVIOR	EXAMPLE PROVIDER STATEMENT
Empathy	Acknowledge sexual health need and concerns	"I understand that this problem has been painful for you."
Validation	Share normative data and patient resources	"You are not alone. Other women experience this, but few talk about it."
Healing	Convey appropriateness of treating sexual health needs	"I would like to work with you to help solve this problem."
Expectations	Communicate that care may require multiple visits and limits of evidence in field	"More information is needed to fully understand and solve this problem."
Hope	Communicate positive outlook and realistic prognosis	"I am optimistic that we can make some changes to improve this problem."

FEMALE SEXUAL DYSFUNCTION

Use of terms like “dysfunction,” “normal,” and even “healthy” in relation to human sexuality requires caution and has been criticized, particularly in the feminist and psychology literatures. What is a normal level of sexual desire for older women? Is celibacy unhealthy? Few older women report same-sex partners, so is lesbianism abnormal? Is a distressing sexual difficulty a “dysfunction” or a “normal” response to unhappy circumstances in a relationship? Critiques are rooted in a painful history of sexual discrimination, particularly in the United States, and partially in medical history; as recently as the early 1990s, female sexual dysfunction could be diagnosed as a sexual problem experienced by a woman even if it was only troublesome to her partner. In addition, skeptics of the “medicalization” of female sexuality question how “normal” or “functional” sexuality can be defined as the absence of problems, given the high prevalence of sexual problems in the population.

Diagnostic Classification of Female Sexual Dysfunction

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) updates classification of female sexual dysfunction for clinical diagnosis (**Table 41-8**). The DSM-5 merges the conditions dyspareunia and vaginismus (classified separately in the DSM-IV) as genitopelvic pain/penetration disorder. Hypoactive sexual desire disorder and female arousal disorder are now defined as female sexual interest/arousal disorder.

TABLE 41-8 ■ DEFINITIONS OF FEMALE SEXUAL DYSFUNCTION FROM THE DSM-5

Female Sexual interest/arousal disorder

Diagnostic Criteria

302.72 (F52.22)

1. Lack of, or significantly reduced, sexual interest/arousal, as manifested by at least three of the following:
   1. Absent/reduced interest in sexual activity.
   2. Absent/reduced sexual/erotic thoughts or fantasies.
   3. No/reduced initiation of sexual activity, and typically unreceptive to a partner’s attempts to initiate.
   4. Absent/reduced sexual excitement/pleasure during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).
   5. Absent/reduced sexual interest/arousal in response to any internal or external sexual/erotic cues (e.g., written, verbal, visual).
   6. Absent/reduced genital or nongenital sensations during sexual activity in almost all or all (approximately 75%–100%) sexual encounters (in identified situational contexts or, if generalized, in all contexts).
2. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.
3. The symptoms in Criterion A cause clinically significant distress in the individual.
4. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress (e.g., partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

- **Lifelong:** The disturbance has been present since the individual became sexually active.
- **Acquired:** The disturbance began after a period of relatively normal sexual function.

Specify whether:

- **Generalized:** Not limited to certain types of stimulation, situations, or partners.
- **Situational:** Only occurs with certain types of stimulation, situations, or partners.

Specify current severity:

- **Mild:** Evidence of mild distress over the symptoms in Criterion A.
- **Moderate:** Evidence of moderate distress over the symptoms in Criterion A.
- **Severe:** Evidence of severe or extreme distress over the symptoms in Criterion A.

Female orgasmic disorder

Diagnostic Criteria

302.73 (F52.31)

1. Presence of either of the following symptoms and experienced on almost all or all (approximately 75%–100%) occasions of sexual activity (in identified situational contexts or, if generalized, in all contexts):
   1. Marked delay in, marked infrequency of, or absence of orgasm.
   2. Markedly reduced intensity of orgasmic sensations.
2. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.
3. The symptoms in Criterion A cause clinically significant distress in the individual.
4. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of severe relationship distress (e.g., partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

- **Lifelong:** The disturbance has been present since the individual became sexually active.
- **Acquired:** The disturbance began after a period of relatively normal sexual function.

Specify whether:

- **Generalized:** Not limited to certain types of stimulation, situations, or partners.
- **Situational:** Only occurs with certain types of stimulation, situations, or partners.

Specify if:

- **Never experienced an orgasm under any situation.**

Specify current severity:

- **Mild:** Evidence of mild distress over the symptoms in Criterion A.
- **Moderate:** Evidence of moderate distress over the symptoms in Criterion A.
- **Severe:** Evidence of severe or extreme distress over the symptoms in Criterion A.

Genito-pelvic pain/penetration disorder

Diagnostic Criteria

302.76 (F52.6)

1. Persistent or recurrent difficulties with one (or more) of the following:
   1. Vaginal penetration during intercourse.
   2. Marked vulvovaginal or pelvic pain during vaginal intercourse or penetration attempts.
   3. Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of vaginal penetration.
   4. Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration.
2. The symptoms in Criterion A have persisted for a minimum duration of approximately 6 months.
3. The symptoms in Criterion A cause clinically significant distress in the individual.
4. The sexual dysfunction is not better explained by a nonsexual mental disorder or as a consequence of a severe relationship distress (e.g., partner violence) or other significant stressors and is not attributable to the effects of a substance/medication or another medical condition.

Specify whether:

- **Lifelong:** The disturbance has been present since the individual became sexually active.
- **Acquired:** The disturbance began after a period of relatively normal sexual function.

Specify current severity:

- **Mild:** Evidence of mild distress over the symptoms in Criterion A.
- **Moderate:** Evidence of moderate distress over the symptoms in Criterion A.
- **Severe:** Evidence of severe or extreme distress over the symptoms in Criterion A.

Note: For more information on substance/medication-induced sexual dysfunction or other specified and unspecified sexual dysfunction refer to the DSM-5.
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright ©2013). American Psychiatric Association. All Rights Reserved.

Population estimates of sexual problems from the cross-sectional NSHAP study (**Figure 41-8**) and other studies

are useful for quantifying the baseline prevalence of sexual problems in later life, or even bothersome sexual problems, but should not be expected to translate precisely into population rates of female sexual dysfunction, clinically defined. Prevalence estimates for older women can be estimated from prior studies, but are needed for the newly defined classes of genitopelvic pain/penetration disorder and female sexual interest/arousal disorder.

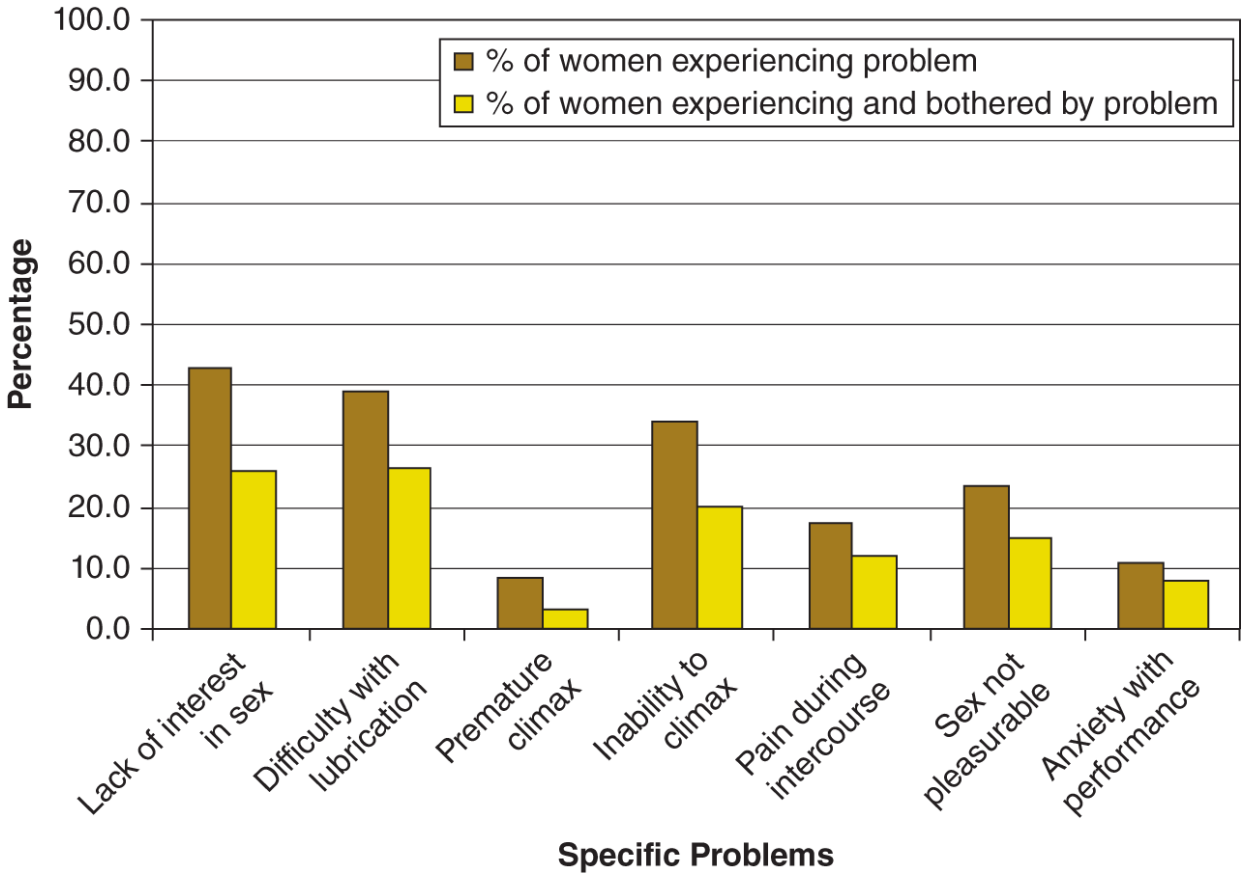


FIGURE 41-8. Prevalence of sexual problems and associated distress among a population-based sample of older women in the United States (n = 1550). *Note: Estimates are weighted to account for differential probabilities of selection and differential nonresponse. Data in this graph reflect prevalence among those of 1550 women surveyed in the National Social Life, Health and Aging Project who reported having sex in the last 12 months and having at least one sexual problem*. (Data from Lindau ST, Schumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *N Engl J Med*. 2007;357(8):762–774.)

Causes of Female Sexual Dysfunction

Sexual dysfunction in later life can be primary, such as a lifelong history of bothersome low sexual desire, or secondary. Secondary causes include (1) interpersonal and personal psychological factors including depression and substance use, (2) biological factors including a wide spectrum of illnesses, injuries, physical disabilities, and their medical and surgical treatments (note that earlier life illness such as cancer and its treatment have been shown to have long-lasting effects on sexual function in survivors), and (3) social factors. The patient's psychosexual history and her current partner's physical and mental health, medication, and substance use and sexual function must also be investigated in order to gain a full picture of the patient's sexual functioning and to appropriately tailor therapeutic interventions. Common medications implicated among iatrogenic causes of sexual dysfunction are summarized in **Table 41-9**. Evidence for the effects of drugs on sexual dysfunction is mixed overall and very limited with respect to older females, specifically. Treatment of underlying disease and health concerns, including common problems like incontinence, vaginal atrophy, sleep dysfunction, and depression, is an essential first step to addressing sexual function problems. Sexual side effects of medications can be offset by improvement of disease-related symptoms and better overall health.

TABLE 41-9 ■ DRUGS IMPLICATED IN SEXUAL DYSFUNCTION, ALTHOUGH RESEARCH IS NEEDED TO BUILD THE EVIDENCE BASE FOR THE EFFECTS OF MEDICATION ON FEMALE SEXUAL FUNCTION

Antiepileptics

Carbamazepine, phenobarbital, phenytoin

Cardiovascular and antihypertensive medications

β-Adrenergic blockers,[a] calcium channel antagonists (diltiazem, nifedipine), clonidine, digoxin, diuretics (hydrochlorothiazide), lipid-lowering agents, prazosin, reserpine, spironolactone

Drugs affecting hormones

Aromatase inhibitors, cimetidine, raloxifene, spironolactone, tamoxifen

Histamine H_2 receptor blockers

Hormones

Estrogens, gonadotropin-releasing hormone agonist, progestins

Ketoconazole

Narcotic analgesics

Psychoactive/psychotropic medications

Amphetamines and related anorexic drugs, antipsychotics, barbiturates, benzodiazepines, lithium, monoamine oxidase inhibitors (MAOIs), opioids, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants

Steroids

[a]No one class of antihypertensives has been consistently associated with female sexual dysfunction, particularly in older women.

Adapted from Phillips NA. Female sexual dysfunction: evaluation and treatment. Am Fam Physician. 2000;62(1):127–136.

Phillips adapted this with permission from Drugs that cause sexual dysfunction: an update. Med Lett Drugs Ther. 1992;34:73–78.

We have further edited this table based on Kingsberg S. Taking a sexual history. Obstet Gynecol Clin North Am. 2006;33:535–547, and Walsh KE, Berman JR. Sexual dysfunction in the older woman. Drugs Aging. 2004;21(10):655–675.

Clinical Evaluation of Sexual Dysfunction

Questions to assess sexual dysfunction are summarized in **Table 41-10**. Identification of the level of personal distress caused by each problem can be assessed informally by asking, "How much does this problem bother you?" and can be noted as a lot, somewhat, or not at all. Not uncommonly, an older woman will say she is not bothered by the problem, but is motivated to address it for relational purposes. A validated instrument, the Derogatis Female Sexual Distress Scale (2002), can be used to track change in distress over time, but is primarily a tool for research purposes and has not been validated in geriatric-age women. Many other research tools have been developed to track female sexual function over time. Few have been validated in older women. We recommend the PROMIS sexual function measures developed with funding from the US National Cancer Institute (http://www.nihpromis.org/measures/availableinstruments).

TABLE 41-10 QUESTIONS TO ASSESS SEXUAL DYSFUNCTION IN THE PRIMARY CARE SETTING

WHO	QUESTIONS
Individual *(Interview patient alone; interview partner alone if patient gives permission for partner to be interviewed)*	1. Clarify individual's view of the problem(s) and how s/he thinks s/he is coping 2. Review individual's sexual response to self-stimulation (see note in text regarding older women and masturbation) 3. Ask about individual's past partnered sexual experiences, including positive and negative aspects 4. Determine individual's developmental history: any losses or traumas, and how s/he coped 5. Inquire if individual ever experienced sexual, emotional, or physical abuse, whether as a child or as an adult
Couple	1. Ask couple to explain their sexual problem(s) in their own words 2. Establish duration of problems, generalized or situational 3. Determine context of sexual problems, including relationship quality

	4. Ask about the erotic context: • What frequency of sex is expected or attempted? • Are there concerns about safety from STIs or privacy? • Adequacy of partner's sexual skills? • Is there mutual communication about sexual needs? 5. Determine the rest of the sexual response for each partner 6. Inquire how each partner has reacted to the problem(s) 7. Note any previous treatment(s), their compliance and benefit; clarify why couple is seeking help now and assess their motivation to make changes

Adapted from Basson R. Women's sexual dysfunction: revised and expanded definitions. CMAJ. 2005;172(10):1327–1333.

Although many adult female sexual function problems have a psychosocial component, a physical examination is needed for thorough evaluation and treatment. The physical examination should include examination of the inguinal lymph nodes, perineum, vulva, vagina, internal reproductive organs, anus, rectum, rectovaginal septum, and pelvic floor musculature. A vulvar cotton swab test can be used to quantify and localize vulvar pain. Graded vaginal dilators can be used to demonstrate to the patient her vaginal capacity and to educate her about dilation, a useful modality in women seeking to resume sexual intercourse after a long hiatus, in women with vaginal stenosis related to radiation or extreme atrophy, and in women with vaginismus. Using a hand mirror during the pelvic examination allows the patient to visualize genital findings and the depth of penetration with the examining finger, speculum, or a vaginal dilator. This information can be therapeutic and facilitate education about the patient's genital anatomy and any physical findings.

Details of the routine gynecologic examination can be found in Chapter 42. The geriatrician or gynecologist should be prepared to provide accommodations for older women undergoing a gynecologic examination such as alternatives to the dorsal lithotomy position; a small-sized, warm, Pederson-type speculum with ample lubricant; extra padding and pillows on the examination table; lower or electric examination tables with padded stirrups. Under the Americans with Disabilities Act of 1990, medical care providers must examine patients with disabilities as they would any patient, and if a medical provider cannot provide an examination table that a patient can access, they must provide assistance to help patients onto the examination table including assisting with transfer if necessary. Patients may be examined in a wheelchair if they wish, although they should be advised that this evaluation is suboptimal. The physician should assure the patient that the patient is in control and the examination can be stopped at her will.

Clinical Management of Female Sexual Dysfunction

Although the evidence base for treatment of sexual problems in women is growing, few studies to date include women older than 65 years. Treatment of many sexual problems benefits from an interdisciplinary approach when possible, including thorough medical evaluation, and in some cases, physical and/or psychotherapy. The 2008 US Medicare Improvements for Patients and Providers Act aims to improve coverage of mental health services for Medicare beneficiaries, which could benefit women with sexual dysfunction and comorbid depression or other mental health issues, although very few mental health professionals with expertise in geriatrics are also certified in sex therapy. The overview of clinical management presented here draws heavily on recommendations by Basson et al. (2010) from the 2009 3rd International Consultation on Sexual Medicine convened by the International Consultation on Urological Diseases and the International Society for Sexual Medicine and uses DSM-5 classifications. It aims to give primary care providers initial treatment options. If available and affordable, referral to a specialist with experience in treatment of female sexual dysfunction may be optimal. Psychotherapy, including couples' and sex therapy, cognitive-behavioral approaches, and sensate focus techniques have long been implemented for treatment of female sexual dysfunction and can be adapted to the needs of older women and couples.

Genitopelvic Pain/Penetration Disorder

Genitopelvic pain/penetration disorder is more common during and after menopause, exacerbated by thinning of the vaginal mucosa, decreased vaginal lubrication, prolapse of the pelvic organs, and shortening of the vagina caused by natural or iatrogenic loss of estrogen. Pain is a common reason for cessation of sexual activity among older women and couples. Management involves treatment of the underlying condition. Conjugated equine estrogen and, more recently,

ospemifene (a SERM) have FDA approval for treatment of moderate to severe dyspareunia caused by vulvovaginal atrophy in menopausal women. For women who cannot or who prefer not to use estrogen or SERM therapy, over-the-counter vaginal moisturizers used two or three times weekly over an extended period can reduce chronic vulvovaginal irritation and increase comfort with intercourse. Lubricants are typically used to reduce friction during vaginal or anal penetration in women with dyspareunia and are also available in hundreds of variations over the counter (**Table 41-11**). Pelvic physical therapy is an effective modality for treating dyspareunia when there is a pelvic, abdominal, and/or low-back component to the dyspareunia and when vaginismus is present. Vaginal dilation with graded dilators or other devices and behavioral, sex, or couples' therapy are additional modalities that benefit many women with sexual pain disorders.

TABLE 41-11 OVERVIEW OF VAGINAL LUBRICANTS AND MOISTURIZERS

	PROS	CONS
Lubricants *(Use immediately before or during intercourse to reduce friction)*		
Water-based	Inexpensive Compatible with latex and silicone Some varieties do not decrease sperm motility Best for women prone to yeast infections	Can dry out quickly Can feel tacky May contain glycerin and/or paraben[a]
Silicone-based	Does not dry easily Can be used in water Feels lush Compatible with latex	More expensive than water-based Difficult to wash off Incompatible with silicone and rubber Impairs sperm motility Not recommended for women prone to yeast infections
Oil-based	Stays slick longer Good for masturbation Natural Inexpensive Food-grade (eg, vegetable, olive, coconut, vitamin E oil)	Degrades condoms Impairs sperm motility
Moisturizers *(Use routinely, 2–3 times per week)*		
	Helps moisturize vaginal lining May make vaginal/surrounding tissue stronger and more pliable Works for several days Compatible with condoms	May contain glycerin[a]

[a]Glycerin has been suggested to increase the risk of yeast infection, although vaginal candidiasis is unlikely in a hypoestrogenic woman; paraben preservative is a common allergen.

Orgasm Disorder

Management depends heavily on whether the disorder is lifelong or acquired and situational or generalized. Acquired situational orgasmic disorder is most common and occurs in the setting of decreased libido and/or relational strain. Because older women, particularly those 75 years and older, have less experience with masturbation (some report they have never masturbated), ability to assess orgasmic ability may be limited. Encouragement to self-stimulate either manually or with a vibrator, a technique sometimes used with younger women, must take into account the older woman's experience and attitudes about masturbation. Psychotherapy to assess psychological issues and attitudes regarding orgasm and to complement physical interventions may be necessary. Education about vulvar anatomy, the role of the clitoris in orgasm, and variations in female orgasm may be therapeutic for some women. Women with

arousal disorders also typically do not experience orgasm so evaluation of arousal should be included in women with this complaint. Sleep dysfunction is a common comorbidity in women with arousal and orgasm disorders.

Medical Therapy for Female Sexual Dysfunction

Currently there are two FDA-approved medical treatments for postmenopausal women experiencing sexual dysfunction, conjugated equine estrogen and ospemifene, as discussed earlier. Other systemic and local exogenous estrogen products, especially local vulvovaginal estrogen cream and vaginal estrogen tablets and rings, are commonly used off-label to treat dyspareunia in menopausal women.

Androgen therapy, including testosterone and DHEA formulations, is being used off-label in some cases for treatment of sexual arousal/interest disorder. Side effects can be irreversible and safety is not established in older women. Tibolone, a synthetic steroid hormone, has been investigated for the treatment of sexual dysfunction in postmenopausal women but evidence of its benefits is limited and it is not approved by the FDA. Treatment of depression can improve sexual desire and interest, but some antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), can inhibit sexual interest. There is limited clinical data to inform treatment options for SSRI-induced sexual dysfunction, but decreasing or ceasing the SSRI dose, switching antidepressants, or using bupropion in combination with SSRIs to offset this side effect may be effective for some women.

Off-label use of phosphodiesterase inhibitors has also been tried for women with genital arousal disorder (a very small subset of women with sexual dysfunction); again, safety has not been established in older women and there is no convincing evidence that benefit outweighs risk. Tricyclic antidepressants and anticonvulsants are being used by some practitioners for treatment of vulvovestibulitis (a cause of dyspareunia), but these should be used with caution because of central nervous system side effects that may be exaggerated in older women, particularly those taking other medications.

Funding for intervention research in the area of female sexual dysfunction comes primarily from pharmaceutical sources supporting clinical trials of small numbers of young, healthy subjects followed for brief periods; even studies of postmenopausal women include only small numbers of older women. Building an evidence base is a necessary step to offering safe and effective medical, psychological, and other treatments for female sexual dysfunction in later life. Several drugs for treatment of female sexual dysfunction, particularly sexual interest/arousal disorder, are currently in preclinical and clinical trials. The FDA has held a patient-focused drug development public meeting and scientific workshop on female sexual dysfunction to learn from patients about their perspectives on female sexual dysfunction and the treatments currently available. Of note, among men aged 57 to 64 surveyed in two nationally representative cohorts conducted 10 years apart, a greater proportion of men interviewed in the more recent cohort reported an increase in sex, perhaps because the later cohort was surveyed after highly effective erectile dysfunction drugs became available. This suggests that as more treatment options for female sexual dysfunction become available, an increase in sexual activity among women in later life may occur.

CONCLUSION

Older women comprise more than half the population of older adults in the United States and will outnumber older men through 2050. Nevertheless, many aspects of older women's health are neglected by researchers and clinicians, including sexuality. Sexual and intimate relationships in later life can promote health and well-being and sustain a basic human need. Many older women engage in sexual relationships despite sexual problems and pain, while others discontinue sex caused by problems that could be treated. Physicians caring for older women can positively impact their patients' sexual functioning and overall well-being by initiating and fostering an open and ongoing dialogue about sexual matters in the context of healthy aging or in relation to medical conditions and their treatments. Public health messaging and medical education addressing the continued importance of sexual health discussions past reproductive age could help normalize late life female sexuality and validate older women's sexual health concerns. Research is needed to establish trajectories of older women's sexuality with aging especially among people identifying with racial, ethnic, and sexual minority groups, and to provide an evidence base for diagnosis and treatment of female sexual dysfunction in later life.

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Chapter 42

Gynecologic Disorders

Karen L. Miller, Tomas L. Griebling

Learning Objectives

- Establish personal and familial risk factors for gynecologic cancer in each female patient.
- Discontinue screening for cervical cancer only after adequate screening criteria have been met.
- Describe the approach to the initial evaluation of vulvovaginal complaints.
- List multiple options to treat atrophic vaginitis.
- Understand the indications for specialty referral in a woman with pelvic organ prolapse (POP).
- Provide reassurance to women who have POP but no medical indication for specialist referral.

Key Clinical Points

1. **Primary care providers will become increasingly responsible for routine gynecologic care.**
2. **Cervical cancer has a higher case-fatality rate in older women, and if a cervix is in situ, screening should be discontinued only in low-risk women age 65+ after three negative cytologies or two negative cotests in the previous decade.**
3. **Endometrial cancer associated with a false-negative screening ultrasound is frequently of the more aggressive type.**
4. **Although ultrasound and serum (CA-125) screening for ovarian cancer is ineffective in a low-risk population, imaging should be considered in women with suspicious symptoms involving abdominal and pelvic pain/discomfort, bloating, gastrointestinal disturbances, and urinary complaints.**
5. **Pelvic pain is not commonly due to pathology of reproductive organs; the urinary tract, gastrointestinal (GI) tract, and musculoskeletal systems should be thoroughly investigated with history and physical examination.**
6. **Pessaries can successfully relieve symptoms for many types of POP and stress urinary incontinence, and should be encouraged.**

INTRODUCTION

The preponderance of women (> 60%) compared to men (< 40%) in a geriatrics practice is not news, but their gynecologic care is changing. With recommendations against routine Pap smears and pelvic examinations over age 65, fewer women will have occasion to see a gynecologist. Gynecologic care will be provided mostly by primary care practitioners, who must be more mindful than ever about risks, symptoms, and unspoken issues. Lifetime risk of a gynecologic cancer (excluding breast cancer) is over 5%, greater than a woman's lifetime colorectal cancer risk. Pelvic floor symptoms bother 40% of women age 70 to 79 and more than 50% of women greater than or equal to 80 years. Sexual problems are prevalent in half of older women who are still sexually active. Fortunately, compared to reproductive years, gynecologic care for older women is relatively straightforward and well within the scope of

primary care management or triage. Urinary and pelvic floor issues are the exception; they increase in complexity with age, but are not foreign to geriatrics practitioners. This chapter seeks to address the most common or important gynecologic and urogynecologic issues encountered in a geriatrics practice, with practical tips and suggestions. Use of the term gynecologic in this chapter usually includes urogynecologic issues as well, except when the topic is cancer. Urinary incontinence is not included in this chapter, but is covered in detail in Chapter 53. Topics are presented anatomically, in approximately the same order as a physical examination is approached, along with the major corresponding clinical issues.

GYNECOLOGIC WELL-WOMAN VISIT

In a geriatrics practice it could be argued that the only important gynecologic history is a gynecologic review of systems and a medication list. However, to assess cancer and infectious disease risks, to anticipate and interpret problems, and to promote function and quality of life, more detail is required. If a new patient visit is consumed with other concerns, vaginal bleeding and pelvic or vulvovaginal pain should be queried, since these are most indicative of urgent issues. A more complete gynecologic history and examination could be rescheduled.

Key points in the gynecologic history and physical are listed in **Table 42-1**. If gynecologic surgery was performed, note the indication. For pain, prolapse, and incontinence surgeries, determine whether symptoms resolved. Lifetime hormonal status and exposure, family cancer history, and cancer screening since age 55 are important in assessing current cancer risks. Additional useful history includes parity (term/preterm deliveries especially), age at first delivery, delivery route (vaginal or cesarean), major obstetrical complications, and lactation. Since pelvic floor issues may develop regardless of parity, the older the patient, the less relevant the obstetrical history, but it does inform cancer risk.

TABLE 42-1 GYNECOLOGIC HISTORY AND EXAMINATION

	COGNITIVELY INTACT	COGNITIVELY IMPAIRED[a]
History	Hormones: menarche, menopause, past and current hormone use.	Current hormone use.
	Breast complaints: pain, lump, nipple discharge.	Staining of brassiere or clothing, pain.
	Vulvovaginal issues: bulge, bleeding, discharge, pain.	Apparent discomfort in perineal area.
	Urinary issues: incontinence, urinary frequency, urinary urgency, hesitancy, nocturia, dysuria, hematuria, infections.	Toileting practices, pad use.
	Defecation issues: constipation, fecal incontinence (gas, liquid, solid stool).	Defecation frequency, stool consistency.
	Sexual health issues: sexual activity, contacts, satisfaction, potential sexual abuse.	Sexual behaviors.
	Family history of gynecologic, breast, intestinal, endocrine malignancies.	
Physical examination	Breast examination (annually)	Breast examination if tolerated.
	Pelvic examination - Upon assuming care for new patient - For symptoms - For vague concerns - To ensure optimal referral Routine examinations controversial, low yield	Annual inspection of the external genitalia is probably useful. Initial internal examination may also be worthwhile. Subsequent internal examinations are indicated for symptoms or to rule out fecal impaction.
	External genitalia and perineum: architecture and integument	
	Urethra: meatus, caruncle	

	Bladder: tenderness, fullness	
	Vagina: mucosal tissue quality, discharge, mass, prolapse	
	Cervix: lesions, mobility	
	Uterus: size and mobility	
	Adnexa: palpability or mass	
	Rectum: anal sphincter tone, mass, stool for occult blood	

[a]Suggestions for examination in the cognitively impaired older woman (moderate or severe impairment) are based on clinical experience (Level D evidence).

Diethylstilbestrol (DES) is an often-forgotten cancer risk factor. It was synthesized in 1938 and prescribed to pregnant women until the early 1980s in some European countries, although not after 1971 in the United States. An estimated 5 to 10 million women worldwide took DES during pregnancy. An increased breast cancer risk has been seen in both women who received DES and their female fetuses exposed in utero (DES daughters). The increased risk of vaginal clear cell adenocarcinoma and cervical neoplasia in DES daughters continues into the fifth decade, but little is known about epidemiology of these conditions in advanced age.

Physical Examination

The physical examination serves four main purposes: (1) to understand the patient's anatomic status, (2) to detect unrecognized problems at an early stage, (3) to detect significant current problems in the cognitively or neurologically impaired, and (4) to provide the patient an opportunity to discuss embarrassing and private issues. A surprising number of gynecologic and urologic symptoms are only voiced or discovered during the pelvic examination, despite a thorough history and denial of problems. While the utility of an annual pelvic examination is low, a strong argument can be made for examination of a new patient or by a new practitioner assuming care. For example, a forgotten vaginal surgery such as colpocleisis may be discovered. Periodic examination of "asymptomatic" but concerned women is wise. A patient may not be able to articulate the concerns she has. A variety of speculum sizes is essential for a painless examination, including regular, long and narrow, small, and large. Topical lidocaine at the posterior introitus as needed limits discomfort. Local anesthetic can also be applied liberally to the vulva and vagina to facilitate examination in cognitively impaired women. Fecal impaction should be ruled out in older women as a cause of a difficult vaginal examination. Fecal impaction can compress the urethra and bladder (**Figure 42-1**), can cause urinary symptoms in addition to abdominal discomfort, and requires evaluation of underlying causes (especially poor fluid intake) as well as treatment (see Chapter 95).

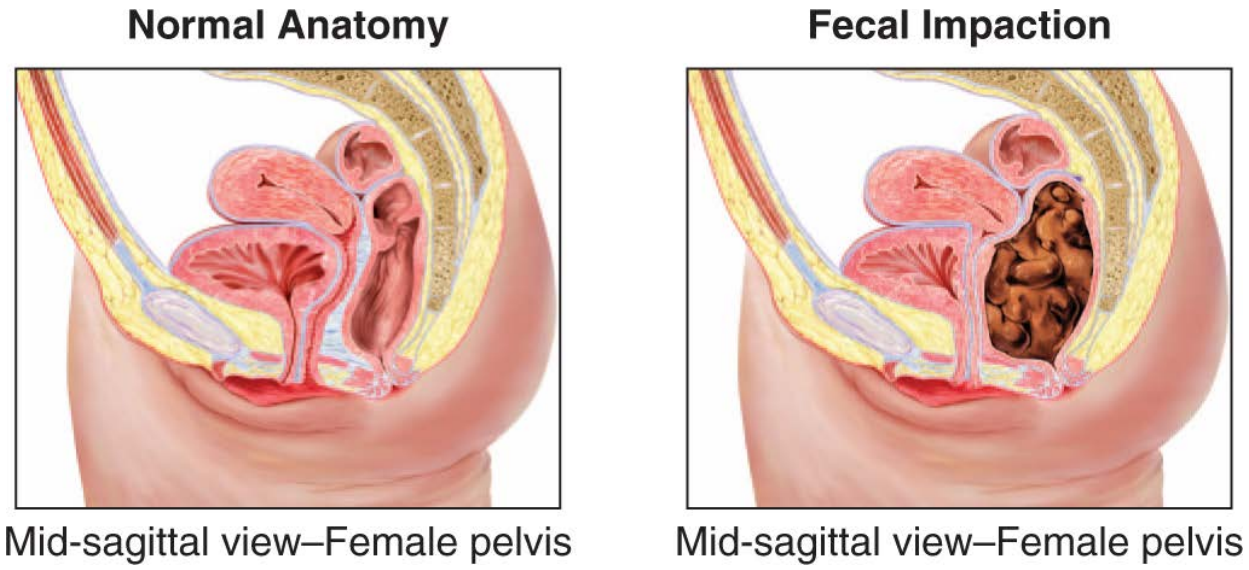


FIGURE 42-1. Sagittal view of normal pelvic anatomy (*left*) and fecal impaction (*right*). Note how a large impaction can compress the bladder, urethra, and surrounding innervation and other tissues.

The American College of Obstetricians and Gynecologists (ACOG) is unique in clearly recommending that "annual examination of the external genitalia should continue" beyond age 65. This is prudent but may not be cost-effective, especially in cognitively intact women who would usually report symptoms. The utility of annual external genitalia examination could be more important in women who are cognitively impaired. Given the possible association with vaginal cancer, ACOG also recommends continuing annual internal pelvic examinations indefinitely in DES daughters, even those who have had a hysterectomy. The benefit of this is unknown.

BENIGN BREAST DISEASE

Screening for breast cancer is addressed in Chapter 97. While numerous studies address cancer, little is known about the epidemiology of benign breast disease in older women. The breast is a complex structure subject to many pathologic conditions, both intrinsic and extrinsic. These may involve skin, connective tissue, ligaments, nerves, vasculature, lymphatics, and muscles in addition to mammary ducts and alveoli.

A clinical breast examination includes axillary, supraclavicular, and infraclavicular lymph nodes. Pertinent negative findings should be documented, ideally in all patients, but especially if there is any breast complaint. These may include "No skin changes, nipple discharge, dominant masses, tenderness, or adenopathy." Fibrocystic changes in breast tissue are present asymptomatically in the majority of women. Symptomatic problems can be categorized as a lump, pain, nipple discharge, or inflammation.

Breast Lump

Evaluation of a lump includes noting the size, position, consistency, and character. Location can be described referencing the areola as a clock face and measuring distance from the areolar border. While a myriad of pathologic entities could result in a breast lump, such as tuberculosis, age is a consistent risk factor for malignancy. A large mammography database study found "lump" to be the only breast symptom significantly associated with cancer, in up to 8% of cases. All discrete lumps should be evaluated by a breast specialist. The diagnostic mammogram and ultrasound may be performed before or after consultation, per consultant preference. If a lump found by the patient is not palpated by the physician, additional consultation is in order. If both the patient and physician agree that now there is no palpable abnormality, reassessment in 2 months to reconfirm is advisable.

Breast Pain

Breast pain is common and rarely indicates dangerous pathology. It may be unilateral or bilateral, intermittent or persistent, sharp or aching. Only half of women with significant breast pain seek medical attention. Cancer uncommonly presents with breast pain, and mastalgia is not an indication for a diagnostic mammogram. Focal persistent pain may be associated with cancer in 1% to 3% of patients, but primarily in younger women seen at a tertiary care center. If focal persistent pain is concerning, a diagnostic mammogram and ultrasound can adequately rule out cancer, or the patient may be referred.

Pain sources intrinsic to the breast include fibrocystic disease, duct ectasia, trauma, sclerosing adenosis, and stretching of Cooper ligaments. Conditions external to the breast but perceived as breast pain include costochondritis (Tietze syndrome), cervical radiculopathy, intercostal neuralgia, thrombophlebitis of the thoracoepigastric vein (Mondor disease), herpes zoster, angina, cholecystitis, and hiatal hernia. Palpate the breast bimanually to differentiate breast from chest wall pain. If findings are negative and mammographic screening is current, the patient can be offered reassurance and/or analgesics. Interference with activities such as hugging, exercising, and sleeping may indicate a need for more aggressive pain management, starting with a well-fitted brassiere with good support. Caffeine reduction is not likely beneficial. Pharmacologic agents for mastalgia are not without side effects. If needed, however, tamoxifen is one of the top considerations.

Nipple Discharge

Breasts are secretory organs. Important nipple discharge characteristics are whether it is spontaneous or expressed, unilateral or bilateral, involving single or multiple ducts, and the color. The examiner should try to elicit discharge palpating each breast quadrant from the outside toward the areola, and then gently squeezing the areola. A mass should be ruled out, particularly under the areola. Whereas unilateral, single-duct, spontaneous, bloody or watery discharge is more concerning for neoplasia, bilateral, expressed, nonbloody discharge from multiple ducts is not associated with

cancer. Consultation should be obtained for all bloody or recurrent spontaneous discharge. A thick grumous or purulent discharge may indicate duct ectasia (dilated lactiferous ducts with inspissated secretions) or subareolar abscess. Duct ectasia is also the most common cause of blood-stained discharge from multiple ducts. Duct ectasia is benign, but may be excised to rule out underlying cancer. Hyperprolactinemia is rare in older women. A serum prolactin is indicated if galactorrhea is observed or suspected, but is not necessary in most cases. Eczematous and other skin conditions may imitate nipple discharge.

Breast Inflammation

Inflammatory conditions intrinsic to the breast include duct ectasia, fat necrosis, ruptured inflammatory cyst, inflammatory abscess due to obstructed ducts, idiopathic granulomatous mastitis, foreign body, radiation, and inflammatory carcinoma. Smoking, diabetes, and rheumatoid arthritis predispose to abscesses. The most common pathogen is *Staphylococcus aureus*. Risk factors for methicillin-resistant *S aureus* include diabetes and residence in long-term care. Most abscesses respond well to drainage and antibiotics. Conditions extrinsic to the breast that may present with inflammation include metastatic lung cancer, Wegener granulomatosis, sarcoidosis, and other skin diseases.

PELVIC PAIN

Perceived "pelvic" pain may arise from any component between the umbilicus and the upper thigh. Bladder pain including interstitial cystitis (IC) is discussed later in this chapter. A strictly gynecologic cause of either acute or chronic pelvic pain is uncommon in older women except with advanced malignancy. Although many women fear that the pain indicates an ovarian problem, other causes are more likely. The ovaries have shrunk to the size of an almond in its shell and are largely inactive, making painful cysts rare and torsion highly unlikely. Benign ovarian cysts and masses are usually asymptomatic until they are quite large. A complaint of "pain" is not likely to herald a gynecologic malignancy; nonspecific abdominal and pelvic discomfort are more common descriptions with cancer. Infection and neoplasm could be gynecologic causes of acute pain. But a nongynecologic cause would be more likely, such as constipation, diverticulitis, herpes zoster, or pelvic insufficiency fracture.

Anecdotally, older women rarely experience the same type of chronic pelvic pain (≥ 6 months) that plagues women in their reproductive years, with "cross-talk" between pelvic organ structures, pelvic tension myalgia, and central sensitization. POP may cause low back or low pelvic pain. Pelvic floor repair with synthetic mesh may result in chronic pain, usually remediable. More likely etiologies of chronic pelvic pain involve the gastrointestinal and musculoskeletal systems. The abdomen, low back, and hips should be evaluated. Myofascial pain with trigger points in the lower abdomen is a particularly notorious pelvic pain impostor. This occurs in 30% of patients with chronic abdominal pain, frequently misrepresented as visceral or functional pain. A finding of myofascial trigger points with Carnett test (increased point tenderness with partial sit-up tensing the abdominal muscles) does not completely rule out internal causes of pain, but initial treatment of this will clarify the etiology.

Following evaluation of the abdomen, back, bony pelvis, and hips, the pelvic examination should proceed slowly, assessing tenderness from external to internal. Urethra, bladder, and pelvic musculature can be sequentially palpated. If abdominal pain or tenderness is present, begin the "bimanual" examination of the uterus and ovaries using only the vaginal hand. After assessing cervical, uterine, and adnexal tenderness without abdominal palpation, then proceed to bimanual evaluation. If the cause is unknown, repeating the examination at subsequent visits is valuable, as the findings typically vary somewhat. Vulvovaginal pain examination is addressed below.

VULVAR AND VAGINAL ISSUES

Examination of the Vulva

Normal vulvar architecture consists of definite labia minora, labia majora, clitoris, clitoral hood, and intact urethral meatus (**Figure 42-2**). Advanced age and estrogen deficiency may lead to a nonpathologic loss of vulvar architecture, especially of the labia minora. Cherry angiomata and epithelial inclusion cysts on the labia majora are common and not concerning. Asymmetrical pigmented lesions should be noted and considered for either biopsy or follow-up examinations. Punch biopsies of the vulva are simple and rarely become infected. Bartholin glands are located in the

inferior (dorsal) aspect of each labium majus. An asymptomatic Bartholin cyst does not require referral if there is no detectable mass associated with the cyst, but rare Bartholin gland malignancies do occur. A new swelling in an older woman is suspicious.

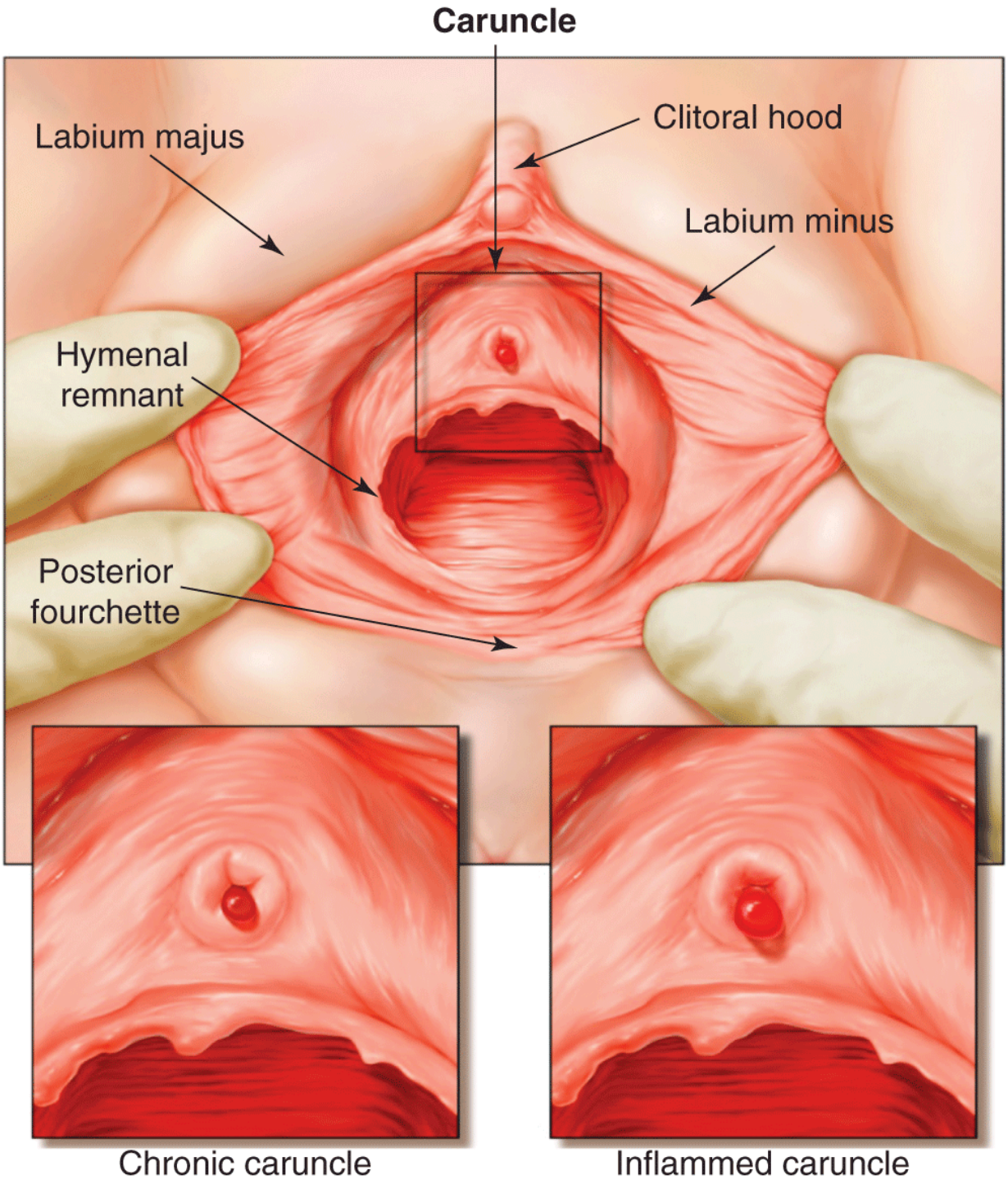


FIGURE 42-2. Illustration of pelvic examination landmarks and a urethral caruncle.

Benign Conditions of the Vulva

The hundreds of benign vulvar disorders generally fall into categories of infection, neoplasia, and dermatosis, some of which may reflect systemic disorders. Inflammatory disorders may be difficult to recognize, even by dermatologists, because the warm, moist, frictional environment alters their otherwise typical appearance. Establishing a nomenclature that is both clinically useful and pathologically appropriate is challenging. Furthermore, as Lynch et al. aptly stated, “Nomenclature regarding the eczematous and lichenified diseases is particularly confusing and controversial.” The

current International Society for the Study of Vulvar Diseases classification relies primarily on histologic morphology (**Table 42-2**). Realizing its limitations, they have since formulated an approach that allows highly accurate diagnoses with just clinical observations. Estrogen deficiency may increase susceptibility to trauma, irritation, and secondary infection, but is not a primary cause of vulvar problems.

TABLE 42-2 CLASSIFICATION OF VULVAR DERMATOSES: PATHOLOGIC SUBSETS AND CLINICAL CORRELATES (2006 INTERNATIONAL SOCIETY FOR THE STUDY OF VULVOVAGINAL DISEASE CLASSIFICATION)

Spongiotic pattern
Atopic dermatitis
Allergic contact dermatitis
Irritant contact dermatitis
Acanthotic pattern (formerly squamous cell hyperplasia)
Psoriasis
Lichen simplex chronicus
Primary (idiopathic)
Secondary (superimposed on lichen sclerosus, lichen planus, or other)
Lichenoid pattern
Lichen sclerosus
Lichen planus
Dermal homogenization/sclerosus pattern
Lichen sclerosus
Vesiculobullous pattern
Pemphigoid, cicatricial type
Linear IgA disease
Acantholytic pattern
Hailey-Hailey disease
Darier disease
Papular genitocrural acantholysis
Granulomatous pattern
Crohn disease
Melkersson-Rosenthal syndrome
Vasculopathic pattern
Aphthous ulcers
Behçet disease
Plasma cell vulvitis

Vulvar Dermatitis

Another term for vulvar dermatitis is vulvar eczema, the most common vulvar dermatosis. Hallmarks are pruritus (often disrupting sleep), scaling, and lichenification. Vulvar architecture is usually normal. When this occurs on previously normal skin, it is termed lichen simplex chronicus, formerly squamous hyperplasia. Lichenification can also occur where there is an underlying dermatologic disorder such as lichen sclerosus or psoriasis.

Vulvar dermatitis can be endogenous or exogenous. Endogenous refers to atopic dermatitis of the vulva, usually with a familial predisposition and extragenital occurrence of eczema. Exogenous vulvar dermatitis is more common in older adults, also called contact dermatitis. It may be initiated by irritants (80%) or allergens (20%). Vulvar epithelium is more vulnerable to irritants than other body areas. All soaps, feminine hygiene products, topical medications, urine, incontinence pads, and synthetic underwear are potential culprits. Effective treatment requires identifying and

eliminating offending factors and applying topical anti-inflammatories. As a general rule, ointments are preferred to creams, because they are less prone to cause further irritation. Secondary infections with yeast and bacteria should be considered. When symptoms have resolved, a daily protective barrier cream or ointment may be necessary, such as when a patient cannot forgo incontinence products. Solid vegetable or mineral oil are among the least irritating.

Other Inflammatory Dermatoses of the Vulva

Lichen sclerosus is a chronic inflammatory disease that can occur at any age, its highest prevalence being after menopause. It may have an autoimmune etiology and is frequently associated with other autoimmune disorders. Pruritus is characteristic, but it may be asymptomatic. Typical lesions are porcelain white papules and plaques, often with areas of ecchymosis or purpura. Perianal involvement can create the classic "figure of eight" appearance. In more advanced cases, vulvar architecture is lost, with labial fusion, clitoral hood phimosis, and fissures. Scarring may lead to introital narrowing. The malignant potential of lichen sclerosus is debated, but may be as high as 4% to 5%. Biopsy confirmation of the diagnosis and visual inspection at least annually are advisable. Treatment is necessary only to control symptoms. Typical regimens involve potent topical glucocorticoids for a few weeks, then tapering to a lower dosing frequency. A subsequent maintenance regimen of daily or twice-daily emollient probably reduces the frequency of symptomatic flares. Estrogen has little or no effect on lichen sclerosus but can improve the resilience of unaffected areas, and estrogen cream can serve as an emollient.

Lichen planus exhibits a wide range of morphologies. Of women with oral lichen planus, approximately 20% to 25% have vulvovaginal lesions. The erosive form may cause pain and vaginal discharge, and lead to agglutination and resorption of labial architecture, rarely with complete obliteration of the vaginal orifice. Other autoimmune disorders to consider are Zoon disorder (plasma cell vulvitis), Behçet disease, Crohn disease, aphthous ulcers, and Hailey-Hailey disorder (fragile and inflamed vulvar and axillary skin). Psoriatic lesions of the genitalia do not exhibit the silver appearance seen elsewhere on the body, and are more often simply erythematous. There is usually a personal or family history of psoriasis.

Ulcerations and Infections of the Vulva

The differential diagnosis of genital ulceration includes sexually transmitted diseases, the most common of which in United States is herpes simplex virus (HSV). Immune suppression, including very advanced age, is a risk factor for HSV infection in the absence of sexual contact, and for herpes zoster of the S3 dermatome. A primary infection is usually accompanied by lymphadenopathy, vaginal discharge, urinary frequency and urgency, and painful ulcers on the labia and/or cervix. Zoster can inhibit detrusor function resulting in an inability to void. Lesions clear more quickly with antiviral agents. Other causes include syphilis, the autoimmune disorders listed above, blistering dermatologic disorders and, of particular concern in older women, excoriated or ulcerated neoplasia.

Vulvar Neoplasia

Vulvar intraepithelial neoplasia (VIN) is now divided into two types. Usual-type VIN associated with human papilloma virus (HPV) occurs mainly in younger women. Differentiated or simplex type classically occurs in postmenopausal women with chronic skin conditions (lichen sclerosus, lichen simplex chronicus). Differentiated VIN has a higher malignant potential, but both types may progress to squamous cell cancer (SCC). Pruritus is the most common symptom. VIN lesions cannot be reliably distinguished by inspection alone. Any focal, raised, irregular, or pigmented lesion warrants biopsy. Of these, pigmentation is the most difficult to interpret, possibly requiring surveillance over time.

Vulvar cancer (**Table 42-3**) is the fourth most common malignancy of the female genital tract, with 3400 new cases reported annually in the United States. SCC is the most common type, and malignant melanoma a distant second. The incidence of both types of SCC (with and without HPV) rises steadily with age, reaching 12 to 20 per 100,000 in the ninth decade. HPV is associated with 15% to 50% of vulvar cancers in older women. For unclear reasons, the incidence of vulvar SCC in the United States and Canada is rising in all age groups over 40 and the 5-year relative survival is declining. These trends become more pronounced in each successive age group. Between 1992 and 2008 in women aged greater than or equal to 80, the 2-year relative survival decreased 10% and the 5-year relative survival declined over 15%. These alarming statistics are all the more disturbing because research has been limited and the causes are not well understood. Pruritus, pain, and a palpable lesion are typical presenting complaints. Malignant melanoma is rare. Concerning characteristics are the same as in sun-exposed skin. Mainstays of therapy for vulvar

cancer treatment are radical vulvectomy with inguinal lymphadenectomy, radiation, and chemotherapy. Wide local excision may suffice for some early cancers and may be used for palliation in frail women.

TABLE 42-3 ESTIMATED 5-YEAR GYNECOLOGIC CANCER SURVIVAL BY DISEASE STAGE

CANCER TYPE	STAGE I	STAGE II	STAGE III	STAGE IV
Endometrial	54%–88%	40%–76%	22%–57%	12%–18%
Ovarian	80%–90%	65%–70%	30%–59%	17%
Cervical	80%–95%	74%–77%	46%–52%	20%–29%
Vulvar	85%	69%	40%	22%
Vaginal	74%	50%	32%	0%–18%

Data summarized from FIGO Annual Report. J Epid Biostat. 2001;6:1.Includes both clinical and surgical staging.

Vulvar Pain, Vaginal Pain, and Dyspareunia

To evaluate vulvar or vaginal pain, the perineum from the mons pubis to the anus should be meticulously inspected for vulvar architectural changes, which may or may not be pathologic, including fissures, ulcers, erythema, and other signs of inflammation. Palpation of the vulva and around the vaginal introitus with a cotton swab or other narrow instrument will better establish the location and extent of tenderness than digital palpation. Particular areas to assess are the base of hymeneal remnants, posterior fourchette, and periurethral Skene glands.

Vulvar pain in the absence of any clinically identifiable condition is now called simply vulvodynia. It may be provoked, unprovoked, or both, and generalized or localized. “Localized provoked vulvodynia” denotes the condition formerly termed vulvar vestibulitis. The suffix “itis” is technically inaccurate, since inflammation is not usually present. Pain located specifically in the vestibule may be called vestibulodynia. This is not particularly common with aging or atrophy. The condition is frustrating, poorly understood, and difficult to treat. Neuropathy is thought to be one of the many components. Estrogen and/or glucocorticoid topical preparations rarely improve symptoms. Daily to twice-daily solid mineral or vegetable oil may provide relief over time by protecting from irritants. Neuromodulators used for chronic pain may be beneficial. Herpes zoster and postherpetic neuralgia should be considered in unilateral cases.

Unlike the vulva, the vagina is rarely an isolated source of pain unless the patient is sexually active. Simple postmenopausal vaginal atrophy is usually asymptomatic, but dyspareunia is common. Dyspareunia evaluation is guided by historical factors such as past sexual experiences, exact symptoms during intercourse, and examination. The anterior, lateral, and posterior vaginal walls and apex should be inspected and palpated as separately as possible. Atrophic vaginitis considerations are presented below. Patients with “atrophic vaginitis” that has not responded to estrogen frequently have an unrecognized vulvar condition. Isolated vaginal pain in the absence of intercourse should prompt consideration of surrounding organs and structures.

Vaginitis, Vaginosis, and Vaginal Discharge

Symptoms of vaginitis, vaginosis, and vaginal discharge overlap with each other and with those of vulvar conditions. A true bacterial vaginitis is uncommon in the absence of an underlying epithelial disorder. Bacterial vaginosis incidence increases with age, but only requires treatment for bothersome symptoms or planned vaginal surgery. Yeast infection incidence declines with age, but antibiotics, diabetes, immune suppression, and estrogen therapy are risk factors. *Trichomonas* can be carried asymptomatically for at least 3 months, but eventually becomes symptomatic. Coexistence with bacterial vaginosis is common. Either estrogen initiation or replacement of a large vaginal prolapse with a pessary may cause benign white discharge in the first few months from an increase in epithelial turnover. Desquamative inflammatory vaginitis is an uncommon cause of discharge, burning, and dyspareunia, and may be a manifestation of erosive lichen planus. Rare causes of purulent malodorous discharge include an enterovaginal fistula secondary to diverticulitis and bacterial endometritis.

Evaluation in younger and older women is largely the same except for vaginal bleeding. Any history of a brown or red color necessitates endometrial evaluation. Physical examination is essential to evaluate vaginal discharge, because definitive description is difficult for anyone. Findings often differ from the presumption based on history. However, when symptoms are classic for yeast infection and follow-up is likely, a trial of antifungal treatment prior to

examination is reasonable. Potassium hydroxide and normal saline wet mounts plus pH paper are the usual evaluation tools, but useful triage information is gleaned even without them. With aging and estrogen deficiency vaginal pH rises, so that a higher pH (> 4.5) is less indicative of bacterial vaginosis, but a low pH may help identify a yeast infection. If microscopy is not available, commercial tests are available for bacterial vaginosis and *Trichomonas vaginalis*, and yeast can be cultured. A trichomoniasis diagnosis should prompt sexually transmitted infection screening and treatment of partner(s). Current recommendations for detection and treatment of sexually transmitted diseases are maintained on the website of the Centers for Disease Control and Prevention (www.cdc.gov/std/default.htm).

Vaginal atrophy secondary to hypoestrinism involves several changes including mucosal thinning; loss of rugae, elasticity, and distensibility; an increase in subepithelial connective tissue and vaginal pH (> 4.5); and reduced secretions. Changes in the vaginal microbiome predispose to urinary tract infections, but traditional assumptions about specific organisms such as lactobacilli are changing and not yet clarified. Atrophic “vaginitis” is poorly defined apart from simple atrophy, but is usually diagnosed when symptoms (dryness, itching, irritation, burning, dyspareunia, irritative voiding) or signs (pale, thin, shiny vaginal mucosa, telangiectasias, petechiae, patches of inflammation, discharge) are present (**Figure 42-3**). A cytologic maturation index would reveal 60% to 100% parabasal cells, but is not necessary for the diagnosis.

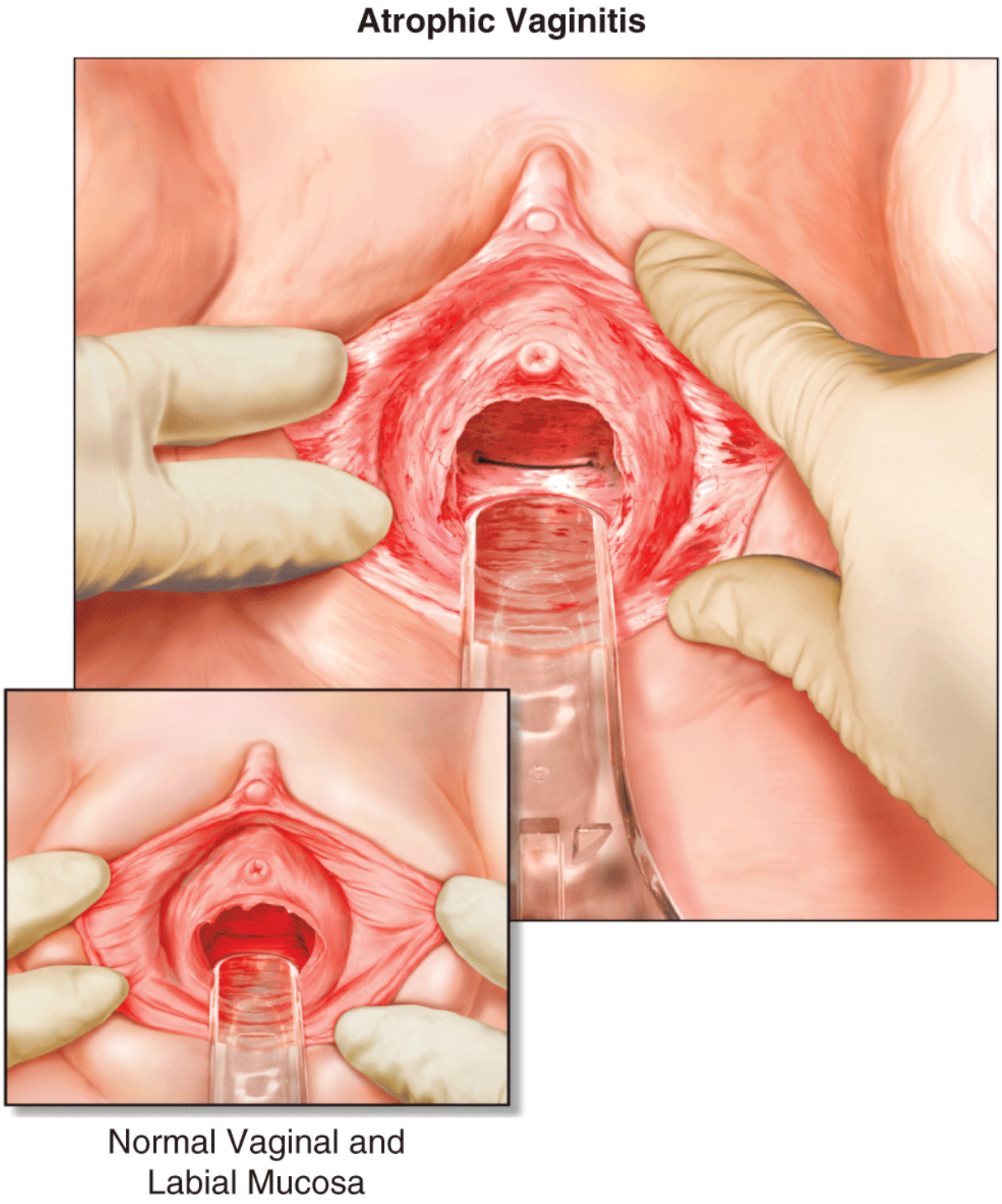


FIGURE 42-3. Illustration of atrophic vaginitis versus normal mucosa. Signs of atrophic vaginitis may include pale, smooth, shiny mucosa with patches of inflammation and petechiae.

Low-dose topical estrogen remains the preferred treatment for atrophic vaginitis in most women. It is the most proven for symptom relief, and there are several delivery options, via ring, tablet, or cream. The ring can remain in the vagina for 3 months without being removed, releasing 6 to 9 μg of estradiol daily. Tablets containing 10 μg of estradiol are inserted nightly for 2 weeks, then twice a week. Daily use is required initially to stimulate mucosal remodeling, because the very low maintenance dose alone is not sufficient. The dose and absorption of both the ring and the tablet are specific and well studied. Serum estradiol rises briefly in the first 24 hours then remains within the postmenopausal range.

Exact low dosage is difficult to achieve with creams, but cream has other advantages. The vehicle soothes the mucosa. Creams are often the least costly approach. The amounts needed to treat atrophic vaginitis are smaller than the lowest measurements on the applicator; using an estimated 1/4 to 1/2 g twice weekly is reasonable. Some women find

fingertip application of a pea- or chocolate chip–size amount at the introitus easier than inserting an applicator.

Vaginal estrogen use in breast cancer survivors is controversial and best prescribed in consultation with an oncologist. Estrogen is contraindicated during breast cancer treatment, but no harm has been detected from use of low-dose topical preparations in survivors. Patients taking aromatase inhibitors may achieve undesirably high premenopausal serum estrogen levels, warranting extra precaution or consultation before and during any estrogen treatment. Concerns seem to only apply to hormone-sensitive cancers. No increased recurrence of hormone receptor negative cancers has been found with any type of postmenopausal hormone therapy. Nonetheless, survivors should try nonhormonal vaginal moisturizers first, then if necessary estrogen tablets or ring so a controlled dose can be given.

With these low doses, progestins to prevent endometrial hyperplasia are not required. However, estrogen absorption varies considerably between individuals, and endometrial growth could possibly be stimulated. Any brown or red discharge necessitates evaluation of the endometrium (see below). Occasionally it may be useful to investigate whether estrogen is causing endometrial growth. The simplest and cheapest method is to prescribe medroxyprogesterone acetate 5 mg or similar progestin for 12 days, to see whether she has “withdrawal bleeding” thereafter.

Ospemifene is an oral estrogen agonist/antagonist, or selective estrogen receptor modulator (SERM), indicated for atrophic vaginitis. It is effective for vulvovaginal atrophy, and appears to have favorable effects on bone, neutral effects on the endometrium and the cardiovascular system, and possibly favorable but as yet unknown effects on breast cancer risk. Long-term data are lacking. Risks and contraindications are similar to those for estrogen, including venous thromboembolism. Vasomotor symptoms are bothersome in 10% of patients.

Other nonestrogen therapies are less reliable in reducing dyspareunia and irritative voiding symptoms, but often relieve mild symptoms. Vaginal moisturizers are used on a regular basis, daily to weekly, to maintain epithelial moisture and vaginal pH. In addition, vaginal lubricants may be used for intercourse. Frequent sexual activity helps maintain supple tissues. Alternative hormonal agents (dehydroepiandrosterone, other SERMs, testosterone) are promising but not yet sufficiently studied.

Vaginal Cancer

Vaginal cancer accounts for 1% or less of female genital tract cancers. Metastatic disease of the vagina is more common than primary vaginal cancer, notably from cancers of the endometrium, cervix, vulva, ovary, breast, rectum, and kidney. The most common primary vaginal cancer is SCC, but adenocarcinoma, sarcoma, melanoma, and others occur. Vaginal SCC is often preceded by vaginal intraepithelial neoplasia, which is associated with concomitant cervical or vulvar neoplasia in about 50% of cases. It is usually asymptomatic and not easily visible, but induration may be palpable. Two-thirds of cases occur in the upper vagina. Risk factors for primary vaginal cancer are the same as those for cervical cancer, including prior gynecologic cancer and radiation therapy. Bleeding, discharge, pain, and urinary or rectal complaints are presenting symptoms. Survival drops precipitously beyond stage II (see **Table 42-3**).

CERVIX UTERI

Examination of the Cervix

The location of the squamocolumnar junction, the border between squamous (ectocervical) and mucous (endocervical) epithelia, changes location over a lifespan. It is usually within the endocervical canal in older women and not visible. Its importance lies in the fact that it is the most common site of cervical neoplasia. Cystic structures near this border are almost invariably nabothian cysts. These are not true cysts, but collections of mucus trapped during metaplastic transition, when squamous cells cover mucus-secreting crypts. They do not require biopsy. Any lesion whose benignity is uncertain should be biopsied or referred. Cytology alone is not an appropriate evaluation of an abnormality.

Cervical Cancer

Cervical cancer is the third most common gynecologic malignancy diagnosed in the United States, but the most common one in developing nations. The risk of cervical cancer increases with age, and the case-fatality rate is higher in older women (see **Table 42-3**). While women over age 65 represent 14% of the US female population, 20% of new cervical cancer cases and 34% of cervical cancer deaths are in this group. Most of these are in unscreened or inadequately screened women. Three-fourths of cervical cancers are SCC. The remaining adeno-, adenosquamous, and clear cell carcinomas have higher mortality rates. In older women only half to two-thirds of cervical cancers are associated with HPV. Postcoital bleeding may occur at an early stage, but other symptoms (pain and bowel or bladder

symptoms) are absent. Radical hysterectomy is the primary treatment for early-stage cervical cancer. Radiation therapy is used for locally advanced disease, as adjunctive treatment, when surgery is not an option, and along with chemotherapy for palliation.

Cervical Cancer Screening

The excess deaths from this mostly preventable malignancy are only avoided through screening, including "adequate" screening of older women. Screening older women provides equivalent benefit to screening younger women, that is, an equivalent reduction in severe cervical intraepithelial neoplasia (CIN) and, by inference, of cancer. But due to low cancer incidence and long lead time, routine screening after age 65 provides little benefit *if women have been adequately screened prior to this*. The key to safe discontinuation is knowing the patient's screening and risk factor history. The three main issues in older women are (1) when to discontinue screening, (2) in whom to *not* discontinue screening, and until what point, and (3) the best screening modalities.

Cervical cancer screening has evolved from microscopy of exfoliated cells in the vagina to detect current cancer, introduced by Georgios Papanikolaou in 1928, to prevention of cancer through HPV genotyping, with or without cervical cytology. Testing options, recommendations, and guidelines have changed at a dizzying rate in recent years, and will continue to evolve. Experts are still debating optimum screening based on current techniques, and will need to further debate the improved methods for abnormality triage that are in development. HPV genotyping has not been studied enough in older women to abandon cytology, but "cotesting" with both HPV DNA and cytology is wise. HPV testing detects adenocarcinoma and its precursors better than cytology alone, and adenocarcinoma is relatively more frequent at older ages. Updated guidelines are available from the American Society for Colposcopy and Cervical Pathology (www.asccp.org).

ACOG and other organizations recommend discontinuing cervical screening after appropriate criteria are met. The patient should be age 65 or older, low risk, and have had adequate negative screening. Adequate is defined as three consecutive negative cervical cytology tests or two negative cotests in the past 10 years, the most recent of which was within the past 5 years. Ideally the final test would include HPV genotyping to minimize the chance of adenocarcinoma, but this is not a specific recommendation. Women older than 65 should continue with screening until these criteria are met. Having a new sexual partner does not necessitate additional screening.

Screening of women who have undergone a total hysterectomy (*corpus et cervix uteri*) is not recommended unless the hysterectomy was performed for cancer or the woman is a DES daughter. The positive predictive value of vaginal cuff cytology after hysterectomy for benign disease is approximately zero. Many women do not know whether their hysterectomy was total or supracervical (*corpus* alone). This can be determined at the initial pelvic examination. If a cervix is unexpectedly discovered, adequate screening should be performed before discontinuation.

It may be premature to recommend against screening a population with a much higher case-fatality rate. A case-control study estimated that 36% of cervical cancer deaths in women 55 to 79 years old could have been avoided by screening. Cervical cancer screening discontinuation guidelines are based on public health statistical modeling and cost concerns. As such, they do not necessarily apply in all cases. Discontinuation at any age because of medical issues is appropriate. Likewise, continued screening in concerned individuals is medically appropriate, albeit with a greater chance for unnecessary interventions than for benefit. Symptom investigation is not equivalent to screening. Although neither cytology nor HPV genotyping sufficiently evaluates signs or symptoms, these tests are appropriate as part of the initial evaluation.

Risk factors for cervical cancer include an abnormal Pap smear within the past decade, a history of moderate or severe CIN (CIN 2 or 3) within the past 20 years; a history of cervical, vaginal, or vulvar cancer; immune suppression; and DES exposure in utero. These groups are excluded from major society guidelines for lengthening screening intervals and discontinuation, but without sufficient alternative recommendations. Annual screening should continue for at least 20 years following successful treatment for CIN 2+. Women infected with human immunodeficiency virus (HIV) should continue annual screening indefinitely. Other causes of immune suppression including solid organ transplant, autoimmune disorders, treatment with glucocorticoids, and chronic antineoplastic therapies are not addressed. The relevance of DES exposure in utero to cervical or vaginal cancer risk in advanced age is uncertain. Although ACOG recommends continuing annual internal pelvic examinations indefinitely in DES daughters, it does not specifically address cervical or vaginal cytology.

CORPUS UTERI AND VAGINAL BLEEDING

Benign Conditions of the Uterus

Both the uterus and leiomyomata (fibroids) shrink after menopause. A palpably large uterus (navel orange or grapefruit sized) is unusual. Previous medical records would probably clarify whether this is a new finding. If unclear, sonographic evaluation would inform the need for further evaluation. Uterine tenderness is also unusual. Bacterial endometritis is uncommon, but occurs even in the absence of uterine manipulation. It is usually associated with a purulent, odorous discharge and/or bleeding.

Uterine Cancer

Ninety percent of uterine cancers originate in the endometrium. Endometrial cancer is the most common gynecologic malignancy in developed countries and the second most common in developing countries. It accounts for 7% of all cancers in women in the United States. The mortality rate has been declining slowly, but more than 10,000 women still die annually in the United States of this disease (see **Table 42-3**). Incidence rates in Europe and North America have risen since the 1980s, possibly related to increases in obesity and life expectancy with a concomitant decrease in birth rates. Three-fourths are type I, endometrioid adenocarcinoma. Type II is more aggressive and characterized by clear cell and papillary serous tumor histologies. Papillary serous carcinoma accounts for only 10% of uterine cancers but 40% of uterine cancer deaths.

Type I endometrial cancer is associated with traditional risk factors related to estrogen abundance and inadequate progestin. It tends to present at an earlier stage and younger age than does type II. Risk factors include early menarche and late menopause, obesity, chronic anovulation, type 2 diabetes, hypertension, and nulliparity. Pregnancy, lactation, hormonal contraceptives (including a progesterone-releasing intrauterine device), and postmenopausal hormone therapy with continuous (not intermittent) progestins are protective historical factors. Pathogenesis and risk factors for type II endometrial cancer are less well understood. Although the effect size of risk and protective factors is stronger in most studies for type I cancer than for type II, the factors are surprisingly similar. Risk factors include body mass index, early menarche, and diabetes; protective factors are higher parity, oral contraceptive use, and cigarette smoking.

Endometrial cancer is the most common sentinel cancer in Lynch syndrome, an autosomal dominant condition caused by germline mutations in mismatch repair genes. Lynch syndrome accounts for 2% to 5% of endometrial cancers and is more associated with younger age and type I histomorphology, but not reliably so. The question of universal versus selective genetic screening in endometrial cancer patients remains to be resolved. The 2014 Society for Gynecologic Oncology recommends that “all women who are diagnosed with endometrial cancer should undergo systematic clinical screening for Lynch syndrome (review of personal and family history) and/or molecular screening. Molecular screening of endometrial cancers for Lynch syndrome is the preferred strategy when resources are available.”

Interest in endometrial cancer prevention is growing, centering on interventions for obesity and diabetes, such as lifestyle changes and use of metformin. Metformin may directly inhibit endometrial cancer cell proliferation in addition to its other benefits. Progestins could theoretically prevent many endometrial cancers in obese women, but this has not yet been adequately studied. As obesity prevalence peaks in the 65 to 74 year age range, geriatrics practitioners will likely become key in endometrial cancer prevention strategies.

A hysterectomy with bilateral salpingo-oophorectomy, lymph node sampling, and tumor debulking is required for endometrial cancer staging and is the mainstay of treatment. Radiation and/or chemotherapy may be used adjunctively or in women who are too frail to undergo surgery. Overall 5-year survival is estimated at 82%, since bleeding usually leads to early diagnosis. Older age is associated with a worse prognosis because more aggressive tumors are relatively more common, as well as due to comorbidity, late diagnosis, and lack of aggressive treatment.

Malignant lesions of the myometrium include leiomyosarcoma and other sarcomatoid tumors. These do not typically cause bleeding in early stages, and may only be detected by the presence of an enlarging uterus or pelvic mass, or be discovered after hysterectomy. Incidence of leiomyosarcoma peaks in the sixth and seventh decades. They are aggressive tumors with high metastatic potential. Treatment involves surgery, chemotherapy, and radiation. Extension of tumor beyond the confines of the uterus is associated with a poor prognosis.

Approach to Vaginal Bleeding

Abnormal vaginal bleeding occurs in up to 20% of postmenopausal women, 10% to 20% of the time due to endometrial hyperplasia or neoplasia. Studies invariably analyze “postmenopausal” as one group, so these statistics misrepresent the risks in older women. Older women bleed less often, but older age increases the risk of malignancy

and of a higher-grade cancer. Although most women with postmenopausal bleeding will be referred to a gynecologist, a focused history and examination will ensure the best referral. A rectal polyp, urethral mucosal prolapse, or neglected pessary may be discovered.

All pelvic bleeding sources should be screened out, including hematuria, hematochezia, vulvovaginal pathology, and trauma (**Table 42-4**). Examination generally begins with the breast and abdomen, including axillary, supra- and infraclavicular, and inguinal lymph nodes. External genitalia, vagina, and cervix are inspected for ulcerations, atrophy, abrasions, polyps, etc. If the cervix appears normal, cancer screening with both cytology and HPV genotyping is advisable unless recently performed. Bimanual and rectal examinations will help rule out pelvic masses, tissue induration, and rectal pathology.

TABLE 42-4 DIFFERENTIAL DIAGNOSIS OF VAGINAL BLEEDING IN OLDER WOMEN

Uterus *(corpus uteri)*	Endometrial atrophy Endometrial proliferation from estrogen stimulation Endometrial polyp Endometrial hyperplasia Endometrial cancer Endometritis Myometrial cancer
Cervix *(cervix uteri)*	Cervical polyp Cervicitis Cancer
Vagina	Atrophy Infection Cancer Trauma Foreign body Prolapse with abrasion
Vulva	Ulcerations Excoriations Cancer Trauma
Urinary tract	Urethral caruncle Urethral mucosal prolapse Hematuria
Gastrointestinal tract	Rectal polyp Rectal prolapse Hemorrhoids Hematochezia
Other (rare causes)	Oviduct cancer Ovarian cancer Metastatic nongynecologic cancer Endometriosis
Systemic illness	Coagulation disorder Hepatic cirrhosis
Iatrogenic	Anticoagulation Estrogen therapy

Regardless of other findings, the endometrium must be evaluated with a biopsy or transvaginal ultrasound. Office biopsy can have greater than 99% sensitivity, but not all devices achieve this. Sonographic sensitivity depends on whether a 3-, 4-, or 5-mm endometrial thickness is used to define abnormal, which then requires biopsy. Defining greater than 5 mm as abnormal can miss up to 10% of cancers. Lowering the acceptable thickness to 3 mm or less increases sensitivity to 98%. ACOG recommends against proceeding immediately to biopsy at an intermediate cutoff of 4 mm or less. At any cutoff level, the cancers missed tend to be the more aggressive type II, for which age is a risk factor. Therefore a biopsy for tissue diagnosis is preferable to sonography to evaluate the endometrium in older women. Persistent or recurrent bleeding requires a more thorough evaluation without delay.

No guidelines have been established for the evaluation of vaginal bleeding in frail, impaired older women. Even if aggressive treatments are not an option, palliative management improves when the disease process is understood. Evaluation of vaginal bleeding including biopsy can always be recommended, guided by clinical judgement and the patient's wishes.

OVARY AND ADNEXAL MASSES

Benign Conditions of the Ovary

Menopause occurs when the ovary ceases its cyclic reproductive function and shrinks to an average volume of less than 4 cm^3. It continues to be an important source of androgen production, but not of estrogen. Functional cysts, normally associated with development of mature ova, still occur fairly often after menopause. These generally resolve without intervention. Benign lesions are overwhelmingly epithelial tumors, usually cystadenomas. Tumors may also arise from stromal or germ cells, but most of these occur at younger ages. An endometrioma may persist indefinitely, but is unlikely to grow or become newly symptomatic in older women.

Ovarian Cancer

Each year 22,000 women in the United States are diagnosed with epithelial ovarian cancer and 15,500 women die of this disease. The median age at diagnosis is 63. The age-specific incidence peaks at age 80 to 84, and subsequently plateaus. Survival rates are poor primarily because of diagnosis at late stages (see **Table 42-3**). Initial symptoms are nonspecific, such as abdominal or pelvic pain, bloating, urinary complaints, and constipation. It is now appreciated that early-stage cancers are often symptomatic. In retrospect, most ovarian cancer patients have had symptoms for several months prior to diagnosis. While a transvaginal ultrasound and CA-125 blood test perform poorly as screening tests in low-risk women, they are useful to rule out ovarian cancer when abdominal, pelvic, gastrointestinal, or urinary symptoms are present. Early evaluation of symptoms has not been proven to improve survival, but some evidence suggests it identifies more women with completely resectable disease. Genetic testing is evolving rapidly. It is now thought that approximately 25% of ovarian cancers have a germline mutation.

The vast majority of ovarian malignancies in older women are epithelial. The paradigm of epithelial ovarian cancer pathogenesis has undergone radical changes in the past decade. Rather than arising from the ovarian cortex, most cancers are likely derived from the fallopian tube or the endometrium. Epithelial ovarian cancers are now divided into two broad categories. The relatively indolent type I tumors are comprised of low-grade serous, low-grade endometrioid, clear cell, and mucinous carcinomas, and Brenner tumors. Type II tumors are high-grade serous, high-grade endometrioid, and other aggressive carcinomas. While these new distinctions have few direct implications for geriatrics practice, they have expanded preventive surgical strategies. ACOG recommends performing incidental bilateral salpingectomy whenever possible. Older women already routinely undergo bilateral salpingo-oophorectomy incidental to abdominal hysterectomy, but not routinely during vaginal surgery. This should be considered in preoperative planning, but no data inform the decision.

Surgery is indicated for most women with ovarian cancer, even in advanced age, both for staging and improved survival with optimal tumor debulking. Treatment outcomes are better on average when the initial surgery is performed by a gynecologic oncologist rather than a general gynecologist, due to more complete staging and debulking. Having one surgery for diagnosis and partial treatment, then a subsequent one to finish the staging and treatment is associated with worse outcomes. This may have implications for referrals from a geriatrics practice.

Adnexal Mass

"Adnexa" is a plural word meaning "parts." *Adnexa uteri* refers to the fallopian tube and ovary. Adnexal masses can

be, accordingly, of either the tube or ovary, but many other gynecologic and nongynecologic pathologies masquerade as adnexal masses. Diagnosis of an ovarian mass requires excisional surgery, as any biopsy risks seeding the peritoneal cavity and needle track. However, imaging can obviate surgery in the majority of patients. Although the chance of malignancy is increased after menopause, most adnexal masses are benign.

Transvaginal ultrasound is the preferred imaging study for adnexal masses. Magnetic resonance imaging (MRI) is best suited to clarify the malignant potential if ultrasound is unreliable or cannot be performed transvaginally. When extraovarian disease is suspected or needs to be ruled out, computed tomography (CT) scan is the most reliable technique. Ultrasonography may be useful even when the adnexal mass was discovered on another imaging study, sometimes adding information that better characterizes the ovaries and uterus. For cysts that will be followed, it is best to measure size over time with the same imaging modality, and ultrasound is less expensive.

Simple cysts less than 10-cm diameter will resolve spontaneously in half of older patients, indicating they were functional cysts. Most of the persistent ones eventually excised are benign epithelial tumors. Complex ovarian masses, with loculations or solid components, comprise 3% of postmenopausal adnexal masses. These are more concerning for neoplasia, but up to half may also resolve spontaneously. If an asymptomatic simple cyst is smaller than 10-cm diameter on transvaginal ultrasound and the serum CA-125 is not elevated, the usual plan is to repeat these studies in 3 to 6 months. Indications for urgent gynecologic consultation include size greater than or equal to 10 cm, complex components, or an elevated CA-125.

HORMONES

Hormone Replacement Therapy

Estrogen and estrogen plus progestin hormone replacement therapy (HT) following menopause has a complex constellation of statistically small risks, mostly outweighed by other risk and protective factors, and benefits, which can usually be managed with nonhormonal alternatives. While initiation of HT after age 65 is contraindicated, continuation of HT taken since menopause must be decided on an individual basis. The major professional society recommendations that “Even though short-term use of hormone therapy may be useful for menopausal symptom relief, such as for vasomotor instability, long-term use of hormone therapy for chronic disease prevention is not warranted” does not inform management in the majority of older women still taking HT. In health-conscious women, the marginal risk of continuation is very small. However, given the association with stroke and cardiovascular events, most women over age 65 will choose to discontinue HT. The issue then becomes how to discontinue without suffering excessive menopausal symptoms.

Four randomized trials studying fewer than 300 women have evaluated abrupt discontinuation versus tapering over 2 weeks, 4 weeks, 4 months, and 6 months. Overall successful discontinuation rates were similar, but symptoms were generally greater in the abrupt groups. Roughly half of women tolerate sudden cessation, but do better with ongoing clinical support for up to 3 years. Others experience unacceptable vasomotor symptoms, insomnia, irritability, short-term memory loss, or fatigue and resume HT. Anecdotally, tapering over an even longer time would effect greater success with fewer symptoms. Unless urgent, this can be done as slowly as necessary, reducing the dose every few months or annually. When the lowest commercially available dose has been reached, the taper can be continued dropping one weekly dose at a time, once a month or as tolerated. Vasomotor symptoms can be ameliorated with progestins, neuromodulating medications, low-dose vaginal estrogens, and a few other medications.

Occasionally an older woman not taking estrogen experiences new-onset vasomotor symptoms. Pertinent history includes onset, frequency, duration, timing during the day or night, facial erythema, perspiration, flushed feelings, associated activities, and her symptoms at the time of menopause. Medications or supplements are often the culprit. While hormone-related vasomotor symptoms do not suddenly arise years after a decline in estrogen, it is unclear in some cases whether hormones could be involved. A trial of estrogen therapy for 1 to 3 months can be informative or educational. Transdermal administration would minimize the risk of a vascular event.

UROGYNECOLOGIC AND PELVIC FLOOR SUPPORT ISSUES

A variety of bladder and pelvic floor support disorders can occur in older adults. Urinary incontinence and urinary tract infections are among the most common. These are covered in more detail in Chapters 53 and 127, respectively. This section will focus on several specific conditions common in female urology and urogynecology including urethral

disorders such as urethral caruncle, urethral cancer, urethral stricture, and urethral diverticulum; interstitial cystitis and painful bladder syndrome; and POP.

Urethral Disorders

Several disorders of the female urethra occur with greater incidence and prevalence in older women compared to their younger counterparts. Urethral caruncle generally appears as a polypoid red mass protruding from the urethra at the 6 o'clock position. This is often asymptomatic and identified incidentally on physical examination. Some patients may notice it and are often concerned for possible malignancy. Urethral caruncles are typically soft to palpation, although they may bleed due to irritation. They represent a prolapse of the urethral mucosa with possible loss of support of the periurethral fascia. Topical estrogen is generally effective, and may lead to reduction in size or complete involution of the caruncle. In contrast, urethral cancers in women may present with bleeding and are typically hard or firm to palpation. The tumor can extend proximally toward the bladder neck, or into the vagina. Treatment is typically surgical, although radiation may also be used in select cases or for palliation.

Urethral strictures in women are uncommon. Surgical excision and reconstruction is the most effective form of therapy. Urethral dilation should be avoided in women and is not particularly effective for long-term therapy. There are no data to support routine urethral dilation for treatment of urinary tract infection or voiding dysfunction in most women. Urethral diverticulum results from an outpouching of tissue in the urethra in association with a defect in the midline fusion of the urethral plate. Women often experience the "3-Ds" of dysuria, dyspareunia, and dribbling incontinence. Surgical excision with urethral closure or reconstruction is typically indicated. Women with urethral diverticulum are at somewhat increased risk of urethral malignancy.

Interstitial Cystitis and Painful Bladder Syndrome

Interstitial cystitis (IC), sometimes called painful bladder syndrome (PBS), is a chronic condition of the bladder typically associated with a constellation of symptoms including urinary urgency, frequency, and pelvic pain. Patients generally experience worse pain with bladder filling, which is relieved at least temporarily by voiding. Pain is a hallmark symptom, and helps to differentiate the condition from overactive bladder (OAB) and other forms of lower urinary tract dysfunction. The exact etiology of IC is unknown although theories including autoimmune components, direct chemical irritants in the urine, effects from inflammatory mediators, and defects in the bladder epithelial barrier layer are known. Other conditions that should be considered in cases of possible IC include bladder cancer, bladder carcinoma in situ, urinary tract infection, and bladder stones. Continued symptoms in the context of persistent negative urine cultures should prompt the clinician to consider IC.

Diagnosis can be made on the basis of clinical symptoms. Cystoscopy with hydrodistension of the bladder under anesthesia is a useful diagnostic tool, and may also be therapeutic for many patients. Reduced bladder capacity and visual changes including petechial hemorrhage are commonly seen in cases of IC. Ulcerations of the bladder mucosa occur less commonly, but may represent more severe disease. Cystoscopy also offers the clinician the opportunity to visually examine the bladder to rule out other serious conditions such as bladder cancer, particularly in older women where the rates of bladder cancer increase compared to young women. Bladder wash cytology and biopsies may also be used to help aid in the diagnosis of bladder cancer. Patients may be treated for IC or PBS without cystoscopic confirmation of the condition, but in older patients it is wise to eliminate other potential pathologies.

Successful treatment of IC and PBS often requires multimodal therapy. Diet modification includes avoiding trigger foods and beverages including caffeine, carbonated drinks, alcohol, spicy and acid-rich foods, and tomatoes. Medical therapies include low-dose antihistamines, antispasmodics, and anticholinergic medications. Low-dose tricyclic antidepressant medications may be used for this purpose, but they should be used with caution in older women who may be at higher risk for side effects. Pentosan polysulfate is a low-molecular-weight heparin derivative that is administered orally. It is excreted in urine and helps to rebuild the glycosaminoglycan layer of the bladder. Instillation of medications inside the bladder including anti-inflammatory agents, heparin, lidocaine, and others can also be useful. Injection of botulinum toxin in the wall of the bladder for chemodenervation can be useful particularly for treatment of associated urinary urgency and frequency. The effect generally lasts for up to 9 to 12 months, and may need to be repeated at that time. Patients must understand the potential for urinary retention after this type of therapy, which could require clean intermittent catheterization at least temporarily. Surgical therapy with removal of the bladder is generally avoided because symptoms may recur even in the absence of the bladder.

Pelvic Organ Prolapse

Prolapse of the genital organs can be quite bothersome for older women. Incidence and prevalence rates of POP increase with advancing age. Risk factors include prior hysterectomy, obesity, smoking, and poor tissue quality. Several different types of prolapse occur depending on the involved anatomy. Patients may experience a bulging sensation from the vagina, or may complain of pressure or discomfort in the pelvis or lower back. Bleeding and discharge are also common symptoms, particularly in women with large prolapse extending out of the vaginal canal, and may be associated with erosion or ulceration of the vaginal mucosa.

Evaluation of Pelvic Organ Prolapse

Clinical evaluation includes careful history and physical examination (**Table 42-5**). Symptoms should be identified to help gauge the degree of bother experienced by the patient, which in turn can help determine the types of treatment that can be considered. In patients with little symptomatic bother and minimal other signs or symptoms, observation may be adequate. Careful pelvic examination is critical in making the correct diagnosis of POP. Prolapse of the anterior vaginal wall is a cystocele, and the posterior vaginal wall is typically a rectocele. Loss of support of the vaginal apex may include small bowel which is known as an enterocele. Uterine prolapse may also occur due to loss of support of the cardinal or uterosacral ligaments. Complete vaginal eversion may occur in women with a prior hysterectomy, or "procidentia" if the uterus is in situ.

TABLE 42-5 EVALUATION AND MANAGEMENT OF PELVIC ORGAN PROLAPSE

History
Vaginal bulge, pressure or pain (often worse in late afternoon or evening)
Vaginal bleeding or discharge
Urinary frequency or incontinence
Difficulty initiating urinary stream
Sense of incomplete bladder emptying
Constipation
Fecal incontinence
Need to elevate the bladder to urinate or "splint" the perineum or rectum to defecate
Physical examination
Vaginal bulge
Mucosal abrasions or ulcerations
Degree of descent of prolapse
Does prolapse extend beyond midpoint of vagina
Does prolapse extend beyond the vaginal introitus/hymenal ring
Does prolapse increase with maximal Valsalva or cough effort
Anterior vaginal wall, posterior vaginal wall, vaginal apex
Cervix and uterus—support and mobility
Urethra and bladder neck—support and mobility
Postvoid residual urine volume and urinalysis
Management
Nonsurgical
Observation
Pessary
Estrogen cream -to prevent and treat ulcerations and improve mucosal quality
Barrier creams or ointments to protect vaginal mucosa
Truss-strong elastic support
Surgical-reconstructive

	Transvaginal
	Transabdominal
	Laparoscopic/robotic
	Uterosacral or sacrospinous ligament fixation of vaginal vault
Surgical-vaginal obliterative	
	Colpocleisis
	Colpectomy

Physical examination is important for complete assessment. On simple inspection, it can be difficult to differentiate the portion of the vagina involved in the prolapse. A single-blade speculum is useful for this purpose. The speculum is initially inserted to depress the posterior vaginal wall. The speculum is then reinserted in the reverse position to elevate the anterior vaginal wall allowing inspection of the posterior compartment for evidence of rectocele. Asking the patient to cough and Valsalva can help to demonstrate prolapse that may increase with abdominal straining. However, some older women cannot generate adequate pressure with this technique. It can be useful to also examine the patient in the standing position if possible, as some prolapse may only be evident with standing.

Cystocele occurs because of a weakness of the anterior vaginal wall fascia. The bladder descends into the space, and in some cases may protrude beyond the hymenal ring. Cystoceles may or may not be associated with stress urinary incontinence. Some women with large cystoceles may experience difficulty voiding due to angulation of the urethra or poor bladder contraction (**Figure 42-4**). In some cases, women with large cystoceles may report having to put their fingers in the vagina to elevate the tissue in order to straighten out the urethra to urinate. Despite this, high-grade obstruction in women is rare, and development of upper tract deterioration with hydronephrosis and renal insufficiency is uncommon. Hydroureter and hydronephrosis can occur if there is substantial ureteral kinking at the insertion into the bladder in cases of complete vaginal vault prolapse. This is more likely if the uterus is present. Serum blood urea nitrogen and creatinine level and renal ultrasound are useful in determining the extent of renal impairment.

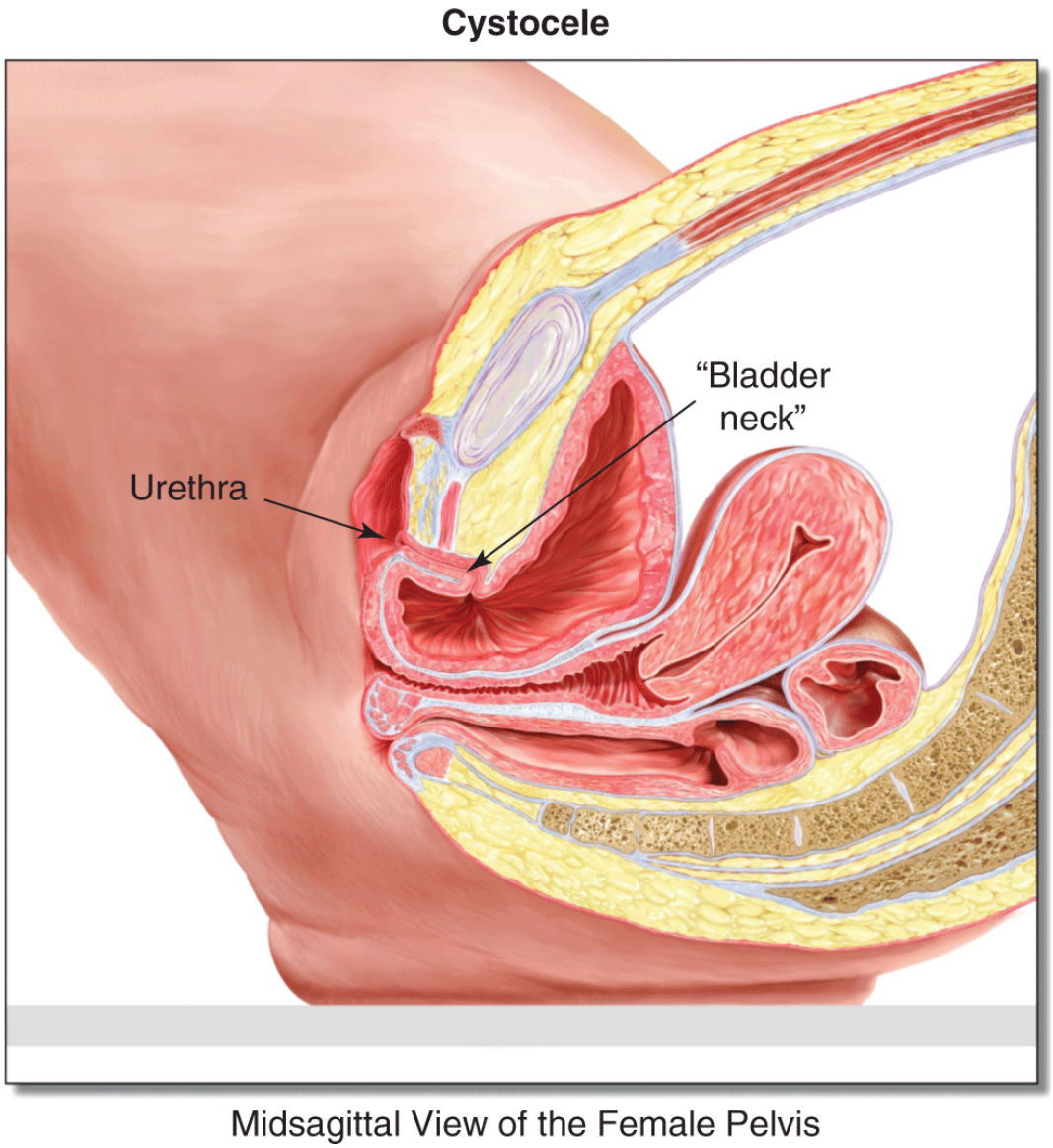


FIGURE 42-4. Sagittal view of a cystocele. Note how a cystocele can cause angulation of the urethra and contribute to symptoms of voiding difficulty and urinary retention.

A rectocele is a protrusion of the rectum through the posterior wall of the vagina, and is caused by weakness in the perirectal fascia. Some patients may experience difficulty with defecation, including an increased sense of pressure or need to strain. Some women describe needing to "splint" or press on the posterior vaginal wall or perineum in order to completely evacuate their stool.

An enterocele is a herniation of small bowel and peritoneum through the apical vagina or between the uterosacral ligaments and rectovaginal space. It is the only true hernia among the various forms of POP. It is more common in women who have undergone prior hysterectomy. However, it can be present in any posterior vaginal wall prolapse, and rarely in anterior compartment prolapse.

Rectal prolapse involves protrusion of the rectum through the anal sphincter with tissue extending beyond the anal verge. It may or may not be associated with hemorrhoids. Symptoms of rectal prolapse can include pain, bleeding, or problems with defecation. Many patients experience both fecal incontinence and constipation. Careful examination is needed to determine if the rectal prolapse can be reduced. In cases where reduction is not possible, tissue incarceration and necrosis may develop. Patients with rectal prolapse should be referred to a colorectal surgeon or gastroenterologist for additional evaluation and treatment.

Several different systems have been designed to grade the degree of POP based on anatomic changes. The Baden-Walker system is commonly used in clinical practice, and classifies the degree of prolapse based on whether it extends beyond the midpoint of the vagina or beyond the vaginal introitus, when it is more likely to become symptomatic. The POP-Q system is more commonly used in research settings. It includes multiple anatomic measurements in relation to the vaginal introitus. In most systems, the hymenal ring is used to define the vaginal introitus. A clear understanding

and documentation of the extent of prolapse is useful for surgical planning and for following progress over time.

Treatment of Pelvic Organ Prolapse

Most treatments are aimed at reducing the prolapse back into the vaginal canal and correcting vaginal anatomy (see **Table 42-5**). Ulcerations of the vaginal mucosa may respond to topical estrogen therapy. Barrier compounds may also be helpful to reduce tissue irritation.

Treatment of POP may be surgical or nonsurgical, and depends to some degree on the amount of bother experienced by the patient. It also depends on overall health status, and goals of therapy. The main conditions necessitating definitive treatment or specialist referral include nonhealing ulcerations, bleeding, elevated postvoid residual urine volume causing recurrent infections, and hydronephrosis. If none of these are present and the patient is not particularly bothered by her symptoms, then reassurance and observation are appropriate. Application of estrogen cream once or twice a week is advisable for preventive care and can help reduce tissue irritation and ulceration. On other days, use of a topical barrier cream such as solid vegetable oil may be helpful. Some patients may find comfort in using supportive underwear.

Pessaries

Pessaries are the main nonsurgical therapy used in the management of POP. These intravaginal devices come in a wide range of shapes and sizes, and are designed to reduce the prolapse. When correctly fit, most women cannot feel the pessary when it is in place. Selection of specific pessaries is based on patient anatomy and the experience and preference of the clinician. A pessary that is too large may be painful and increases the risk for tissue erosion. A pessary that is too small will tend to fall out with ambulation or other activity. Topical estrogen cream is useful to reduce the risk of tissue erosion and irritation. The pessary should be periodically removed and cleaned. If a patient is unable to do this herself, she should be seen by a clinician at least every 1 to 3 months for pessary cleaning and inspection of the vaginal tissues. Neglected pessaries can cause odor and increase the risk for infection or erosion. Case reports have shown that neglected pessaries can erode into the peritoneum, rectum, or bladder. Careful follow-up for pessary care is particularly important in older women with any degree of cognitive impairment to prevent forgetting that the pessary is in place.

Pessaries may also be used for the treatment of urinary incontinence. Special designs include a “button” that is placed under the urethra to increase outlet resistance and help reduce stress incontinence with increased abdominal pressure. Rarely women may need to remove the pessary in order to void to completion. Incontinence pessaries may be useful to identify women who might benefit from surgical correction of stress incontinence. A variety of urethral plugs and patches have also been designed for treatment of female stress urinary incontinence, although patients often find them difficult to use and compliance is generally low.

Surgeries

Surgical management of POP includes either reconstructive or obliterative procedures. Reconstructive options aim to reduce the prolapse and reestablish normal vaginal anatomy. Examples include anterior and posterior colporrhaphy and enterocele repair. Prolapse of the vaginal apex may require more advanced repair techniques. These include either open or robotic and laparoscopic uterosacral or sacrospinous ligament fixation, in which the apex of the vagina is sutured to a fixed point in the pelvis. In some cases, mesh or other supporting material is needed to perform this type of repair. Potential complications include mesh erosion through the vaginal wall or other surrounding structures. Colpocleisis is an obliterative procedure in which the prolapse is reduced and the vagina is essentially closed to prevent recurrence. It is technically easier and may offer an option for older women with substantial comorbidity who may not be good candidates for more involved reconstructive procedures. However, patients need to be carefully counseled that penetrative sexual activity will not be possible after colpocleisis. Studies have shown that in carefully selected patients, satisfaction rates are high with low rates of regret regarding the procedure. Rectal prolapse is typically treated surgically with either reduction or fixation, or excision of the prolapsed portion of the rectum. Treatments to prevent chronic constipation are indicated after all types of POP repair to avoid significant straining with bowel movements and prevent prolapse recurrence.

SUMMARY

Although gynecologic issues comprise a small part of geriatric care, large impacts can be made on function and quality of life. A thorough personal and family history will guide cancer prevention and detection. An initial pelvic examination will provide the basis for understanding symptoms and anticipating problems, potentially for years to come. Querying problems will encourage the patient to voice symptoms when they arise. Persistence in addressing chronic incontinence and pelvic floor issues will prevent hopelessness and isolation. Ensuring adequate cervical cancer screening, early recognition of endometrial and vulvar cancer, and early investigation of abdominopelvic complaints to rule out ovarian cancer will reduce disease burden.

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Chapter 43

Sexuality, Sexual Function, and Androgen Replacement Therapy in the Aging Male

J. Lisa Tenover

Learning Objectives

- Identify the factors affecting sexual function in the older man, including changes in sexual physiology, coexisting medical problems, and psychosocial issues.
- Describe the initial evaluation of erectile dysfunction (ED) in an older man, using knowledge of possible etiologies to guide evaluation and treatment recommendations.
- Recognize the components necessary for the diagnosis of testosterone deficiency in an older man and be able distinguish the expected outcome(s) of testosterone replacement therapy.

Key Clinical Points

1. **Male sexual activity declines with aging, due to social factors and changes in physical and psychological health; yet many older men are sexually active into late life.**
2. **The most common causes for ED in older men are vascular in origin, not hormonal, and thus current predominant therapies are phosphodiesterase-5 (PDE-5) inhibitors and vacuum devices.**
3. **The diagnosis of testosterone deficiency in an older man requires both low testosterone levels and symptoms of hypogonadism. Consideration for testosterone replacement therapy should involve a careful discussion of possible benefits and risks.**

Sexuality is a basic human need which exists throughout life in one form or another and is a significant component to quality of life of many older individuals. Although 70% of adult patients in a large sample study considered sexual matters to be an appropriate topic for a general clinician or geriatrician to discuss, sexual problems are noted in fewer than 2% of primary care physicians' notes. It is not easy to find physicians and other health care providers who are knowledgeable about sexuality in general and among the aging population in particular. Sexuality and sexual function in the aging female is addressed in Chapter 41. Sexuality, sexual function, and dysfunction in the aging male will be addressed in the first part of this chapter, with the second part of the chapter being devoted to androgen replacement therapy in the older man.

SEXUALITY AND SEXUAL FUNCTION IN OLDER MEN

Sexual Behaviors

Idealized societal concepts of older people do not include sex or the facility for sexual function. A poll conducted by the National Council on Aging, regarding attributes of people over 65 years, reported that older persons were frequently thought of as being "warm and friendly" (74% of respondents) or "wise from experience" (70% of respondents), but being "sexually active" was attributed to older persons by only 5% of the survey respondents. Nonetheless, numerous cross-sectional and longitudinal epidemiologic studies of sexuality and aging report that,

although sexual activity decreases with age, many older adults are sexually active. These surveys have reported that, by all measures evaluated, men have a stronger sex drive than women; sexual activity, good-quality sex life, and interest in sex were higher for men than for women and this gender gap widened with age. Sexual expression can encompass many forms, including sexual intercourse, oral sex, masturbation, touching and caressing, physical appearance, erotic stimuli (reading, movies), and fantasies (daydreams), but most study data involve the first three components.

Figure 43-1 depicts the age-related prevalence of male sexual activity from two large studies, the University of Chicago study of 3000 US adults, aged 57 to 85, and the Health in Men Study of over 3000 Australian men, ages 75 to 95. Both studies defined sexual activity as activity with a partner and occurring within the 12 months prior to the data collection. In these studies, the likelihood of sexual activity with a partner did decline with age, but nearly 40% of men at age 75 to 80 reported some sexual activity, and 54% of these reported sex at least two to three times a month.

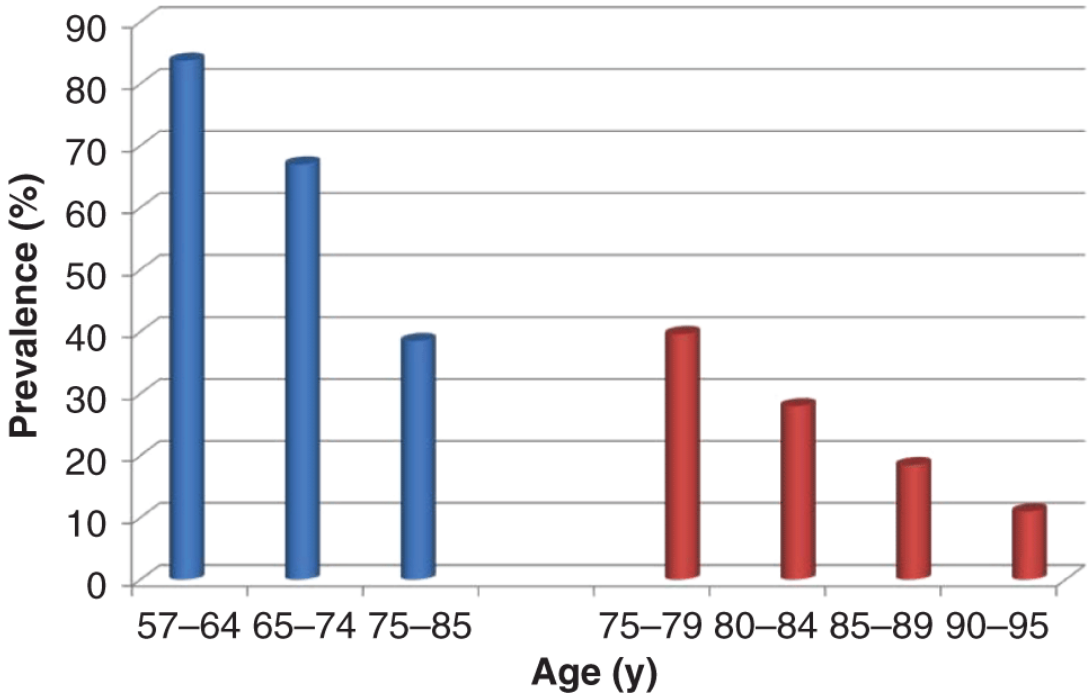


FIGURE 43-1. Prevalence, by age group, of male sexual activity with a partner in previous 12 months as obtained from a survey of a probability sample of 3000 US adults age 57 to 85 (Blue bars, data from Lindau ST, Schumm LP, Laumann EO, et al. A study of sexuality and health among older adults in the United States. *N Engl J Med*. 2007;357:762) and from a population-based cohort study of 3274 men age 75 to 95 (Red bars, data from Hyde Z, Flicker L, Hankey GJ, et al. Prevalence of sexual activity and associated factors in men aged 75 to 95 years. *Ann Intern Med*. 2010;153:693).

Reasons reported by older men for not engaging in sexual activity are varied and involve social factors and physical and psychological health. In addition to lack of partner availability (no partner, partner not interested, or partner with physical limitations), one of the other main factors is health status, both psychological and physical. Psychological conditions, such as anxiety and depression, can affect libido and sexual function. There are many medical problems that are linked to sexual dysfunction. Diseases such as arthritis, especially when it involves the hips and pelvis, can affect sexual positions, endurance, and comfort. Urinary incontinence, with or without the need of urinary catheters, or the presence of ostomies can affect body image and may raise physical barriers to sexual activity. Chronic diseases, such as diabetes, stroke, or cardiovascular disease also will have significant impact, especially in regards to erectile function in the aging male, as will be discussed later. Older men across all age ranges who report excellent or good health are more likely to be sexually active than men who report fair or poor health. Medications also may have an impact on the level of sexual activity and function, particularly for men, as many medications can impact erectile function; this will be discussed in detail later in this chapter.

Changes in Male Sexual Physiology With Age

Overall there is a gradual slowing of sexual physical response time as men age. It takes more time to achieve sexual arousal, complete the sexual act, and become rearoused for further sexual activity. **Table 43-1** lists the specific changes in the male sexual response cycle with age. Some of the changes have been shown to be impacted, at least in part, by

low testosterone levels, while others are unaffected by hormone levels. The aging male may need reassurance that slowing of the sexual response is normal and predictable in order to avoid the fear and anxiety that may ensue without such information. Lengthening of the period of foreplay is one approach to adapting to these normal aging changes.

TABLE 43-1 CHANGES IN THE MALE SEXUAL RESPONSE CYCLE WITH AGE

Lengthening of the excitement (plateau)
Decreased penile rigidity[a]
Longer interval to ejaculation (plateau) phase
Fewer and less forceful contractions of the urethra
Lower ejaculatory volume
Less well-defined sense of impending orgasm[a]
Shortening of the ejaculatory event and orgasmic phase[a]
Increased occurrence of resolution without ejaculation[a]
More rapid detumescence
Lengthening of the refractory period

[a]Aspects that may be somewhat affected by testosterone levels.

The Aging Male Homosexual

Older homosexual men have similar sexual problems as older heterosexual men, but may suffer additional problems. Homosexual older men can face discrimination when seeking health care, and only a minority of service providers is prepared to work with them. Additionally, these older men are likely to suffer stress while trying to find a partner, especially if their living situation changes and they move into assisted living facilities or nursing homes. More than 50% of lesbian, gay, bisexual, and transgender (LGBT) people surveyed in 2010 felt that nursing homes were not LGBT friendly; 59% of the surveyed individuals said they would prefer to live in a facility that specifically catered to people who did not identify as heterosexual. Specific organizations that address issues of aging gay and bisexual persons have formed across the country.

Unprotected sex occurs in approximately 10% of older homosexuals. Compared to younger homosexual men, older homosexual men get tested less often for sexually transmitted diseases, including testing for acquired immunodeficiency syndrome (AIDS). The incidence of AIDS is increasing in older men. Education about safe sex practices is important in the older population. Older males with a history of anal sex need to be regularly examined for anal cancer, as the prevalence increases in such persons.

Older male homosexuals should be encouraged to get advanced directives for health and to specifically designate their durable power of attorney for health care. This should facilitate the ability of their partners to make their health decisions.

Sex in Long-Term Care

While there is no reason to believe the desire for intimacy is lost on entering a residential long-term care facility, persons who live in nursing homes frequently have no opportunity for a private, social, or sexual life; many couples are separated due to the residential care admission. Federal regulations provide some right to privacy, but it is limited to married couples and to nursing homes that participate in federal Medicare and Medicaid programs. Specifically, the regulations state that (1) the nursing home resident has the right to share a room with his/her spouse when married residents live in one facility and both spouses consent; and (2) the resident has the right to privacy during a visit with his/her spouse. These regulations are not enforced uniformly, however, and the majority of long-term care staff possess minimal understanding about how to deal with the sexuality of their nursing home residents. Education programs for nursing staff around resident sexuality issues are important.

Additional barriers to sexual expression in long-term care include lack of a partner and physical or mental illness. Issues surrounding romantic liaisons between two unmarried residents in a nursing home can be especially problematic. Many ethical concerns can arise around the assessment of sexual behaviors in the residential care setting and whether the behaviors are “sexually inappropriate” or not. These include balancing a resident’s need for sexual expression against expectations and beliefs of caregivers and family members. If the sexual conduct involves one or

both persons who are cognitively impaired, then the individual's capacity to consent to sexual activity needs to be assessed. There is considerable variability by state in the definitions of capacity to consent to sexual activity. Sexual consent is complicated and involves knowledge, capacity, and voluntariness. There are no surrogate decision makers for sexual relations. Psychological evaluation for capacity to consent to sexual activity may need to be sought.

Sex and Dementia

Issues of sexuality are especially complex for those individuals who have cognitive impairment, as the diagnosis of dementia does not determine in which domains a person is capable of making decisions. Some men with dementia become impotent, but others remain quite interested and capable, and a few older men with dementia become hypersexual. Physicians of demented male patients need to ask the spouse about sexual issues, as the wife may be embarrassed to reveal sexual difficulties. If the problems are placed in the context of dementia, it can assist with discussion of coping strategies. Nonsexual ways of expressing ones' intimacy, such as touching, holding hands, and massages, might be suggested.

Inappropriate sexual behavior (ISB) can be seen in those with mild cognitive impairment, but more often occurs in persons with moderate to severe dementia. ISB occurs much more frequently in men. There is no universally accepted definition of ISB, but it has been described as sexually related activities or heightened sexual drive that interferes with function and is pursued at inappropriate times or with nonconsenting persons. Included in ISB are unwanted verbal remarks, unwanted touching, disrobing, public masturbation, unwanted sexual advances, and sexual aggression. ISB can cause conflict between a patient's autonomy and the preventing of psychological and physical trauma for the person and others. It impacts families, care providers, and, especially in long-term care facilities, may threaten others who might be unable or unwilling to give informed consent.

There are no established treatment protocols for ISB. Some environmental and behavioral strategies that have been tried include redirection, distraction, clothing modification, avoidance of external cues, and in long-term care facilities, provision of single rooms and for conjugal visits. Supportive psychotherapy for spouses and families can be helpful. There are no controlled trials of pharmacologic therapies for ISB, but medications that have been reported to reduce ISB include the selective serotonin reuptake inhibitors (SSRIs), venlafaxine, both first-generation and atypical antipsychotics, medroxyprogesterone, gonadotropin-releasing hormone (GnRH) analogues, cyproterone acetate, cholinesterase inhibitors, pindolol, and gabapentin.

SEXUAL DYSFUNCTION IN THE AGING MALE

Categories of Male Sexual Dysfunction

The major categories of sexual dysfunction in older men include ED, lack of interest in sex (low libido), performance anxiety, and inability to climax. ED is by far the most prevalent. ED (also called impotence) is defined as the inability to obtain and sustain a penile erection adequate for intercourse. Age alone is a significant risk factor for ED, and its incidence, prevalence, and severity increase with age. However, many older men do not lose the capacity for erections and ejaculation. Severe ED is estimated to be present in over 20 million men in the United States. In the Massachusetts Male Aging Study, a community-based study of middle-aged and older men, the reported incidence of any ED was 55% for men at age 60, and 65% for men at 70 years; the prevalence of total ED at age 70 was 15%. In a population-based prospective cohort study in Olmsted County, Minnesota, ED prevalence was 6% in men aged 50 to 59, 17% in men aged 60 to 69, and 39% in men aged 70 and older (**Figure 43-2**).

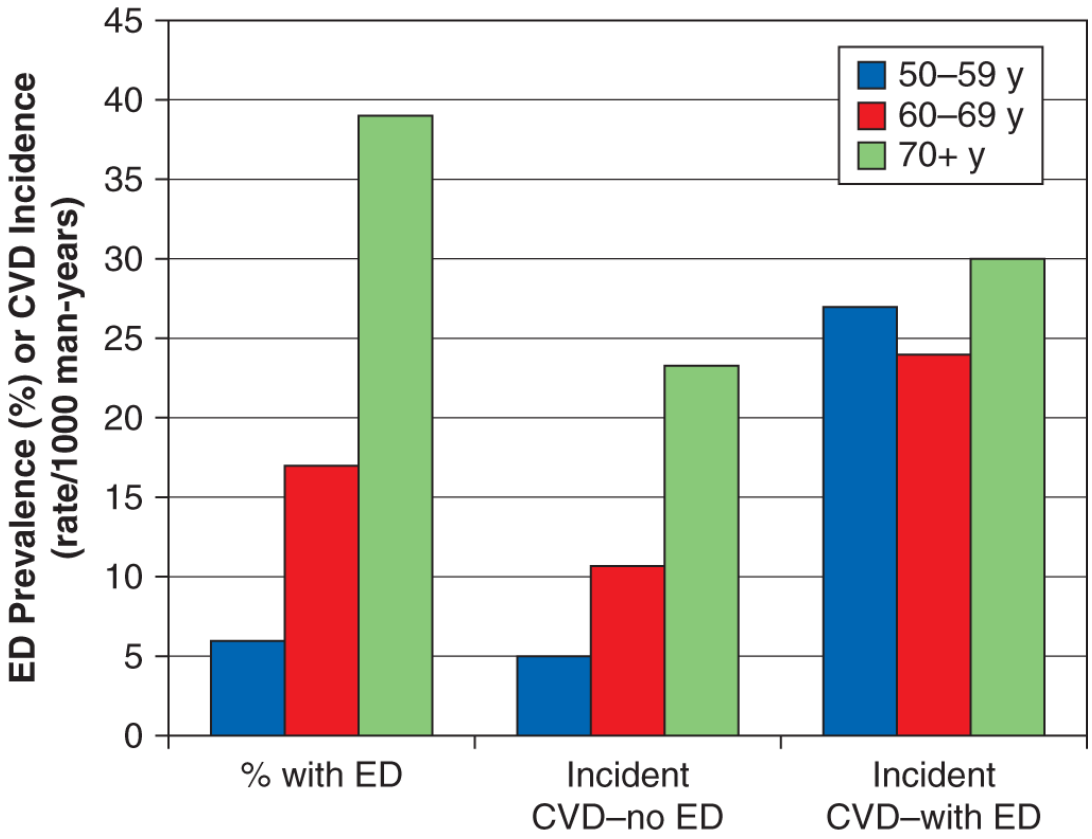


FIGURE 43-2. Prevalence, by age group, of erectile dysfunction (ED) from a longitudinal population-based study of community-dwelling men, and the 10-year follow-up incidence of cardiovascular events as a function of baseline presence or absence of ED. (Data from Inman BA, St. Sauver JL, Jacobson DJ, et al. A population-based, longitudinal study of erectile dysfunction and future coronary artery disease. *Mayo Clin Proc*. 2009;84:108.)

Libido, the enthusiasm for sex, or sexual desire, is dependent on learned responses, general health-related quality of life, and, to some extent, serum testosterone levels. As will be discussed later in this chapter, testosterone levels decline in men with normal aging, and some men may reach levels that are low enough to affect libido. However, testosterone replacement studies in hypogonadal men suggest that the level of testosterone needed to maintain libido is likely below the serum "normal" range for most men.

Performance anxiety is common in older men and often a result of equating masculinity with speed and magnitude of sexual activity. A man may become so preoccupied by his performance that his confidence and sexual capacity lessen, leading to ED. Depression and psychosocial stresses also are prevalent in older men and contribute to sexual problems. "Widower's syndrome," where a man fails to achieve erection after the death of spouse, is a reported entity.

Inability to reach climax or to resolve without ejaculation can occur. In the University of Chicago study, this occurred in about 16% in the 57- to 64-year age range, but increased to 33% in the 75-year and older age group.

Erectile Dysfunction

Physiology To better understand how diseases and medications impact erectile function, it is important to have at least a cursory understanding of the physiology of penile erection. An erection of the penis is obtained in three ways: through local sensory stimulation of the penile shaft and glans penis, through visual or auditory stimuli, and spontaneously during rapid eye movement (REM) sleep. As men age, erection becomes more dependent on physical stimulation of the penis and less responsive to visual and other nongenital stimulation, yet mechanical sensitivity of the penis decreases with age.

When the penis is flaccid, there is α-adrenergic–mediated vasoconstriction of arterioles and sinusoidal spaces of the corpora cavernosa. During erection, parasympathetic input results in vasodilatation, which leads to an increase in arterial blood flow and pressure in the cavernosal sinusoids, resulting in occlusion of the venous outflow system and penile erection. A number of neurotransmitters play a role in this process. Nitric oxide is released by penile endothelial cells and cavernous sinus nerves during sexual stimulation. This release of nitric oxide, along with other agents such as prostaglandins E1 and E2 (PGE1 and PGE2) and vasoactive intestinal peptide, results in smooth muscle relaxation

within the corpora, which leads to an erection.

Etiologies **Table 43-2** lists the major etiologies of ED. The prevalence of the specific etiology depends on the type of reporting center (primary care, urology, endocrinology). Vascular disease, which includes both atherosclerotic arterial occlusive disease and corpora cavernosal venous leak, is the most common cause of ED across referral centers. The likely mechanism is that penile hypoxia leads to replacement of corpora smooth muscle by connective tissue, which results in impaired cavernosal expandability and inability to compress subtunical venules.

TABLE 43-2 MAJOR ETIOLOGIES OF ERECTILE DYSFUNCTION

1. Vascular disease
   Atherosclerotic arterial occlusive disease, corpora venous leak
2. Neurologic disease
   Neuropathy, cord injury, stroke, multiple sclerosis, temporal lobe epilepsy, Parkinson disease
3. Diabetes mellitus
   Both vascular and neurologic effects
4. Other systemic diseases
   Renal failure, chronic obstructive pulmonary disease
5. Hormonal
   Hyper- and hypothyroidism, hypercortisolemia, severe hypogonadism
6. Urologic
   Lower urinary tract symptoms (LUTS) due to BPH
7. Surgery/trauma
   Prostate cancer surgery, Peyronie disease
8. Lifestyle related
   Obesity, smoking, heavy alcohol use
9. Medications
10. Psychogenic
    Depression, anxiety

The vascular endothelium of the penis modulates vascular tone and blood flow to the penis and releases factors that affect the contractility of the vascular smooth muscle. In this response cardiovascular disease (CVD) and ED share etiologies, having many of the same risk factors and similar pathophysiology (endothelial dysfunction). Diabetes mellitus, hypertension, hyperlipidemia, and smoking are major risk factors for both ED and CVD. The penis is a high blood flow system during erectile function, so ED may be an early sign of vascular inadequacy on the basis of atherosclerosis. In fact, numerous studies suggest that ED is one of the sentinel symptoms of occult CVD. ED is clearly associated with CVD and the symptoms of ED often precede the clinical consequences of CVD, such as myocardial infarction or stroke. Presence of ED is associated with increased risk of incident CV events, but this effect is much more pronounced in men under the age of 70 (see **Figure 43-2**). The predictive value of ED for subsequent CVD in men less than 70 years is equal to or greater than the risk effect of family history of myocardial infarction, cigarette smoking, or hyperlipidemia. Therefore, men under the age of 70 with ED of suspected vascular etiology should be provided with appropriate screening and treatment for CVD.

Men with uncontrolled hypertension can develop ED as well, and ED can improve when the blood pressure normalizes. Men with mild to moderate hypertension need not restrict themselves sexually, but because systolic blood pressure can increase significantly with sexual activity, those with uncontrolled or severe hypertension should postpone sexual activity until blood pressure is controlled.

Diabetes mellitus is the most common single disease to cause ED. The pathophysiology involves neuropathic, angiopathic, and general vascular changes. Although the severity of hyperglycemia has been suggested as a predictor of ED, age, duration of diabetes, and other diabetic complications appear to be better predictors of ED than degree of hyperglycemia. Sometimes ED is the first symptom of diabetes mellitus, so all men who present with newly diagnosed ED should be evaluated for undiagnosed diabetes.

Neurologic diseases, such as peripheral neuropathy, spinal cord injury, stroke, multiple sclerosis, temporal lobe epilepsy, and Parkinson disease all can cause ED. In men who develop multiple sclerosis, about half of them present initially with ED. In these men, ED may be present for a time, then disappear and reappear at the next exacerbation. Men with stroke-related ED also tend to have ejaculatory problems.

Significant other systemic diseases that can cause ED are renal failure and chronic obstructive pulmonary disease (COPD). Chronic renal failure impacts erectile function through effects on the vascular system and via the development of autonomic neuropathy. In addition, many men with end-stage renal disease are severely hypogonadal. Neither hemodialysis nor testosterone replacement in men with renal failure has been shown to improve ED. Men with COPD and low PaO_2 have decreased cavernosal nitric oxide. Oxygen therapy may improve erectile function in some men with COPD.

Hypercortisolemia and hyper- and hypothyroidism have been associated with hypoactive sexual desire and ED. Hypothyroidism also is associated with delayed ejaculation, with a prevalence of up to 64%, and hyperthyroidism is associated with a 50% prevalence of premature ejaculation. Normalization of thyroid function frequently leads to improvement in both ED and ejaculatory dysfunction, although it may take up to 6 months after achievement of a euthyroid state for these functions to normalize.

Many studies have shown a clear association of ED with aging, but there have been no consistent correlations of ED in older men with low serum testosterone levels. In the Massachusetts Male Aging Study, where serum testosterone levels were measured throughout the study duration, 16% of the men who had no ED at baseline developed erectile problems within the next 8 years. Of the men who developed ED, 22% were in lowest tertile for serum testosterone levels, but 12% were in the highest tertile. Other studies in healthy older men have shown that testosterone levels may correlate with sexual desire, but not with erectile function or coitus frequency.

ED and lower urinary tract symptoms (LUTS), occurring as the result of benign prostatic hyperplasia (BPH), have significant effects on each other. Treatment of one can often improve the other. Both LUTS and ED are prevalent in the older male and frequently coassociate, contributing to diminished quality of life. Epidemiologic studies have shown strong associations between LUTS and ED, with a temporal relationship in onset and cessation and a dose response. A study in older men who had both ED and LUTS and were treated with the PDE-5 inhibitor, sildenafil, reported that both ED and LUTS symptoms improved with the sildenafil treatment.

While transurethral resection of the prostate (TURP) for BPH seldom results in ED, surgery for prostate cancer is more extensive and results in some degree of ED in about 60% of men. Nerve-sparing surgery offers a greater chance of preserving sexual potency. In addition, penile rehabilitation with PDE-5 inhibitors immediately following surgery helps prevent complete ED. Peyronie disease, where fibrosis of the corpora occurs, also can lead to erectile problems.

A number of lifestyle factors have been associated with the development of ED. Obesity alone is associated with a 20% increased risk of developing erectile problems. Although men with obesity often have low serum total testosterone levels, their free testosterone levels usually are normal, making hypogonadism an unlikely cause for obesity-associated ED. Often, however, obese men have elevated serum estrogen levels, due to the conversion of androgens to estrogens in adipose tissue. Improving obesity can improve erectile function. Smoking also can cause ED, both from direct effects of nicotine on penile smooth muscle and from longer-term effects on accelerating atherosclerosis. High levels of alcohol consumption are associated with ED, but moderate to low alcohol use has been associated with a lowering of the risk of ED. Physical activity alone, regardless of weight, can improve or delay development of ED.

A large number of medications have produced adverse drug events reports involving male sexual dysfunction, usually ED. By and large, the effects on sexual function are medication class effects, based on mechanisms of action. Above average prevalence for ED has been reported among men treated with vasodilators, cardiac drugs, antihypertensive agents, antihyperglycemic agents, and antidepressants. It is unlikely that medications would precipitate symptomatic ED in a man who had absolutely no erectile problems prior to initiating the medication, but for men with mild preexisting ED, these medications may precipitate clinically significant erectile problems. Sometimes, when relying on adverse drug event reports in the absence of large randomized trials, conclusions regarding the potential of a medication to impact sexual function may be exaggerated or incorrect. For example, although the 5α-reductase inhibitor, finasteride, has been reported to cause ED, analysis of the prospective quality-of-life data from the large Prostate Cancer Prevention Trial showed finasteride had no significant effect on sexual function.

Evaluation of Sexual Dysfunction

The first step in evaluation of sexual dysfunction is often the most difficult: eliciting the information that the patient has sexual dysfunction. Screening for sexual dysfunction can be done by asking a brief question or two about sexual activity in all patients and can legitimize the topic for conversation. Examples of possible screening questions include: "Are you satisfied with your sexual activity?"; "How has your illness affected your sex life?", if the patient has a chronic illness; or "Many of my male patients your age have noticed some change in their sexual function; how about you?"

If sexual dysfunction is discovered during screening, then a more extensive sexual and health history and physical examination are warranted. A careful history from the man's sexual partner can be helpful as well. If psychological or couples' problems exist, or if the patient is depressed, these should be treated before pursuing the direct management of other problems, such as ED. As noted earlier, an evaluation for general vascular disease and for diabetes, as well as a medication evaluation, should be done.

Treatments for Erectile Dysfunction

The initial step in the treatment approach to ED is to identify reversible causes and then to change them if possible. This includes making alterations in a medication regimen, facilitating smoking cessation and weight loss, and encouraging physical exercise. If there is evidence for a significant psychological component to the ED, couples' counseling or treatment for depression, if appropriate, are warranted.

Table 43-3 lists the current medical treatments for ED that are available in the United States. Vacuum erection devices consist of a vacuum cylinder connected to a pump to create controlled negative pressure, and one or more constriction rings that go at the base of the penis after vacuum-induced engorgement has occurred. Intercourse occurs with rings in place, but the ring should not be left on for more than 30 minutes. Erection satisfactory for intercourse occurs in 75% to 90% of users. Overall satisfaction rate is 65% to 70% if the method is chosen and used, but only about 12% of men select the vacuum device as an initial choice of therapy. Side effects or reasons for dissatisfaction include pain, inconvenience, and premature loss of rigidity. There are few contraindications to its use, but if on anticoagulants, these devices should be used with care.

TABLE 43-3 CURRENT MEDICAL TREATMENT OPTIONS FOR ERECTILE DYSFUNCTION AVAILABLE IN THE UNITED STATES

Vacuum erection devices
Penile prosthetic implants
Medications
Intracavernous injections
Papaverine (PDE inhibitor) ± phentolamine (α-adrenergic blocker)
Alprostadil (PGE1)
Transurethral
Alprostadil (PGE1)
Oral
PDE-5 inhibitors
Sildenafil, vardenafil, tadalafil, avanafil
α-Adrenergic blockers
Yohimbine, phentolamine
Other
Testosterone

Penile prosthetic implants are either semirigid (noninflatable) or inflatable. Designs have improved over the last decade, and the 5-year failure rates for the inflatable prosthesis are now about 5%. Infection is the most significant complication and varies from less than 1% to 16%.

Erection predominantly requires arterial dilation and venous sinusoidal relaxation, facilitated by α-adrenergic blockade and smooth muscle relaxation via mechanisms involving nitric oxide, PGE1, acetylcholine, or vasoactive

intestinal peptide (VIP). Nitric oxide activates guanylate cyclase in smooth muscle cells, leading to a rise in cGMP, which leads to muscle relaxation. cGMP is degraded in the penis predominantly by PDE-5. The major medications approved for use in the United States for treating ED are PGE1, PDE-5 inhibitors, or α-adrenergic blockers. Delivery methods for these medications are by intracavernous injections, transurethral, or oral.

Intracavernous injections with PGE1 or a PDE-5 inhibitor, with or without an α-adrenergic blocker, have efficacy of 65% to 90%. Side effects include mild local pain (10%–15%), penile fibrosis, prolonged erections, and rhinitis. PGE1 also can be delivered via urethral insertion, followed by vigorous penile massage to assist with medication delivery. Reported efficacy is between 45% and 65% and side effects include mild pain, minor urethral bleeding, dizziness, and lowered blood pressure.

The most common first-line therapy of ED is one of the PDE-5 inhibitors because of their efficacy (from 45% to 90%), ease of use, and generally favorable side effect profiles. The PDE-5 inhibitors available currently in the United States are sildenafil, vardenafil, tadalafil, and avanafil. There are no good data to support one PDE-5 inhibitor as being more efficacious than another. Tadalafil has a longer duration of action and avanafil may have a more rapid onset of action compared to the others. Sildenafil and vardenafil must be taken on an empty stomach, as high-fat meals and/or alcohol delay their absorption, but food does not interfere with the absorption of tadalafil or avanafil. PDE-5 inhibitors have some vasodilatory activity and interact with nitrates. Therefore they are contraindicated in men taking nitrates. Most common side effects of these agents are headaches, flushing, rhinitis, dyspepsia, and lowering of blood pressure. Sildenafil and vardenafil have some cross-reactivity with PDE-6, which may explain some reports of visual disturbances (usually a “blue haze”) with use of these medications.

Oral α-adrenergic blockers, such as yohimbine or phentolamine, have been used to treat ED, but with low efficacy (10%–20%). Testosterone replacement therapy, with or without concomitant PDE-5 inhibitor treatment, has been used successfully to treat ED in some hypogonadal men (see next section).

Testosterone and Male Sexual Dysfunction

In animal models, testosterone modulates multiple cellular components in the corpus cavernosum, leading to a penile erection. Probably the main action in erectile function is to stimulate nitric oxide synthesis, but it is also needed to maintain the ultrastructure of the dorsal penile nerve.

The human male requires at least a minimal amount of testosterone for normal sexual behavior. Profoundly hypogonadal young and middle-aged adult men need testosterone to restore both libido and normal erectile function. Overall dose-response studies in men seem to suggest, however, that androgen dependency of erectile function is maintained at threshold values far below levels required by other androgen target organs. In the hypogonadism in men (HIM) study, for example, ED did not occur until serum total testosterone level fell below 100 ng/dL, well below the low end of what is considered “normal” range for serum testosterone. Overall, there is not a strong cause and effect relationship between testosterone levels and ED. There are men with very low serum testosterone levels and no overt sexual dysfunction and men with complete ED who have high serum testosterone.

Decreased libido is considered the most prominent symptom of low testosterone and can impact erectile function. Using low libido as a screening for low testosterone, however, is not very sensitive. In the Massachusetts Male Aging Study, assessment of the association of low testosterone with low libido demonstrated that the two were associated when evaluated on a population level, but decreased libido was not a strong predictor of testosterone level in an individual man. If a man had low libido, the positive predictive value that he also would have a low serum testosterone level (< 300 ng/dL) was only about 23%.

A meta-analysis of testosterone replacement trials in men 50 years and older showed overall a positive impact on libido, but moderate and inconsistent effects of testosterone on ED. In 2014, there was another review of 20 randomized controlled trials of testosterone replacement in men with sexual dysfunction; this review also reported large discrepancies in clinical response. In this latter review, no effect of testosterone treatment on ED was seen in men who had a baseline serum total testosterone level greater than 12 nmol (> 350 ng/dL). For truly hypogonadal men, there was a beneficial effect of testosterone therapy on erectile function. In assessing the efficacy of testosterone treatment in ED, the length of treatment is an important factor. Effects of testosterone therapy on libido and ejaculation occur in 2 to 3 weeks of treatment onset, but effects on erectile function may take up to 6 months to manifest.

Testosterone facilitates the effects of PDE-5 inhibitors on erectile function, and may be beneficial as additional therapy in men in whom PDE-5 inhibitor treatment alone has failed. Again, this synergistic effect of testosterone and PDE-5 inhibitors appears to be present only in men who are truly hypogonadal, with the most benefit being seen in those men who have the most severe testosterone deficiency.

The value of hormone measurements in the routine evaluation of men with ED is unclear. The European Association of Urology and the British Society of Sexual Medicine currently recommend that all men with ED have some initial endocrine evaluation. The American Urological Association, on the other hand, recommends hormonal testing in men with ED only if they have other signs or symptoms of low testosterone, such as decreased libido, small testes, or low-volume seminal fluid, or if they have failed PDE-5 inhibitor therapy.

In summary, testosterone replacement therapy is not the primary treatment for the majority of older men with ED, but may be beneficial in some older men in whom decreased libido is a significant complaint or in whom serum testosterone levels are very low. In addition, testosterone therapy might be considered as adjunctive therapy for hypogonadal men who have failed PDE-5 inhibitor therapy alone.

ANDROGEN REPLACEMENT THERAPY IN OLDER MEN

When an older man presents with decreased libido and/or ED, androgen deficiency is considered a potential cause. However, androgens have effects on a broader range of organs and physiologic functions than those involved with sexual function. Testosterone levels decline with normal aging, a decline that may parallel changes in muscle, bone, and other androgen-responsive tissues. This has led to the concept that replacing androgens, mainly testosterone, in testosterone-deficient older men might prevent, stabilize, or even reverse some of the detrimental target-organ changes seen with aging.

Androgen Physiology and Changes With Aging

A further discussion of this topic appears in Chapter 108. Nearly all testosterone, which is the most plentiful androgen in the human male, circulates in blood bound to two proteins, albumin and sex hormone–binding globulin (SHBG); only about 1% to 2% of testosterone circulates totally free in plasma. Testosterone is tightly bound to SHBG, whereas its affinity for albumin is weak. Because of the strong affinity of testosterone for SHBG, the portion of plasma testosterone not bound to SHBG is often called *bioavailable* testosterone. Bioavailable testosterone best correlates with parameters such as bone mineral density and sexual function in older men, and is predictive for the development of frailty in inner-city African-American males. It is not known, however, if non-SHBG (*bioavailable*) testosterone is the component of testosterone that is truly bioavailable to every androgen target organ; for example, testosterone bound to SHBG may be available to the prostate.

Not all target-organ effects of testosterone are the result of the steroid directly, but may be the result of one of its metabolites. Testosterone can be converted to 17β-estradiol through the action of an aromatase enzyme. In men, the majority of estrogen is felt to come from the action of an aromatase enzyme in adipose tissue rather than from direct production by the testis. Testosterone also can be converted, via a 5α-reductase, to dihydrotestosterone (DHT), which is the predominant androgen in some organs, such as the prostate. Although some DHT is found in serum, most of the effects of DHT at the target-organ level are felt to be due to its local formation from testosterone. Both testosterone and DHT affect target organs through their interaction with the same intracellular androgen receptor.

Figure 108-6 and **Table 108-9** in Chapter 108 summarize age-related changes in the hypothalamic-pituitary-testicular axis. Serum levels of total testosterone, free testosterone, and bioavailable testosterone, but not DHT, decline with aging in many normal men. Both cross-sectional and longitudinal studies demonstrate these age-related changes. Most data on testosterone levels and age are from studies where the men were predominantly Caucasian of western European descent. Some smaller cross-sectional evaluations of men of African-American or Asian descent suggest that these ethnic groups also may demonstrate age-related testosterone decline. **Figure 43-3** demonstrates the longitudinal effects of aging on total testosterone, bioavailable testosterone, or free testosterone as reported from several longitudinal studies. While age alone has a strong predictive value for lower serum testosterone levels, concomitant disease such as diabetes mellitus, liver disease, depression, metabolic syndrome, or hemochromatosis can contribute; smoking also is significantly associated with low testosterone levels. Use of certain medications has been associated with lower testosterone levels, including ketoconazole, cimetidine, glucocorticoids, and chronic opioids.

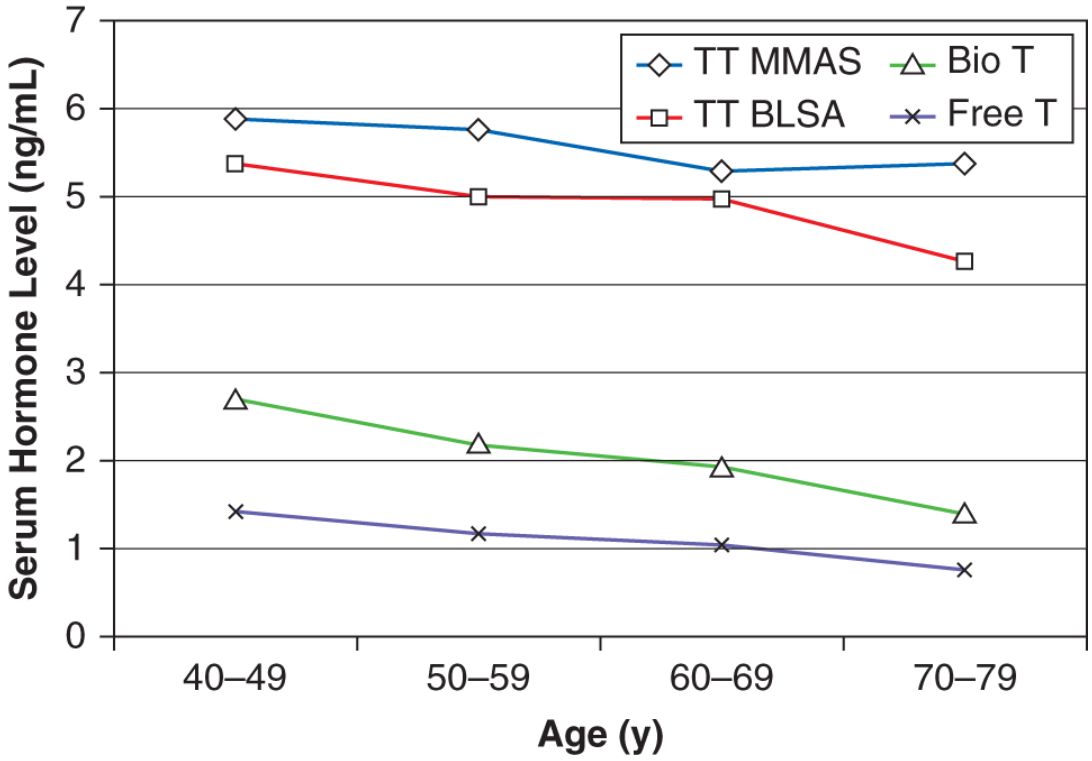


FIGURE 43-3. Serum total testosterone (TT, ng/mL), bioavailable testosterone (Bio T, ng/mL), and free testosterone (Free T; ng/mL × 10^{-1}), by age group from Baltimore Longitudinal Study of Aging (BLSA) (data from Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab*. 2001;86:724) or the Massachusetts Male Aging Study (MMAS) (data from Mohr BA, Guay AT, O'Donnell AB, McKinlay JB. Normal, bound and nonbound testosterone levels in normally ageing men: results from the Massachusetts Male Ageing Study. *Clin Endocrinol*. 2005;62:64).

Only some men, as they age, develop testosterone levels that are low enough to cause obvious hypogonadism. The prevalence of "late-onset" hypogonadism in the older male population is uncertain, largely because there is still no agreement on how to define testosterone deficiency in this age group. There is no target-organ change, physiologic finding, or symptom that readily assists with this definition, and in general, serum luteinizing hormone (LH) levels are not helpful. Unlike the thyroid hormone axis, where an elevated serum thyroid-stimulating hormone level can establish the diagnosis of hypothyroidism, serum LH levels in most older men, even those men with quite low testosterone levels, are usually within the "normal" range for young adult men. It is also possible that a single cut point for serum level of testosterone cannot define hypogonadism for all older men; the desired level of testosterone that maximizes target-organ effects may vary by the androgen target organ of interest, as well as being different among individuals.

Defining Hypogonadism in Older Men

The American Academy of Clinical Endocrinology, the Endocrine Society, the American Society of Andrology, and the International Society of Andrology have published clinical guidelines for diagnosis and treatment of testosterone deficiency in adult men. Within these guidelines are included some recommendations related to late-onset hypogonadism. All of the societies have agreed that late-onset hypogonadism should not be just a biochemical diagnosis, but must include age-related pathology or symptoms that would warrant treatment. There is no role for the use of testosterone therapy in older men for "prevention."

All these societies also have agreed that total testosterone levels are the appropriate initial test for hormonal evaluation. In these guidelines, cutoff values for serum total testosterone levels, above which older men are not likely to have testosterone deficiency, vary, but usually are in the normal range given for young adult men. In general total testosterone levels above 350 ng/dL do not merit testosterone treatment, and levels below 200 ng/dL are considered "low."

Reproducibility of testosterone level measurements is an issue. In addition to assay variability, serum testosterone levels show a wide range of intraindividual variability due to pulsatile secretion, diurnal variation, circannual rhythm, stress, acute illness, or excessive exercise. This volatility of testosterone levels is reflected in a broad normal range for total testosterone levels and is a reason that more than one morning serum sample should be used to characterize an individual.

Obesity, metabolic syndrome, diabetes, hyperthyroidism, and use of antiepileptic medications can cause significant changes in SHBG levels. In men where at least one of these is present, the second testosterone level evaluation also should include an SHBG level, and then, using the measured total testosterone and SHBG levels, a calculation of free testosterone can be done using an established formula (one example: http://www.issam.ch/freetesto.htm). At this time, direct radioimmunoassays for free testosterone are extremely unreliable. The level of free testosterone that is considered to be "low" also is not definitive, and ranges from 50 to 75 pg/mL.

The signs and symptoms that might be related to low serum testosterone levels in older men are listed in **Table 43-4**. These are based on extrapolation from the clinical syndrome of androgen deficiency in young men. All the listed signs and symptoms are nonspecific and could be indicators of many other diseases that are common in an aging male, making the diagnosis of late-onset hypogonadism less than straightforward. Many older men with testosterone levels that are in the hypogonadal range (for young adult men) are relatively asymptomatic, making the prevalence of testosterone deficiency in the older age group lower than that based on serum testosterone levels alone. On the other hand, some symptoms in older men, such as sexual dysfunction and fatigue, have shown to be more prevalent in those with low testosterone levels. None of the questionnaires available to date for screening for hypogonadism in older men, such as the ADAM questionnaire, the Massachusetts Male Aging Study questionnaire, or the Aging Males Survey scales, has high enough specificity to help either with clinical diagnosis or monitoring response to therapy.

TABLE 43-4 SIGNS AND SYMPTOMS OF POSSIBLE TESTOSTERONE DEFICIENCY IN OLDER MEN

Reduced muscle mass
Increased visceral fat
Low bone mineral density
Loss of libido
Fatigue; diminished physical or work performance
Decreased energy, motivation, aggressiveness
Depression, dysphoria, or irritability
Vasomotor symptoms
Poor concentration and memory
Sleep disturbances

The general assumption behind the consideration of giving testosterone replacement therapy to older men is that the symptoms that may be attributable to testosterone deficiency will improve significantly with replacement. Early trials of testosterone therapy in older men directed at treatment of symptoms were suggestive of possible benefit in a number of areas, but changes with therapy were small and inconsistent across studies. In 2004, the Institute of Medicine highlighted the lack of data to support substantial benefits from testosterone therapy in older men with low to low-normal testosterone levels and called for more research to better define the benefits.

Testosterone Therapy Effects on Specific Target Organs

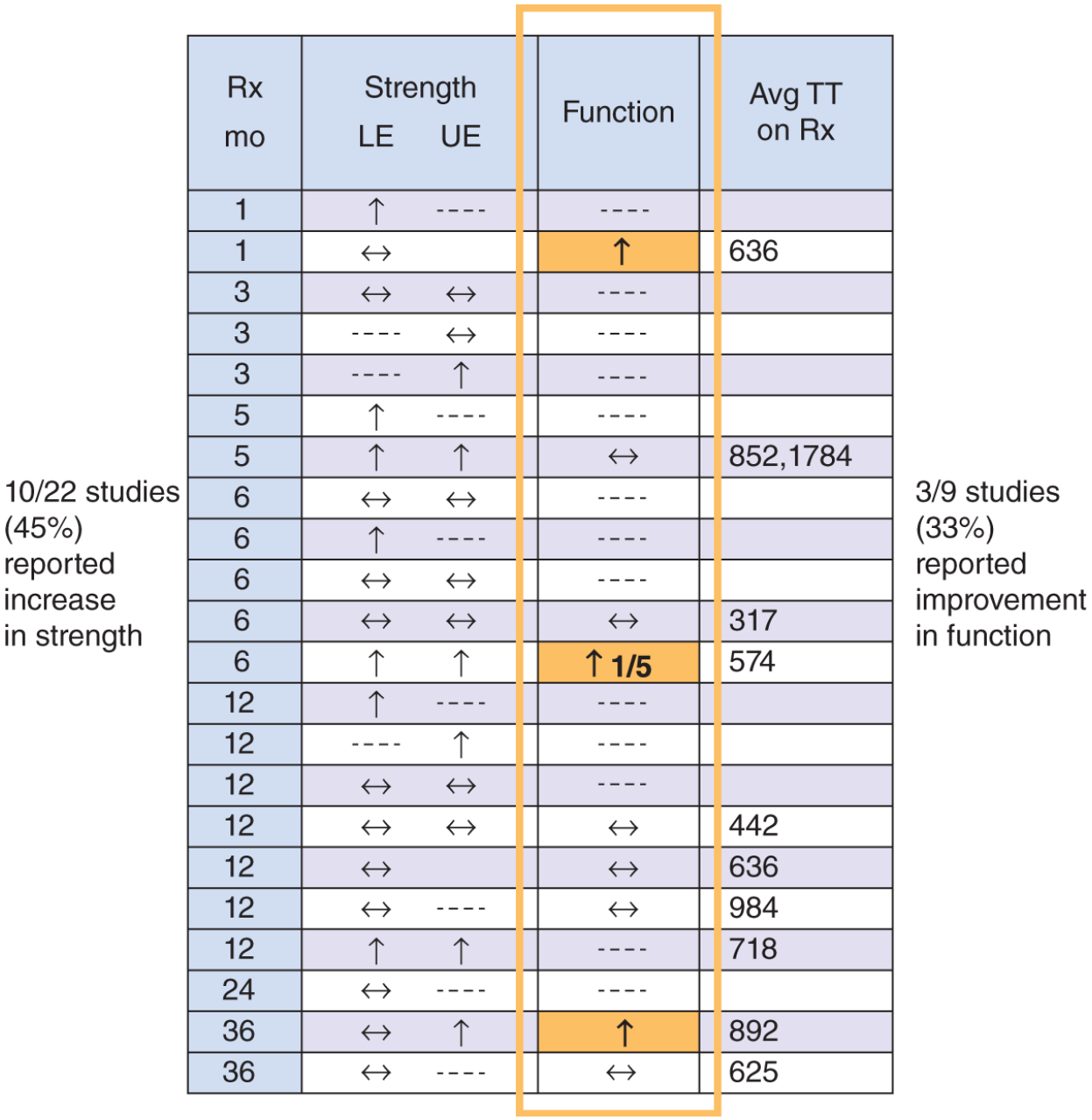
Bone The Institute of Medicine report in 2004 did not recommend pursuing additional studies of testosterone therapy for treatment or prevention of male osteoporosis, largely because other efficacious therapies are available. Nonetheless, testosterone is known to be anabolic to bone. Long-standing testosterone deficiency is a known risk factor for male osteoporosis and androgen deprivation therapy for prostate cancer is associated with a rapid loss in bone mineral density and an increase in fracture risk. The studies of androgen replacement therapy in older men which have evaluated an effect on bone have all utilized testosterone as the treatment androgen. This may be important, since testosterone is converted to estradiol in vivo, and older men receiving testosterone often show a substantial increase in plasma estradiol levels. Since bioavailable estradiol has been shown to be a better predictor of bone mineral density in older men than any component of testosterone, it is possible that the effects of testosterone replacement on bone in older men could be mediated through its conversion to estradiol.

The published studies of testosterone replacement in older men which have evaluated bone-related outcomes have lasted from 3 to 36 months, with the shorter studies measuring biochemical parameters of bone turnover and the longer studies evaluating bone mineral density. In general, the rate of bone degradation is slowed by testosterone replacement

and bone mineral density increases, more so in the spine than in the femoral neck. Whether positive effects on bone density can be maintained over longer periods of time than have been studied and what might be the optimal level of testosterone replacement to achieve the maximal benefit for bone in older men are both currently unknown. There are as yet no data on the effect of testosterone replacement therapy on fracture rates in older men.

Muscle mass, strength, and physical function Sarcopenia, the loss of muscle mass with age, leads to decreased muscle strength and a decline in physical function. Testosterone is known to have anabolic effects on muscle, through alterations in intramuscular gene expression. Testosterone therapy can lead to an increase in muscle mass. Whether increases in muscle mass will then translate to improvement in muscle strength and improvement in physical function are key to its therapeutic potential in the older individual. There have been at least 25 clinical studies in older men in which muscle mass has been evaluated during androgen therapy. Changes in lean body mass (predominantly muscle mass) with testosterone therapy have occurred consistently, with 85% of the studies showing at least some increase with testosterone. The magnitude of the changes in muscle mass in older men appears similar in magnitude to that seen with testosterone replacement in young hypogonadal men.

The effects of testosterone replacement therapy on strength in older men have not been as consistent as have been the changes in muscle mass. A meta-analysis published in 2006 reported a modest increase in overall muscle strength from testosterone replacement in older men, but the magnitude of improvement was largely from one trial. Subsequent trials have not altered the overall finding that there are small increases in muscle strength in some older men receiving testosterone therapy. In the 22 controlled testosterone replacement trials in older men, which have been published through 2014 and which measured strength, 45% reported an increase in either lower extremity strength, upper extremity strength, or both (**Figure 43-4**). In terms of improvement of the more meaningful outcome, physical function, the data generated so far do not show a major impact of testosterone therapy. Only a few testosterone replacement trials have reported improvement in any measure of physical function (see **Figure 43-4**), and improvement occurred in only certain subgroups in some of these trials. Unfortunately, although small early studies suggested that testosterone therapy in conjunction with functional strength training might prove more beneficial, three of the four randomized controlled trials in older men published to date which have evaluated the effect of exercise, with or without testosterone, have reported no benefit of adding testosterone to exercise alone on either muscle strength or physical function.



Rx mo	Strength LE	Strength UE	Function	Avg TT on Rx
1	↑	----	----	
1	↔		↑	636
3	↔	↔	----	
3	----	↔	----	
3	----	↑	----	
5	↑	----	----	
5	↑	↑	↔	852,1784
6	↔	↔	----	
6	↑	----	----	
6	↔	↔	----	
6	↔	↔	↔	317
6	↑	↑	↑ 1/5	574
12	↑	----	----	
12	----	↑	----	
12	↔	↔	----	
12	↔	↔	↔	442
12	↔		↔	636
12	↔	----	↔	984
12	↑	↑	----	718
24	↔	----	----	
36	↔	↑	↑	892
36	↔	----	↔	625

FIGURE 43-4. Reported effect from controlled studies of testosterone replacement therapy in older men on lower extremity (LE) and upper extremity (UE) strength (22 studies) and physical function (9 studies). Column 1 is the months on testosterone treatment for each study and column 4 is the average serum total testosterone level obtained during the study, if provided. ↑, increase; ↓, decrease; ↔, no change.

Fat mass In the many testosterone replacement studies in older men in which fat mass has been evaluated, 74% reported a decline in body fat with the therapy. The clinical significance of the fat mass changes with testosterone therapy in older men, however, remains to be delineated, especially in regard to possible use of testosterone therapy in men with metabolic syndrome (MetS). MetS denotes a cluster of signs and symptoms which include visceral adiposity (obesity), dyslipidemia (elevated triglycerides and low high-density lipoprotein [HDL] cholesterol), hypertension, insulin resistance, and increased inflammatory markers. Epidemiologic studies, such as the Baltimore Longitudinal Study of Aging, have demonstrated that the prevalence of MetS increases with age until about age 80 and is associated with an increase in body mass index. Lower serum total and free testosterone levels and higher SHBG levels also were seen in men with MetS compared to those without MetS. A meta-analysis published in 2011 also reported that men with MetS had lower serum total testosterone levels. Much of this is linked to obesity, as obese men tend to have lower serum testosterone levels; weight loss alone has been shown to increase serum testosterone. The question, therefore, is whether MetS results in lower testosterone, whether lower testosterone participates in the pathophysiology of MetS, or whether both of these might be occurring.

Testosterone replacement studies in older men, in which the location of the fat mass loss was measured, have

demonstrated that it is primarily subcutaneous fat, not visceral fat, that decreases with treatment. These studies have not reported any weight loss, or significant changes in HbA_{1C}, fasting insulin, or glucose levels, with testosterone treatment, although total cholesterol and low-density lipoprotein (LDL) cholesterol levels were lowered. On the other hand, there have been some testosterone replacement studies in predominantly middle-aged hypogonadal men with MetS and/or type 2 diabetes that have demonstrated modest (15%) improvement in insulin resistance and some weight loss with the therapy. One single-blind study in middle-aged hypogonadal men with MetS compared effects of diet and exercise to diet, exercise, and testosterone treatment. The group receiving testosterone had larger improvements in HbA_{1C} and lipid profiles than did the nontestosterone-treated group. Thus, whether testosterone replacement therapy has any role in the management of MetS in older men remains uncertain.

Mood Young men with profound testosterone deficiency have symptoms of dysphoria, fatigue, and irritability, all of which improve with normalization of testosterone levels. There also is some epidemiologic support for a relationship between low androgen serum levels and dysphoria or depression in older men. There have been several studies of testosterone replacement in hypogonadal middle-aged men with depression or dysthymia which reported improvement in depression scales either with testosterone treatment alone, or with testosterone as adjunctive therapy to antidepressant treatment.

There have been no studies of the efficacy of testosterone replacement therapy in older men with diagnosed depressive disorder. In older men who were not frankly depressed, there have been at least nine blinded controlled clinical trials which have evaluated effect on mood; only one of these studies reported any benefit with testosterone replacement.

Cognition Cross-sectional studies of older men have found an association of higher serum total testosterone levels with higher scores on some cognitive tests. In the Baltimore Longitudinal Study of Aging, a higher baseline free testosterone index correlated with better scores on visual and verbal memory at baseline and a slower decline of visual memory after 10 years of follow-up. A higher baseline free testosterone index, after adjustment for a number of risk factors, also was correlated with 26% reduction in risk for development of Alzheimer dementia at 10 years.

To date, there have been at least 10 randomized controlled clinical trials evaluating cognitive function with testosterone replacement therapy in older men without significant cognitive deficits at baseline. Five of these studies enrolled older men with baseline low or low-normal serum total testosterone and four had men with normal baseline total testosterone levels. One study evaluated the effects of inducing a temporary severe hypogonadal state compared to maintaining a controlled midrange eugonadal state. In the study where older men made severely hypogonadal were compared to those in the eugonadal state, there was no difference in the various measured cognitive domains between the two groups. For the other studies, about half of the trials in each category showed some improvement on aspects of cognition such as visuospatial memory, total memory, or verbal memory, and half reported no detectable effect of testosterone on cognitive test scores. No consistent effect of testosterone replacement has been observed in older men with dementia, but only small numbers of patients have been studied thus far.

Cardiovascular system Testosterone in older men could be beneficial, detrimental, or neutral with regard to the cardiovascular system. Factors associated with risk for cardiovascular disease that might be affected by androgens include serum lipoprotein levels, vascular tone, platelet and red blood cell clotting parameters, and direct atherogenesis. There are currently little data on the effects of testosterone or testosterone therapy in older men on many of these parameters. On the other hand, as noted previously in this chapter, low testosterone levels in men are associated with cardiovascular disease risk factors, such as obesity, diabetes, and dyslipidemia, although it is unclear if low testosterone is independently associated with these risk factors.

Most prospective observational studies have reported that low endogenous testosterone in men is predictive of increased risk for development of cardiovascular disease and/or mortality. There were two meta-analyses of these studies, both published in 2011. One meta-analysis concluded that, in men under the age of 70, testosterone levels seemed to have no effect on subsequent cardiovascular outcomes, but for men over 70 years, having a higher serum testosterone level offered a small protective effective against cardiovascular disease. The other meta-analysis reported that low testosterone levels were associated with a subsequent increase in mortality, but that this was likely due to those men with lower testosterone being older and sicker. Other observational studies seem to indicate that lower serum testosterone levels may be linked to earlier all-cause and cardiovascular-related mortality, suggesting that testosterone deficiency might have important long-term negative cardiovascular consequences. It is not clear, however, that improving testosterone levels by testosterone therapy will improve those negative consequences.

As yet there have not been any randomized controlled trials of testosterone replacement where assessment of

cardiovascular-related events or morality was a primary or secondary outcome. The data on testosterone therapy and cardiovascular outcomes come from small controlled clinical studies, retrospective observational analysis, retrospective analysis of large databases, or meta-analyses of testosterone replacement trials. In men with preexisting cardiovascular disease and low testosterone levels testosterone administration appeared to increase time to ischemia when challenged on a treadmill. In two retrospective observational analyses of middle-aged and older men, some with preexisting cardiovascular disease, and comparing the reported cardiovascular and/or mortality outcomes of those who received testosterone with those who did not get testosterone, one of the studies reported lower incidence of subsequent mortality in men who received testosterone, while the other study reported increased risk of stroke, myocardial infarction, or death in the group getting testosterone. An analysis of a large database from middle-aged and older men in regards to risk of myocardial infarction after receiving a prescription for testosterone was published in early 2014. It found that those men filling an initial prescription for testosterone were at higher risk of having a myocardial infarction within 90 days of getting that prescription than those men who did not get a testosterone prescription; that risk was higher for men who were older or/and if the man had preexisting coronary artery disease.

In terms of cardiovascular effects seen in randomized controlled trials of testosterone replacement, two meta-analysis, one published in 2005 and one in 2010, both reported no effect of testosterone therapy on occurrence of cardiovascular events. Subsequently, the TOM trial, a randomized controlled study of testosterone replacement in older men with limited mobility, many of whom had cardiovascular disease at baseline, was discontinued early due to increased number of cardiovascular-related events in the testosterone-treated group. A meta-analysis, published in 2013 and which analyzed 27 randomized controlled trials, including the TOM trial, reported that testosterone replacement resulted in an increased relative risk of 1.54 for all cardiovascular events compared to placebo treatment. Given the conflicting data in regards to cardiovascular disease and testosterone, the US Food and Drug Administration (FDA) launched an investigation in 2014. As of summer 2015, the FDA required revisions to the labels of all testosterone products stating that testosterone replacement therapy may increase the risk of heart attack and stroke.

The retrospective cohort analysis of a large database that reported increased risk of myocardial infarction within 90 days of an initial testosterone prescription suggests that perhaps there might be some early effect of testosterone treatment on the cardiovascular system, perhaps as regards hemostasis. Data in men as regards testosterone and the hemostatic/fibrinolytic system are from observational studies or small interventional studies. Cross-sectional studies have shown a positive association between higher testosterone levels and antithrombotic factors, such as tissue plasminogen activator (tPA), and a negative correlation with prothrombotic factors, such as plasminogen activator inhibitor-1 (PAI-1), fibrinogen, factor VIIc, and protein C. However, testosterone replacement for 1 year in older hypogonadal men or for 3 months in middle-aged to older hypogonadal men with stable angina did not affect tissue factor-induced coagulation or levels of coagulation factors. There have been some reports of deep venous thrombosis (DVT) in men on testosterone replacement therapy, with most events occurring within the first 3 to 4 months of therapy initiation. In these reports, the large majority of the men had undiagnosed hypofibrinolytic thrombophilia. Overall the incidence of DVT in men on testosterone therapy is quite low (< 1%), but risk is likely to be increased in men who previously have had a DVT.

Adverse Effects of Testosterone

Table 43-5 lists potential or reported adverse effects of testosterone therapy in older men. In addition to the possible cardiovascular adverse outcomes, as discussed above, fluid retention is possible, especially during the first few months of therapy. With testosterone this fluid retention is not as dramatic as in the case of oral anabolic steroids. In the large majority of older men, testosterone replacement therapy does not appear to cause peripheral edema or exacerbation of hypertension, but there was at least one reported case of precipitation of congestive heart failure in a study in which very high doses of testosterone were used. Nearly all the studies of testosterone replacement therapy in older men have enrolled relatively healthy men. In chronically ill, frail older men, fluid retention might pose more of a concern. On the other hand, there have been at least four studies where testosterone was given to hypogonadal men with systolic heart failure in order to evaluate whether replacement therapy could improve exercise capacity. A meta-analysis of these studies reported small overall improvement in exercise capacity with testosterone treatment, but more importantly, no exacerbation of congestive heart failure.

TABLE 43-5 POTENTIAL OR REPORTED ADVERSE EFFECTS OF TESTOSTERONE REPLACEMENT THERAPY IN OLDER MEN

Increase risk of cardiovascular system events

Myocardial infarction
Ischemic stroke
Deep venous thrombosis
Fluid retention
Peripheral edema
Worsening of congestive heart failure
Breast tenderness or gynecomastia
Liver toxicity (only with oral methylated formulations)
Exacerbation of sleep apnea
Development of polycythemia
Exacerbation of benign or malignant prostate disease

Tender breasts or gynecomastia occurs in a small number of older men receiving testosterone therapy, perhaps because of the relatively greater increase in serum estradiol levels (as compared with serum testosterone levels) that occurs with the therapy. Liver toxicity, although known to occur with oral methylated testosterone, has not been seen with parenteral forms of therapy. Testosterone supplementation has been reported to exacerbate sleep apnea, but this adverse effect has not been found uniformly.

Testosterone replacement therapy in older men often increases red blood cell mass and hemoglobin levels. In a meta-analysis of testosterone replacement trials in older men, there was a nearly fourfold relative risk of developing a hematocrit level over 50%. The increases in hemoglobin and hematocrit seen in older men with testosterone therapy are much larger than those usually observed when young hypogonadal men are given testosterone replacement. In some cases in which polycythemia has developed in older men, it has been necessary to either terminate therapy or decrease the dose of testosterone used. While the coexistence of sleep apnea and elevated body mass index seems to contribute to the development of polycythemia in certain older men, this has not been the case for many of the men studied. Methods of testosterone replacement that give a more uniform level of testosterone within the physiologic range throughout the dosing period, such as the transdermal patch or gels, appear to have less of an effect on red blood cell mass than replacement methods such as the injections or implants.

Androgens have a role in promoting both benign prostatic hyperplasia (BPH) and prostate cancer, and androgen deprivation therapy has been used in the treatment of both these disorders. The issue of whether testosterone replacement therapy will promote prostate disease in older men, however, has not been resolved. To date there are no prospective studies with sufficient power to resolve the issue. Observational studies, such as the Massachusetts Male Aging Study and the Baltimore Longitudinal Study of Aging, have reported no relationship between serum testosterone levels and subsequent development of symptomatic BPH. A collaborative analysis of 18 prospective observational studies of endogenous sex hormone levels and prostate cancer showed no association between serum concentrations of any sex steroids and the risk of prostate cancer; a few studies even have found a relationship between low total testosterone levels and increased prostate cancer risk.

A number of testosterone replacement studies in older men have evaluated serum levels of prostate-specific antigen (PSA), prostate size, or functional prostate parameters. The majority of these studies have reported no significant change in PSA serum levels or other prostate parameters. A meta-analysis of adverse events from 19 double-blind, placebo-controlled testosterone replacement trials in 651 middle-aged and older men reported that the rates of prostate cancer, the number of prostate biopsies performed, and a rise in PSA to greater than 4 ng/mL or a PSA increase of more than 1.5 ng/mL over baseline were numerically higher in men on testosterone compared to placebo, but none of the individual prostate parameters were significantly different between the testosterone and placebo treatment groups. However, the rate of all prostate events combined was higher in the testosterone therapy groups compared to placebo, with those men receiving testosterone having a 1.8-fold higher likelihood of having some "prostate event." A more recent 2014 meta-analysis of 22 randomized controlled trials of testosterone replacement (total of 2352 patients) concluded that testosterone treatment in the short term (up to 36 months) did not promote prostate cancer development. Testosterone therapy has been initiated in small numbers of men after either radical prostatectomy or brachytherapy for prostate cancer. These studies have reported that, in up to as long as 12 years of follow-up, there has been no increase in cancer recurrence or increase in PSA levels.

One of the reasons why testosterone treatment may not promote prostate disease in most hypogonadal older men is

that the maximum threshold serum level for testosterone effects on the prostate may be lower than the pretreatment testosterone level. For example, one study in middle-aged and older men who were treated for 6 months with testosterone to raise their baseline average testosterone from about 280 ng/dL to an average of 640 ng/dL, reported that intraprostatic levels of androgens, androgen action biomarkers, and gene expression did not change with the testosterone treatment. This suggests that the threshold for maximum testosterone effects on the prostate for these men was a serum level less than 280 ng/dL.

To date, therefore, the preponderance of evidence suggests that the risk of testosterone treatment in promoting either prostate cancer or BPH is low; however, it has not been proven to be zero. Since both prostate cancer and BPH are diseases with long natural histories, and the observation time for studies of testosterone therapy in older men is limited, the long-term effects of testosterone supplementation on the prostates of older men is still in question. Screening for prostate cancer prior to initiation of testosterone therapy, especially in older men, is mandatory, and periodic monitoring of PSA levels and digital rectal examinations of the prostate should be done while men are on testosterone therapy.

Testosterone Preparations for Replacement Therapy

The testosterone delivery systems that are currently available in the United States for use in replacement therapy include long-acting injectable testosterone esters, such as testosterone enanthate or cypionate; transdermal patches; transdermally applied gels; or buccal patch (**Table 43-6**). The 17-alkylated testosterone oral preparations, although available, are not recommended for male hormone replacement because of hepatotoxicity and unfavorable alterations in serum lipoprotein profiles that occur with their use. All preparations of testosterone should be efficacious for replacement therapy if adequate serum testosterone levels are achieved, so selecting the specific preparation will depend on patient preference with regards to acceptability, dosing regimen, and cost, as well as possible adverse effects related to the specific preparation (see **Table 43-6**).

TABLE 43-6 ■ TESTOSTERONE DELIVERY PREPARATIONS AVAILABLE IN NORTH AMERICA: RECOMMENDED DOSING IN OLDER MEN AND POTENTIAL SPECIFIC ADVANTAGES AND DISADVANTAGES

PREPARATION	RECOMMENDED INITIAL REGIMEN	ADVANTAGES	DISADVANTAGES
Oral			
17-alkylated testosterone	Not recommended[a]		
Injectable esters			
Testosterone enanthate cypionate (100–200 mg/cc)	75 mg IM/wk or 150 mg IM/2 wk	Reliable delivery Good dosing flexibility Low cost	Widely variable serum T levels over dosing period Mood swings Significant increase in hemoglobin Increase in serum estradiol levels Pain at injection site
Implantable pellets	225 mg/4–6 mo	May last up to 6 mo Steady serum T levels	Local site infection Extrusion of pellet Significant increase in hemoglobin Poor dosing flexibility
Transdermal patch			
(2.5 or 5 mg)	5-mg patch/d	Easy self-application Steady serum T levels	Dermatitis at application site Limited dosing adjustment Poor absorption in some patients

Transdermal gel			
(2.5- or 5-g packets, or pump; 5-g gel delivers 5 mg/d)	5 mg/d	Good dosing flexibility Easy self-application Steady serum T levels Invisible	Occasional skin irritation Poor absorption in some patients Mildly elevated serum DHT levels
Buccal			
(30-mg adherent tab)	30-mg q12h	Easy self-application Not transdermal	Gingival irritation Poor adhesion No dosing flexibility

[a]Not recommended because of increased incidence of hepatotoxicity and unfavorable alteration in lipoprotein profiles.

The injectable esters deliver reliable testosterone serum levels, offer a wide range of dosing, and are relatively low in cost, especially if the patient or a family member can give the intramuscular injections. The disadvantages of injectable esters include the necessity for intramuscular injection, with possible discomfort at the injection site, and the large variation in serum testosterone levels over a single dosing period. Especially with the 2- and 3-week dosing regimens, supraphysiologic testosterone levels occur within the first few days after injection, and levels then fall below the normal range just prior to the next dose. This may result in mood swings and significant increases in hemoglobin and estradiol levels, and is why an every 3-week dosing regimen is not routinely recommended. Since testosterone metabolism slows with aging, the recommended initial dose of injectable testosterone for older men is lower than that used in younger adults.

The pellet formulation delivers relatively stable serum testosterone levels for periods up to 6 months. However, it requires a skin incision and trocar to implant, site infection or extrusion of the pellet are possible, and there is no significant dosing flexibility.

The transdermal patch is easy to apply and provides physiologic levels of serum testosterone throughout most of the 24-hour dosing period. The disadvantages of transdermal patch include possible local skin irritation and limited dosing adjustment (the patch comes in two sizes and cannot be cut). The testosterone gels also are easy to apply, deliver physiologic serum testosterone levels, and offer more dosing flexibility than the patch, because less than a full packet (or pump dose) can be applied. Disadvantages of the gels include their cost, production of mildly elevated serum DHT levels, and some occasional skin irritation. It is important to note that a small percentage of men are unable to achieve normal serum testosterone levels with *any* transdermal preparation. In that case, the injectable esters, the pellet, or the buccal formulation must be used. The disadvantages of the buccal preparation include gingival irritation and loss of the patch due to poor adhesion.

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Chapter 44

Benign Prostate Disorders

Catherine E. DuBeau

Learning Objectives

- Understand the epidemiology and pathophysiology of benign prostate disease in older men.
- Perform an evaluation of older men with lower urinary tract symptoms (LUTS) that incorporates an understanding of the role of etiologic factors beyond benign prostate disease.
- Manage evidence-based stepped treatment of LUTS, including appropriate specialist referral.

Key Clinical Points

1. **Benign prostate hyperplasia (BPH), prostate hypertrophy, and bladder outlet obstruction are related but not always coincident common conditions in older men.**
2. **The natural history of benign prostate disease and lower urinary symptoms is variable and includes symptom regression.**
3. **Multimorbidity, medications, and functional and cognitive impairment may be the predominant cause of LUTS even in men with benign prostate disease.**
4. **Many men with LUTS can be effectively managed with medical treatment.**

DEFINITIONS

Many terms are used to describe benign prostate disease, often interchangeably. Precision is important, however, because the conditions overlap only partially (**Figure 44-1**). benign prostate hyperplasia (BPH) is a histologic condition characterized by benign proliferation of stromal and/or epithelial prostate tissue. Its prevalence increases with age and is nearly universally present in men by the ninth decade. Benign prostate enlargement (BPE) occurs in about half of men with BPH, and is quantified by milliliters of prostate tissue (eg, as measured by ultrasound). Bladder outlet obstruction (BOO) occurs in only a subset of men with BPE.

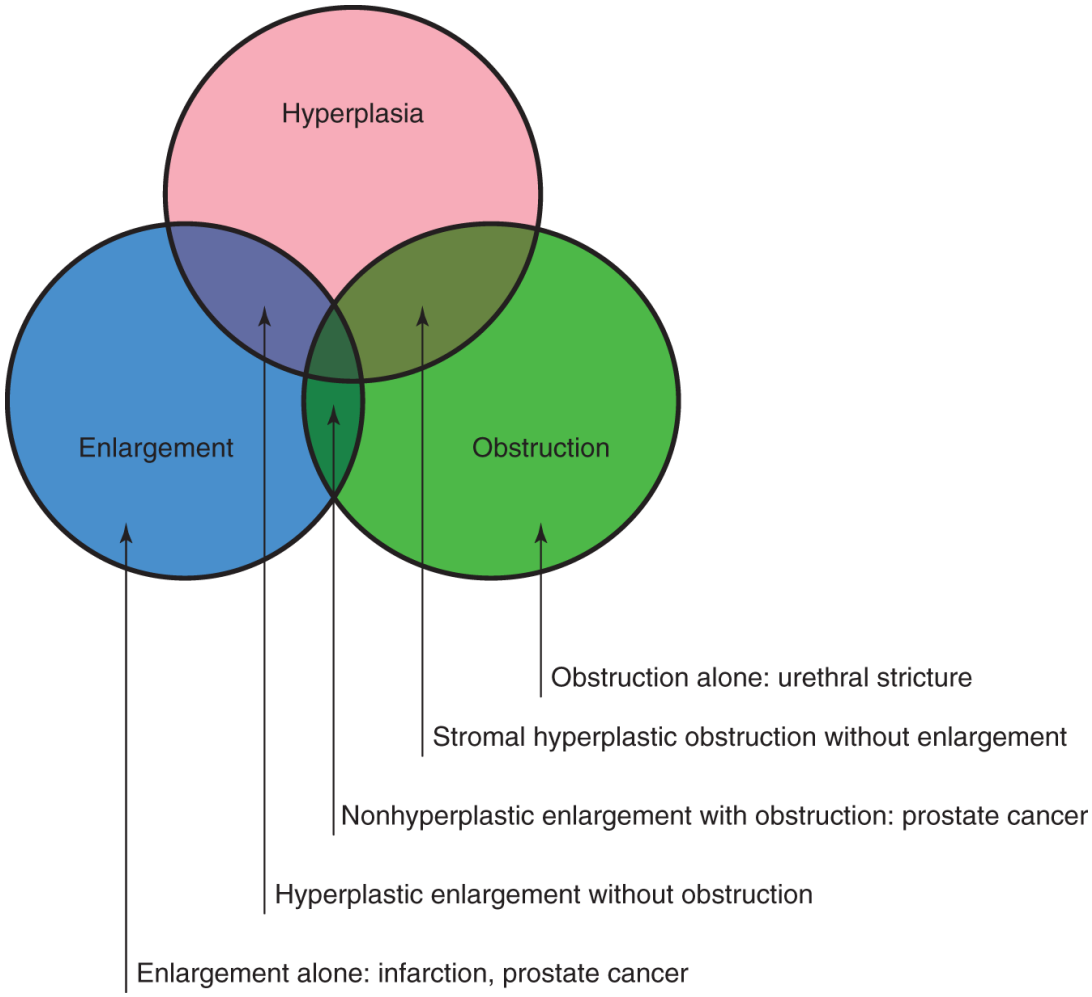


FIGURE 44-1. Examples of overlap between benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE), bladder outlet obstruction (BOO), and lower urinary tract symptoms (LUTS) in men.

Common voiding symptoms are urgency, frequency, nocturia, slow stream, hesitancy, incomplete emptying, postvoiding dribbling, and incontinence, which may be related to BPH, BPE, BOO, age-related physiologic changes in the lower urinary tract, or comorbid conditions and medications. Therefore, voiding symptoms are best described by the nonspecific term lower urinary tract symtoms (LUTS).

EPIDEMIOLOGY AND NATURAL HISTORY

Early autopsy and epidemiologic studies demonstrated a marked rise in prevalence of BPH and BPE with age, especially during the sixth and seventh decades, and a similar relationship between age and "clinical BPH" (LUTS and BPE on examination) (**Figure 44-2**). In a racially, ethnically, and socioeconomically diverse population in the United States, the overall prevalence of LUTS was 18.7% and increased with age (10.5% at age 30–39 to 25.5% at age 70–79) but did not differ by sex or race/ethnicity. Other studies suggest that 28% to 35% of older men without previous prostate surgery have moderate to severe LUTS. More recent data from longitudinal epidemiologic studies and placebo arms of treatment trials confirm that the incidence of benign prostate disease gradually and variably increases with age until the ninth decade (**Figure 44-3**). Only weak correlations exist between BPE, BOO, and LUTS, suggesting that their relationships are nonlinear and complex.

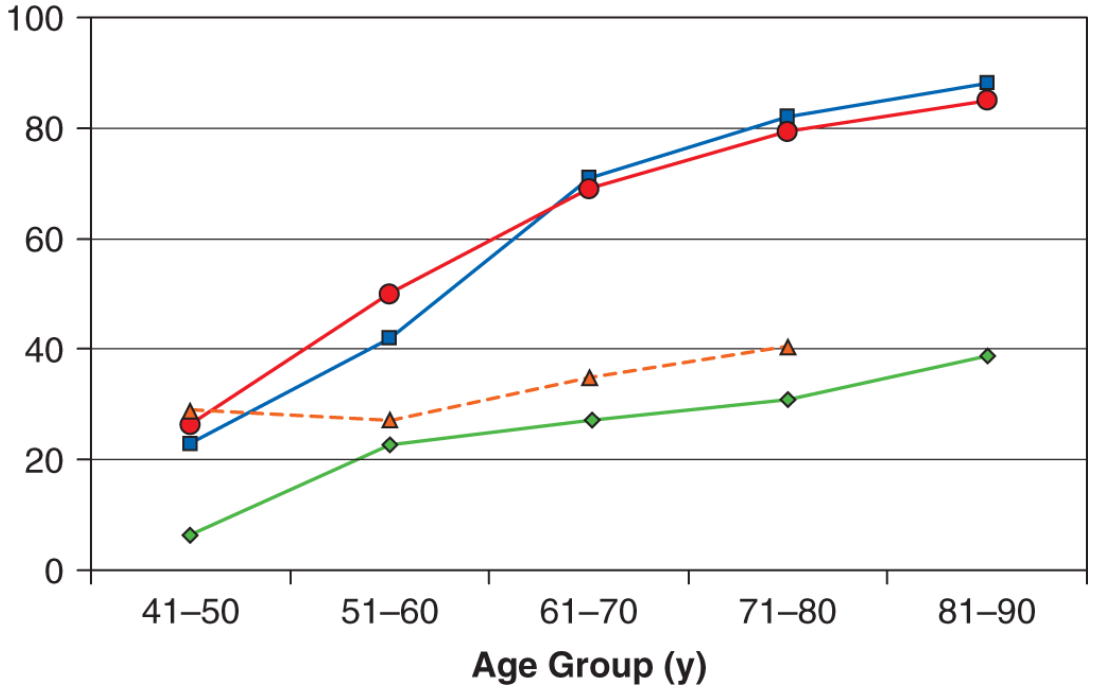


FIGURE 44-2. Autopsy evidence of prostate hyperplasia (percentage of prostates, solid line with ■), mean weight (mL) of all prostates (solid line with ♦), mean weight of prostates with hyperplasia (dashed line with ▲), and percentage of men with lower urinary tract symptoms (LUTS) (solid line with •).(Data from Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol*. 1984;132:474–479; Guess HA, Arrighi HM, Metter EJ, Fozard JK. Cumulative prevalence of prostatism matches the autopsy prevalence of benign prostatic hyperplasia. *Prostate*. 1990;17:214–216.)

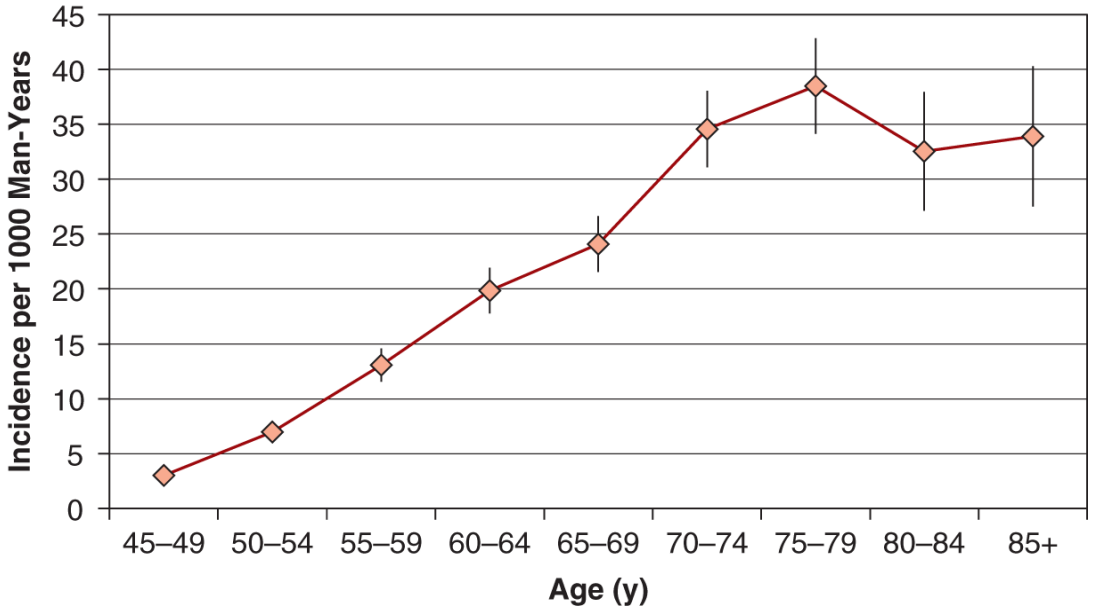


FIGURE 44-3. Incidence of benign prostatic hyperplasia (BPH) by age. (Data from Verhamme KM, Dieleman JP, Bleumink GS, et al. Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care—the Triumph project. *Eur Urol*. 2002;42:323–328.)

Some data suggest that African-American men have a higher risk of benign prostate disease, urinary retention, and BPE/BOO surgery, possibly because they have higher levels of 5α-reductase and larger prostate transitional zone volume (see section "Pathophysiology"). The very limited available data suggest that Hispanic men have similar risk of BPH and characteristics of BPE as non-Hispanic white men. Asian men generally have lower rates of benign and malignant prostate disease, although this may differ by country of origin.

Progression of benign prostate disease is defined as worsening LUTS, acute urinary retention (AUR), and/or the need for surgical treatment. LUTS can vary significantly over time, and abate as well as progress. In a prospective

cohort of men with moderate LUTS, by 1 year, symptoms had improved in 16% and worsened in only 24%, and at 4 years, symptoms were only mild in 13%, unchanged in 46%, and worse in 41%. The worsening of LUTS and the need for medication and surgery differ by age, with the proportion developing severe LUTS and treatment increasing with age (**Figure 44-4**). The incidence of AUR in men with LUTS and benign prostate disease is low; in a meta-analysis including 6100 moderately symptomatic men, the incidence of AUR was 13.7 per 1000 patient-years in all men although considerably higher in men aged greater than or equal to 70 or taking anticholinergic agents (34.7 per 1000 patient-years). Higher baseline prostate-specific antigen (PSA) levels are associated with greater risk of AUR and surgery; 7.8% of men with PSA levels up to 1.3 ng/mL develop AUR and/or require surgery by the fourth year, compared with 12.6% of men with PSA levels 1.4 to 3.2 ng/mL, and 19.9% with PSA levels 3.3 to 12 ng/mL. Change in PSA over time (PSA velocity), however, is not associated with AUR or surgery. As PSA is strongly correlated with prostate volume, it is not surprising that higher volumes (> 30–40 mL by ultrasound) are associated with worsening LUTS and AUR. Other factors that increase AUR risk include previous episode(s) of retention, baseline postvoiding residual volume (PVR) greater than 100 mL, worsening LUTS, and failure to respond to α-blocker treatment.

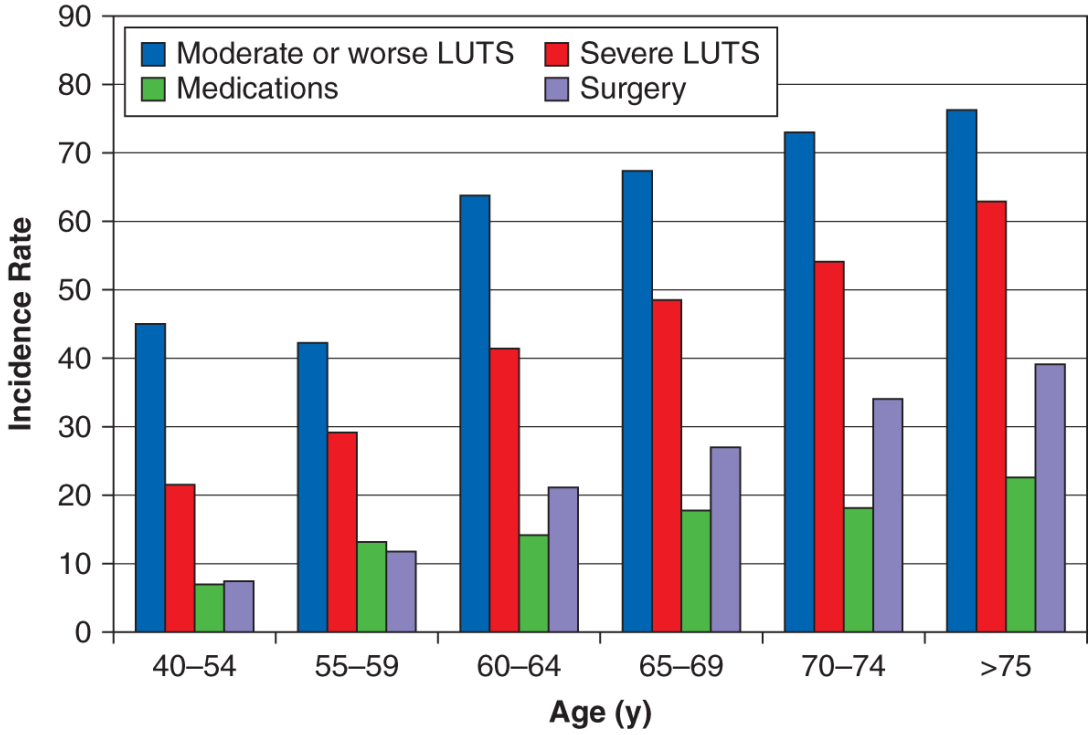


FIGURE 44-4. Progression of lower urinary tract symptoms (LUTS) to worsening symptoms, need for medication, and need for surgery over 18 years, by age group. Data are incidence rates per 1000 man-years over 18 years from the Physicians Health Study. At baseline, all men had International Prostate Symptom Score (IPSS) of < 7. Progression to "moderate or worse" LUTS was defined as IPSS of ≥ 15, surgery, or medication use. Progression to "severe" LUTS was defined as IPSS of ≥ 20, surgery, or medication use. (Data from Platz EA, Joshu CE, Mondul AM, Peskoe SB, Willett WC, Giovannucci E. Incidence and progression of lower urinary tract symptoms in a large prospective cohort of US men. *J Urol*. 2012;188:496–501.)

LUTS are strongly related to poorer health and decreased quality of life. Bother from urinary symptoms and poorer health status (self-reported health, SF-12 Physical Summary Scale, or difficulty with instrumental activities of daily living [IADLs]) are strongly associated with older age. Over half of men with severe LUTS report they would feel unsatisfied, unhappy, or terrible if they were to spend the rest of their life with their urinary condition.

PATHOPHYSIOLOGY

Hyperplasia

Prostate hyperplasia occurs when prostate cell proliferation exceeds programmed cell death (apoptosis) as a result of stimulated cell growth, inhibition of apoptosis, or both. BPH occurs predominantly in the prostatic periurethral transitional zone, unlike prostate cancer, which tends to occur in more peripheral areas. BPH and prostate cancer are genetically distinct, and one is not a risk factor for the other.

The development of stromal and epithelial hyperplasia in BPH is androgen- and aging-dependent, and involves numerous paracrine and autocrine factors. The trophic androgen for prostate growth is dihydrotestosterone, produced from testosterone within the prostate by the enzyme 5α-reductase (thus the utility of 5α-reductase inhibitors [5αRIs] for treatment). In the absence of 5α-reductase, even high serum levels of testosterone will not cause BPH. Additional factors supporting prostate cell growth include inflammatory cytokines (eg, interleukin-8), autocrine cytokine growth factors, and neuroendocrine cell products. Stromal-epithelial interactions regulating proliferation also involve interactions between androgens, estrogens, and stimulatory and inhibitory peptide growth factors (eg, fibroblast growth factor-2, transforming growth factor-β). Other regulatory factors include nitric oxide (nitric oxide synthetase levels are low in BPH), vitamin D, and local autonomic innervation and activity. Thus the development of BPH is the end result of numerous pathways involved in regulating sympathetic activity, androgen-estrogen balance, and smooth muscle proliferation.

The divergence in prevalence between BPH, BPE, BOO, and LUTS results from many lower urinary tract factors (**Table 44-1**). In addition, numerous medical conditions, medications, and functional impairment may cause or worsen LUTS independent of prostate disease (see Chapter 53).

TABLE 44-1 ■ LOWER URINARY TRACT FACTORS UNDERLYING THE DIVERGENCE IN PREVALENCE BETWEEN BPH, BPE, BOO, AND LUTS

FACTOR	IMPACT
Ratio of stromal to epithelial hyperplasia (stromal proliferation predominates in 50%, glandular in 25%, and mixed in 25%)	Stromal glands tend to be smaller, more symptomatic, and have worse symptomatic outcomes to prostatectomy
Location of BPH nodules	Adenomas, which occur predominantly in central transitional and periurethral zones of the prostate, predispose to prostatic urethra compression. Adenomas in the median lobes may compress the bladder base without causing BOO.
Fibroelastic properties of prostate capsule	Altered compliance may increase urethral compression in the absence of mechanical BOO.
α-Adrenergic innervation of prostate	Increased number of α-adrenergic receptors promotes smooth muscle contraction.
Variability in detrusor muscle structure and function	Detrusor contractility can be affected by BPE/BOO-associated increased connective tissue infiltration; smooth muscle hypertrophy and disintegration; decreased autonomic neuronal number; and conversion from predominantly β-adrenergic (inhibitory) to α-adrenergic (stimulatory) responsiveness.
Detrusor overactivity	Detrusor overactivity (DO) is found in about two-thirds of men with BOO. Causality is unclear as DO occurs in normal asymptomatic older men and women. DO resolves in up to two-thirds of men after TURP, yet tends to persist in older adults.
Atherosclerotic disease	May cause detrusor ischemia leading to impaired contractility, and acute BOO from prostate infarction.
Neurologic disease	Depending on type and location of involvement, may cause DO, impaired contractility, and/or sphincter dysfunction including neurologically mediated BOO.

BPH, benign prostatic hyperplasia; BPE, benign prostatic enlargement; BOO, bladder outlet obstruction; LUTS, lower urinary tract symptoms; TURP, transurethral resection of the prostate.

Risk Factors

Factors associated with the development of benign prostate disease and LUTS include age, physical inactivity, high meat and fat intake (especially polyunsaturated fats), diabetes, high insulin levels, obesity, low high-density lipoprotein levels, and arteriovascular disease. Vasectomy is not a risk factor and the data on smoking are inconclusive. Obesity, a diet high in meat and fat, medications (antidepressants), and physical inactivity are potentially modifiable risk factors for BPH and/or LUTS.

EVALUATION

Benign prostate disease may be asymptomatic, but most commonly presents with LUTS; other symptoms include urinary retention, recurrent urinary tract infections (UTI), or hematuria (from prostatic varices). **Figure 44-5** lists the recommended evaluation and management in men presenting with LUTS suggestive of benign prostate disease from the American Urological Association (AUA) 2010 guideline on the management of benign prostatic hyperplasia. The sections below highlight aspects of the evaluation especially relevant to older men.

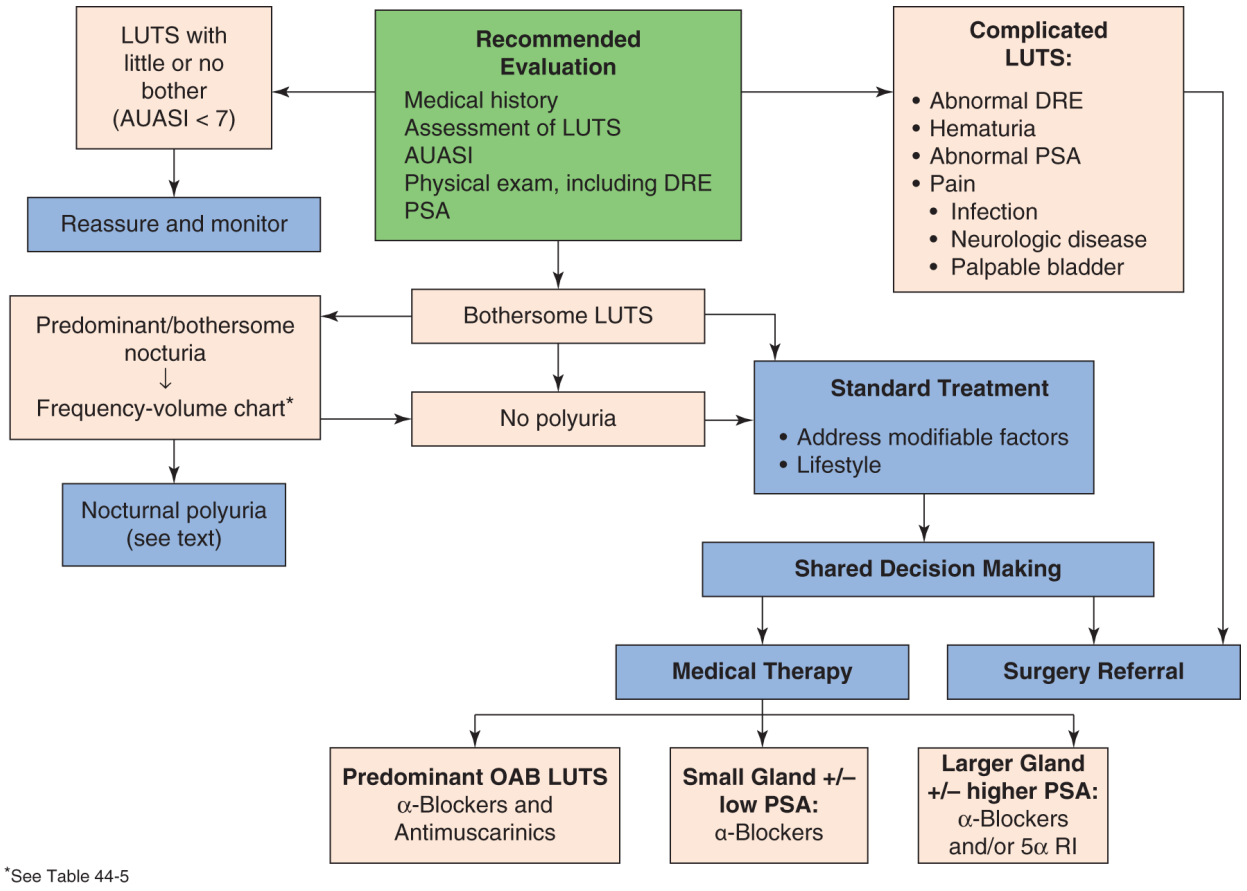


FIGURE 44-5. Algorithm for management of symptomatic benign prostatic hyperplasia (BPH). AUASI, American Urological Association symptom index; DRE, digital rectal examination; PSA, prostate-specific antigen; PVR, postvoiding residual volume; UTI, urinary tract infection. (Adapted from American Urological Association guideline: Management of Benign Prostatic Hyperplasia (BPH), revised 2010. http://www.auanet.org/common/pdf/education/clinical-guidance/Benign-Prostatic-Hyperplasia.pdf. Accessed April 24, 2015.)

History

The evaluation of older men with LUTS closely parallels that of older persons with urinary incontinence (UI; see Chapter 53). The history should include the onset, progression, and associated factors for the common LUTS (slow stream, urgency, nocturia, etc.), and quantification of LUTS using the AUA symptom index (see below). Distinguishing between "irritative" and "obstructive" LUTS is not useful, because the terms are poorly specific and do not correlate with symptom bother, severity, or physiologic measures. Older men always should be evaluated for causes of LUTS other than prostate disease. The history and review of systems should question patients about hematuria, dysuria, and pelvic pain (rare in benign prostate disease, more suggestive of infection, bladder stone, prostate or bladder cancers); episodes of urinary retention; cardiac symptoms (regarding possible congestive heart failure in patients with nocturia); bowel and sexual function; type and amount of fluid intake (in relationship to frequency and nocturia symptoms); and sleep disturbance. All medications (including nonprescription drugs) must be reviewed, with a focus on drugs that can decrease detrusor contractility (anticholinergics, calcium channel blockers), diuretics, drugs that can cause pedal edema, and α-adrenergic agents.

American Urological Association Symptom Index

The American Urological Association symptom index (AUASI) quantifies the severity of BPH-associated LUTS on a scale 0 to 35; scores of 0 to 7 indicate mild symptoms, 8 to 19 moderate, and 20 to 35 severe (**Table 44-2**). An additional question, not tallied in the total score, assesses disease-specific quality-of-life impact. The similar International Prostate Symptom Score (IPSS) is widely translated and identically scored. A change in AUASI of ± 5 points has an 80% probability of indicating a true clinical change. The threshold for clinical change varies with symptoms severity (minimum perceptible difference is two points for AUASI < 20 and six points for AUASI ≥ 20). Any magnitude of change, however, may be caused by interval changes in comorbidity and medications and not prostate disease.

TABLE 44-2 AMERICAN UROLOGICAL ASSOCIATION SYMPTOM INDEX

1. Incomplete emptying: Over the past month, how often have you had the sensation of not emptying your bladder completely after you finished urination?

Not at all	Less than 1 time in 5	Less than half of the time	About half of the time	More than half of the time	Almost always	Your score
0	1	2	3	4	5	

2. Frequency: Over the past month, how often have you had to urinate again less than 2 h after you finished urinating?

Not at all	Less than 1 time in 5	Less than half of the time	About half of the time	More than half of the time	Almost always	Your score
0	1	2	3	4	5	

3. Intermittency: Over the past month, how often have you found that you stopped and started again several times when you urinated?

Not at all	Less than 1 time in 5	Less than half of the time	About half of the time	More than half of the time	Almost always	Your score
0	1	2	3	4	5	

4. Urgency: Over the past month, how often have you found it difficult to postpone urination?

Not at all	Less than 1 time in 5	Less than half of the time	About half of the time	More than half of the time	Almost always	Your score
0	1	2	3	4	5	

5. Weak stream: Over the past month, how often have you had a weak stream?

Not at all	Less than 1 time in 5	Less than half of the time	About half of the time	More than half of the time	Almost always	Your score
0	1	2	3	4	5	

6. Straining: Over the past month, how often have you had to push or strain to begin urination?

Not at all	Less than 1 time in 5	Less than half of the time	About half of the time	More than half of the time	Almost always	Your score
0	1	2	3	4	5	

7. Nocturia: Over the past month or so, how many times did you get up to urinate from the time you went to bed until the time you got up in the morning?

None	1 time	2 times	3 times	4 times	5 times	Your score
0	1	2	3	4	5	

ADD UP THE SCORES FOR THE TOTAL AUA SCORE =

Quality of Life Due to Urinary Symptoms: If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? (circle)

Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible

Adapted from Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. J Urol. 1992;148:1549–1557.

The Benign Prostatic Hyperplasia Impact Index (BII) measures the impact of BPH-associated LUTS on a scale 0 to 13 (**Table 44-3**). Results from randomized controlled treatment trials suggest that the minimal clinically perceptible difference for the BII is a mean decrease of 0.5 to 1.7 points. BII correlates well with the AUASI, but not with objective measures of BPH-associated LUTS severity (eg, urine flow rate or prostate size).

TABLE 44-3 BENIGN PROSTATE HYPERPLASIA IMPACT INDEX

Over the past month:	**0**	**1**	**2**	**3**		Score
1. How much physical discomfort did any urinary problems cause you?	None	Only a little	Some	A lot		
2. How much did you worry about your health because of any urinary problems?	None	Only a little	Some	A lot		
3. Overall, how bothersome has any trouble with urination been during the past month?	Not at all bothersome	Bothers me a little	Bothers me some	Bothers me a lot		
	0	**1**	**2**	**3**	**4**	
4. How much of the time has any urinary problem kept you from doing the kind of things you would usually do?	None of the time	A little of the time	Some of the time	Most of the time	All of the time	
					Total Score:	

Adapted from American Urological Association Education and Research, Inc. McVary K, Roehrborn C, Avins A, et al. American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH), Revised 2010.

Other Measures of LUTS and Quality of Life

There are a variety of other measures of LUTS and their impact. Some of the more widely used are the International Consultation on Incontinence Questionnaire (ICIQ) male module (ICIQ-MLUTS). To assess sexual function, the Derogatis Interview for Sexual Functioning Self-Report and the International Index of Erectile Function can be used. Depending on the patient's symptoms, other potentially useful scales are the Incontinence Impact Questionnaire and ICIQ Urinary Incontinence Short Form, and UI-specific and general quality-of-life measures; for example, ICIQ-LUTSqol, Urogenital Distress Inventory, Urge Impact Scale, and the SF-12.

The impact of LUTS on quality of life is critical to evaluate because it is the primary determinant of treatment. Quality-of-life impact may include interference with daily activities, work, sleep, and sexual function; worry, embarrassment, and impaired self-esteem; and physical discomfort. Patients' perception of bother may be independent of LUTS severity, and bother from an individual symptom may be more important than from all symptoms. Determining a patient's most bothersome symptom can help target evaluation and treatment; for example, nocturia is often extremely bothersome, yet many prostate-specific treatments are not very effective for it.

Nocturia

Nocturia is defined as voiding at least once during the normal hours of sleep. Almost 80% of older men have nocturia, which is the most bothersome of all of the LUTS associated with benign prostate disease. The three main causes of nocturia are LUT pathophysiology, nocturnal polyuria, and sleep disturbance (**Table 44-4**). The latter two causes are

especially important in older men because of the many age-related changes, comorbid conditions, and medications that can cause them.

TABLE 44-4 CAUSES OF NOCTURIA

- **1. Nocturnal polyuria**
  - a. Age-related delay in urine excretion
  - b. Fluid intake
    - i. Late afternoon and evening intake
    - ii. Caffeine
    - iii. Alcohol
  - c. Peripheral edema
    - i. Venous insufficiency
    - ii. Congestive heart failure
    - iii. Medications
      1. Gabapentin
      2. Pregabalin
      3. Thiazolidinediones
      4. Nonsteroidal anti-inflammatory agents
      5. Pyridine calcium blockers (eg, nifedipine)
  - d. Medical conditions
    - i. Obstructive sleep apnea
    - ii. Uncontrolled diabetes mellitus
- **2. Sleep disturbance**
  - a. Insomnia
  - b. Depression
  - c. Congestive heart failure
  - d. Obstructive sleep apnea
  - e. Pain (eg, arthritis)
  - f. Restless leg syndrome
  - g. Medications
    - i. Stimulants
    - ii. β-Blockers
    - iii. Steroids
    - iv. Thyroxine
    - v. Selective serotonin reuptake inhibitors antidepressants
    - vi. Withdrawal from alcohol, narcotics, benzodiazepines
- **3. Lower urinary tract dysfunction**
  - a. Decreased functional bladder capacity
    - i. Detrusor overactivity
    - ii. Increased postvoiding residual volume
      1. Impaired contractility
      2. Outlet obstruction

Nocturnal polyuria is defined as the excretion of one-third or greater of the daily (24-hour) urine output during normal sleeping hours. Older persons are prone to nocturnal polyuria, possibly due to higher nocturnal atrial natriuretic peptide levels and/or altered secretion of vasopressin. Some older person may excrete 50% or more of their 24-hour

urine output during the night. For this reason, one episode of nocturia is considered normal in older persons and even the best treatment may not be able to completely eliminate nocturia. Another cause of nocturnal polyuria is peripheral edema when fluid mobilizes when the patient reclines, leading to increased urine output. Sleep apnea is an underappreciated cause of nocturnal polyuria; apnea should be suspected when the patient or his partner report loud snoring, apneic periods, excessive daytime sleepiness, and morning headaches, and in men who are obese and/or have hypertension.

When aroused owing to primary sleep disorders, patients may sense their bladder volume (which tends to be higher at night) and get up and void, and report these episodes as "nocturia." Common causes of sleep disturbance in older persons include age-related changes in sleep architecture (see Chapter 49), pain (eg, from arthritis), depression, restless leg syndrome, gastric reflux, pulmonary and cardiac diseases, dementia, Parkinson disease and the effects of many medications.

Physical Examination

Given the many medical causes of LUTS in older men, a complete physical examination is required and should include evaluation of cognition, function, and mobility. In men with impaired emptying without other evident cause, a neurologic examination should include the bulbocavernosus reflex, anal wink, and perineal sensation to assess sacral nerve integrity. Digital rectal examination (DRE) should be done to assess prostate nodularity, rectal tone, masses, and stool impaction. DRE is not accurate for assessing prostate volume, even when performed by specialists, because BPH adenomas can occur in the anterior and median lobes that are inaccessible to rectal palpation. Prostate volume is not associated with BOO, and is important only for decisions regarding surgical approach for prostatectomy. Although higher volume is associated with disease progression, it should not be routinely assessed for this purpose because accurate measurement requires ultrasound.

Laboratory Tests

Only urinalysis is needed in routine assessment, primarily to check for microscopic hematuria. The decision of whether to do PSA testing in men with LUTS should follow the recommended guidelines for prostate cancer screening (see Chapter 98). The US Protective Services Task Force recommends against all screening, while the 2013 updates of the AUA and American Cancer Society guidelines both recommend shared decision making for men greater than 50 to 55 years and against screening men greater than 70 or with fewer than 10 years remaining life expectancy. Serum creatinine is not required because of the extremely low prevalence of renal insufficiency in men with LUTS. Vitamin B_{12} level may be considered in men with a high PVR or urinary retention.

Postvoiding Residual and Urine Flow Rate

PVR is not needed in the initial evaluation, especially in men with mild-moderate LUTS who can be managed with watchful waiting or medical therapy. PVR is small in randomly selected community men (75th percentile, 35 mL). In a large trial of men with moderate LUTS, the baseline mean PVR was 110 ± 74 mL. PVR correlates modestly with prostate volume, but is not significantly associated with age, AUASI, quality-of-life indices, BOO, or the need for invasive therapy.

PVR should be considered in men with complex neurologic disease (eg, Parkinson disease, spinal cord injury), new impairment in renal function without other evident cause, medications that can decrease detrusor contractility (anticholinergics, opiates, calcium channel blockers), or who have failed empiric therapy. Inability to pass a urethral catheter for PVR measurement is more likely a result of sphincter spasm than BOO; this can be overcome using intraurethral lidocaine jelly and patient relaxation. Older men tend to have a larger PVR in the morning, which can increase within-patient PVR variability.

Urine peak flow rate measurement is commonly used in urologic practice and is recommended in the AUA guideline. Low urine flow rate is not specific for BOO, as it can also occur with in impaired detrusor contractility (intrinsic or extrinsic [eg, from medications]) and/or a low bladder volume. A normal peak flow rate is very sensitive for BOO (peak flow > 12 mL/s with void ≥ 150 mL excludes BOO).

Bladder Diaries (Frequency-Volume Charts)

Although not specified by the AUA guideline, bladder diaries can be very helpful to determine if polyruria contributes to frequency and/or nocturia symptoms (**Table 44-5**). To complete the diary, the patient records the time and volume

of all voids (continent and incontinent). Several studies (albeit primarily in women) confirm that bladder diaries are reliable and valid, especially when done for 3 days.

TABLE 44-5 USE OF A FREQUENCY-VOIDING CHART IN THE EVALUATION OF LUTS AND NOCTURIA

DATE	TIME	VOIDED VOLUME (ML)	ARE YOU WET OR DRY?	ESTIMATED LEAKAGE	COMMENTS	
4/5	3:05 PM	240	Dry			
	6:10 PM	210	Dry		Beer with dinner	
	8:15 PM	150	Dry			
	10:20 PM	150	Dry			
	10:30 PM	45	Dry		Went to bed	
4/6	3:15 AM	270	Wet	Tablespoons		
	5:50 AM	300	Dry			
	7:40 AM	120	Dry		Coffee	Total nocturnal output = 690
	9:50 AM	60	Dry			
	11:20 AM	90	Dry			
	12:50 PM	120	Dry			
	1:40 PM	120	Dry			
	3:35 PM	90	Dry			
	6:00 PM	90	Dry			
	8:40 PM	215	Dry			
	10:25 PM	180	Dry		Went to bed	Total daytime output = 965
4/7	1:00 AM	240	Dry			
	3:50 AM	400	Dry		Almost didn't make it	
	5:20 AM	200	Dry			
	8:00 AM	180	Dry		Coffee	Total nocturnal output = 1020
	11:15 AM	90	Dry			
	4:00 PM	120	Dry			

Bladder diary of 75-year-old man with LUTS and bothersome nocturia. Shaded portions are the nighttime urine output (from time of sleep up to and including first morning void). The diary demonstrates nocturnal polyuria ranging from 690 to 1020 mL. On 4/6, nocturnal polyuria constituted ~ 50% of the 24-hour urine output (965/[1020 + 965]). The diary also demonstrates the common finding of lower voided volumes during the day compared to night (60–240 mL vs 45–400 mL). Even with the higher functional bladder volume at night, the volume of polyuria ensures that he would have to awaken to void almost three times (1020 mL/400 mL = 2.6 voids). Thus, the evaluation of this patient should first focus on possible non-LUT causes of nocturnal polyuria.
Adapted from DuBeau CE, Resnick NM. Evaluation of the causes and severity of geriatric incontinence: a critical appraisal. Urol Clin N Amer. 1991;18:243–256.

Specialized Testing

Urodynamic studies Urodynamic studies are not needed in the initial evaluation of men with LUTS, especially for those manageable with watchful waiting or medical therapy. Even for men considered for surgery, the AUA guideline considers urodynamics, cystoscopy, and prostate ultrasound optional. Urodynamics should be considered: (1) for frail older men (especially those with Parkinson disease or spinal cord injury) who desire surgical treatment, in order to exclude conditions such as detrusor hyperactivity with impaired contractility; and (2) for men who have failed empiric therapy and in whom further management is desired. The urodynamic tests to evaluate LUTS are cystometry and pressure-flow study. Cystometry measures bladder pressure during filling to determine detrusor stability (vs overactivity), contractility, and compliance. The standard for diagnosing BOO is pressure-flow study, which

simultaneously measures flow rate versus bladder pressure during voiding.

Other tests Cystoscopy is needed only in men with hematuria (especially those with risk factors for bladder carcinoma such as smoking), positive cytology, or pelvic pain; it should not be used to diagnose BOO. Renal ultrasound may be considered in men with new renal impairment, yet even in this group, hydronephrosis is usually only found in men with PVR greater than 150 mL.

MANAGEMENT

Overview

For the majority of men, treatment of benign prostate disease will focus on management of LUTS. Generally, fewer than 10% will need upfront surgical intervention for severe obstruction, urinary retention, or gross hematuria. This section focuses on stepped, evidence-based management of LUTS based on the AUA BPH guideline (see **Figure 44-5** and **Table 44-6**), emphasizing shared decision making. The discussion assumes that contributory multimorbidity, medications, and impairments have been addressed and minimized to the extent possible.

TABLE 44-6 2014 AMERICAN UROLOGICAL ASSOCIATION GUIDELINE: MEDICAL TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

Watchful Waiting
Standard: Patients with mild symptoms of LUTS secondary to BPH (AUASI score < 8) and patients with moderate or severe symptoms (AUASI score ≥ 8) who are not bothered by their LUTS should be managed using a strategy of watchful waiting (active surveillance).
α-Blockers
Option: Alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate and effective treatment alternatives for patients with bothersome, moderate to severe LUTS secondary to BPH (AUASI score ≥ 8). Although there are slight differences in the adverse events profiles of these agents, all four appear to have equal clinical effectiveness. The effectiveness and efficacy of the four α-blockers appear to be similar (no published efficacy data on silodosin at time of review).
Option: The older, less costly, generic α-blockers remain reasonable choices. These require dose titration and blood pressure monitoring.
Option: The combination of an α-blocker and a 5αRI is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, PSA (as a proxy for volume), and/or enlargement on DRE
Recommendation: Prazosin should not be considered.
5α Reductase Inhibitors
Option: 5αRIs may be used to prevent progression of LUTS secondary to BPH and to reduce the risk of urinary retention and future prostate-related surgery.
Option: The 5αRIs are appropriate and effective treatment alternatives for men with LUTS secondary to BPH who have demonstrable prostate enlargement.
Recommendation: 5αRIs should not be used in men with LUTS secondary to BPH without prostatic enlargement.
Antimuscarinic Agents
Option: Antimuscarinic agents are appropriate and effective treatment alternatives for the management of LUTS secondary to BPH in men without an elevated postvoid residual and when LUTS are predominantly irritative (storage).
Recommendation: Prior to initiation of anticholinergic therapy, baseline PVR urine should be assessed. Anticholinergics should be used with caution in patients with a postvoid residual greater than 250–300 mL.

5αRIs, 5α-reductase inhibitors; AUASI, American Urological Association symptom index; BPH, benign prostatic hyperplasia; DRE, digital rectal examination; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen; PVR, postvoiding residual volume.

Definitions: Standard: A guideline statement is a standard if: (1) the health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions and (2) there is virtual unanimity about which intervention is preferred. **Recommendation**: A guideline statement is a recommendation if: (1) the health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions, and (2) an appreciable but not unanimous majority agrees on which intervention is preferred. **Option**: A guideline statement is an option if: (1) the health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or (2) preferences are unknown or equivocal. Options can exist because of insufficient evidence or patient preferences are divided and may/should influence choices made.

Data from American Urological Association Guideline: Management Of Benign Prostatic Hyperplasia (BPH), revised 2010. http://www.auanet.org/common/pdf/education/clinical-guidance/Benign-Prostatic-Hyperplasia.pdf. Accessed April 24, 2015.

Shared Decision Making

Treatment decisions must be patient centered because benign prostate disease has variable impact on patients and only a small absolute risk of morbidity. No treatment prolongs life or guarantees durable cure, and watchful waiting and lifestyle changes provide relief with little risk for many men. Only the small minority of men with hematuria, significant renal impairment, hydronephrosis, recurrent UTIs, retention, and large PVR (eg, over 200 mL) require immediate referral to a urologist. Issues to discuss in making management decisions include symptom severity and quality-of-life impact, risk for disease progression, preferences for immediate versus delayed symptom improvement, likely treatment outcomes and adverse effects, short- and long-term costs, and ability to comply with long-term monitoring. Providers should offer guidance in tailoring treatment so that men are supported in—and not burdened by—decision making. There are video and print decision aids to help both patients and providers weigh treatment risks and benefits. Men with nocturia should be offered prostate-specific medical and invasive therapy *only* after treatment of any contributing polyuria and/or sleep disturbance.

Multiple medical problems, frailty, and short life expectancy need not preclude treatment of benign prostate disease. The broad range of available therapies permits tailoring to the desired immediacy of symptom relief, avoidance of specific adverse effects, and patient comorbidity. Noninvasive treatment is possible in care settings where adequate clinical monitoring and medication adjustment are possible. Assisted-living residents and other vulnerable men will require either community or inpatient skilled nursing after surgical interventions. Across settings, surgery may not be desirable for men at high risk for in-hospital functional and cognitive decline.

Treatment decisions include the efficacy, durability, and associated adverse effects of therapy. **Table 44-6** summarizes outcomes for the major therapies based on meta-analyses and systematic reviews. **Figure 44-5** shows the suggested treatment algorithm.

Geriatric Medicine Considerations

Management of benign prostate disease and LUTS in older men should incorporate important principles central to the practice of geriatric medicine. These are as follows:

- Goals of care: Specific treatments may be effective for some but not other individual LUTS, and have differing time to maximum effect. It is important to ask these questions: Which LUTS are the most bothersome or troubling to the patient and/or caregiver? How urgent is symptom relief? To what degree is the patient accepting of possible surgical treatment? How does the time course of treatment fit within the patient's remaining life expectancy?
- Avoiding harms from treatment. Several medications used to treat LUTS are included in the Beers criteria of potentially inappropriate medications in older persons. These include antimuscarinics and α-blockers (in patients with falls and previous fractures). LUTS management frequently involves medications or treatments that can cause or worsen erectile dysfunction (ED). The likely harm from a specific treatment in a particular patient must be carefully considered.
- Appropriate prescribing. These principles include starting at the lowest possible dose, and avoidance of drug-drug and drug-disease interactions. For example, all α-blockers can cause significant hypotension (especially in patients with hypertension), several interact with other drugs that induce or inhibit the P450 system, and doxazosin can exacerbate congestive heart failure. The half-lives of silodosin (34 hours) and tamsulosin (15 hours) may permit for off-label, less than daily dosing.

Indications for Urology Referral

Absolute indications for prompt urologic referral and intervention are urinary retention (acute or chronic), recurrent UTIs, bladder stones, and hematuria (gross and microscopic). Urology referral should also be considered for men with LUTS and prior bladder or prostate cancer, history of urethral stricture, complicated neurologic disease (Parkinson disease, spinal cord injury), and those who fail noninvasive treatment.

Medical Therapy

Watchful waiting The natural history of benign prostate disease and the large placebo effects seen in randomized

controlled treatment trials support the use of watchful waiting as a specific intervention. Men most appropriate for watchful waiting have mild to moderate LUTS, are comfortable with this approach, and can be reliably followed. Clinicians should be "watchful" and not passive in following these patients, with regular follow-up, instruction in voiding hygiene, and behavioral approaches to decrease LUTS (see Chapter 53), counseling to avoid medications that can cause retention (eg, over-the-counter "cold" tablets containing α-agonists and antihistamines), and careful monitoring for men on anticholinergics or calcium channel blockers.

Self-management techniques can be effective. One such program, comprising education and reassurance, lifestyle modifications, and behavioral interventions (eg, adjustment in fluid intake), resulted in 30% to 50% less need for medication or surgery than standard care.

In the largest randomized trial of watchful waiting versus transurethral resection of the prostate (TURP) (n = 556 men with moderate LUTS), TURP had significantly greater symptom improvement at 3 years, yet the watchful waiting results were not trivial (mean decrease in symptom score 66% and 38%, respectively). One-third of men on watchful waiting crossed over to TURP, but absolute failure rates with watchful waiting were low (urinary retention 2.9%, PVR > 350 mL 5.8%, worsening LUTS 4.3%). There were no significant differences in sexual function, general well-being, or social activities. The improvement in LUTS was less in men with the least symptom bother, especially after TURP. In the Medical Therapy of Prostatic Symptoms (MTOPS) trial, only 17% of men in the placebo (watchful waiting) arm had "clinical progression" at 4 years, and 80% of these cases were considered "progression" because of AUASI increase of greater than or equal to four points.

Medications (Table 44-7)

TABLE 44-7 MEDICATIONS FOR TREATMENT OF LOWER URINARY TRACT SYMPTOMS IN MEN

α-Blockers	
Nonselective	Doxazosin 4–8 mg once daily Terazosin 2–10 mg once daily
Selective	Tamsulosin 0.4–0.8 mg once daily Alfuzosin 10 mg once daily Silodosin 4–8 mg once daily
5α-Reductase inhibitors	Finasteride 5 mg once daily Dutasteride 0.5 mg once daily
Antimuscarinic agents[a]	Tolerodine ER 4 mg once daily Solifenacin 5–10 mg once daily Fesoterodine 4–8 mg once daily
Phosphodiesterase type 5 inhibitors[a]	Tadalafil 5 mg once daily

[a]Includes only those agents and doses with published evidence.

α-Adrenergic Blockers α-Adrenergic blockers reduce BPH-related LUTS by several proposed mechanisms: decreased contractility of prostatic tissue, capsule, and urethra; increased apoptosis caused by higher levels of tumor growth factor-β; and improved vascular flow to the detrusor. The nonselective agents—terazosin and doxazosin—target α_{1B} and α_{1D} receptors, which are found outside the LUT. Prazosin is not recommended for treatment of BPH-associated LUTS. Selective agents target the α_{1A} receptors that are specific to the prostate, and include tamsulosin (0.4–0.8 mg daily), alfuzosin (10 mg daily), and silodosin (8 mg daily [4 mg with renal impairment]).

Time to onset of action for all α-blockers is 2 to 4 weeks. Randomized controlled trials show no significant differences in LUTS reduction between these agents. Efficacy is greater in men with more severe LUTS, and appears durable, although most long-term data are from open–label trials. α-Blockers do not prevent urinary retention and are not very effective in reducing nocturia.

For all of these agents, withdrawal rates in published trials are 10% to 15%, and may be higher in clinical practice. All can cause asthenia, headache, dizziness, and hypotension. Slow titration from minimal starting doses and nighttime dosing help mitigate first-dose hypotension. Alfuzosin should be taken within an hour of a meal to maximize bioavailability. Although seemingly parsimonious, α-blockers should not be used as first-line antihypertensive agents

in men with LUTS and hypertension.

Nonselective agents have higher rates of dizziness and orthostatic hypotension, and can precipitate or worsen congestive heart failure. The selective agent tamsulosin is associated with retrograde ejaculation and a high risk of floppy iris syndrome during cataract surgery. To prevent the latter complication, special surgical approaches are necessary and men taking tamsulosin should alert their ophthalmologist. The impact of stopping tamsulosin preoperatively is unclear, as some cases occurred months after discontinuation. Concomitant use of phosphodiesterase type 5 inhibitors (PDE-5) for ED can cause potentially dangerous hypotension with all α-blockers except tamsulosin.

5α-Reductase Inhibitors The 5αRIs finasteride and dutasteride decrease prostate size by blocking the 5α reduction of testosterone to dihydrotestosterone, the active androgen for prostate growth. 5αRIs decrease prostate volume over 6 months by a maximum of 30%. They have a slow onset of action, and improvement in LUTS may take 6 to 10 months; they should not used when men want rapid symptom improvement or life expectancy is short. Lifetime use is necessary to prevent recurrent BPE and LUTS, raising the potential for higher lifetime treatment costs. In one study, finasteride was more cost-effective for men with moderate LUTS than watchful waiting (up to 3 years) and TURP (up to 14 years), but cost-effectiveness decreased over time.

Unlike α-blockers, 5αRIs are considered "disease modifying" because they decrease the risk of BPE-related complications (ie, worsening symptoms, AUR, need for surgery). This was first established in the PLESS trial (Proscar Long-term Efficacy and Safety Study) in men with moderate to severe LUTS and BPE. Finasteride decreased the incidence of AUR (absolute risk reduction [ARR] 5% [95% CI 10%–5%], number needed to treat [NNT] 26–49), and prostatectomy (ARR 4% [95% CI 7%–3%], NNT 18–31). Risk reduction was apparent by 1 year and was greatest in men with large glands (prostate volume > 58 mL and/or PSA ≥1.4 ng/mL). Similar results were seen with dutasteride in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial. At baseline men had prostate size greater than 40 mL and AUASI less than 8. At 4 years, clinical progression occurred in 21% in men taking dutasteride versus 36% in men on placebo (NNT 7). Sexual dysfunction with finasteride was 8% greater than placebo (absolute difference).

Although 5αRIs maintain or even increase serum testosterone levels, they can cause adverse sexual effects including decreased libido (6%) and impotence (8%). A subanalysis of PLESS found no effect of finasteride on bone density, and a subsequent case-control study found no association between 5αRIs and hip fracture.

The relationship between 5αRIs and prostate cancer is complex. 5αRIs decrease PSA levels by 40% to 60% in the first year. In older men treated with 5αRIs for whom prostate cancer screening is appropriate (which should be uncommon), PSA should be monitored and biopsy done if PSA remains stable or rises. There is concern about an increased risk of high-grade prostate cancer with long-term use of 5αRIs (ie, 4 years). In the initial report from the Prostate Cancer Prevention Trial (PCPT), finasteride lowered prostate cancer rates (18% vs 24% with placebo), but there was a statistically significant increase in high-grade cancer in the finasteride group (6.4% vs 5.1%). Results were very similar in the subsequent REDUCE trial with dutasteride: overall prostate cancer rates were lower with the 5αRI (22.8% relative reduction, absolute reduction 5%), but there were significantly more high-grade tumors. However, a higher rate of high-grade tumors was still present but no longer statistically significant in the 2013 PCPT analysis with an extra year of data. Furthermore, at 10-year analyses, there were no differences in overall or prostate cancer–specific mortality.

Antimuscarinic Agents for Urgency Incontinence and Overactive Bladder Men typically are most bothered by the LUTS storage symptoms (urgency, frequency, nocturia), which are less responsive to prostate-specific interventions than the LUTS voiding symptoms. This lead to interest in antimuscarinic agents. Tolterodine, fesoterodine, and solifenacin have been the primary agents studied, with most studies done in combination with α-blockers (see Combination Therapy below). Available data suggest that antimuscarinic monotherapy has minimal to moderate efficacy, although the risk of retention appears small (eg, 5% with fesoterodine). The TIMES trial (tolterodine and tamsulosin in men with LUTS including overactive bladder: evaluation of efficacy and safety) compared tolerodine ER, placebo, and tamsulosin alone with tolterodine ER plus tamsulosin. Patient report of benefit occurred in 65.1% of men on tolterodine alone versus 61.7% on placebo (NNT 333); however, urgency incontinence was significantly reduced with tolterodine ER versus placebo. Further analysis found no effect of tolterodine ER monotherapy on the IPSS storage subscale.

Phosphodiesterase Type 5 Inhibitors Randomized trials demonstrate statistically significant but modest decreases in AUASI with daily doses of PDE-5 inhibitors used for ED. Trials have included tadalafil 5 mg daily, vardenafil 10 mg daily (only studied in men < 65 years), and sildenafil 25 mg daily, but only daily tadalafil is FDA approved for

treatment of male LUTS.

PDE-5 inhibitors may decrease BPH-associated LUTS by regulation of smooth muscle tone and tissue oxygenation. However, there is ongoing controversy about whether the observed efficacy of PDE-5 inhibitors for LUTS is a direct effect or secondary to subjects being "unblinded" to their randomization to drug by improvement in ED symptoms. A review of four randomized trials found no significant interaction of baseline ED severity and improvement in IPSS, and similarly no significant interaction between baseline IPSS severity and ED outcomes.

Combination Therapy

α-Adrenergic blockers and 5αRIs. Because of their different mechanisms of action, combination treatment with α-blockers and 5αRIs have the potential for additive benefit. The pivotal Medical Therapy of Prostate Symptoms (MTOPS) study randomized nearly 3000 men with moderate LUTS to placebo, doxazosin, finasteride, or both drugs with a mean follow-up of 4.5 years. The primary outcome was "clinical progression," not LUTS reduction. At 1 year, only doxazosin (alone or in combination) was significantly more effective than placebo, but at 5 years, finasteride was more effective than doxazosin, and combination therapy more effective than either finasteride or doxazosin alone (albeit with high withdrawal rates and adverse effects). Men with baseline prostate volume greater than 40 mL and/or PSA greater than 4 ng/mL benefited the most from combination therapy. Disease progression was associated with rising PSA and prostate volume during the trial in men on placebo or doxazosin, but not finasteride or combination therapy. The Symptom Management After Reducing Therapy (SMART) trial evaluated whether the efficacy of short-term combination therapy could be maintained with a 5αRI alone. After 24 weeks of dutasteride ± tamsulosin, stop tamsulosin-caused increased symptoms only for men with severe baseline LUTS. The CombAT trial (Combination of Advodart and Tamsulosin) randomized men with symptomatic LUTS to tamsolusin 0.4 mg, dutasteride 0.5 mg daily, or both. At 4 years, AUR or surgery occurred in 4.2% on combination therapy, versus 5.2% with dutasteride and 11.9% with tamsulosin. Symptom progression was less likely with combination (12.6%) than dutasteride (17.8%) or tamsulosin (21.5%).

α-Adrenergic blockers and antimuscarinics. The appeal of this combination is targeting of both storage and voiding symptoms. Although most studies of these combinations show general safety and efficacy, studies usually added antimuscarinic on to established α-blocker therapy, only included men with PVR less than 200 mL, and had a relatively short follow-up (12 weeks, maximum in one study for 4 months). For example, in a 12-week trial of tamsulosin and extended-release tolterodine (n = 979, 25% aged ≥ 70 years), 80% of men on combined therapy had subjective improvement, versus 71% with tamsulosin alone, 65% with tolterodine, and 62% with placebo. AUR occurred in three men on placebo, two on tolterodine, and two on combination therapy. Fesoterodine (flexible dose 4–8 mg) was not more effective than placebo in reducing urgency in men already on an α-blocker, but it did statistically improve overactive bladder—specific quality of life and urinary frequency. Acute retention occurred in 2% to 3% of men on fesoterodine versus 1% on placebo.

α-Adrenergic blockers and PDE-5 inhibitors. Trials of this combination have been small; a meta-analysis included only 278 patients, and the decrease in IPSS was statistically significant but small (1.8 points). Tadalafil is approved as a single agent for treating LUTS and ED.

Phytotherapy Plant-derived compounds that have been used to treat BPH-related LUTS, especially outside of the United States, include saw palmetto, β-sitosterols, and cernilton. Most phytotherapy trials suffer from short-term treatment (typically 4–24 weeks) and lack of standardized preparations. Although a Cochrane systematic review concluded that saw palmetto significantly improved LUTS and decreased nocturia, in a recent 1-year trial saw palmetto had the same AUASI and quality-of-life outcomes as placebo among men with moderate to severe LUTS. Cochrane meta-analyses also have concluded that β-sitosterols and cernilton significantly reduce LUTS, but the source trials were heterogeneous and small. Phytotherapeutic agents have few reported side effects, but long-term data are lacking.

Emerging Therapies Several agents that act on neurotransmitters and trophic factors other than α-adrenergic systems and androgens are under active investigation. In small trials, intraprostatic injection of botulinum toxin A decreases prostate size and IPSS. There are limited data yet on effect size and duration, impact on other outcomes and disease progression, and adverse effects. A randomized trial of the calcitriol analog BXL-353 is underway. Several reviews suggest that nonsteroidal anti-inflammatory agents may have efficacy, yet their toxicity in older patients would limit long-term therapy.

SURGERY

Transurethral Resection of Prostate

TURP remains the gold standard surgical treatment for symptomatic benign prostate disease, with level 1 evidence of robust and durable symptom improvement. The absolute indications for TURP are high-grade BOO, urinary retention (medical causes excluded), recurrent urinary infections, gross hematuria, bladder stones, and hydronephrosis with renal insufficiency. Outside of these situations, the primary reasons for surgery are moderate to severe symptoms with patient bother and lack of efficacy or poor tolerability of medical therapy.

TURP is highly effective, resulting in up to 90% decrease in LUTS and 10-point decrease in AUASI. Impact on symptoms may be less in older men (< 80% decrease in symptoms). TURP is superior to watchful waiting in preventing worsening LUTS, elevated PVR, and AUR over 5 years (10% vs 21%, NNT 9). Urodynamic evaluation may be helpful in identifying men most likely to have the best symptomatic outcomes, that is, those with BOO and without detrusor overactivity or underactivity. Efficacy declines over time, from 87% decrease in LUTS at 3 months to 75% at 7 years, and reoperation rates average 1% to 2% per year. Symptom reduction tends to be lower in older men (< 80%).

There are two types of TURP, the original monopolar resection (M-TURP) and the newer bipolar resection (B-TURP); the difference is that the electrical generator of B-TURP allows for isotonic irrigation fluid. Although the overall quality of evidence is low, four meta-analyses of the more than 30 randomized controlled trials to date suggest that 1-year (and likely longer) symptomatic and objective outcomes from M-TURP and B-TURP are similar, but B-TURP has shorter duration of postoperative catheterization, and less post-TURP syndrome (hyponatremia) and clot retention.

Perioperative complications of TURP have declined over time. Adverse effects of TURP include retrograde ejaculation (74%); ED (mean ~ 14%, and increases with age); immediate surgical complications (12%); UI (5%); bleeding requiring transfusion (2%); failure to void; and infection. In one trial, there was no difference in erectile dysfunction and UI rates between TURP and watchful waiting. Men over age 80 have higher rates of complications (early 30%–40%, late 13%–22%), reoperation (4% per year), and perioperative mortality (2%–3% vs 0.4%), but no change in long-term survival. Older men may be at higher risk of postoperative myocardial infarction, although the level of evidence is weak. Many of the studies in older men, however, did not adjust for increased comorbidity, and there is some evidence that higher Charlson scores are associated with increased morbidity post-TURP.

Laser Prostatectomy

Laser technology is increasingly used as an alternative to TURP. The two main laser systems currently used are holmium laser enucleation of the prostate (HoLEP) and the GreenLight photovaporization of the prostate (PVP). HoLEP provides similar outcomes to open prostatectomy for men with AUR with significant BPE. In a multicenter, industry-sponsored randomized controlled trial in 269 patients, PVP was noninferior to TURP regarding symptom score outcomes and postoperative interventions at 6 months. PVP patients had shorter catheterization times (by ~ 20 hours) and shorter hospital stay (by ~ 30 hours). A systematic review of PVP versus TURP trials reported similar results, except that quality-of-life scores were better with TURP at 6 months. HoLEP provides results similar to TURP with less bleeding and shorter recovery time, but the technique can be more difficult to learn. Initial studies suggest that HoLEP may produce more durable results than other laser surgeries. Photoselective vaporization of the prostate also has similar efficacy as TURP, with less bleeding and a shorter recovery; it appears to work better for smaller prostates. Transurethral evaporation of the prostate is used less frequently.

In one randomized controlled trial, TURP was superior to noncontact lasers in improving LUTS and quality of life at 7 months, but outcomes were equivalent at 1 year. The sole 5-year study found higher reoperation rates with laser (38%), despite a TURP reoperation rate (16%) higher than nearly any other study. Laser procedures require longer postoperative catheterization and cause more infections and urethral irritation than TURP. Side effects vary by technique, and can include impotence, retrograde ejaculation, increased urgency and frequency, UI, and bladder neck stricture.

Open Prostatectomy

Men with very large prostate volume (> 60 mL) require open prostatectomy (via an abdominal or perineal approach) because the operative time needed for TURP in these cases significantly increases perioperative complications. Open

procedures account for less than or equal to 5% of prostatectomies, and some surgeons prefer to perform an "incomplete" TURP to avoid the morbidity of abdominal or perineal surgery. In retrospective studies, open prostatectomy has lower reoperation rate and mortality than TURP, but these analyses did not adequately control for the higher age and comorbidity in TURP patients or the secular trend of decreasing TURP mortality.

Minimally Invasive Procedures

Prostate incision Transurethral incision of the prostate (TUIP) is a technically simpler procedure used in men with small glands (< 30 mL). TUIP is done under local anesthesia with shorter operation time and less bleeding than TURP. TUIP has similar symptomatic efficacy to TURP at 1 year. In a select case series, at 2 years only 8% of TUIP patients had required a subsequent TURP. TUIP has the potential to be a safe and effective alternative for obstructed older men with smaller prostates who have high operative risk and have failed noninvasive treatment.

Thermotherapy Transurethral needle ablation (TUNA) employs transurethrally placed radiofrequency needles to heat prostate tissue, causing coagulation necrosis and a tissue defect. Symptomatic efficacy is lower and less durable than with TURP, and no studies compare TUNA to other procedures, medical therapy, or watchful waiting. Transurethral microwave thermotherapy is a related outpatient procedure that requires repeated treatments. Symptomatic improvement is typically modest, and in short-term trials is inferior to TURP, sham procedures, and terazosin. The future of these procedures is uncertain.

Stents Urethral stents to facilitate voiding should be reserved for high-risk patients with recurrent AUR who are unfit for surgery or for whom long-term indwelling catheterization is undesirable. Permanent absorbable stents are complicated by encrustation, pain, and infection, and failure rates run 20% to 30%. Nonabsorbable temporary stents are complicated by migration, UTI, stricture, and encrustation.

PREVENTION

Data on risk and protective factors suggest that increased physical activity, a diet low in meat and fat and high in vegetables and micronutrients, and moderate alcohol consumption may prevent or slow the progression of benign prostate disease. Weight loss for obese men, glycemic control in diabetes, and treatment of high cholesterol also may be important. However, there are no intervention trials to support these suggestions.

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Part III

Geriatric Syndromes

Chapter 45.	Aging and Homeostatic Regulation
Chapter 46.	Frailty
Chapter 47.	Delirium
Chapter 48.	Falls
Chapter 49.	Sleep Disorders
Chapter 50.	Dizziness
Chapter 51.	Syncope
Chapter 52.	Pressure Ulcers
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Chapter 45

Aging and Homeostatic Regulation

George A. Kuchel

Learning Objectives

- Understand the concepts of homeostasis and homeostenosis.
- Describe the impact of aging on homeostatic mechanisms which help maintain a normal physiologic body temperature in the face of lowered or increased ambient temperature.
- Describe the clinical features—including epidemiology, symptoms, signs, results of diagnostic tests and treatment—of both hypothermia and hyperthermia.
- Describe the impact of aging on the ability to maintain a normal blood pressure in the face of orthostasis, meal ingestion, and hypovolemia.

Key Clinical Points

1. **Homeostasis reflects the aggregate effect of varied mechanisms that maintain normal physiologic constancy in the face of different extrinsic challenges. Aging is associated with impaired homeostasis, or homeostenosis, in the form of diminished capacity to respond to varied challenges.**
2. **Aging is associated with a failure of several different homeostatic mechanisms that enhance the risk of hypothermia in the face of decreased ambient temperature.**
3. **Aging is associated with a failure of homeostatic mechanisms which enhance the risk of hyperthermia and heatstroke in the face of increased ambient temperature.**
4. **The clinical presentation of hypothermia and hyperthermia may be subtle in the older adults, requiring a high index of suspicion and careful supportive management in order to avoid the high rate of mortality associated with these conditions in late life.**
5. **Aging is also associated with homeostatic deficits when confronted with the assumption of the upright posture, eating, hypovolemia or a fluid challenge, increased or decreased sodium level, increased or decreased glucose level, bladder filling or bladder outlet obstruction, major burns or trauma, bed rest, or exercise.**
6. **Features of homeostatic dysregulation in old age include diminished physiologic reserve, loss of complexity, enhanced variability, normal or enhanced basal activity, excess response to stressors in terms of the sympathetic nervous system, diminished end-organ responsiveness, and loss of negative feedback.**
7. **The accumulation of repeated exposure of such challenges resulting in an increased biological burden—termed allostatic load has been shown to be predictive of mortality and frailty including future declines in cognitive and physical function.**

"Besides more or less obvious physical changes in old age, physiological investigation may reveal increasing limitation of the effectiveness of homeostatic devices which keep the bodily conditions stable."

BACKGROUND

Older patients present the clinician with many unique challenges. Many of these are fully discussed in chapters that address the care of older adults in the context of individual organ systems and diseases. However, some of the most complex, common, debilitating, and costly clinical problems seen in geriatrics are extremely challenging precisely because they defy conventional medical wisdom by crossing traditional organ- and discipline-based boundaries. Termed "geriatric syndromes," conditions such as frailty (Chapter 46), delirium (Chapter 47), falls (Chapter 48), sleep disorders (Chapter 49), dizziness (Chapter 50), syncope (Chapter 51), pressure ulcers (Chapter 52), incontinence (Chapter 53), and elder mistreatment (Chapter 54) are discussed individually. Nevertheless, given the central importance of these diverse conditions to the practice and science of geriatric medicine, it is also important to address their common features.

In addition to being highly prevalent in frail olders, geriatric syndromes also exert a substantial impact on quality of life and disability. Moreover, these are complex multifactorial conditions in which large numbers of underlying and provocative risk factors involving different organ systems interact in influencing ultimate clinical presentation, course, response to treatment, and outcome. These unusual features present important challenges for the clinician since the patient's chief complaint may point away from, rather than toward, the specific pathologic condition that actually underlies the change in health status. At times, the two processes may involve distinct and distant organs with an apparent "disconnect" between the site of the underlying insult and the site involved in specific functional declines and/or clinical symptoms as reported by the patient. For example, when an infection involving the urinary tract precipitates delirium, it is the altered neural function in the form of cognitive and behavioral changes, which permits the diagnosis of delirium and determines many functional outcomes.

Grouping distinct conditions together as geriatric syndromes also highlights those common features that may help in the development of innovative clinical and research strategies. One of the primary goals of geriatric medicine has been to maintain functional independence in frail older adults, addressing the very common scenario of an older patient who is able to maintain usual function under basal conditions, yet decompensates when exposed to seemingly common day and even minor challenges. In fact, the clinical dilemma of a frail older adult who is at significant risk of delirium, falls, or incontinence can be restated within a homeostatic framework. Viewed in this manner, function is determined by a complex balance between underlying physiology and health, the nature, number, and intensity of the challenges being experienced, as well as overall physiologic plasticity expressed as the effectiveness of relevant homeostatic mechanisms. This approach has several advantages, above all, permitting a clinical and research conceptualization of health and aging which moves beyond traditional paradigms and to an approach which is able to capture the highly dynamic and multifactorial reality of geriatric care.

HOMEOSTASIS IN A HISTORICAL CONTEXT

The term homeostasis was first coined by Claude Bernard in the mid-nineteenth century and is now extensively used in the medical literature. Unfortunately, it is often forgotten that homeostasis has always referred to the body's attempts at maintaining an internal constancy, which is required for optimal function. Far from reflecting physiologic "stasis," effective homeostasis actually requires that all relevant compensatory mechanisms remain suitably vibrant, responsive, and well calibrated. During the twentieth century, it became increasingly clear that overall health status, as well as many individual disease processes may impair an individual's ability to appropriately respond to common homeostatic challenges. The recognition that aging can also exert a measurable impact on homeostatic mechanisms came later, but is not recent, as illustrated by the 1932 quote preceding this chapter from the great physiologist Walter Cannon. Finally, in the modern era, several events have greatly impacted upon our understanding of homeostasis. In an extension of the concept of homeostasis, Yates has introduced the term homeodynamics to emphasize the concept that the resiliency of living organisms requires a dynamic interplay of multiple regulatory mechanisms rather than a constancy of the internal environment. Advances in basic research have also permitted investigators to explore homeostatic principles at the level of subcellular processes ranging from gene expression to protein turnover. Most recently, some of the limitations inherent in purely reductionist studies have led to a trend toward systems biology, emphasizing an integration of relevant homeostatic processes from the level of individual cells to tissues and

organisms. Moreover, it is now possible to begin defining mechanisms in a manner which reflects the multifactorial and systemic nature of typical geriatric conditions or syndromes.

HOMEOSTATIC REGULATION IN OLD AGE

General Considerations

Physiologic systems responsible for maintaining homeostatic regulation may control variables as divergent as body temperature, blood pressure, intracellular calcium, or serum cortisol. At the same time, even among distinct systems, it is possible to observe shared common physiologic principles by which they all exert homeostatic control (**Table 45-1**). With these considerations in mind, a number of investigators have sought to identify unifying and preferably specific "fingerprints" by which aging affects homeostatic control within different physiologic systems.

TABLE 45-1 ■ COMMON FEATURES OF HOMEOSTATIC DYSREGULATION IN OLD AGE

CONCEPT	EXAMPLES
Homeostenosis	Diminished capacity to respond to varied homeostatic challenges such as changes in ambient temperature, orthostasis, fluid load, or dehydration
Diminished physiologic reserve	Increased homeostatic vulnerability as a result of a critical loss in numbers of neurons or a decline in glomerular filtration rate
Loss of complexity	Declines in bone or neuronal architecture; narrowing of hearing frequency responses or loss of long-range correlations in blood pressure readings
Enhanced variability	Greater inter- and intraindividual variability in sympathetic activity or blood pressure readings
Higher basal activity	Basal sympathetic activity is elevated in older adults
Excessive response to stressors	Sympathetic responses to common challenges are excessively large and prolonged
Diminished end-organ responsiveness	Ability of peripheral catecholamines to increase heart rate via β-adrenergic receptors or to mediate arterial vasoconstriction via α-adrenergic receptors is decreased
Loss of negative feedback	Ability of corticosteroids to downregulate activity of the hypothalamic-pituitary-adrenal system via negative feedback is diminished
Allostatic load	Increased biological burden in terms of estimates of cumulative exposure exacted by attempts to adapt to life's demands predicts future mortality, as well as declines in cognitive and physical function

Systemic Patterns of Change

Homeostenosis of old age has been viewed as the diminished capacity to respond to various homeostatic challenges. Even healthy older adults may exhibit homeostenosis when exposed to a cold or hot environment, on rapidly assuming the upright posture, and while responding to an acute fluid challenge or hypovolemia. Traditionally, these deficits were attributed to a loss of physiologic reserve, an appealing, yet somewhat ill-defined concept emphasizing static (eg, losses in neuronal numbers, declines in glomerular filtration rate) rather than dynamic explanations. In an effort to better define physiologic factors responsible for the dynamic nature of stability in old age, disease, and frailty, Lipsitz has instead focused on categories of relevant complexity that decline with aging. For example, study of aged bone and brain demonstrates evidence of declining complexity in terms of trabecular or neuronal architecture. Other examples of declining complexity involve physiologic processes such as narrowing of auditory frequency responsiveness, decreased long-range correlations in time series data such as blood pressure measurements, as well as increased randomness or stochastic activity in terms of cardiac intervals. It has been proposed that such alterations in dynamics of physiologic systems contribute to functional decline and frailty. However, changes in complexity should not be confused with those involving variability. These are two distinct concepts, with aging often having distinct and at times directly opposite, effects on complexity and variability. For example, aging *increases* interindividual and intraindividual variability in blood pressure measurements, while long-range correlations involving the complexity of these readings *decrease* with aging. Finally, proponents of the concept of allostatic load have used population-derived measurements

(eg, blood pressure, waist-hip ratio, cholesterol, glycosylated hemoglobin, cortisol, catecholamines, and dehydroepiandrosterone sulfate [DHEA-S]) as an estimate of cumulative physiologic burden exacted on the body through attempts to adapt to life's demands.

Alterations in Specific Homeostatic Mechanisms

In addition to systemic perspectives of homeostasis, there has also been a growing interest in uncovering specific homeostatic mechanisms that are impaired in old age. For example, markers of sympathetic activity such as peripheral norepinephrine (NE) levels are elevated in older adults under basal conditions. At the same time, a variety of different stimuli result in an elevation in peripheral NE levels, which are both enhanced and prolonged in older adults. Another common feature is a decline in end-organ responsiveness of many, but not all, receptors to their relevant ligand in the form of a neurotransmitter or hormone. Finally, decreased tissue responsiveness translates in many cases to lessened effectiveness of negative feedback mechanisms as shown for a number of hormones, including corticosteroids.

Reconciling Different Views of Homeostatic Dysregulation

Many different aspects of homeostatic dysregulation in old age have been emphasized in published studies, often in support of a specific concept or theory. Nevertheless, common unifying principles can sometimes be identified. For example, research conducted using simple gene circuits has shown that negative feedback loops enhance the complexity and stability of such systems, permitting more precise and rapid responses to homeostatic challenges. Thus, declines in negative feedback demonstrated for many mammalian homeostatic systems could also contribute to some of the other commonly described features of homeostatic dysregulation in old age and frailty. Moreover, a marker of "allostatic load" such as peripheral cortisol, is not only a predictor of future cognitive and functional impairment, but can also contribute to neuronal cell death involving hippocampal cells involved in cognition, while also contributing to a decline in the ability of cortisol to downregulate its own synthesis and release.

SPECIFIC HOMEOSTATIC CHALLENGES

General Considerations

As discussed earlier, under normal basal conditions, many older adults are able to maintain their usual level of function even in the presence of a large number of health problems. However, once exposed to additional challenges, the same individuals may experience rapid and at times even catastrophic declines in their health status and functional independence. A growing understanding of normal homeostatic mechanisms has led many investigators to conduct studies evaluating the impact of aging on such responses. **Table 45-2** provides an overview of our current understanding of the impact of aging on the ability to effectively respond to specific homeostatic challenges in terms of the most relevant biomarkers or physiologic measurements. However, it must also be noted that aging may influence some of these measurements under basal conditions. Moreover, since some of these topics are discussed in far greater detail elsewhere in this book, relevant chapter numbers are also provided. Finally, when evaluating the large body of literature that supports the information provided in **Table 45-1**, several overarching principles must be kept in mind. First, while animal studies largely support results of human research, occasional species-specific differences have been noted. Thus, all summary findings in **Table 45-1** are based on human research. Second, clinicians deal with older adults who represent the full spectrum of health, comorbidity, disability, and frailty. Nevertheless, in order to attribute a specific physiologic change to aging, it is important to make a distinction between changes that are caused by confounding illness from those associated with usual or successful aging. With these considerations in mind, most of the changes reported in **Table 45-1** can be attributed to normal or "usual" aging, with common geriatric illnesses often enhancing such vulnerability. In many cases, it remains unknown whether individuals who age particularly well or successfully also exhibit some or all of these changes.

TABLE 45-2 ■ IMPACT OF AGING ON PHYSIOLOGIC RESPONSES TO SPECIFIC HOMEOSTATIC CHALLENGES

HOMEOSTATIC CHALLENGE	SELECTED BIOMARKERS UNDER BASAL CONDITIONS	IMPACT OF AGING ON RESPONSE TO SPECIFIC CHALLENGE	RELEVANT CHAPTERS
"Fight or flight" challenge or	—Norepinephrine ↑	Enhanced and prolonged ↑ in	109

mental stress	—Epinephrine N.C. —Sympathetic neural recordings ↑ —Cortisol levels N.C.	norepinephrine levels, sympathetic neural activity, and cortisol levels	
Decreased ambient temperature	—Temperature N.C. —Metabolic rate ↓	—Sensation of cold ↓ —Shivering intensity ↓ —Thermogenesis ↓ —Vasoconstriction ↓	
Elevated ambient temperature	—Temperature N.C.	—Sweating responses ↓ —Vasodilatation ↓ —Ability to raise cardiac output ↓	
Orthostasis, meals, and hypovolemia	—Blood pressure N.C.	—Hypotension risk ↑ with frailty, comorbidity, and concurrent challenges	51, 75, 89
Hyperglycemia and hypoglycemia	—Fasting glucose N.C. or small ↑	—Glucose clearance ↓ —Response to hypoglycemia N.C. or small ↓	108, 110
Fluid challenge and dehydration	—Serum sodium N.C. —Osmolarity N.C. —Osmolality N.C.	—Ability to retain Na^+ in salt depletion ↓ —Ability to excrete Na^+ in salt loading ↓	89
Bladder outlet obstruction	—Detrusor contractility mildly ↓	—Ability to raise detrusor pressure ↓ —Likelihood of detrusor decompensation with muscle degeneration and fibrosis ↑	53
Major burns and trauma		—With comorbidity favorable outcome ↓	33, 69
Altered physical activity		—Extent and speed of deconditioning ↑ —Extent and speed of gains in muscle mass and strength ↓	29, 33, 116, 117
Anticholinergic medications		—Xerostomia, cognitive problems, constipation, urinary retention ↑	24, 47, 49, 64
Antidopaminergic medications		—Rigidity, poverty of movement ↑	64, 67
Neuronal degeneration		—Compensatory neuronal plasticity ↓	62

N.C., no change

"Fight or Flight Response"

When confronted with a stressful situation, animals and humans respond in a fairly predictable fashion involving a series of predetermined responses collectively referred to as the fight or flight response. Although thought to have evolved as a response to the risk of attack by a predator, in the context of our patients, such responses are more commonly activated during mental stress for any reason, while caring for an ill or disabled spouse or during bereavement. Stress results in the activation of hypothalamic and brainstem neurons, leading to increased stimulation of sympathetic preganglionic neurons, which regulate cardiac and adrenal medullary function. Stress also promotes the release of corticotropin-releasing factor, which in turn increases adrenocorticotropic hormone (ACTH) release. All of these events result in both local and systemic release of corticosteroids and catecholamines, which are ultimately responsible for mediating most of the clinical features of the response to stress. The above sequence of reactions can

ultimately influence a broad range of systemic functions ranging from cardiac performance, energy metabolism, as well as immune and inflammatory responses.

Under basal conditions, the overall sympathetic nervous system (SNS) activity appears to be increased with aging. This basal activity increase is manifested in the form of increased sympathetic nerve activity on microneural recordings, elevated basal plasma NE, and less consistently epinephrine (E) levels, while basal cortisol levels do not appear to be altered with aging. In contrast, both systems demonstrate somewhat similar patterns of dysregulation in old age with enhanced and prolonged responsiveness following exposure to varied challenges. For example, assuming the upright posture, an oral glucose meal, insulin infusion, isometric exercise, and mental stress all result in enhanced elevation of peripheral NE levels in older subjects, while cortisol responses to surgical stress are also increased. Moreover, demonstrated deficits in terms of decreased negative feedback have been proposed as being major contributors to exaggerated SNS and hypothalamic-pituitary-adrenal (HPA) axis activation with aging. For example, the ability of clonidine or elevated blood pressure to downregulate SNS activity via central nervous system (CNS) α_2-receptors or baroreceptor activation, respectively, is impaired in old age. This is in addition to well-described declines in the ability of peripheral catecholamines to increase heart rate via β-receptors or to mediate arterial vasoconstriction via α-adrenergic receptors. Similarly, the ability of circulating corticosteroids to downregulate HPA activity via hypothalamic and hippocampal receptors is also diminished in old age.

Lowered Ambient Temperature

Epidemiology Older adults are less able to adjust to extremes of low temperature. Hypothermia has historically received greatest attention in the United Kingdom, at least in part as a result of a tendency to maintain lower indoor ambient temperatures in the winter than is the custom in the United States. Some of this earlier British literature described hypothermia among 3.6% of individuals 65 years and older admitted to the hospital, with nearly 10% of community-dwelling older adults found to demonstrate evidence of borderline hypothermia. Nevertheless, recent literature has demonstrated a significant prevalence of hypothermia in North America. The US Centers for Disease Control and Prevention statistics point to the fact that hypothermia-related deaths may also occur in sunbelt states and illustrate the importance of advanced age, chronic medical conditions, substance abuse, and homelessness as contributing risk factors. Moreover, a number of individual case series have highlighted the need to remain vigilant to the development of hypothermia among frail and immobile residents of air-conditioned long-term care facilities. Concerns have also been raised about the role played by medications, which may enhance the risk of hypothermia.

Pathophysiology While basal body temperature remains unaltered with aging, older adults are less able to sense and respond to cold challenges when exposed to lowered ambient temperatures. Relevant mechanisms include a decreased sensation of cold, as well as declines in shivering intensity, thermogenesis, and vasoconstriction. Such changes may be related to both physiologic declines associated with aging or with specific diseases. For clinical purposes, hypothermia is generally defined as a body core temperature of less than 35°C (95°F), obtained using tympanic, rectal, or esophageal probes. Nonetheless, significant clinical consequences may occur outside of the boundaries of these definitions. Moreover, the development of frank hypothermia depends on a balance between the severity and length of the cold exposure and an individual subject's ability to sense and mount an effective response to such a challenge. Ultimately, aging, frailty, comorbidity, and diseases may all contribute to determining an individual's specific vulnerability.

Normal body temperature is regulated by the thermoregulatory center, which controls heat loss and heat generation by regulating sweating, blood vessel tone, as well as shivering and nonshivering (chemical) thermogenesis. Older adults demonstrate evidence of deficits in both afferent and efferent thermoregulatory pathways. For example, a diminished sensitivity to changes in environmental temperature may have both physiologic and behavioral consequences. As a result, already compromised compensatory mechanisms may be overwhelmed by the fact that older individuals may be less likely to seek suitable shelter or clothing in the cold. Declines in shivering thermogenesis may be particularly catastrophic in older adults, given the importance of these mechanisms in normal responses to the cold. Other contributing physiologic risk factors for hypothermia include deficient autonomic mechanisms with a decreased vasoconstrictor response, which is more common among older adults with orthostatic hypotension, as well as decreased ability of β-adrenergic stimuli to effect thermogenesis. Of course, decreases in lean body mass with a lower metabolic rate also enhance the vulnerability of older adults. Absence of fat mass may also provide frail older adults with less insulation against heat loss.

A large number of potentially reversible factors also need to be considered. For example, malnutrition,

hypothyroidism, hypoglycemia, as well as immobility and decreased physical activity may all contribute to decreased thermogenesis. Medications, which have been linked to hypothermia, include alcohol, phenothiazines, barbiturates, benzodiazepines, opioids, and general anesthetics, as well as antidepressants and neuroleptics. Central thermoregulatory control may also be affected by hypothalamic neural injury following anoxic, vascular, traumatic, or malignant lesions. Severe sepsis, especially in frail older adults, can occasionally overwhelm host defenses, resulting in a blunted and even paradoxical response to infection with hypothermia. The association of infection with hypothermia is generally viewed as a poor prognostic sign and is felt to reflect altered hypothalamic regulatory function. Finally, a clinician's approach to hypothermia is incomplete without an assessment of the cognitive, social, and economic factors, which may result in self-neglect, poor judgment, or lack of financial resources to provide for adequate heating.

Clinical presentation Early manifestations of hypothermia may be subtle and nonspecific. Moreover, older adults may become hypothermic even without exposure to extremely cold temperatures. Thus, a high index of suspicion is essential, as is a thermometer capable of recording very low temperatures. Early hypothermia (core temperatures of 32°C–35°C or 90°F–95°F) can be associated with fatigue, lethargy, apathy, slow gait, slurred speech, confusion, and cool skin. Challenging the diagnosis is the nonspecific nature of these symptoms and signs, combined with the finding that some hypothermic older patients may not complain of feeling cold and may not shiver. With more advanced hypothermia (core temperatures of 28°C–32°C or 82°F–90°F), skin becomes cold and cyanotic, while hypopnea and altered consciousness first become apparent. Bradycardia and atrial and ventricular arrhythmias represent common cardiac abnormalities. These cardiac events, combined with volume contraction resulting from fluid redistribution, as well as cold-induced water and solute diuresis, contribute to the risk of hypotension and cardiovascular collapse in these individuals. Altered consciousness may progress to coma with slowing of neurologic reflexes and sluggishness of pupillary responses. Finally, with core temperatures below 28°C (82°F), individuals may be mistaken for dead since they may be unresponsive and apneic, with very cold skin, ventricular fibrillation, absent neurologic reflexes, as well as fixed and dilated pupils. Individuals who have survived early cardiovascular complications of severe hypothermia are at risk for pneumonia, aspiration, pulmonary edema, pancreatitis, gastrointestinal hemorrhage, acute renal failure, and intravascular thrombosis. Abnormal J (Osborne) waves may follow each QRS on the electrocardiogram (ECG). These relatively specific changes disappear as temperature returns to normal. Much less specific ECG changes include bradycardia, prolongations of P-R interval, QRS complex, and QT segment, as well as atrial fibrillation, premature ventricular contractions, and ventricular fibrillation. ECG changes may mimic those seen with acute myocardial ischemia or infarction. Finally, hypothermic individuals may also present with hypothyroidism. Not only do myxedema coma and hypothermia share some clinical features, but hypothyroidism may contribute to the development of hypothermia. On occasion, a history of previous thyroid disease, a surgical scar in the thyroid region, or a delay in the relaxation phase of deep tendon reflexes may provide the only clues.

Treatment

Emergency Care Severe hypothermia represents a medical emergency. If outdoors, such individuals need to be immediately moved away from severe cold, wet clothing must be removed, and warmed blankets applied. Early cardiac monitoring is essential since even minor stimuli can trigger significant dysrhythmias. Procedures such as chest compression or pacemaker placement should be avoided as long as a heartbeat is detectable and patient is breathing spontaneously. In individuals who are asystolic or in ventricular fibrillation, resuscitation should be pursued. Since a cold heart may be relatively unresponsive to drugs or electrical stimulation, such efforts must be pursued aggressively and need to include warmed intravenous fluids (eg, 5% dextrose normal saline without potassium).

General Support Severe hypothermia is associated with a mortality exceeding 50%. These figures worsen further with advanced age and with associated comorbidity. As a result, such patients require close supportive care in an intensive care unit. Such supportive care must include treatment of contributing conditions such as infection, hypoglycemia, and hypothyroidism. Clinicians need to have a high index of suspicion for infection in hypothermic older adults, administering broad-spectrum antibiotics without waiting for results of confirmatory cultures. When administering thyroid hormone for suspected hypothyroidism, corticosteroids may also be required in order to avoid inducing adrenal insufficiency. While ECG monitoring is necessary, central lines should be avoided, given cardiac irritability in these subjects. Pharmacodynamic and pharmacokinetic properties of many commonly used drugs may become dramatically altered in hypothermic patients, creating therapeutic challenges. Such drugs may accumulate as metabolism is delayed and as ever increasing doses are administered because of a lack of response at lower temperatures, causing potential problems as responsiveness to accumulated doses of these medications increases during body warming. Since insulin is ineffective at temperatures below 30°C (86°F), it should not be administered at low temperatures. Volume depletion as

well as hypoxemia needs to be corrected. Intubation may be required and blood gases should be monitored. Nevertheless, rewarming strategies may need to be undertaken immediately following stabilization, since cardiac arrhythmias, acidosis, fluid, and electrolyte disorders may be resistant to treatment until body core temperatures are raised.

Rewarming For patients who are only mildly hypothermic (core temperatures of 32°C–35°C or 90°F–95°F), passive rewarming techniques using insulating materials and transfer to a warm environment generally suffice. For such individuals, active external rewarming using electric blankets, warm mattresses, hot water bottles, or warm water baths are generally not necessary. Moreover, such treatment can be associated with significant risk as warmth-induced peripheral vasodilatation may precipitate hypovolemic shock in vulnerable individuals.

For individuals in more severe hypothermia (core temperatures under 32°C or 90°F), active core rewarming becomes necessary. A variety of techniques are available, with peritoneal dialysis rewarming representing the most practical solution in most institutions. Mediastinal lavage involves a major surgical procedure, while extra corporeal circulation requires special equipment and carries risks of hypotension and heparin-induced hemorrhage. Gastric lavage using balloons filled with warm fluid is simple, yet rate of warming may be slow and pharyngeal irritation may induce arrhythmias. Peritoneal dialysis with rapid instillation and removal of warm (40°C or 104°F) potassium-free dialysate can provide for safe core warming within six to eight fluid exchanges.

Raised Ambient Temperature

Epidemiology Heatstroke is a major public health problem with 7415 US deaths attributed to extreme heat between 1999 and 2010—an average of 618 each year with nearly 40% of these deaths occurring in those older than 65 years. Heat waves in the United States (eg, Chicago) and abroad (eg, France) have graphically illustrated the tremendous vulnerability of older adults to excessively high temperatures. Given a growing awareness of the need to be vigilant for the development of hyperthermia in institutional settings, nursing home cases have fortunately become rarer. Nevertheless, older adults living in the community, especially those who are frail, suffer from disabilities, and live alone are at great risk. In addition to the risk of heatstroke, hyperthermia also contributes to excessive cardiac mortality and morbidity.

Pathophysiology As in the case of hypothermia, heatstroke represents an example of homeostatic decompensation in which older adults' deficient or sluggish compensatory mechanisms are unable to maintain normal body temperature in the face of increased environmental temperature. Excess mortality in older adults during heat waves may be attributed to heat-provoked cardiac events or to primary thermoregulatory failure. In recent years, there has been a growing awareness that heatstroke is a form of hyperthermia, which is associated with an excessive systemic inflammatory response contributing to multiorgan dysfunction. Impairments of thermoregulatory systems may occur at a number of different levels and, as in the case of hypothermia, may result from aging or from associated comorbidity and diseases. Sweating responses to thermal, pharmacologic, and chemical stimuli are reduced with aging, representing a significant contributor to homeostatic decompensation by older adults faced with significant heat challenges. Moreover, older adults require higher body core temperatures before compensatory sweating mechanisms are activated. During times of heat stress, younger individuals depend on being able to increase their skin heat loss by shunting blood flow from core toward peripheral blood vessels. In older individuals, the extent and speed of these important compensatory homeostatic mechanisms is impaired as a result of decreased cardiac output and a diminished vasodilatation of peripheral blood vessels. However, some of the above changes may also be the result of occult cardiac disease or physical deconditioning. For example, maximum oxygen uptake appears to be a much more important predictor of sweat rate and forearm flow during exercise than is chronological age. Moreover, with increased physical activity, older adults are able to improve some of these physiologic responses to heat challenge toward those seen in younger individuals. Finally, as for hypothermia, presence of significant comorbidity, medications, as well as social and environmental factors may further place older adults at risk of homeostatic decompensation during heat waves. For example, decreased mobility or impaired judgment caused by dementia or psychiatric illness may keep some older adults from seeking assistance and from taking sensible precautions such as removal of heavy clothing and increasing fluid intake. Moreover, air conditioning may not be an option for individuals living on a fixed income. Common chronic conditions such as congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and alcoholism further enhance the risk of heatstroke. Anticholinergic agents used for urge incontinence, depression, or behavioral problems may also contribute to hyperthermia by inhibiting normal sweating mechanisms, while diuretics may lead to hypovolemia. Finally, neuroleptic medications have been associated with an increased risk for

hyperthermia in the rare but highly dangerous neuroleptic malignant syndrome.

Clinical presentation Earliest warnings of thermoregulatory failure or heat exhaustion may be subtle and nonspecific. In addition to a feeling of warmth, such individuals may also present with a sense of lethargy, weakness, dizziness, anorexia, nausea, vomiting, headache, and dyspnea. Frank heatstroke is defined clinically as a core body temperature above 40°C (105°F) that is accompanied by hot, dry skin, and major central nervous system abnormalities, which may include delirium, convulsions, and coma. Nonneurologic multiorgan dysfunctions are also common and may include congestive heart failure, cardiac arrhythmias, hepatic necrosis, hypokalemia, respiratory alkalosis, metabolic acidosis, and hypovolemic shock. Rhabdomyolosis, disseminated intravascular coagulation, and acute renal failure may occur in older adults, but are more common in exertional heatstroke typically seen in younger athletes.

Treatment Heatstroke is a medical emergency, requiring prompt and aggressive therapy. Rapid cooling is essential since its pathophysiology involves thermoregulatory failure rather than a reset thermostat point. Immediate on site management must include removal of clothing, cooling the patient's skin with cold water or ice packs, and transfer to cooler setting. Cool intravenous fluids should be considered, but oral hydration may lead to aspiration. Other effective cooling techniques include ice water baths, cold water gastrointestinal lavage, or the administration of cool water followed by warm air to promote evaporation. Irrespective of the technique chosen, speed is of the essence with careful continuous monitoring in order to prevent hypothermic overshoot. Careful fluid balance management and cardiovascular monitoring are also essential. However, given the high prevalence and mortality associated with heatstroke, preventive measures are extremely important. Above all, vulnerable older adults, as well as their families and neighbors must be educated as regards both the seriousness of this problem and commonsense strategies, which can help reduce its toll.

Orthostasis, Meals, and Hypovolemia

An ability to appropriately respond to the challenge of assuming the upright posture is absolutely critical to remaining independent. Under normal conditions, significant or symptomatic orthostatic hypotension is rare among healthy older adults. However, aging does blunt the ability of older individuals to defend against more major hemodynamic challenges, especially among frail individuals, in the presence of significant comorbidity and following exposure to multiple provocative factors. The presence of hypertension increases the risk of hypotension by decreasing baroreceptor sensitivity and ventricular compliance beyond declines observed in normal aging. Use of hypotensive medications and the presence of diseases such as diabetes mellitus, aortic stenosis, and Parkinson disease are all important risk factors. Some risk factors can be synergistic as seen with a modest diuretic-induced sodium depletion, which can induce orthostatic hypotension in previously well-compensated healthy older adults. Similarly, while meal ingestion induces only negligible and asymptomatic blood pressure changes in most healthy older adults, frail older nursing home residents may develop symptomatic postprandial hypotension, which may even contribute to altered mental status and syncope.

Hyperglycemia and Hypoglycemia

Aging has been shown to be associated with glucose intolerance. Even in healthy individuals who do not meet criteria for diabetes mellitus or for impaired glucose tolerance, aging is associated with a dramatic slowing in the return of glucose levels back to normal following glucose ingestion. In contrast, most healthy older adults are able to respond adequately to hyperglycemia. Nevertheless, diabetes, malnutrition, medications, as well as a number of comorbidities may significantly attenuate older adults' ability to recover from a hypoglycemic episode.

Fluid Challenge and Dehydration

When given a major water challenge, older adults tend to have greater difficulty in appropriately diluting their urine. While less well studied, declines in glomerular filtration rate (GFR) tend to compromise the ability of the aged kidney to deal effectively with a sodium load.

Difficulties with water disposal can predispose older individuals to develop hyponatremia, while decreased capacity to adapt to increased salt load may contribute to dependent edema, nocturia, hypertension, and congestive heart failure. The aged body's capacity to prevent dehydration is also affected. Aging is associated with a decreased sensation of thirst even in the setting of significant dehydration. Moreover, aging is associated with a delay in the time required for the kidney to appropriately concentrate urine in response to sodium restriction. Large numbers of

medications, as well as the presence of significant comorbidity, can further enhance the clinical impact of these aging-related changes.

Bladder Filling and Bladder Outlet Obstruction

The ability of older adults to sense and respond appropriately to bladder filling appears to be diminished. These sensory processing deficits may be contributing to a form of homeostatic dysregulation involving lower urinary tract mechanisms in response to bladder filling. It remains to be seen to what extent these changes contribute to common voiding disorders of late life involving urgency and/or impaired bladder emptying.

Bladder outlet obstruction is a relatively common complication of benign prostatic hyperplasia and older men with this problem are much more likely to develop urinary retention with detrusor decompensation than are their younger counterparts. Normally, during a compensatory phase, bladder emptying is maintained with an increased bladder muscle mass, mostly caused by hypertrophy of individual muscle cells. During a subsequent decompensation phase, the bladder undergoes muscle loss, collagen infiltration, and axonal degeneration. Aging appears to increase the likelihood of detrusor decompensation, with its associated degenerative changes.

Major Burns and Trauma

For any given total percentage of body surface burned, advanced age contributes to a measurable decrease in survival. Such systemic vulnerability has been attributed to a combination of progressive reductions in the function of many organs, together with simultaneous reductions in varied homeostatic capabilities and functional impairments associated with specific disease states. In spite of remarkable improvements in the perioperative care of older adults, older individuals have significantly worse outcomes than their younger counterparts following burns, road traffic injuries, and head trauma. While more research is needed, this differential vulnerability may be related to the catastrophic nature of these events, as well as underlying vulnerabilities and presence of significant comorbidity.

Altered Physical Activity

Older adults are particularly vulnerable to the loss of function and the development of individual adverse events following bed rest. With immobilization, muscle mass can be lost at a rate of up to 5% a week, which together with disruptions in subcellular muscle structure, can result in losses in muscle strength, which may approach 40% by 6 weeks. When unloaded, aged muscle cells are more likely to atrophy or to degenerate via apoptotic mechanisms. Strategies, which can diminish the impact of bed rest, include opting for minimally invasive surgery whenever possible, rapid mobilization following surgery or injury, exercise, nutritional supplementation, as well as efforts to decrease offending medications and to address relevant comorbidity. Increased physical activity represents an extremely attractive option since contrary to conventional wisdom, even frail institutionalized older adults are able to benefit from exercise, experiencing significant benefits in terms of muscle mass, muscle performance, and improvements in relevant homeostatic mechanisms.

Anticholinergic Medications

While systematic literature is lacking, older adults appear to be highly sensitive to anticholinergic effects of commonly used medications including altered cognitive function, dry mouth, constipation, and urinary retention. Some of this vulnerability can be attributed to the presence of underlying disease or preclinical pathology. For example, subjects with Alzheimer disease develop new learning deficits at lower scopolamine doses than do age-adjusted normal controls, while the presence of detrusor underactivity predisposes older adults to develop urinary retention when treated with anticholinergic agents. However, aging in itself contributes to an enhanced anticholinergic vulnerability as shown by the presence of an augmented and prolonged inhibition of stimulated parotid flow rate in healthy older adults following exposure to an intravenous anticholinergic drug (glycopyrrolate). Increased blood-brain permeability in old age and in the setting of specific diseases has been proposed as one mechanism that could mediate an augmented vulnerability to develop cognitive or other CNS problems with anticholinergic medications. Other relevant contributing mechanisms include a decreased homeostatic capacity with declines in both numbers and complexity of relevant cellular elements, as well as an aging-associated loss in the ability of muscarinic receptors to be upregulated when exposed to anticholinergic agents.

Antidopaminergic Medications

Older adults often develop extrapyramidal side effects when given neuroleptic agents with potent antidopaminergic properties. Interestingly, adverse events such as acute dystonia are relatively rare in old age, while others including rigidity, poverty of movement, and tardive dyskinesia appear to be more common in old age. In many cases, early or preclinical Parkinson disease may render individuals more vulnerable to pharmacologic disruption of relevant CNS dopaminergic circuits. Moreover, aging-associated declines in numbers and function of CNS dopaminergic neurons, as well as a decreased capacity to compensate for additional losses by upregulation of dopaminergic receptors or by neuronal plasticity involving surviving dopaminergic fibers, are also likely to contribute to the loss of such homeostatic mechanisms.

Neuronal Degeneration

Past dogma has held that aging is associated with a significant, progressive, and inevitable decline in all categories of neurons. In recent years, this pessimistic view has been greatly modified with evidence of selective neuronal vulnerability, as well as dramatic demonstrations of the brain's continued plasticity throughout the lifespan. The observation that specific neurons and neural circuits are vulnerable to aging- and disease-associated declines, while others are quite resistant, has raised considerable hope for the development of physiologically sound interventions, which could help maintain normal neural function into old age. First, evidence of selective neural vulnerability raises the possibility of developing interventions designed to specifically target the most vulnerable cellular elements. Second, many decades of research have demonstrated the presence of neuronal plasticity, in particular collateral sprouting, the formation of new nerve terminals by intact nerve cells, which represents a compensatory homeostatic mechanism with the potential of maintaining normal function following declines in neural circuits, which are similar and in near proximity. Collateral sprouting involving peripheral and central nerve cells tends to decline in old age, yet the ability of modifiable factors such as hormonal levels and nerve activity or experience to influence this category of neural plasticity raises hope for the development of effective interventions.

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Chapter 46

Frailty

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Learning Objectives

- Gain perspective about the general concept of frailty in older persons.
- Understand alternative operational definitions of frailty.
- Recognize frailty in older persons.

Key Clinical Points

1. **Frailty is an important predictor of serious adverse outcomes, such as disability, health care utilization, and death. The phenotype of frailty includes the five following characteristics: unintentional weight loss, weakness, slow gait, exhaustion, and low activity. In addition there is a complex relationship between frailty and cognitive functioning.**
2. **Aging phenotypes that are closely related to frailty and late-life decline include (1) signalling networks that maintain homeostasis, (2) body composition, (3) balance between energy availability and energy demand, and (4) neurodegeneration/neuroplasticity.**
3. **A pervasive biological feature of aging and frailty is the presence of a chronic and mild proinflammatory state.**
4. **Multimorbidity is the clinical manifestation of frailty.**
5. **Frailty has become a key feature in evaluation of a number of specific medical conditions.**
6. **The paradigm of precision medicine provides an almost ideal entry for the frailty concept into the mainstream of modern medicine.**

INTRODUCTION

Over the past century, the science of clinical medicine based on the identification of risk factors and pathophysiologic mechanisms of diseases has accomplished outstanding results. Since 1960, death rates for chronic diseases have changed dramatically, mainly as a consequence of smoking reduction and treatment of hyperlipidemia and hypertension. For example, heart disease death rates declined by almost two-thirds during the past 50 years, and stroke rates declined by more than three-quarters (http://www.cdc.gov). In spite of the relative success in performing early diagnosis, slowing down the clinical development and moderating the symptoms of many chronic diseases, the witnessed gain in longevity has helped to push older adults into the part of life characterized by multimorbidity and disability, unfortunately with very little expansion of the period of life free from any illness (**Figure 46-1**).

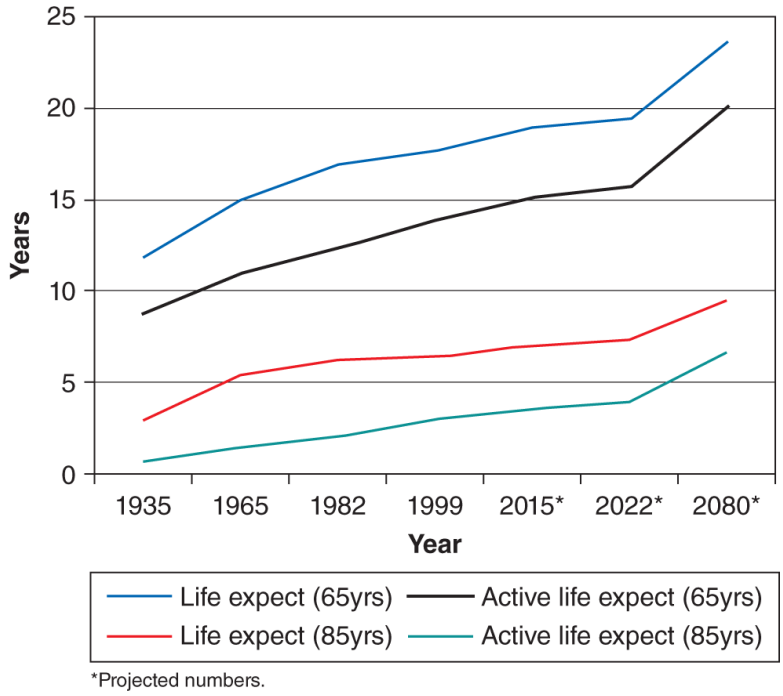


FIGURE 46-1. Life expectancy and active life expectancy at age 65 and 85, US population, 1935 to 2080, selected years (redesigned from published data). (Data from Manton KG, Gu X, Lamb VL. Long-term trends in life expectancy and active life expectancy in the United States. *Popul Dev Rev*. 2006;32(1):81–105.)

Geriatrics is the medical specialty that first perceived the limitations of traditional medicine: that a specific disease diagnosis or an assemblage of diagnoses could not encompass the substantial heterogeneity and complexity of the health problems presented by many older patients. Knowing the diseases and their clinical stage is not enough to explain presence and severity of physical and cognitive limitations. It has become more and more evident that the traditional biomedical principles that had been so effective in the care of patients with single disease were not similarly effective in the care of older patients. For geriatricians, understanding diseases is necessary but not sufficient to improve the health of their patients.

FROM COMPREHENSIVE GERIATRIC ASSESSMENT TO FRAILTY

The history of geriatric medicine has been focused on attempts to conceptually capture the complexity of older patients and develop standard tools for measuring it. This effort has demonstrated unequivocally that health status in older patients is best measured by the ability to function in the environment and that functional status provides powerful prognostic information on multiple adverse health outcomes independent of disease status. Consequently, one goal of geriatric medicine has been to elaborate a comprehensive care plan that would maximize functional status and quality of life of patients and their families. Progress in the field of functional assessment encompasses some of the most important research in the areas of clinical geriatrics and epidemiology of the last three decades. Self-report standard questionnaires were created and validated, followed by objective assessment of performance-based measures. An array of large epidemiologic studies provided robust evidence that even minor declines in physical function are associated with substantial deterioration of quality of life, are good metrics of disease severity, are more accurate and predictive than traditional organ-specific measures, and provide prognostic information for multiple health-related outcomes, including health care resources utilization, progression of disability, and mortality.

FRAILTY CONCEPTUAL DEVELOPMENT AND THE “LAYERS” OF FRAILTY

Most health care professionals recognize that there are complexities that are unique to geriatric patients. In spite of extensive research, the focus described above on functional status and the development of functional assessment tools has failed to fill the vacuum of knowledge about the complexity of aging and its relationship with diseases and disability. Understanding physical and cognitive function is important, but does not provide clear and specific paths to

interventions. Furthermore, since addressing each single disease did not require information on functional status, the assessment of functional status has often been left out of the clinical assessment.

Overall, there is diffuse awareness that recognizing diseases is a necessary component of care, but it is often not enough to infer prognosis and fully understand health and functional status in older patients. The conceptualization and operationalization of frailty is an attempt to capture the missing components of deteriorating health status that are often overlooked in the traditional medical approach.

While creating a standard definition of frailty is a daunting task, it is often argued that most geriatricians can easily recognize frail older persons when they see and interact with them. This hypothesis was examined by a formal multistage Delphi process conducted between 2011 and 2012 that asked a large number of geriatricians, health care providers, and experts to identify the critical characteristics that define a frail older person. Not unexpectedly, results were mixed. The majority of participants agreed that frailty should be considered a clinical syndrome that involves multiple physiologic systems, characterized by decreased reserve and impaired ability to respond to stress, and useful in different settings to identify individuals at high risk of developing adverse health outcomes. However, there was very little agreement on a specific set of clinical/laboratory biomarkers useful for diagnosis. Because of the lack of clarity and the need to determine whether there was sufficient information available to justify systematic screening for frailty, a consensus conference was convened in Orlando, Florida, on December 7, 2012. The project was endorsed by experts from six major international scientific societies and included the participation of other independent top experts in the field. Consistent with the previous experience, a construct of frailty emerged as a "medical syndrome with multiple causes and contributors characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" (Morley et al., 2013). There was consensus that because frailty screening is particularly important to identify individuals at risk of disability, the definitions of frailty and disability should not overlap and that frailty cannot be exhaustively defined by the presence of sarcopenia or multimorbidity. The published report from the conference supported screening for frailty in all individuals 70 and older using some of the operational criteria developed and validated. However, the rationale provided in support of population screening was less than robust. In fact, while frailty can be prevented (eg, by regular exercise) and even partially reversed (possibly by vitamin D or simplification of polypharmacy), so far no randomized controlled trial has definitively demonstrated that screening older individuals for frailty is associated with significant benefits. In addition, there are not specific clinical guidelines available on how frail older adults might be managed differently. However, as described later in this chapter, there is evidence supporting screening of specific subgroups and indicating the need for more research in this area.

Starting from the conclusions of the consensus documents reported earlier, the complexity of typical frail patients can be conceptualized by considering their features in concentric layers, like the layers of an onion (**Figure 46-2**).

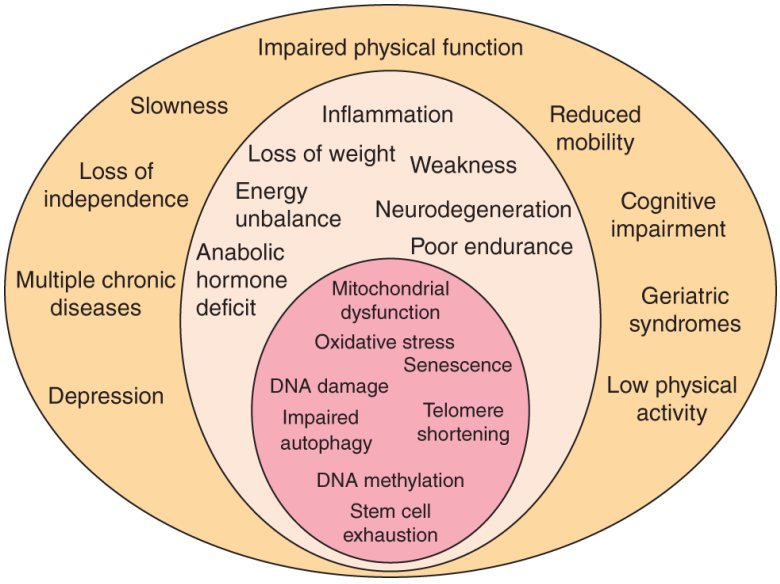


FIGURE 46-2. Frailty can be conceptualized as a construct with three overlaying dimensions, similar to layers of an onion. The clinical presentation, including cognitive and physical impairments, is in the first, most superficial layer. The second layer includes a number of hypothetical pathophysiologic mechanisms and can also be considered as the "area of biomarkers." The third, most inner layer includes the biological mechanisms that are hypothesized to be primary causes of frailty. (From Ferrucci and Fabbri, unpublished data.)

The first layer is the clinical presentation characterized by *multimorbidity*, *impaired physical function* (including mobility), and *cognitive impairment*. These characteristics can be considered as the common beacon at the confluence of all frailty characteristics that contribute to the clinical syndrome. The clinical elements in this layer convey most of the prognostic information for disability, mortality, and many other adverse health outcomes. Examples are *walking speed*, *lower extremity performance*, *reduced physical activity*, *poor muscle strength*, *poor memory*, *number of diseases*, *number of drug treatments*, and many others. Part of this first layer is also a dynamic dimension that is clinically observable, characterized by *reduced functional reserve*, *impaired resilience* to a number of stresses, and *delayed and incomplete recovery* after homeostatic perturbations, health instability, and impending deterioration of health and functional status.

Older patients who come to the observation of geriatricians often present these characteristics and show a spiral of progressive health deterioration in spite of medical treatment aimed at promoting recovery and stabilization (**Table 46-1**). Often these patients develop one or more "geriatric syndromes," common clinical conditions that do not fit into specific disease categories but have substantial implications for functionality and life satisfaction in older adults. Conditions most commonly considered geriatric syndromes are pressure ulcers, incontinence, falls, gait problems, delirium, malnutrition, sleeping problems, dizziness, syncope, and self-neglect. In describing the main physiologic changes that occur with aging, we will come back to this point and explain how it can be quite useful to consider the geriatric syndromes as an overt manifestation of different combinations of the aging phenotypes.

TABLE 46-1 CHARACTERISTICS OF FRAILTY

Increased vulnerability
Reduced physiologic reserves
Decreased resistance to stressors
Reduced capacity to maintain internal homeostasis
Loss of resilience
Multisystem dysregulation
Failure to thrive
Accumulation of deficits
Functional decline
Dependence in daily activities
Impaired mobility
Disability
Comorbidity
Cognitive impairment
Poor health function
Poor psychological functioning
Depression
Unintentional weight loss
Sarcopenia/muscle wasting
Weakness
Low strength
Slow motor performance
Slow walking speed
Decreased balance
Low energy expenditure
Low physical activity
Low fitness
Poor endurance
Exhaustion

Gait abnormality
Impaired vibration sense tremor
Vision and/or hearing deficits

The next, second layer closer to the frailty core could be defined as the “area of biomarkers,” and departs from a purely descriptive interpretation of frailty by providing some information on possible mechanisms. Research on frailty has pointed to multisystem impairments across multiple physiologic systems and organs: (1) Muscle mass and strength are reduced and fat mass increased over and beyond what is expected from the pure effect of aging, and these changes are accompanied by extreme bone fragility; (2) level of fitness is poor and accompanied by altered resting metabolic rate and reduced energetic efficiency, which likely contribute to fatigue and reduced mobility; (3) some homeostatic mechanisms are impaired, show low reserve and reduced ability to respond to perturbation, and have reduced ability to recover a stable level of equilibrium. Examples include the hypothalamic-pituitary-adrenal (HPA) axis cortisol response to stress or the homeostatic response after an oral load of carbohydrates. Perhaps the most pervasive homeostatic dysregulation feature of aging is the acquisition of a proinflammatory state, demonstrated by chronically elevated levels of cytokines and associated with blunted immune response to vaccination and/or to infection, which lead to predisposition to infections. Kidney function is substantially impaired beyond what is expected by aging. Anemia and malnutrition are also almost constant features of aging and frailty. The three main portions of the nervous system (central, peripheral, and autonomic) likely have some degree of involvement and play an important role in the physical and cognitive manifestations of frailty. Imaging studies show that frailty is associated with leukoaraiosis as well as presence of micro- and macroischemic lesions in the white matter, longer reaction time, and reduced performance in dual tasks that involve both cognitive and physical challenges.There is motor neuron loss and fragmentation of the neuromuscular junction, which probably contributes to sarcopenia and poor mobility. Impaired orthostatic hemodynamics, heart rate control, and reduced intestinal peristalsis are signs of autonomic dysfunction. While many studies have considered relationships of frailty with single physiologic and pathologic features, the constant involvement of multiple physiologic systems in frailty suggests that most of them are driven by some unifying cause, although still unknown and hidden.

In parallel to the conceptual development of frailty as a clinical entity with profound functional consequences and poor prognosis, its biological basis is being investigated. The biological basis of frailty represents the deeper, third layer of the onion-like frailty syndrome model, which is purely mechanistic and still largely hypothetical. Attempts to understand the core mechanisms of frailty provide the basis for making a connection between the biology of aging and the experience of geriatric practice. Some hypothesize that aging and frailty are manifestations of the same biological mechanisms, and that frailty is in fact “accelerated aging.” This is consistent with the idea that aging affects resilience, the susceptibility to any stressful event that perturbates the homeostatic equilibrium essential for life and impairs the chances of regaining the lost equilibrium. The accumulation of damage due to loss of resilience across different physiologic systems leads to multimorbidity, the development of the aging phenotype, and decline in many functions that ultimately impact physical and cognitive performance, triggering events that eventually lead to death. Of course, if frailty and aging are made of the same fabric, then understanding the biological mechanisms of frailty may inform our understanding of aging.

FROM SPECULATION TO PRACTICE: OPERATIONAL DEFINITIONS OF FRAILTY

The concept of frailty emerged as a logical extension of comprehensive geriatric assessment, as an attempt to reconstitute clinical and research perspectives under a unique umbrella.

As opposed to functional assessment, which attempts to assess and track the consequence of the physiologic decline that occurs with aging and tries to characterize its consequences regardless of its causes, the concept of frailty implies the existence of underlying pathophysiologic mechanisms responsible for the phenotypical manifestations of aging. Although different interpretative frameworks for frailty have been developed, with different operational criteria, all of them connect frailty directly or indirectly with the biology of aging.

FRAILTY AS A SYNDROME OR PHENOTYPE

The operational model of frailty developed by Linda Fried and other investigators working in the Cardiovascular

Health Study (CHS) is supported by a large body of strong methodological work. According to these authors, frailty is a dysregulation of the stress response systems responsible for organismal resilience, leading to loss of homeostatic capabilities, increased susceptibility to stress, and the emergence of a distinct syndromic phenotype that is predictive of a range of clinical adverse outcomes. The syndromic attribution to frailty in CHS was later validated by research conducted on the Women's Health and Aging Study, and implies that the criteria used for the clinical definition are not exhaustive of the syndrome but rather represent biomarkers that in the aggregate allow for the identification of a group of subjects likely to be affected by the syndrome with some level of sensitivity and specificity.

In describing their theoretical construct of frailty, the authors consider the diagnostic criteria as the milestones of a pathologic vicious cycle that lead to a progressive decline in health and function. The visual representation of this cycle is now part of the background culture in geriatrics and gerontology (**Figure 46-3**). Subsequent models from the same research group have helped to facilitate the testing of biological hypotheses related to frailty and other adverse health outcomes often observed in older adults (**Figure 46-4**). This evolution toward a deeper biological and etiologic understanding is key to progress in this field.

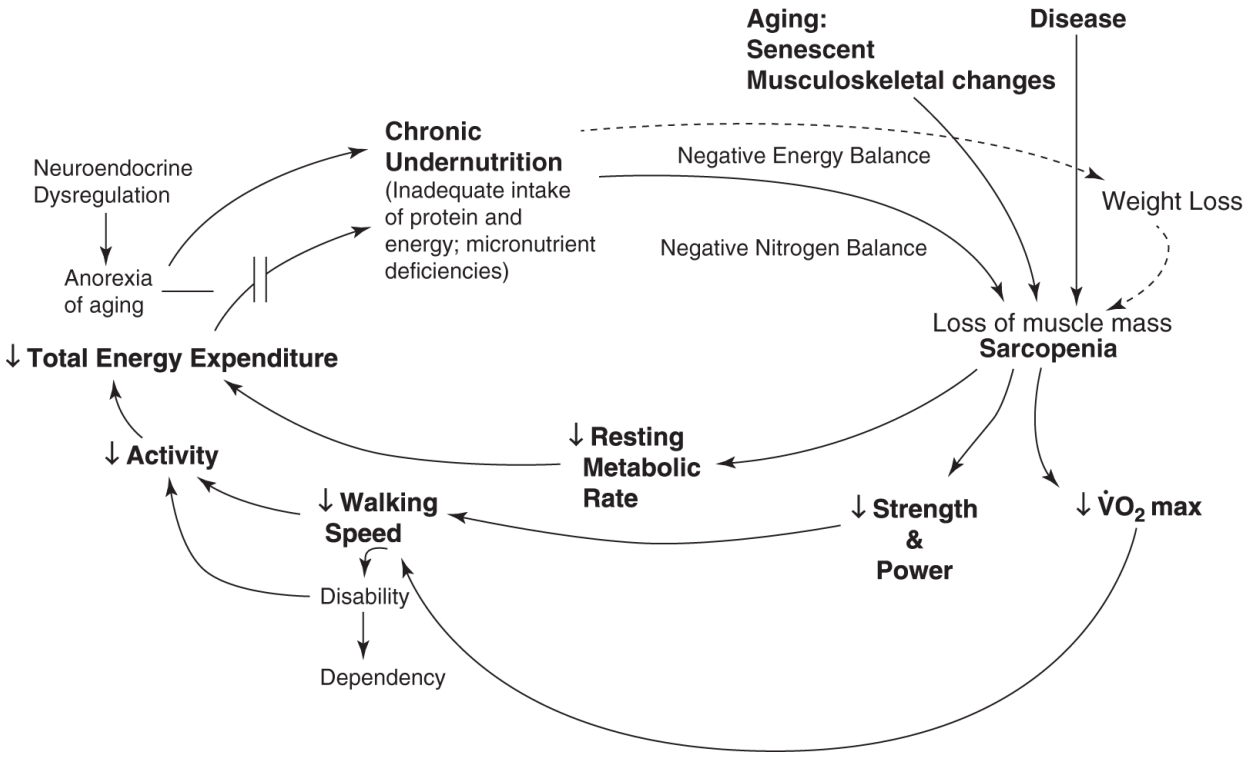


FIGURE 46-3. Schematic representation of the pathologic vicious cycle supposed to lead to a progressive decline in health and function according to the Linda Fried model. (From Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–M156.)

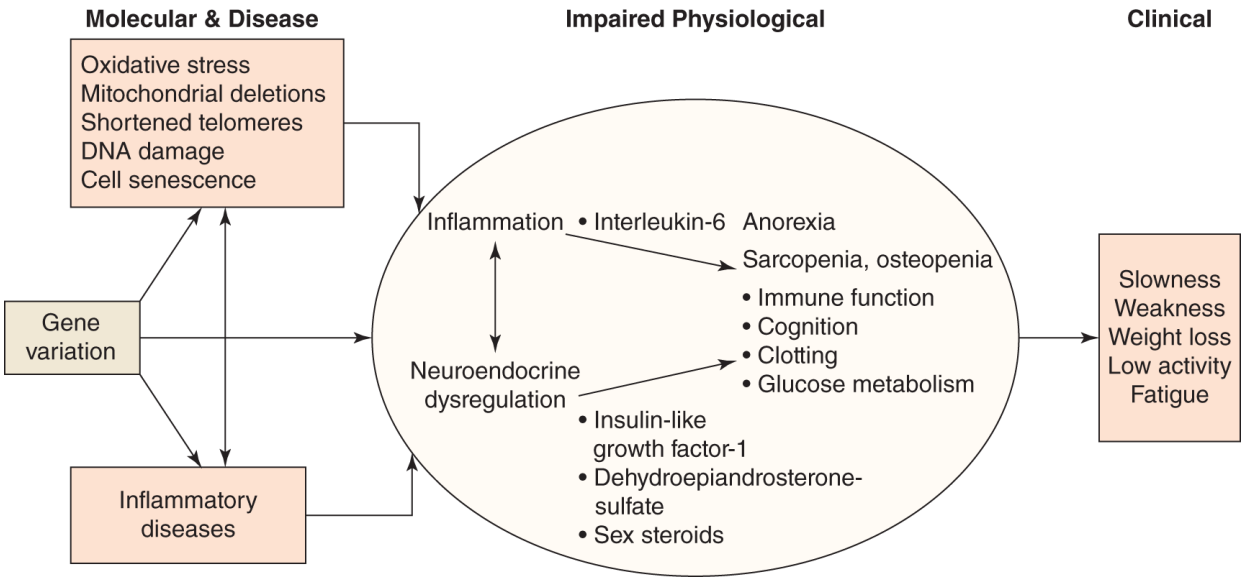


FIGURE 46-4. An updated version of the frailty model presented in **Figure 46-3**, subsequently proposed by Linda Fried and Jeremy Walston. (From Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc*. 2006;54(6):991–1001.)

Based on the clinical observation that frail older individuals often have low lean body mass; poor strength, balance, and walking performance; and low physical activity, Fried and colleagues conceptualized frailty as a vicious circle of declining energetics and reserve, whose elements represent both the diagnostic criteria for the syndrome identification and the core elements of its pathophysiology. In particular, the phenotype of frailty was defined by the five following characteristics (**Table 46-2**): unintentional weight loss, weakness, exhaustion, slowness, and low activity.

TABLE 46-2 CRITERIA FOR FRAILTY SYNDROME ACCORDING TO FRIED AND COLLEAGUES

CHARACTERISTICS OF FRAILTY	CARDIOVASCULAR HEALTH STUDY MEASURE
1. Weight loss (unintentional)/sarcopenia (loss of muscle mass)	> 10 lb lost unintentionally in prior year
2. Weakness	Grip strength: lowest 20% (by gender, body mass index)
3. Exhaustion/poor endurance	"Exhaustion" (self-report)
4. Slowness	Walking time/15 ft: slowest 20% (by gender, height)
5. Low activity	kcal/wk: lowest 20% males: <383 kcal/wk; females: < 270 kcal/wk

Adapted from Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146 - M156.

Those individuals who meet at least three of the five criteria are considered frail, while those individuals who meet two criteria out of five are considered as prefrail. Of note, the presence of one criterion alone may constitute a risk factor but does not represent frailty itself, because frailty is considered a multisystemic syndrome. Using this operational definition, the severity of frailty is associated with risk for disability and loss of independence, even in the absence of an acute precipitant. In addition, frailty is associated with the presence of specific chronic diseases, particularly those with an inflammatory etiology, and patients with chronic multimorbidity are likely to be frail or have high risk of developing frailty. While frailty incidence rises with increasing age independent of chronic diseases, the association with such chronic diseases, including cardiovascular, kidney, and rheumatologic diseases, suggests that there may be both a primary, aging-related frailty and a phenotype of frailty that is secondary to chronic disease or jointly related to a shared etiology.

The Fried approach to frailty is appealing because it is both easy and immediate to operationalize and also is based on a solid pathophysiologic model that directly indicates opportunities for interventions. However, this approach of frailty also has few drawbacks. The first problem is the lack of a cognitive dimension, which is in contrast with the clinical experience that cognitive impairment often accompanies frailty. Brain dysfunction can be captured by the

mobility assessment but still patients in the early stage of frailty who develop mostly cognitive manifestations may be missed. A second problem is the inclusion of weight loss in the syndrome. Unexplained weight loss is a strong biomarker of health decline with aging. However, given the increasing prevalence of obesity, the sarcopenic-obesity variant of frailty is becoming more and more frequent, and this variant may be missed by the weight loss criterion. Third, the threshold selected for the definition of some of the criteria are based on distributions in the CHS population, which may not be fully representative of all clinical populations in the United States. In spite of these limitations, an extensive literature demonstrates that the Fried definition of frailty is a useful tool both for research and clinical applications, and it has been adapted to many studies and uses. Examples of the many successful applications are given later in this chapter.

FRAILTY AS A DEFICIT ACCUMULATION

Another major school of thought that has been a mainstream in frailty research is the approach developed by Ken Rockwood and colleagues. In this approach, frailty is considered an accumulation of illnesses, signs, symptoms, and laboratory abnormalities, based on the observation that "the more things individuals have wrong with them, the higher the likelihood that they will be frail". Using data from two population-based Canadian studies, Rockwood and his collaborators combined a series of 70 measurements (jointly referred to as "deficits") in order to generate a multisystem, broad, graded, and conceptually simple tool into the frailty index (FI). This approach conceptualizes frailty as a stochastic accumulation of structural and functional deficits in almost any physiologic system or organ and operationalizes it as a simple unweighted count of the number of deficits. The FI, in particular, is the ratio of the deficits present in a person to the total number of deficits considered. Therefore, according to this definition, it is the proportion of all potential deficits considered for a given person rather than their specific nature or combination that best expresses the likelihood and the severity of frailty. The FI and multiple shorter versions of the original FI have most often been used as a means of assessing individual aging and risk of mortality as described below.

In building their model of frailty, Rockwood and his colleagues used data from the Canadian Study of Health and Aging (CSHA) and followed three subsequent approaches. First, they developed a rules-based definition of frailty, followed by a method of counting 70 of a patient's various clinical deficits. Items consisted of the presence and/or severity of current diseases, ability in activities of daily living (ADLs), and physical signs from the clinical and neurologic examinations. Each deficit was dichotomized or trichotomized and mapped to the interval 0 to 1, representing the occurrence and severity of the problem. The FI has a strong face validity; it shows an age-specific, nonlinear increase (similar to Gompertz law), higher values in females, strong associations with adverse outcomes (eg, mortality), and a universal limit to its increase (at FI ~ 0.7). The authors interpreted these findings as a proof that FI tracks rate of individual aging. This approach is reproducible and highly correlates with mortality, but it is unwieldy for clinical use. Therefore, more recently, Rockwood and collaborators developed a third approach, based on the determination and validation of a seven-category tool, named the Clinical Frailty Scale, which is easier to use in clinical settings and has similar predictive power for institutionalization and death. The seven categories of the Clinical Frailty Scale are (1) very fit, (2) well, (3) well with treated comorbid disease, (4) apparently vulnerable, (5) mildly frail, (6) moderately frail, and (7) severely frail. The Clinical Frailty Scale mixes items such as comorbidity, cognitive impairment, and disability that some other groups separate in focusing on physical frailty.

The FI approach has several attractive features but some drawbacks as well. First, as a prognostic tool, the FI is a sensitive predictor of adverse health outcomes, in part because it includes multiple related factors known to share causal relationships with adverse outcomes. The clinical version of the tool is very direct and intuitive, has strong face validity, and shorter versions of FI can be generated quickly from medical records. The stochastic approach of the FI approximates the idea of aging as a rise in entropy, which makes intuitive sense and is supported by a wealth of research data and solid mathematical models. On the other hand, a pure stochastic approach is inconsistent with the idea of a specific "hub" biological mechanism that causes frailty. This and the lack of a focused list of measures make the development of specific mechanistic, biological, and intervention development studies needed to move toward focused clinical strategies more challenging. Finally, the FI, even with multilevel variables, is still based on the assumption of equality of deficits. It would be of interest to differently weight the variables to have greater influence at predicting the adverse outcomes.

OTHER OPERATIONAL DEFINITIONS OF FRAILTY

There are many other operational definitions of frailty beyond the two described above, although most of them arise from the already discussed concepts. The most relevant operational definitions are summarized in **Table 46-3**. The wide variety and number of published tools document the very lively discussion in the field about the definition and interpretation of frailty, which has occupied many hours in meetings, workshops, and roundtables, at times louder and more emotional than one would have liked.

TABLE 46-3 SUMMARY OF THE FRAILTY TOOLS PUBLISHED IN THE LITERATURE

INSTRUMENT	PUBLICATION(S)	DOMAINS/ITEMS	SCORING
Physical Frailty Phenotype (PFP)	Fried et al., *J Gerontol*, 2001	Physical function (gait speed, grip strength), physical activity, weight loss, and exhaustion	Score range: 0–5 Frail = ≥ 3 criteria present Intermediate/prefrail = 1–2 criteria present Robust/nonfrail = 0 criteria present
Deficit Accumulation Index (DAI)	Mitnitski et al., *The Scientific World*, 2001; Mitnitski et al., *J Gerontol Med Sci*, 2004; Rockwood et al., *J Am Geriatr Soc*, 2006; Rockwood et al., *J Gerontol Med Sci*, 2007a; Rockwood et al., *J Gerontol Med Sci*, 2007b	Diseases, activities of daily living (ADL), health attitudes/values, and symptoms/signs from clinical and neurologic examinations	Number of deficits present and divided by the number of deficits taken into consideration Higher proportion equates to a higher level of frailty Number of deficits may vary
Gill Frailty Measure	Gill et al., *N Engl J Med*, 2002	Physical function (gait speed, chair stand)	Moderately frail if rapid gait speed back and forth over 10 ft course is > 10 s; or could not stand from the chair. Severely frail if meet both criteria
Frailty/Vigor Assessment	Speechley & Tinetti, *J Am Geriatr Soc*, 1991	Frail: age (over 80), physical function (balance and gait abnormalities, decreased shoulder strength, decrease knee strength), physical activity (infrequent walking for exercise); psychological function (depressed); medications (taking sedatives); disability (lower extremity disability); sensory function (near vision loss). Vigorous: age (under 80), cognition (cognitively intact), physical activity (frequent exercise other than walking), sensory function (good near vision)	Score ranges: Frail 0–9 Vigorous 0–4 Frail: ≥ 4 frail values and ≤ 1 vigor value Vigorous: ≥ 3 vigor values and ≤ 2 frail values Transitional: having median values for either or both frail (3) and vigor (2)
Clinical Frailty Scale	Rockwood et al., *CMAJ*, 2005	Clinical judgment from very fit to severely frail: 1 = Very fit—robust, active, energetic, well motivated, and fit; these people commonly exercise regularly and are in the most fit group for their age; 2 = Well—without active disease, but less	Physician assigns score of 1–7 based on clinical judgment Physicians making the initial assessment given access to diagnoses and assessments related to these variables and other measures of comorbidity,

		fit than people in category 1; 3 = Well, with treated comorbid disease—disease symptoms are well controlled compared with those in category 4; 4 = Apparently vulnerable—although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms; 5 = Mildly frail—with limited dependence on others for instrumental activities of daily living; 6 = Moderately frail—help is needed with both instrumental and noninstrumental activities of daily living; 7 = Severely frail—completely dependent on others for the activities of daily living, or terminally ill	function, and associated features that inform clinical judgments about the severity of frailty A secondary review and scoring performed by a multidisciplinary team
Brief Frailty Instrument	Rockwood et al., *Lancet*, 1999	Four levels of classification, representing fitness to frailty: 0 = Those who walk without help, perform basic activities of daily living (eating, dressing, bathing, bed transfers), are continent of bowel and bladder, and are not cognitively impaired 1 = Bladder incontinence only 2 = One (two if incontinent) or more of needing assistance with mobility or activities of daily living, has cognitive impairment with no dementia (CIND), or has bowel or bladder incontinence 3 = Two (three if incontinent) or more of totally dependent for transfers or one or more activities of daily life, incontinent of bowel and bladder, and diagnosis of dementia	Higher classification means higher grade of frailty
Vulnerable Elders Survey (VES-13)	Saliba et al., *J Am Geriatr Soc*, 2001	Age, self-rated health, physical function, and ADL/IADL disability	Score range: 0–10 Frail = score ≥ 3
FRAIL Scale	Abellan Van Kan, *J Nutr Health Aging*, 2008; Abellan Van Kan, *J Am Med Dir Assoc*, 2008	Fatigue, physical function (resistance: ability to climb a single flight of stairs; and ambulation: ability to walk one block), illnesses (more than 5), weight loss (more than 5%)	Score range 0–5 No frailty = 0 deficits Intermediate frailty = 1 or 2 deficits Frailty = 3 or more deficits

Winograd Screening Instrument	Winograd et al., *J Am Geriatr Soc*, 1991	Cerebrovascular accident; chronic and disabling illness; confusion; dependence in ADLs; depression; falls; impaired mobility; incontinence; malnutrition; polypharmacy; pressure sore; prolonged bed rest; restraints; sensory impairment; socioeconomic/family problems	Frail = presence of any *one* of the 15 screening criteria Participants could instead be categorized as "severely impaired" if they had severe dementia *and* ADL dependence, or terminal illness

Adapted from Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments, Ageing Res Rev. 2016;26:53-61.

A NOVEL APPROACH: FRAILTY AS AGE-RELATED BIOLOGICAL DECLINE

Recently, we and others proposed that while agreeing on an operational definition of frailty is very important for translational purpose, until the pathophysiology of frailty is fully understood, any operational definition of frailty should be considered temporary and amenable to change. Importantly, the theoretical discussion and research on the biological and mechanistic origin of frailty does not completely depend on a specific operational definition. We recently proposed an agnostic approach, which assumes that frailty is, in fact, a syndrome of accelerated aging and, therefore, phenotypes of aging as well as frailty can be identified as those physiologic dimensions that change with aging in all humans and, perhaps, in all living organisms. For example, the risk of developing a clinical disease such as coronary artery disease (CAD) increases with aging but not all individuals develop CAD. Therefore, CAD cannot be considered a phenotype of aging. On the other hand, percent body fat, especially visceral fat, increases with aging in all individuals and, therefore, increased visceral fat could be considered a phenotype of aging. Based on these assumptions, we proposed that the phenotypes of aging can be clustered in discrete interactive domains, whose impairments are pervasive across body systems and, therefore, can serve as proxy measures of the rate of aging. In particular, we identified four main "aging phenotypes" that we hypothesize are closely related to frailty and late-life decline: (1) signalling networks that maintain homeostasis; (2) body composition; (3) balance between energy availability and energy demand; and (4) neurodegeneration/neuroplasticity, whose changes occur in parallel in all aging individuals and are strongly intercorrelated (**Figure 46-5**). Extensive evidence, in fact, shows that frailty is associated with overt changes in these four main interacting domains regardless of its operational definition. Such conceptualization of frailty also recognizes the heterogeneity and dynamic nature of the aging process. Aging is a universal phenomenon, but the progressive multisystem instability and deterioration that characterize aging are very heterogeneous among different individuals. Thus, not only whether an older patient is frail, but also whether the severity of the frailty syndrome is beyond clinical and behavioral thresholds becomes relevant. Furthermore, the conceptualization of frailty as a result of various levels of impairment in the "aging phenotypes" represents an interconnecting and dynamic interface between the clinical presentation of the syndrome (first layer of frailty) (see **Figure 46-2**) and its biological bases (the inner and deeper layer or biological core of frailty). This model provides a causal link to the development of multiple chronic diseases and geriatric syndromes, whose occurrence can be interpreted as clinical expression of alterations in specific combinations of aging phenotypes.

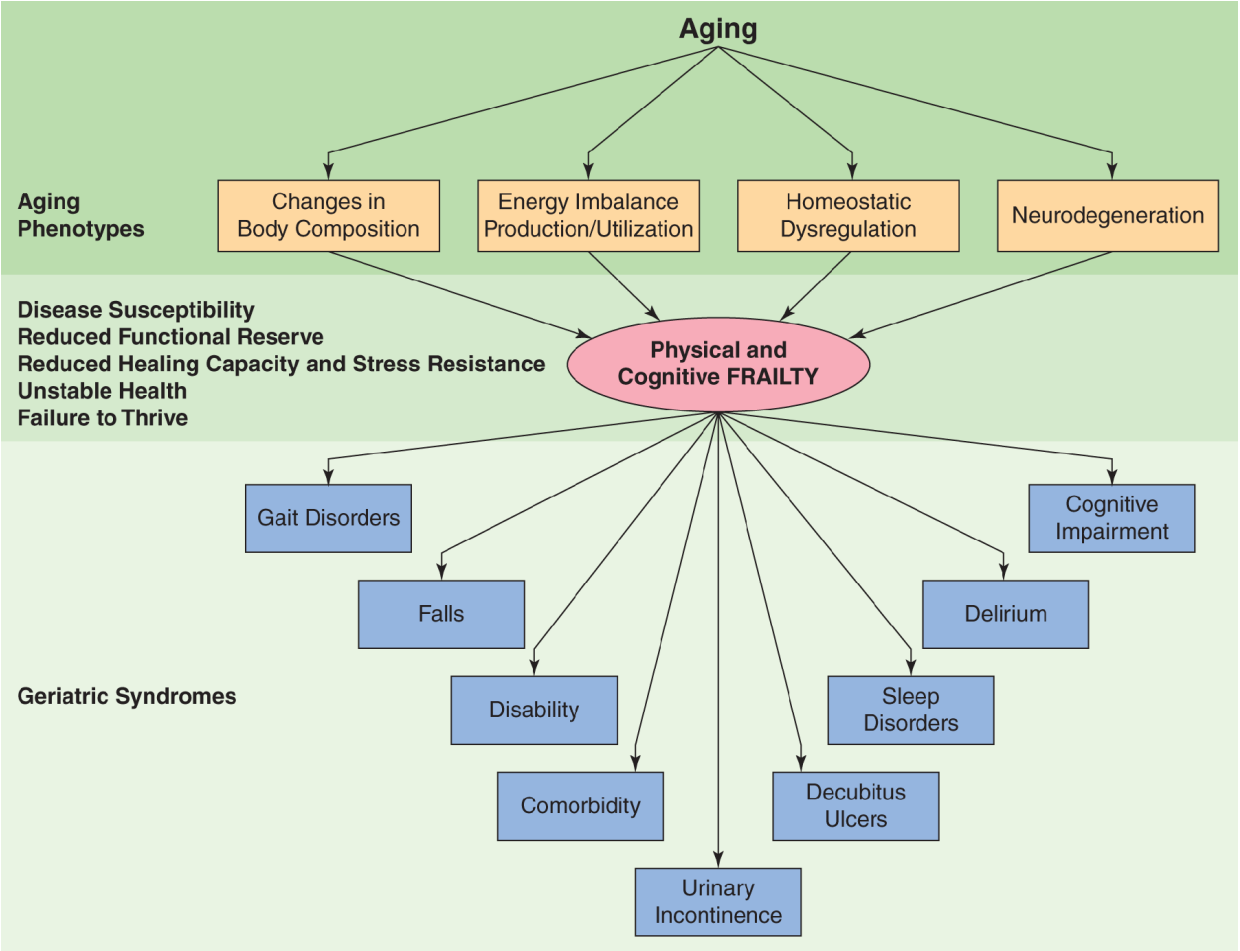


FIGURE 46-5. Schematic representation of the domains of the aging phenotype, and their relationship with frailty and with the geriatric syndrome. (From Ferrucci L, Studenski S. Clinical problems of aging. In: Longo DL, Fauci AS, Kasper DL, et al., eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw Hill; 2012.)

Signalling Networks That Maintain Homeostasis

A remarkable and pervasive biological feature of aging and frailty is the presence of a chronic and mild proinflammatory state, revealed by elevated levels of serum proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α). Such a proinflammatory signature of aging, also called "inflammaging," has been described across different animal models and tissues, and is even present in individuals who are free of diseases, disabilities, and cardiovascular risk factors (Ferrucci et al., 2005). Moreover, higher levels of proinflammatory biomarkers have been associated with loss of physiologic reserve and function across multiple organs and system in older adults. These biomarkers are strong independent predictors of adverse health outcomes including multiple chronic diseases, disability, hospitalization, and mortality.

Research on the biology of aging has shed some light on the underlying mechanisms of the proinflammatory state of aging. For example, one of the possible triggers is defective autophagy, a fundamental cellular housekeeping mechanism that eliminates altered macromolecules, cell membranes, and organelles before they are replaced. In particular, the processing and elimination of aged and degraded mitochondria appears to be impaired. These dysfunctional mitochondria cannot be replaced, are energy inefficient, and produce large quantities of radical oxygen species which are supposed to trigger a chronic inflammatory response. Animal models demonstrate a strong connection between the accumulation of senescent cells and the development of characteristic aging phenotypes. One of the main features of senescence is the senescence-associated secretory phenotype that is characterized by the secretion of proinflammatory mediators, including IL-6 and IL-1, and may account for the proinflammatory state of aging.

An additional and relevant characteristic of the aging process is the occurrence of complex and profound hormonal changes, including a decline in multiple anabolic hormone concentrations (dehydroepiandrosterone sulfate [DHEAS], testosterone, estrogens, growth hormone [GH]/insulin-like growth factor 1 [IGF-1], and vitamin D), with a relative

preservation of catabolic hormones (thyroid hormones, cortisol). A single hormonal alteration, in fact, is unusual in older persons and usually is a sign of a specific impending disease. More often, aging individuals experience a complex "multiple hormonal dysregulation," characterized by simultaneous and synergistic mild multiple anabolic hormonal deficiencies, which may be an important contributor to progressive loss of resilience and high vulnerability in older adults. Multihormonal dysregulation has also been associated with the development of numerous geriatric conditions, including sarcopenia and cognitive decline as well as high risk of disability, comorbidity, and mortality.

Body Composition

Aging is also characterized by major changes in body composition which negatively affect metabolism and functional status. These changes contribute to impaired mobility, disability, and other adverse health outcomes in older adults. Lean body mass, composed predominantly of muscle and visceral organs, starts to decline progressively around the age of 30 with a more accelerated loss after the age of 60, while fat mass increases with age during middle age and declines in late life. Age-related loss of muscle mass is typically offset by gains in fat mass as adults age with resulting stable or slightly increasing body weight. After the age of 70, fat-free mass and fat mass tend to decrease in parallel, with consequent decreasing weight. Furthermore, visceral fat and intermuscular fat tend to increase with age, while subcutaneous fat in other regions of the body declines. The age-related loss of muscle mass, with a shift in muscle fiber composition, due to a selective loss in fast-twitch fibers compared to slow-twitch fibers, was long considered the major determinant of decline in muscle strength in older adults.

However, the decrease in muscle strength actually exceeds what is expected on the basis of the decline in muscle mass alone, especially after the age of 60 to 70, suggesting that other factors related to muscle quality (defined as muscle strength or power per unit of muscle mass) may play a major role in the decline in muscle strength and physical function in older adults. Muscle biomechanical quality, defined at the force that is generated by a volume unit of muscle tissue, is almost constant in children and young adults but starts deteriorating after the age of 40. Progressive muscle denervation secondary to progressive failure of the denervation/reinnervation cycle and to dysfunction of the neuromuscular junction is probably largely responsible for the decline of muscle mass and quality with aging. Furthermore, there is increased fat infiltration within the muscle, which probably results from age-related changes in body composition and includes storage of lipids in adipocytes located between the muscle fibers (also termed intramuscular fat) and between muscle groups (intermuscular fat) as well as lipids stored within the muscle cells themselves (intramyocellular lipids). This fat infiltration is thought to be largely responsible for the deterioration of muscle quality, impaired muscle force production, and mobility decline in older adults.

In addition, an increase of fibroconnective tissue within the muscle contributes to poor muscle quality with aging. Another focus is on the failure of mechanisms of the maintenance and repair of damaged muscle fibers, mainly due to the limited regenerative capacity and dysfunction of satellite cells (stem cells resident in muscle tissue), which may be exhausted before the end of life in situations that require continued and intensive repair. Overall, the decline in muscle mass and muscle strength with aging plays a critical role in the development of the frailty syndrome.

Progressive demineralization and architectural modification in the bone also occurs with aging, with consequent increased skeletal fragility and higher risk of fractures, especially at the hip. Trabecular bone mass "peaks" in early adult life, with decreases in trabecular bone evident in both sexes as early as the third decade, although the rate of decline is clearly accelerated in women compared to men.

Balance Between Energy Availability and Energy Demand

Although the idea that longevity and health are linked to energy metabolism was introduced over a century ago, the role of energy metabolism in human aging and chronic diseases is still not fully understood. As described earlier, Fried and colleagues conceptualized frailty as a vicious cycle of declining energetics and reserves. Indeed, the integrity of energetic metabolism is a prerogative for successful aging. In fact, the degenerative processes that characterize aging occur when the organism's ability to balance energy production and expenditure declines. Lack of energy or even an excess of energy that is not utilized could be the root causes of progressively higher morbidity and mortality with aging. Resting metabolic rate (RMR) is the energy required to maintain structural and functional homeostasis at physical rest, in fasting and neutral conditions. RMR accounts for 60% to 70% of the total daily energy expenditure and can be assessed by indirect calorimetry. RMR normalized by body size declines rapidly from birth up to the end of the third decade, and then continues to decline more slowly from adulthood until death, mostly but not completely, as a consequence of the age-related loss of lean body mass.

In older adults higher RMR has been found to be an independent risk factor for mortality and to predict future

greater burden of chronic diseases; consequently it should be considered a marker of health deterioration in older adults. Specifically, the increased RMR is likely to be due to increasing difficulties to cope efficiently and effectively with internal and environmental challenges and stressors. Therefore, in the presence of overt homeostatic dysregulation, the energy requirement increases because of the extra work required to maintain a stable homeostasis.

Moreover, the maximum energy that can be produced by an organism over extended time periods, or fitness, can be approximately estimated during a maximal treadmill test as peak oxygen consumption (VO_2 max). Oxygen consumption represents the maximal ability to use oxygen to meet the energy demands of physical activity (maximal aerobic capacity) and reflects not only cardiovascular adaption to transport oxygen but also adaptations within muscle to use oxygen to meet the energy demands of physical activity. VO_2 max declines with age, starting around age 30 and continuing at approximately 10% per decade, but at an accelerated rate for increasing age and in those who are sedentary or affected by chronic diseases. Of relevance, the age-related decline in maximal aerobic capacity is a strong predictor of decline in physical function and mobility in older adults.

Neurodegeneration

An important biomarker of aging and frailty is the age-related degeneration of the central and peripheral nervous system (for details see Chapter 45). As result of these changes, declining performance in specific cognitive abilities, like memory, processing speed, executive function, reasoning, and multitasking is commonly experienced with aging. All of these so-called "fluid" mental abilities are important for carrying out everyday activities, living independently and leading a fulfilling life. In fact, there is a strong association between accelerated decline in cognitive performance and in mobility, even in "normal" older adults.

Age-related changes occur also at the level of the peripheral nervous system (PNS), especially after the age of 60, with a progressive degeneration in structure and function from the spinal cord motor neuron to the neuromuscular junction. These changes in the PNS greatly contribute to impaired mobility and decline in physical function in older adults. The number of motor neurons declines with aging and such declines seem to play an important role in the loss of muscle strength and quality with aging. Age-related motor unit remodeling leads to changes in fiber-type composition because denervation occurs preferentially in the fast muscle fibers with reinnervation occurring by axonal sprouting from slow fibers. As a consequence, motor units decrease in number and become progressively larger, but less functional with aging with reductions in fine motor control. Furthermore, the efficiency of segmental demyelination-remyelination process declines with aging, resulting in slower conduction of the impulses, with consequent decreased sensation as well as slower reflexes.

THE EPIDEMIOLOGY OF FRAILTY

The prevalence of frailty varies enormously among studies according to different definitions, countries, and settings. A systematic review reported that the overall prevalence of frailty, in community-dwelling adults aged 65 and older, is on average 10.7% (range 4.0%–59.1%). Of note, use of a broader definition of frailty results in a higher prevalence than use of the Fried tool (13.6% vs 9.9%). Moreover, prevalence of frailty increases with age, reaching 15.7% in individuals aged 80 to 84 and 26.1% in those aged 85 or more. Independent of the type of definition, the prevalence is higher in women than men (Fried Scale: 9.6% vs 5.2%; FI: 39.0% vs 37.3%). Also, frailty, however defined, shows a U-shaped relationship with body mass index (BMI), with higher levels of frailty in individuals with both low and very high BMI. In older hospitalized patients, the frailty prevalence varied from 27% to 80%. The prevalence of frailty in institutionalized older adults is less well defined, but varies from 29.2% to 68.8%.

The clinical relevance of frailty is mainly due to its being an important predictor of serious adverse outcomes, such as disability, health care utilization and death. The broader definition of frailty appears to be more precise than the Fried Scale in discriminating the risk of adverse outcomes, in particular mortality. A linear relationship between mortality rate and frailty as accumulation of deficits has also been demonstrated. In addition, physical frailty indicators are strong predictors of ADLs disability in community-dwelling older people. Slow gait speed and low physical activity/exercise seem to be the most powerful predictors followed by weight loss, lower extremity function, balance, muscle strength, and other indicators. Moreover, increasing frailty is associated with increasing length of hospital stay, nursing home institutionalization, and mortality in hospitalized patients. Consistently, a secondary data analysis in 1851 community-dwelling, Medicare fee-for-service enrollees, greater than or equal to 65 years old, who were discharged from the emergency department between January 2000 and September 2002, demonstrated that frailty was strongly associated with higher risk of hospitalization, nursing home admission, or death. As a consequence, there is

consensus that frailty predicts high health care utilization and costs. Furthermore, frailty negatively impacts quality of life, directly or indirectly (through associated comorbidity). In addition, prescribing drugs for these vulnerable individuals is difficult and frequently complicated by iatrogenesis.

Finally, epidemiologic data on transition of frailty states according to Fried's definition show that nearly 60% of people over age 70 have at least one transition between any two of the three frailty states over 4.5 years. Transitions to states of greater frailty are more common than to states of lesser frailty, and the probability of transitioning from being frail to nonfrail is very low. Although a person who has already entered the frail state is unlikely to transition back to no frailty, the evidence that frailty is a dynamic process with older adults gradually progressing through different frailty states suggests the opportunity for prevention strategies.

COGNITION, DEMENTIA, AND FRAILTY

Traditionally, operationalization of frailty has been mostly focused on the physical aspects of the syndrome. However, the contribution of cognition to frailty has been increasingly recognized, and the complex relationship between frailty and cognitive functioning has been extensively explored. There is a higher prevalence of cognitive impairment and lower cognitive performance in frail older adults than in fit ones. Moreover, frailty increases the risk of future cognitive decline and incident dementia in longitudinal studies. As a consequence, the term "cognitive frailty" has been used to describe a clinical condition characterized by the simultaneous occurrence of both physical frailty and cognitive impairment, in the absence of a diagnosis of dementia or underlying neurologic conditions. In particular, the operational definition of cognitive frailty is based on the following criteria: (1) physical frailty; (2) mild cognitive impairment (MCI), according to the Clinical Dementia Rating (CDR, score equal to 0.5); and (3) exclusion of Alzheimer disease (AD) and other dementias. Moreover, it has been suggested that the occurrence of physical frailty should precede the onset of cognitive impairment, in order to differentiate between a physically driven cognitive decline versus a cognitive deterioration independent of physical conditions. However, despite the increasing interest in the complex relationship between physical deterioration and cognitive decline in older adults, no epidemiologic data on cognitive frailty have been produced yet. Therefore, future research in this field should better define the epidemiology and clinical presentation of this condition as well as the underlying biological and pathophysiologic pathways.

FRAILTY IN THE CONTEXT OF SPECIFIC MEDICAL CONDITIONS

The robust scientific progress generated in understanding functional status as a prognostic marker has induced other specialties to incorporate frailty into clinical decision making.

1. *Frailty to evaluate surgical risk.* Despite progress in medical and anesthesia support techniques, older surgical patients have an excess risk of postoperative adverse outcomes. The main reasons are the frequent presence of comorbid conditions and reduced functional reserve across multiple systems. In addition, surgical diseases and surgery itself are stressors that may alter physiologic homeostasis. Therefore, assessing frailty has a particular clinical relevance for older patients who are considered as candidates for surgery. Frail older adults who undergo surgery, in fact, are more likely than patients who are not frail to experience postoperative complications such as pneumonia, delirium, and urinary tract infections; have prolonged hospital stays; be discharged to nursing homes or long-term care facilities; and have higher mortality. Surgical decision making is very challenging due to the heterogeneity of health status and level of fitness among older adults and the paucity of appropriate assessment tools for predicting operative risks. Traditional risk assessment measures have substantial limitations as they are mostly based on specific comorbid conditions or on single organ system, and they do not estimate individual physiologic reserve. "Alternative" tools, whose cornerstone is the assessment of frailty, are emerging. One example is a multidimensional frailty score based on the following items: benign/malignant disease, comorbidity (Charlson index), albumin level, physical function (ADL and IADL), dementia (MMSE-KC), risk of delirium (Nu-NESC), nutrition (MNA), and mid arm circumference. This multidimensional frailty score was more useful than conventional methods for predicting outcomes in geriatric patients undergoing surgery.
2. *Frailty and cancer.* Emerging evidence suggests that the pathogenesis of age-related degenerative and cancer diseases may share cellular senescence as a common denominator. One of the major issues facing physicians who deal with older adults with cancer is the heterogeneity of their physiologic reserves and level of physical and

cognitive fitness and, consequently, their ability to tolerate treatment and prognosis. Moreover, cancer and its treatments are often associated with comorbid conditions such as weight loss and cachexia, which may negatively affect patients' quality of life, tolerance to treatments, and ability to respond to rehabilitation. Polypharmacy, as result of the presence of comorbidity, is also an important issue in older adults with cancer, and it is associated with high risk of adverse side effects and postoperative complications. Therefore, it is becoming part of oncologic practice to include comprehensive geriatric assessment (CGA) in the evaluation of older adults with cancer, with particular attention to functional status (ADL, IADL), presence of comorbidity, social support, cognitive status, and presence of geriatric syndromes. In geriatric oncology, in particular, CGA identifies reversible conditions that might interfere with the treatment of older patients, it ascertains an estimate of life expectancy and treatment tolerance, and it establishes a common language in the classification of older individuals as an alternative to the use of chronologic age. On the other hand, CGA is very time consuming; therefore, a number of screening tests have been proposed, such as the Vulnerable Elderly Survey 13 (VES-13). Patients who screen positive (ie, VES-13 score of 3 or higher) should undergo a complete CGA. In old and very old patients with a diagnosis of cancer, but who are apparently healthy, physically active, and cognitively intact, a different approach should be considered for estimating the status of individual physiologic reserves and susceptibility to stress. In these cases, the conceptual framework provided by the physical phenotype of frailty is particularly useful to estimate the risk of side effects of potentially harmful treatments and make the most appropriate choices among different treatment options.

3. *Frailty and chronic kidney disease (CKD).* Reduced renal function, even when still in the range considered "normal aging," is one of the main factors associated with unsuccessful aging. Older adults with the more severe stages of CKD are often frail individuals with reduced physiologic reserves, homeostatic dysregulation, comorbid conditions, polypharmacy, geriatric syndromes, disability, need for institutional care, frequent hospitalization, and high mortality rate. CKD even at earlier stages has been associated with clinical manifestations of frailty. The CHS showed that individuals with CKD have twofold risk of being frail and disabled because of disease-related conditions such as protein-energy wasting, anemia, inflammation, acidosis, and hormonal disturbances. Frailty is also extremely common among patients starting dialysis and is associated with adverse outcomes among incident dialysis patients, including higher risk of hospitalization and death. In these patients, frailty may be either a result of uremia or independent of CKD. Frail patients are started on dialysis earlier (at a higher estimated glomerular filtration rate) on average than nonfrail patients, although there are no data to suggest that frail patients derive any benefit from early initiation of dialysis either in the form of improved survival or functional status.
4. *Frailty and cardiovascular disease (CVD).* Frailty has become a high priority in the management of cardiovascular patients due to their increasing aging and complexity. Frailty is about three times more prevalent among persons compared with those without heart disease. In the CHS, frail subjects were more likely to have subclinical CVD, and subjects with subclinical CVD were more likely to have impaired physical or mental function during follow-up. Similarly, the Women's Health Initiative Study revealed that women with coronary artery disease (CAD) were more likely to develop de novo frailty over 6 years (12% vs 5%), and the Health, Aging, and Body Composition study showed that older adults with objectively measured frailty were more likely to develop CAD events (3.6% vs 2.8% per year). Frailty has been reported in 20% of patients aged greater than or equal to 65 years undergoing percutaneous coronary intervention (PCI) and in 27% of patients aged greater than or equal to 70 years with significant CAD at cardiac catheterization and is particularly common in patients undergoing TAVR. Frailty is also prevalent in patients with heart failure, which directly contributes to frailty by reducing exercise capacity and skeletal muscle function. Patients with CVD who are frail have a worse prognosis than nonfrail patients. For example, in one study of patients who underwent PCI, 3-year mortality was 28% for frail patients (using the Fried criteria) compared with 6% for nonfrail patients. Frailty is also a strong predictor of mortality in patients with chronic heart failure. In patients admitted to hospital with acute decompensated heart failure, simple measures of physical function have been associated with length of hospital stay, reduced activities of daily living, higher readmissions, and mortality. In one community-based study, the attributable risk associated with frailty in patients with heart failure was 35% for emergency department visits and 19% for hospitalizations. In patients referred for cardiac surgery, frailty has been associated with postoperative mortality and morbidity, and greater need for rehabilitation and institutional care following the procedure. In patients with severe symptomatic aortic stenosis treated by TAVR, frailty predicts need for institutional care and mortality 6 to 12 months after a successful procedure. Thus, identifying frailty has important implications for clinical care of older patients with CVD. The assessment of frailty is particularly relevant when counseling older patients with CVD regarding their prognosis following a procedure in order to plan personalized management and treatment, and increase their likelihood of

positive outcomes.

5. *Frailty and diabetes.* In the CHS, 25% of frail subjects had diabetes, and 18% of prefrail subjects had diabetes, but only 12% of nonfrail subjects had diabetes. Furthermore, frail CHS participants were more likely to have higher glucose and insulin levels at baseline and on oral glucose tolerance testing than those who were not frail. Thus, there is no doubt that diabetes and frailty are closely interrelated, but what is uncertain is whether frailty leads to glucose disorders, glucose disorders lead to frailty, or that both are casually related to other common factors. Insulin resistance predicts incident frailty, and diabetes accelerates the loss of skeletal muscle strength—an important component of frailty. In old-old women from Women's Health and Aging Study II, an exaggerated and prolonged glucose and insulin response to an oral glucose tolerance test was observed in frail versus nonfrail or prefrail women, suggesting that dysregulation in response to glucose challenge may be a component of physiologic vulnerability associated with frailty. On the other hand, the increased expression of inflammatory markers in frail older adults may negatively influence late-life glucose tolerance leading to the development of diabetes and may also have an adverse impact on the microvascular effects of diabetes itself.
6. *Frailty and HIV.* Patients with HIV experience accelerated aging and greater risk of geriatric syndromes such as frailty and difficulty with daily activities than HIV-negative people of the same age. Prevalence of frailty in younger HIV-infected individuals is similar to that in older adults, ranging from 5% to 20%. A decline in prevalence of frailty was observed with increased use of effective antiretroviral therapy. Duration of HIV infection, in addition to other markers of advanced HIV disease (CD4+ T-cell count < 350 cells/mm^3), are independently associated with the occurrence of a frailty-related phenotype. The presence of clinical AIDS, previous opportunistic illnesses, and CD4+ T-cell count less than 100 cells/mm^3 are further risk factors for HIV-related frailty. A low serum albumin, which may represent an end point of chronic low-grade inflammation from concomitant comorbidities, weight loss, and/or nutritional and metabolic disturbances, is also associated with HIV-related frailty and is an important independent predictor of death in untreated HIV-infected persons. Similarly to older adults, in HIV-infected persons frailty predicts a number of negative clinical and socioeconomic outcomes. For example, frail HIV-infected persons have greater comorbidity including chronic kidney disease, cognitive impairment, and depression. Furthermore, frail HIV-infected persons have higher rates of nonelective hospitalization and longer inpatient admissions.
7. *Frailty and transplantation.* An increasing number of older adults are referred for and have access to organ transplantation and also are donating organs. Organ allocation systems vary by specific organ and by programmatic tendencies. For example, the lung allocation score, which includes age as a variable, grades disease severity and physiologic reserve. The model for end-stage liver disease (MELD) predicts waitlist mortality but predicts posttransplant outcomes only at scores above 35. Although short-term outcomes are acceptable for older transplant recipients across organs, long-term outcomes differ by age. Older donor organs also have been associated with inferior long-term outcomes, for example, increased risk for graft loss. Transplant recipients are often selected based on the likelihood of successful outcomes, and age is often used as a determinant. However, comprehensive risk assessment, based on stronger predictors than age and accounting for end points such as independence and quality of life, is needed to evaluate risk versus benefit for older recipients. One prospective study of 487 patients with end-stage liver disease referred for liver transplant demonstrated that frailty, defined using the Fried criteria, is a better indicator of quality of life than severity of liver disease measured as MELD.

MULTIMORBIDITY IS THE CLINICAL MANIFESTATION OF FRAILTY

As people age, they not only tend to lose their physical and cognitive integrity, but also become highly susceptible to several chronic diseases, such as congestive heart failure, chronic kidney disease, anemia, chronic obstructive pulmonary disease, and others. Both the prevalence and incidence of major chronic diseases increase with aging (**Figure 46-6**). Hence, if only by chance alone, the probability that a person would develop multiple chronic diseases increases with aging. Indeed, the term "multimorbidity", namely the cooccurrence of at least two chronic diseases in the same person at the same time, is mainly used to refer to an age-related phenomenon. But chance is only part of the story. The multisystem dysregulation that occurs with aging causes morphologic and physiologic changes in multiple organs and physiologic processes. These changes result in progressive homeostatic perturbation, functional deterioration, and reduced reserves. When a certain threshold of dysfunction is reached, it becomes clinically manifest at a system level as a chronic disease. In other words, from a gerontologic perspective, multimorbidity is a milestone

for multisystem age-related loss of resilience and increased vulnerability. Because the rate of biological aging between individuals is highly heterogeneous, the predisposition to multimorbidity is also heterogeneous. Therefore, in a population of individuals the severity of multimorbidity is higher than expected by chance. Consistent with this vision, biological aging is widely recognized as the main risk factor for most chronic diseases.

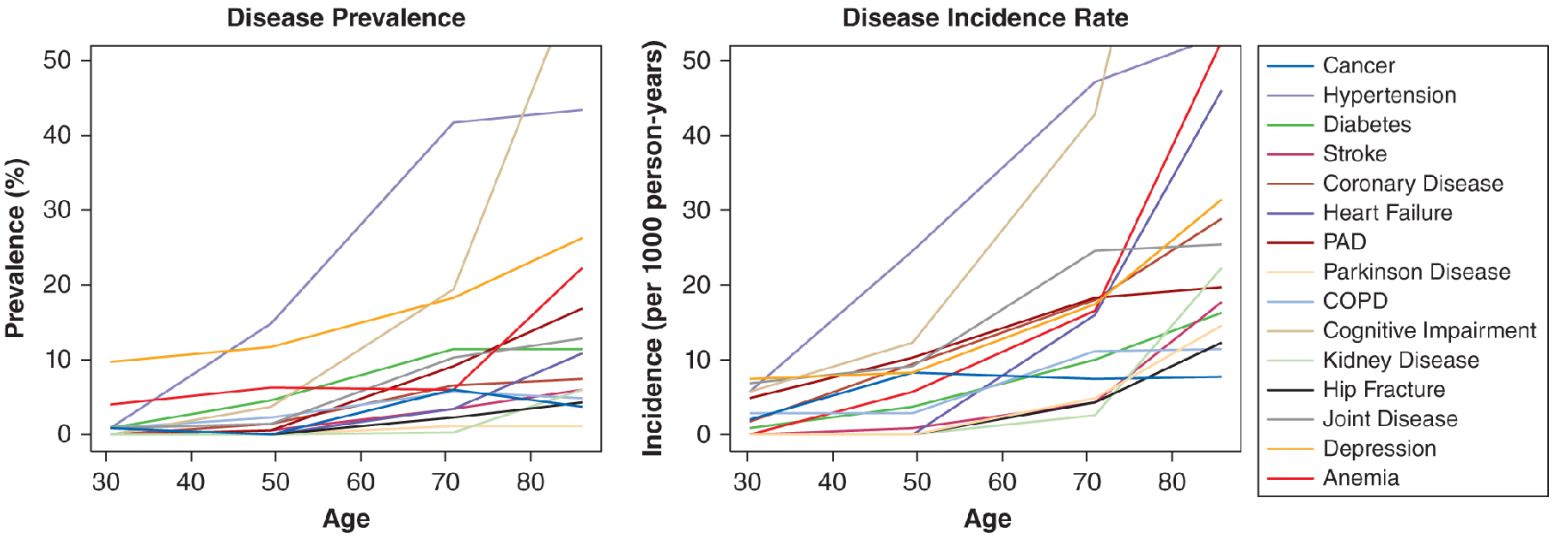


FIGURE 46-6. Prevalence and incidence of major chronic diseases according to age group. InCHIANTI study, 1998–2014. COPD, chronic obstructive pulmonary disease; D, disease; F, fracture; I, impairment; PAD, peripheral artery disease. (From Ferrucci and Fabbri, unpublished data.)

Indeed, the relationship between multimorbidity and frailty has not been fully conceptualized yet. In most cases, despite a certain undiscussed overlap, the two concepts have been considered causally related, but distinct clinical entities, based on the epidemiologic observation that many but not all individuals with multimorbidity meet criteria for the frailty syndrome and vice versa.

If frailty is the aggregation of subclinical losses of reserve across multiple physiologic systems, and multimorbidity is the aggregation of multiple clinically manifested system failures, then frailty and multimorbidity can be viewed as diverse expressions (subclinical and clinical, respectively) of the increasing loss of resilience and homeostatic dysregulation which characterize aging itself. Attempts to operationalize frailty mainly focus on the identification of preclinical measures of high vulnerability to stressors with consequent increased risk to develop adverse outcomes, including disability and death. Similarly, the operationalization of multimorbidity provides a quantification of the clinical manifestations of such vulnerability.

Consistent with this idea, multimorbidity is strongly associated with the main clinical manifestations of frailty such as impaired physical function and cognitive decline. Accordingly, metrics of multimorbidity may be considered proxy measures of age-related multisystem dysfunction and accelerated aging. Indeed, multimorbidity is strongly associated with several aging phenotypes, including inflammation, changes in body composition, energetic impairment, and neurodegeneration (second layer of frailty—**Figure 46-2**). In the InCHIANTI study, higher baseline levels and steeper increases overtime of IL-6 strongly predicted accelerated longitudinal accumulation of chronic diseases in older adults. Moreover, multimorbidity was also related to higher resting metabolic rate (RMR) and RMR higher than expected for a certain age, sex, and body composition predicted future greater development of chronic diseases. In addition, obesity is associated with greater burden of diseases compared to normal weight and overweight status. However, in older adults who are obese at baseline, loss of weight over time rather than gain of weight is associated with the most dramatic rise in number of chronic conditions. In conclusion, weight loss, which is also one of the diagnostic criteria for the physical phenotype of frailty, when it occurs in obese older adults, may represent a sign of ongoing health status deterioration and steeper accumulation of multimorbidity.

The relationship between multimorbidity and the basic biological mechanisms of frailty is still largely unexplored. Age-related pathologies once thought to be distinct from each other are now understood to share the same underlying molecular and cellular mechanisms, some of which are also the biological underpinnings of the aging process. The idea that slowing aging and the biological processes leading to frailty can determine not only a gain in lifespan, but also importantly an increase in health span (the portion of life an individual spends in good health), has driven the birth of a new multidisciplinary branch of science, called geroscience.

GEROSCIENCE AS A POSSIBLE INTERFACE BETWEEN FRAILTY AND PRECISION MEDICINE

The manifesto of geroscience, which embraces the conceptual approach outlined in the onion frailty model, is that health problems in older persons cannot be simply addressed by applying nosologic classification of diseases based on signs and symptoms and by the identification of a specific pathophysiology. Instead, understanding the biological mechanisms of aging would be considerably more informative about the causal nature of diseases, how and why disease manifestations and clinical course are modified by aging, and what treatments are likely to be more effective for prevention and cure of chronic diseases in the older people.

Biological mechanisms of aging are still poorly understood, but research in this area has made great progress over the last few decades (see Chapter 1). Research on the hypothetical mechanisms of aging is gaining momentum, and some of these hypothetical mechanisms of aging can now be tested in humans. Such testing offers the opportunity to verify whether one or more of these mechanisms are related and change in parallel with the major phenotypes of aging and frailty, thereby validating the hypothesis that they are true drivers of the aging process. While it would be difficult and prohibitively expensive to apply routinely sophisticated techniques of molecular biology to the evaluation of frail older patients, it may be possible to identify basic biomarkers that capture the biological nature of the processes at the core of frailty. These processes (illustrated in **Figure 46-7**) could be targeted for potential interventions.

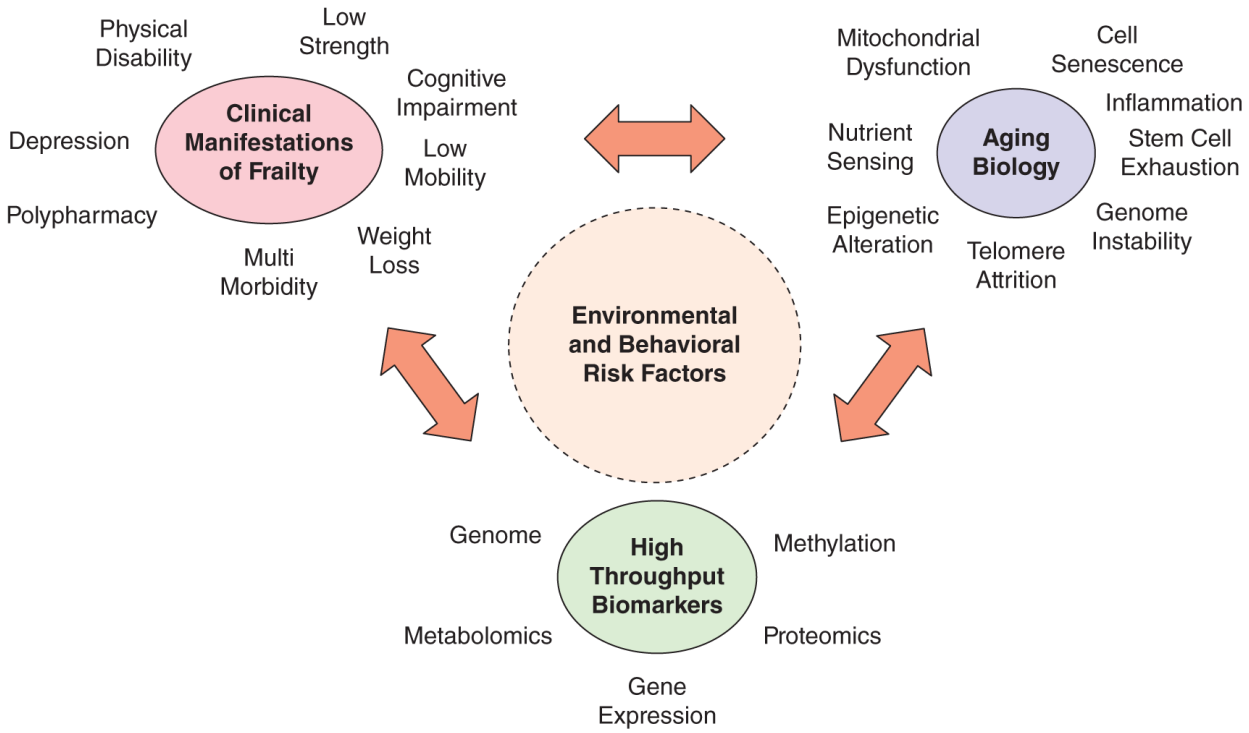


FIGURE 46-7. Operational definition of research aimed at understanding the relationship between accelerated aging and frailty. (From Ferrucci and Fabbri, unpublished data.)

High throughput genetic and genomic biomarkers are increasingly employed to study aging and age-related medical conditions and may have value in understanding the core of frailty and translate this knowledge into clinical applications. Studies that combine measures of aging biology, such as high throughput biomarkers and in-depth phenotyping, may create a convergence between geroscience and "precision medicine." Precision medicine assumes that individual patients can be classified into subpopulations that differ in some biological characteristics that make them susceptible to particular medical conditions or outcomes. Preventive or therapeutic interventions can then be tailored to those patients with specific characteristics, thereby maximizing effectiveness and sparing expense and side effects. Frailty appears to result from perturbing and stressful events that act on a background predisposition leading to multisystem dysregulation. The biological mechanisms responsible for the frailty syndrome could be identified as those that are cross-sectionally and longitudinally correlated with some predefined phenotypes. The nature of these relationships might be further described by a signature biomarker set derived from high throughput technology:

genetic, gene expression, epigenetic, or proteomic biomarkers. Once these relationships have been robustly established, high throughput methods that are becoming progressively less and less expensive could be used to classify patients to receive different targeted therapeutic interventions.

The new paradigm of precision medicine provides an almost ideal entry for the frailty concept into the mainstream of modern medicine. Beyond the variety of operational definitions, at the heart of precision medicine is the attempt to better understand the pathology in the context of the physiology of a specific individual, so that prevention and treatment strategies can be selected that account for variability across individuals. To accomplish this goal, precision medicine relies on state-of-the-art molecular profiling, including but not limited to high throughput genetics, genomics, metabolomics, and proteomics and the emerging ability of computational biology and systems biology to extract meaningful information from "big data." An attractive feature of precision medicine is the agnostic approach to patient subgroup classification that excludes preconceived assumptions about etiology and pathophysiology. The biological mechanisms underpinning the aging process are not known, but research in model organisms suggests that one or a few biological processes are involved. Under the assumption that these processes are also involved in the pathophysiology of chronic diseases and frailty, namely that multimorbidity and frailty result from accelerated aging, the agnostic approach proposed by precision medicine may be able to capture their nature. Prevention and treatment strategies driven by precision medicine will have to take into account the core mechanisms of aging and, perhaps, will be able to distinguish pathologic conditions that have a unique, intrinsic pathophysiology and those that are mostly age related. To accomplish this goal, it is critical that the next-generation studies that derive the molecular signature of pathology include measures of multimorbidity and frailty, and that geriatricians and gerontologists be involved in the development of these new tools.

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Chapter 47

Delirium

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Learning Objectives

- Learn the epidemiology, pathophysiology, clinical presentations, evaluation, and management of delirium in older adults.
- Understand the role of various predisposing and precipitating factors in increasing risk of older persons to delirium and associated prognosis and mortality.
- Recognize the significance and limitations of routine as well as special laboratory and imaging tests commonly used to evaluate an older patient with delirium.
- Learn the special relationship between dementia and delirium and the role of certain medications in predisposing older adults to delirium.
- Gain a clear understanding of the specific indications and efficacy of various treatments, including pharmacologic and nonpharmacologic strategies commonly used to manage delirium.
- Understand the latest concepts about special issues related to delirium, including patient preferences and decision making, delirium in nursing homes, and palliative and end-of-life care.

Key Clinical Points

1. **Delirium is commonly encountered in older adults in various clinical settings and associated with significant morbidity and mortality, especially in intensive care units, inpatient settings, nursing homes, and following major medical illnesses or surgery.**
2. **Delirium is commonly unrecognized in up to 70% of older patients and can lead to long-term functional and cognitive deficits.**
3. **The pathophysiology of delirium is currently unclear, but posited to be the end result of multiple pathogenic pathways eventually culminating in the dysfunction of various neurotransmitters and major brain networks.**
4. **Delirium is commonly due to multiple causes and the most effective treatment strategy is to identify and address as many predisposing and precipitating factors as possible.**
5. **Among the precipitating factors, decreased mobility is strongly associated with delirium and medical equipment and devices may further contribute to immobilization.**
6. **Dementia is the underlying risk factor in almost 75% of cases of delirium, and must be suspected in patients with slowly progressive cognitive and functional deficits.**
7. **Acute onset, varying levels of alertness, and inattention are cardinal features of delirium, and obtaining historical details from a close family member or friend is critical in making a correct diagnosis of delirium.**
8. **Lethargy and reduced psychomotor functioning are common presentations of delirium in older patients, in contrast to the hyperactive form more common in younger patients.**
9. **Nonpharmacologic strategies are the preferred treatment for delirium in older patients, and medications are reserved for more severe symptoms that affect either medical management or**

patient safety.

Delirium, defined as an acute disorder of attention and global cognitive function, is a common, serious, and potentially preventable source of morbidity and mortality for hospitalized older persons. Delirium affects as many as half of all people over age 65 who are hospitalized. With the aging of the US population, delirium has assumed heightened importance because persons aged 65 and older presently account for more than 45% of all days of hospital care. Delirium increases hospital costs by an average of $1000 per patient and posthospital costs by over $10,000 per patient-year, so that annually over $164 billion (in 2011 US dollars) of US health care costs are attributable to delirium. Moreover, delirium is preventable in 30% to 40% of cases. Importantly, substantial additional costs linked to delirium accrue after hospital discharge because of the increased need for institutionalization, rehabilitation services, closer medical follow-up, and home health care. Delirium often initiates a cascade of events in older persons, leading to a downward spiral of functional decline, loss of independence, institutionalization, and ultimately, death. These statistics highlight the importance of delirium from both clinical and health policy perspectives. In fact, a recent consensus panel identified delirium as among the top three target conditions for quality-of-care improvement for vulnerable older adults. With its common occurrence, its frequently iatrogenic nature, and its close linkage to the processes of care, incident delirium can serve as a marker for the quality of hospital care and provides an important opportunity for quality improvement.

DEFINITION

The definition of and diagnostic criteria for delirium continue to evolve. The standardized criteria for delirium that appear in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5, 2013) is the current diagnostic standard. These criteria are based on: (A) a disturbance in attention and awaremeness; (B) an acute onset and fluctuating course; (C) an additional deficit in cognition (such as memory, orientation, language, or visuoperceptual ability); (D) impairments not better explained by dementia and do not occur in context of severely impaired level of consciousness or coma; and (E) evidence of an underlying medical etiology or multiple etiologies. Expert consensus was used to develop these criteria, however, and performance characteristics such as diagnostic sensitivity and specificity have not yet been reported for DSM-5 criteria. A standardized tool, the Confusion Assessment Method (CAM), provides a brief, validated diagnostic algorithm that is currently in widespread use for identification of delirium. The CAM algorithm relies on the presence of acute onset and fluctuating course, inattention, and either disorganized thinking or altered level of consciousness. The algorithm has a sensitivity of 94% to 100%, specificity of 90% to 95%, and high interrater reliability. Given the uncertainty of diagnostic criteria for delirium, a critical area for future investigation is to establish more definitive criteria, including epidemiologic and phenomenologic evaluations assisted by advances in functional neuroimaging and other potential diagnostic marker tests.

EPIDEMIOLOGY

Most of the epidemiologic studies of delirium involved hospitalized older patients, in whom the highest rates of delirium occur. Reported rates vary based on the subgroup of patients studied and the setting of care (eg, hospital, intensive care, surgical). Previous studies estimated the prevalence of delirium (present at the time of hospital admission) at 18% to 35% and the incidence of delirium (new cases arising during hospitalization) at 11% to 29%. The incidence rates of delirium in high-risk hospital venues, such as the intensive care unit and posthip fracture settings, range from 19% to 82% and 12% to 51%, respectively. Delirium occurs in up to 36% of patients in nursing homes or postacute settings, and in up to 83% of all patients at the end of life. The rates of delirium in all older persons presenting to the emergency department in several studies have ranged from 8% to 17%. While less frequent in the community setting, delirium is an important presenting symptom to emergency departments and community physicians, and often heralds serious underlying disease. Delirium is often unrecognized; previous studies have documented that clinicians fail to detect up to 70% of affected patients across all of these settings. Furthermore, the presence of delirium portends a potentially poor prognosis; hospital mortality rates in patients with delirium range from 22% to 76%, as high as mortality rates associated with acute myocardial infarction or sepsis. Following

hospitalization, the additional 1-year mortality rate associated with cases of delirium is 35% to 40%.

PATHOPHYSIOLOGY

The fundamental pathophysiologic mechanisms of delirium remain unclear. Delirium is thought to represent a functional rather than structural lesion. The characteristic electroencephalographic (EEG) findings demonstrate global functional derangements and generalized slowing of cortical background (alpha) activity. Current hypotheses view delirium as the final common pathway of many different but interacting pathogenic mechanisms, causing dysfunction of multiple brain regions and neurotransmitter systems and culminating in disruption of large-scale networks. Evidence from EEG, evoked-potential studies, and neuroimaging studies in acute delirium suggest focal dysfunction localized to the prefrontal cortex, thalamus, basal ganglia, temporoparietal cortex, fusiform, and lingual gyri of the nondominant cortex. Studies using x-ray computed tomography (CT) or magnetic resonance imaging (MRI) have found lesions or structural abnormalities in the brains of patients with delirium. Several studies of cerebral blood flow (CBF) using single-photon emission computed tomography (SPECT) found that delirium is mostly associated with decreased blood flow. However, results from previous studies have been highly variable. Associated neurotransmitter abnormalities involve elevated brain dopaminergic function, reduced cholinergic function, or a relative imbalance of these systems. Serotonergic activity may interact to regulate or alter activity of these other two systems, and serotonin levels may be either increased or decreased. Extensive evidence supports the role of cholinergic deficiency. Acetylcholine plays a key role in consciousness and attentional process, and given that delirium is manifested by an acute confusional state often with alterations of consciousness, it is likely to have a cholinergic basis. Anticholinergic drugs can induce delirium in humans and animals, and serum anticholinergic activity is increased in patients with delirium. Physostigmine can reverse delirium associated with anticholinergic drugs, and cholinesterase inhibitors appear to have some benefit even in cases of delirium that are not induced by drugs. Neurotransmitter systems can also be affected indirectly. For instance, in sepsis, the systemic inflammatory response triggers a cascade of local (brain) neuroinflammation, leading to endothelial activation, impaired blood flow, neuronal apoptosis, and neurotransmitter dysfunction. Neuroinflammation can lead to microglial overactivation, resulting in a neurotoxic response with further neuronal injury. The stress response associated with severe medical illness or surgery involves sympathetic and immune system activation, including increased activity of the hypothalamic-pituitary-adrenal axis with hypercortisolism, and release of cerebral cytokines that alter neurotransmitter systems, the thyroid axis, and modification of blood-brain barrier permeability. Age-related changes in central neurotransmission, stress management, hormonal regulation, and immune response may contribute to the increased vulnerability of older persons to delirium. The description of delirium as “acute brain failure”—involving multiple neural circuits, neurotransmitters, and brain regions—suggests that understanding delirium may help to elucidate the essential underlying mechanisms of brain functioning.

ETIOLOGY

The etiology of delirium is usually multifactorial, like many other common geriatric syndromes, such as falls, incontinence, and pressure sores. Although there may be a single cause of delirium, more commonly in older persons, delirium results from the interrelationship between patient vulnerability (ie, predisposing factors) and the occurrence of noxious insults (ie, precipitating factors). For example, patients who are highly vulnerable to delirium at baseline (eg, such as patients with dementia or serious illness) can experience acute delirium after exposure to otherwise mild insults, such as a single dose of a sedative medication for sleep. On the other hand, older patients with few predisposing factors (low baseline vulnerability) are relatively resistant, with precipitation of delirium only after exposure to multiple potentially noxious insults, such as general anesthesia, major surgery, multiple psychoactive medications, immobilization, and infection (**Figure 47-1**). Moreover, based on validated predictive models for delirium, the effects of multiple risk factors appear to be cumulative. Clinically, the importance of the multifactorial nature of delirium is that removal or treatment of one risk factor alone often fails to resolve delirium. Instead, addressing many or all of the predisposing and precipitating factors for delirium is often required before the delirium symptoms will improve.

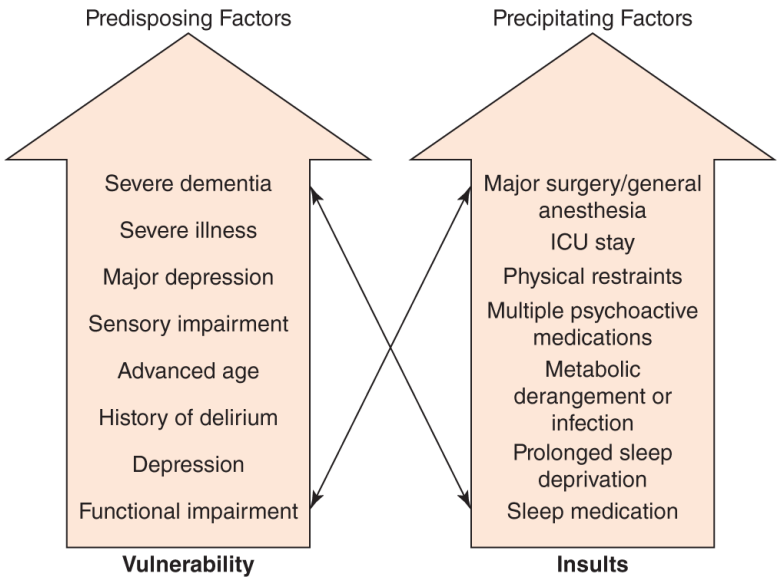


FIGURE 47-1. Multifactorial model for delirium. The etiology of delirium involves a complex interrelationship between the patient's underlying vulnerability or predisposing factors (*left axis*) and precipitating factors or noxious insults (*right axis*). For example, a patient with high vulnerability, such as with severe dementia, underlying severe illness, or hearing or vision impairment, might develop delirium with exposure to only one dose of a sleeping medication. Conversely, a patient with low vulnerability would develop delirium only with exposure to many noxious insults, such as general anesthesia and major surgery, intensive care unit (ICU) stay, multiple psychoactive medications, and prolonged sleep deprivation.

Predisposing Factors

Predisposing factors for delirium include preexisting cognitive impairment or dementia, a history of delirium, advanced age (> 70 years), severe underlying illness and multimorbidity, functional impairment, depression, alcohol abuse, a history of stroke or transient ischemic attack, and sensory impairments (vision or hearing) (**Table 47-1**). Preexisting cognitive impairment, including dementia, is a powerful and consistent risk factor for delirium demonstrated across multiple studies, with patients with dementia having a two- to fivefold increased risk for delirium. Moreover, up to half of delirious patients have an underlying dementia. Nearly any chronic medical condition can predispose to delirium, ranging from diseases involving the central nervous system (eg, Parkinson disease, cerebrovascular disease, mass lesions, trauma, infection), to diseases outside the central nervous system, including infectious, metabolic, cardiac, pulmonary, endocrine, or neoplastic etiologies. Predictive risk models that identify predisposing factors in populations such as general medicine, intensive care, surgical patients (cardiac and noncardiac), cancer patients, and nursing home residents, have been developed and aid in the understanding of baseline patient characteristics contributing to delirium risk.

TABLE 47-1 PREDISPOSING AND PRECIPITATING FACTORS FOR DELIRIUM FROM VALIDATED PREDICTIVE MODELS

Predisposing factors

- Dementia or underlying cognitive impairment
- Severe illness
- Comorbidity
- Depression
- Vision and/or hearing impairment
- Functional impairment
- History of transient ischemia or stroke
- History of alcohol abuse
- History of delirium
- Advanced age (> 70)

Precipitating factors

- Drugs, including polypharmacy, psychoactive, and sedatives or hypnotics
- Use of physical restraints
- Indwelling bladder catheters
- Dehydration
- Poor nutritional status, abnormal serum albumin
- Iatrogenic complications
- Major surgical procedure (eg, aortic aneurysm repair, noncardiac thoracic surgery, and neurosurgery)
- Metabolic derangements (electrolytes, glucose, metabolic acidosis)
- Infection
- Trauma admission
- Urgent admission
- Coma

Precipitating Factors

Major precipitating factors identified in validated predictive models include medication use (see section on "Drug Use and Delirium"), use of indwelling bladder catheters, use of physical restraints, dehydration, malnutrition, iatrogenic events, infections, metabolic and electrolyte derangements, surgery, admissions that are urgent or involve trauma, and coma (see **Table 47-1**). Decreased mobility is strongly associated with delirium and concomitant functional decline. The use of medical equipment and devices (eg, indwelling bladder catheters and physical restraints) may further contribute to immobilization. Major iatrogenic events occur in 29% to 38% of older hospitalized adults (three to five times the risk when compared with adults younger than 65 years). Examples include complications related to diagnostic or therapeutic procedures, allergic reactions, and bleeding caused by over-anticoagulation. Many of these events potentially are preventable. Disorders of any major organ system, particularly renal or hepatic failure, can precipitate delirium. Occult respiratory failure has emerged as an increasing problem in older patients, who often lack the typical signs and symptoms of dyspnea and tachypnea. In older adults, acute myocardial infarction and congestive heart failure may present with delirium or "failure to thrive" as the cardinal feature, and minimal or none of the usual symptoms of angina or dyspnea. Occult infection, caused by pneumonia, urinary tract infection, endocarditis, abdominal abscess, or infected joint, is a particularly noteworthy cause of delirium because older patients may not present with leukocytosis or a typical febrile response. Metabolic and endocrinologic disorders, such as hyper- or hyponatremia, hypercalcemia, acid-base disorders, hypo- and hyperglycemia, and thyroid or adrenal disorders, may also contribute to delirium. The precipitating factors for delirium in hospitalized older patients that have been validated previously in a predictive model include use of physical restraints, malnutrition, more than three medications added during the previous day (more than 70% of these were psychoactive drugs), indwelling bladder catheter, and any iatrogenic event. The presence of these independent factors contributes to delirium risk in a predictable and cumulative manner, yet each risk factor is potentially modifiable.

Drug Use and Delirium

In 40% or more of delirium cases, use of one or more specific medication contributes to its development. While medications often incite delirium, they are also the most common remediable cause of delirium. A broad array of medications and their metabolites can lead to delirium; the most common are those with known psychoactive effects, such as sedative hypnotics, anxiolytics, narcotics, H_2 blockers, and medications with anticholinergic activity (**Table 47-2**). In previous studies, use of any psychoactive medication was associated with a fourfold increased risk of delirium, while use of two or more psychoactive medications was associated with a fivefold increased risk. Sedative-hypnotic drugs are associated with a 3- to 12-fold increased risk of delirium; narcotics with a threefold risk; and anticholinergic drugs with a 5- to 12-fold risk. The incidence of delirium, similar to other adverse drug events, increases in direct proportion to the number of medications prescribed, because of the effects of the medications themselves, as well as to the increased risk of drug-drug and drug-disease interactions. Recent studies provide compelling evidence that suboptimal medication management, ranging from inappropriate use to overuse of psychoactive medications, occurs commonly in older adults in the hospital and in community settings, and suggests that many cases of delirium and other related adverse drug events may be preventable. As the number of prescription and over-the-counter drugs consumed by the older population increases, review of potentially problematic medications

will remain an important step in the search for predisposing factors in the patient with delirium.

TABLE 47-2 MEDICATIONS ASSOCIATED WITH COGNITIVE IMPAIRMENT AND DELIRIUM (BEERS CRITERIA, 2012)

All tricyclic antidepressants
Anticholinergics (including antihistamines, antiparkinsonian agents, skeletal muscle relaxants, antidepressants, antimuscarinics, antispasmodics)
Benzodiazepines
Chlorpromazine
Corticosteroids
H_2-receptor antagonists
Meperidine
Sedative hypnotics
Thioridazine
Zolpidem
Antipsychotics (chronic and as-needed use)

Data from *American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012;60(4):616–631.*

Relationship Between Delirium and Dementia

While delirium and dementia are highly interrelated, the nature of their relationship remains poorly examined. The contribution of delirium itself to permanent cognitive impairment or dementia remains controversial; however, previous studies document that, after delirium, at least some patients never recover their baseline level of cognitive function. Thus, delirium and dementia may represent two ends along a spectrum of cognitive impairment with "chronic delirium" and "reversible dementia" falling along this continuum. Dementia is the leading risk factor for delirium, and fully two-thirds of cases of delirium occur in patients with dementia. Moreover, studies have shown that delirium and dementia are both associated with decreased cerebral metabolism, cholinergic deficiency, and inflammation, reflecting their overlapping clinical, metabolic, and cellular mechanisms. Delirium can alter the course of an underlying dementia, with dramatic worsening of the trajectory of cognitive decline, resulting in more rapid progression of functional losses and worse long-term outcomes. In follow-up studies, patients with dementia in whom delirium develops have worse outcomes than those with dementia alone, including worsened cognitive function and increased rates of hospitalization, institutionalization, and death.

PRESENTATION

Cardinal Features

Acute onset and inattention are the central features of delirium. Determining the acuity of onset requires accurate knowledge of the patient's prior cognitive status. Pinpointing the origin and time course of changes in mental status often entails obtaining historical information from another close observer, such as a family member, caregiver, or nurse. Typically with delirium, the mental status changes occur over hours to days, in contrast to the changes that occur with dementia, which present insidiously over weeks to months. Another key feature is the fluctuating course of delirium, with symptoms tending to wax and wane in severity over a 24-hour period. Lucid intervals are characteristic, and the reversibility of symptoms within a short time can deceive even an experienced clinician. Inattention is manifested as difficulty focusing, maintaining, and shifting attention or concentration. With simple cognitive assessment, patients may display difficulty with straightforward repetition tasks, digit spans, or recitation of the months of the year backward. Delirious patients appear easily distracted, experience difficulty with multistep commands, cannot follow the flow of a conversation, and often perseverate with an answer to a previous question. Additional major features include a disorganization of thought and altered level of consciousness. Disorganized thoughts are a manifestation of underlying cognitive or perceptual disturbances, and can be recognized by disjointed and incoherent speech, or an unclear or illogical flow of ideas. Clouding of consciousness is typically manifested by

lethargy, with a reduced awareness of the environment that may show diurnal variation. Although not cardinal elements, other frequently associated features include disorientation (more commonly to time and place than to self), cognitive impairments (eg, memory and problem-solving deficits, dysnomia), psychomotor agitation or retardation, perceptual disturbances (eg, hallucinations, misperceptions, illusions), paranoid delusions, emotional lability, and sleep-wake cycle disruption.

Classification of Delirium

The clinical presentation of delirium can take two main forms, either hypoactive or hyperactive. The hypoactive form of delirium is characterized by lethargy and reduced psychomotor functioning, and is the more common form in older patients. Hypoactive delirium often goes unrecognized and carries an overall poorer prognosis. The reduced level of patient activity associated with hypoactive delirium, often attributed to low mood or fatigue, may contribute to its misdiagnosis or underrecognition. By contrast, the hyperactive form of delirium presents with symptoms of agitation, increased vigilance, and often concomitant hallucinations; its presentation rarely remains unnoticed by caregivers or clinicians. Importantly, patients can fluctuate between the hypoactive and hyperactive forms—the mixed type of delirium—presenting a challenge in distinguishing the presentation from other psychotic or mood disorders. Moreover, recent recognition of partial or subsyndromal forms of delirium has brought attention to the persistence of symptoms among older patients, particularly during the resolution stages of delirium, when manifestation of the full syndrome may not be apparent. Partial forms of delirium also adversely influence long-term clinical outcomes.

Prognosis

Delirium is an important independent determinant of prolonged length of hospital stay, increased mortality, increased rates of nursing home placement, and functional and cognitive decline—even after controlling for age, gender, dementia, illness severity, and baseline functional status.

Delirium has long been thought to be a reversible, transient condition; however, recent evidence brings this into question. Recent research on the duration of delirium symptoms, however, provides evidence that delirium may persist for much longer than previously recognized. In fact, delirium symptoms generally persist for a month or more; as few as 20% of patients attain complete symptom resolution at 6-months follow-up. In addition, those patients with extant cognitive impairment may experience greater deleterious effects than comparable patients without dementia. The chronic detrimental effects are likely related to the duration, severity, and underlying cause(s) of the delirium, in addition to the baseline vulnerability of the patient.

EVALUATION

Table 47-3 lists instruments for identification of delirium. Of these, the most widely used is the CAM, of which the four-item short form has been applied in over 4000 studies to date and translated into over 14 languages. The CAM has also been adapted for use in other settings, including the intensive care unit (CAM-ICU), nursing home (NH-CAM), and emergency department (CAM-ED and B-CAM). A new adaptation, called the 3D-CAM, provides a brief cognitive assessment that takes fewer than 3 minutes to complete, and identifies delirium with high sensitivity and specificity. The CAM-S derived from the CAM can be used to rate delirium severity, and has demonstrated predictive validity for relevant clinical outcomes. Other delirium severity instruments include the Delirium Rating Scale (DRS-98), the Memorial Delirium Assessment Scale (MDAS), and the Delirium Index (DI). Each instrument has strengths and limitations, and the choice among them depends on the goals for use.

TABLE 47-3 DELIRIUM SCREENING TESTS

DELIRIUM SCREENING TEST	BRIEF DESCRIPTION
4AT	2-min instrument for general practice includes 4 items; scores range from 0–12, with a score ≥ 4 suggesting possible delirium
Bedside Confusion Scale	2-min screening test requiring minimal training, involving observation of alertness and timed attention task, scores range from 0 to 5, with scores > 2 indicating confusion
Clinical Assessment of Confusion (CAC)	Nursing checklist of 25 psychomotor behaviors associated with

	confusion; range, 0–77, higher score indicates more severe confusion
Cognitive Test for Delirium (CTD)	15-min instrument designed for use in ICU settings; scores range from 0 to 30, with lower scores indicating delirium
Confusion Assessment Method (CAM)[a]	Widely adopted 5-min instrument to score 4-item algorithm based on 9 operationalized DSM-IIIR criteria for delirium; involves cognitive assessment; interviewer training recommended for optimal use
Confusion Assessment Method—ICU version (CAM-ICU)	Modification of CAM 4-feature algorithm with nonverbal tasks that can be used in the ICU setting
3D-CAM	3-min version of CAM requires minimal training; algorithm probes 4 cardinal features of delirium, with 2 essential features and at least 1 of 2 secondary features indicating delirium
Confusion Rating Scale (CRS)	Scale involving 4 behavioral domains designed for nurses during 8-h shifts, scores range from 0–24, with higher scores indicating more pronounced delirium
Delirium Index	Designed to be used with MMSE and to track delirium severity over time, includes 7 operationalized items from CAM, ranges from 0 to 21 with higher scores indicating greater severity
Delirium-O-Meter	Adapted from the CAM, 12-item behavioral observation scale, scores range from 0–36, with higher scores indicating higher severity of delirium
Delirium Observation Screening (DOS)	Thirteen-item scale based on DSM-IV criteria for delirium that can be observed during routine nursing care; presence of ≥ 3 items indicates delirium
Delirium Rating Sale Revised 1998 (DRS-98R)[a]	Scale for clinicians with psychiatric training with 2 sections, including 3 diagnostic items for initial ratings and 13 items on a scale ranging from 0 to 46, with higher scores indicating delirium
Delirium Symptoms Interview (DSI)	Structured interview for nonclinicians assesses 7 domains from DSM-III criteria for delirium, including 63 interview questions and 44 observations
Delirium Diagnostic Test—Provisional (DDT-Pro)	3-min, 3-item screening tool designed for nonclinicians and derived from CTD and DRS-98R, range 0–12 with lower scores indicating delirium; originally validated in patients rehabilitating from traumatic brain injury
Intensive Care Delirium Screening Checklist (ICDSC)	8-item screening tool involves focused bedside patient evaluation and observations during 24-h nursing shift, range 0–8, with scores ≥ 4 indicating delirium
Memorial Delirium Assessment Scale (MDAS)[a]	Physician-rated instrument requiring 10–15 min and designed for use multiple times in single day, scores range from 0 to 30 with higher scores indicating more severe delirium
NEECHAM Confusion Scale	Nursing questionnaire requiring 10 min with 3 subscales addressing cognition, behavior, and physiologic parameters, scores range from 0 to 30, with lower scores indicating higher risk of delirium
Nursing Delirium Screening Scale (Nu-DESC)	5-item, 1-min screening scale designed for use by nurses and used during routine care on the hospital floor, scores range from 0 to 10 with higher scores indicating delirium
Single Question in Delirium (SQiD)	Single question, “Do you think (name of patient) has been more confused lately?” posed to informant, positive response indicates delirium

[a]Generally considered too lengthy to serve as screening tools.
ICU, intensive care unit; MMSE, Mini Mental State Examination.

The acute evaluation of suspected or confirmed delirium centers on three main tasks that occur simultaneously: (1) establishing the diagnosis of delirium; (2) determining the potential cause(s) and ruling out life-threatening contributors; and (3) managing the symptoms while assuring patient safety. Delirium is a clinical diagnosis, relying on astute observation at the bedside, careful cognitive assessment, and history-taking from a knowledgeable informant to establish a change from the patient's baseline functioning. Identifying the potentially multifactorial contributors to the delirium is of paramount importance, because many of these factors are treatable, and if left untreated, may result in substantial morbidity and mortality. Because the potential contributors are myriad, the search requires a thorough medical evaluation guided by clinical judgment. The challenge is enhanced by the frequently nonspecific or atypical presentation of the underlying illness in older persons. In fact, delirium is often the *only* sign of life-threatening illness, such as sepsis, pneumonia, or myocardial infarction in older persons. The NICE guidelines on delirium provide a recent systematic review and evidence-based approach to delirium (http://www.nice.org.uk/guidance/CG103). These guidelines highlight both the importance of delirium in older persons, and the need for better recognition and prevention of delirium.

History and Physical Examination

A thorough history and physical examination constitute the foundation of the medical evaluation of suspected delirium. The first step in evaluation should be to establish the diagnosis of delirium through careful cognitive assessment and to determine the acuity of change from the patient's baseline cognitive state. Because cognitive impairment may easily be missed during routine conversation, brief cognitive screening tests, such as the Short Portable Mental Status Questionnaire, Mini-Cog test, or 3D-CAM assessment, should be used to rate the CAM. The degree of attention should be further assessed with simple tests such as a forward digit span (inattention indicated by an inability to repeat five digits forward or three digits backwards) or recitation of the months of the year backward. A targeted history, focusing on baseline cognitive status and chronology of recent mental status changes, should be elicited from a reliable informant (eg, family member or health professional). In addition, such historical data as intercurrent illnesses, recent adjustments in medications, the possibility of alcohol withdrawal, and pertinent environmental changes may point to potential precipitating factors of delirium.

The physical examination should include a detailed review that focuses on potential etiologic clues to an underlying or inciting disease process. Vital sign assessment is important to identify fever, tachycardia, or decreased oxygen saturation, each of which may point to specific disease processes. Ausculatory examination may suggest pneumonia or pulmonary effusion. A new cardiac murmur or dysrhythmia may suggest ischemia or congestive heart failure. Gastrointestinal examination should focus on evidence of an acute abdominal process, such as occult bleeding, perforated viscus, or infection. Patients with delirium may also demonstrate nonspecific focal findings on neurologic examination, such as asterixis or tremor, although the presence of any new neurologic deficit should raise suspicion of an acute cerebrovascular event or subdural hematoma. It is worthy of emphasis that in many older patients and in those with cognitive impairment, delirium may be the initial manifestation of a serious new disease process. Therefore, attention to early localizing signs on serial physical examinations is important.

A complete medication review, including over-the-counter medications, is critical, and any medications with known psychoactive effects should be discontinued or minimized whenever possible. Because of pharmacodynamic and pharmacokinetic changes in aging adults, these medications may cause deleterious psychoactive effects even when prescribed at customary doses and with serum drug levels that are within the "therapeutic range."

Laboratory Tests and Imaging

Despite the growing recognition of geriatric syndromes such as delirium, there is little evidence-based research that assesses the predictive value of laboratory and other diagnostic testing in the evaluation of delirium. Consequently, laboratory evaluation should be guided by clinical judgment and take into account specific patient characteristics and historical data. An astute history and physical examination, medication review, focused laboratory testing (eg, complete blood count, chemistries, glucose, renal and liver function tests, urinalysis, oxygen saturation), and search for occult infection should help to identify the majority of potential contributors to the delirium. Obtaining additional laboratory testing such as thyroid function tests, B_{12} level, cortisol level, drug levels or toxicology screen, syphilis serologies, and ammonia level should be based on a patient's distinct clinical presentation. Further diagnostic work-up

with an electrocardiogram, chest radiograph, and/or arterial blood gas determination may be appropriate for patients with pulmonary or cardiac conditions. The indications for cerebrospinal fluid examination, brain imaging, or EEG remain controversial. Their overall diagnostic yield is low, and these procedures are probably indicated in fewer than 5% to 10% of delirium cases. Lumbar puncture with cerebrospinal fluid examination is indicated for the febrile delirious patient when meningitis or encephalitis is suspected. Brain imaging (such as CT or MRI) should be reserved for cases with new focal neurologic signs, with history or signs of head trauma, or without another identifiable cause of the delirium. Of note, some neurologic symptoms are associated with delirium, including tremor and asterixis. EEG, which has a false-negative rate of 17% and a false-positive rate of 22% for distinguishing between delirious and nondelirious patients, plays a limited role and is most commonly employed to detect subclinical seizure disorders and to differentiate delirium from nonorganic psychiatric conditions.

Differential Diagnosis

Distinguishing a long-standing confusional state (dementia) from delirium alone, or from delirium superimposed on dementia, is an important, but often difficult, diagnostic step. These two conditions can be differentiated by the acute onset of symptoms in delirium, with dementia presenting much more insidiously and by the impaired attention and altered level of consciousness associated with delirium.

The differential diagnosis of delirium can be extensive and includes other psychiatric conditions such as depression and nonorganic psychotic disorders (**Table 47-4**). Although perceptual disturbances, such as illusions and hallucinations, can occur with delirium in about 15% of cases, recognition of the key features of acute onset, inattention, altered level of consciousness, and global cognitive impairment will enhance the identification of delirium. Differentiating among diagnoses is critical because delirium carries a more serious prognosis without proper evaluation and management, and treatment for certain conditions such as depression or affective disorders may involve use of drugs with anticholinergic activity, for example, which could exacerbate an unrecognized case of delirium. At times, working through the differential diagnosis can be quite challenging, particularly with an uncooperative patient or when an accurate history is unavailable, and the diagnosis of delirium may remain uncertain. Because of the potentially life-threatening nature of delirium, however, it is prudent to manage the patient as having delirium and search for underlying precipitants (eg, intercurrent illness, metabolic abnormalities, adverse medication effects) until further information can be obtained.

TABLE 47-4 DIFFERENTIAL DIAGNOSIS OF ALTERED MENTAL STATUS

CHARACTERISTIC	DELIRIUM	DEMENTIA	DEPRESSION	ACUTE PSYCHOSIS
Onset	Acute (hours to days)	Progressive, insidious (weeks to months)	Either acute or insidious	Acute
Course over time	Waxing and waning	Unrelenting	Variable	Episodic
Attention	Impaired, a hallmark of delirium	Usually intact, until end-stage disease	Decreased concentration and attention to detail	Variable
Level of consciousness	Altered, from lethargic to hyperalert	Normal, until end-stage disease	Normal	Normal
Memory	Impaired commonly	Prominent short- and/or long-term memory impairment	Normal, some short-term forgetfulness	Usually normal
Orientation	Disoriented	Normal, until end-stage disease	Usually normal	Usually normal
Speech	Disorganized, incoherent, illogical	Notable for parsimony, aphasia, anomia	Normal, but often slowing of speech (psychomotor retardation)	Variable, often disorganized
Delusions	Common	Common	Uncommon	Common, often complex
Hallucinations	Usually visual	Sometimes	Rare	Usually auditory and more complex

Organic etiology	Yes	Yes	No	No

Algorithm for the Evaluation of Altered Mental Status

Figure 47-2 presents an algorithm for the evaluation of altered mental status in the older patient. The initial steps center on establishing the patient's baseline cognitive functioning and the onset and timing of any cognitive changes. Chronic impairments, representing changes that occur over months to years, are most likely attributable to a dementia, which should be evaluated accordingly (see Chapter 66). Acute alterations, representing abrupt deteriorations in mental status, occur over hours to weeks, although they may be superimposed on an underlying dementia. They should be further evaluated with cognitive testing to establish the presence of delirium. In the absence of notable delirium features (see "Presentation" earlier in this chapter), subsequent evaluation should focus on the possibility of major depression, acute psychotic disorder, or other psychiatric disorders (see Chapters 71–73).

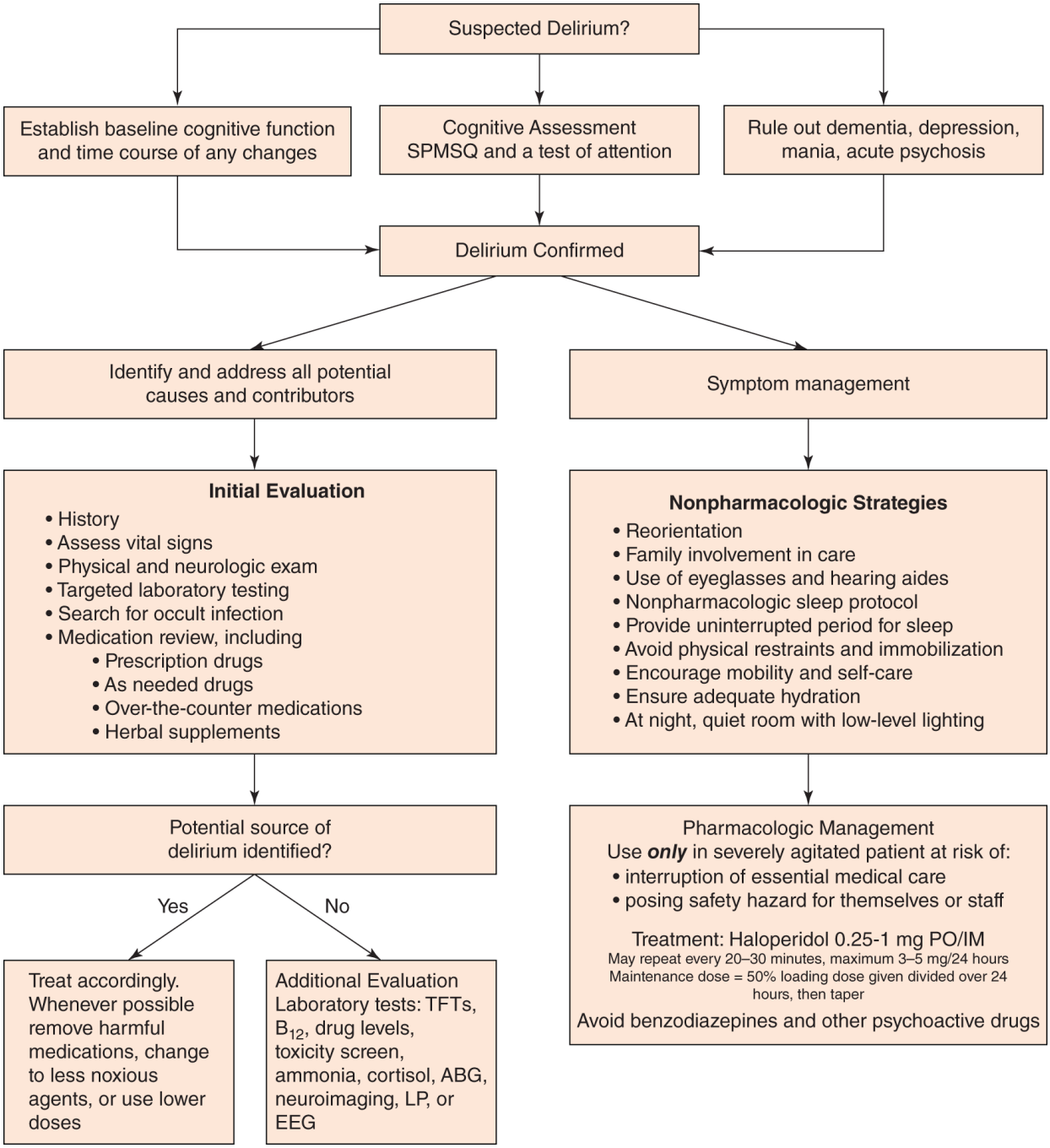


FIGURE 47-2. Flowchart for evaluation of suspected delirium in an older person. ABG, arterial blood gas; B_{12}, cyanocobalamin or vitamin B_{12} level; CAM, Confusion Assessment Method; EEG, electroencephalography; IM, intramuscular; LP, lumbar puncture; PO, by mouth; SPMSQ, Short Portable Mental Status Questionnaire; TFT, thyroid function tests (eg, T_4, thyroid index, thyroid-stimulating hormone).

PREVENTION

Primary prevention—preventing delirium before it develops—is the most effective strategy for reducing delirium and its associated adverse outcomes, which range from functional disability to longer lengths of hospital stay, institutionalization, and death. **Table 47-5** describes well-documented delirium risk factors and tested preventive interventions to address each risk factor. A controlled clinical trial demonstrated the effectiveness of a delirium prevention strategy targeted toward these risk factors. The selection of risk factors was based on their clinical relevance and the degree to which they could be modified by employing practical and feasible interventions. Compared with standard care, implementation of these preventive interventions resulted in a 40% risk reduction for delirium in hospitalized older patients.

TABLE 47-5 DELIRIUM RISK FACTORS AND TESTED INTERVENTIONS

RISK FACTOR	INTERVENTION PROTOCOL
Cognitive impairment	• Orienting communication, including orientation board • Therapeutic activities program
Immobilization	• Early mobilization (eg, ambulation or bedside exercises) • Minimizing immobilizing equipment (eg, restraints, bladder catheters)
Psychoactive medications	• Restricted use of PRN sleep and psychoactive medications (eg, sedative-hypnotics, narcotics, anticholinergic drugs) • Nonpharmacologic protocols for management of sleep and anxiety
Sleep deprivation	• Noise-reduction strategies • Scheduling of nighttime medications, procedures, and nursing activities to allow uninterrupted period of sleep
Vision impairment	• Provision of vision aids (eg, magnifiers, special lighting) • Provision of adaptive equipment (eg, illuminated phone dials, large-print books)
Hearing impairment	• Provision of amplifying devices; repair hearing aids • Instruct staff in communication methods
Dehydration	• Early recognition and volume repletion

Data from Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A clinical trial of a multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1990;340:669.

The Hospital Elder Life Program (HELP; www.hospitalelderlifeprogram.org) represents an innovative strategy of hospital care for older patients, designed to incorporate the tested delirium prevention strategies and to improve overall quality of hospital care. Programs, such as HELP, underscore the importance of an interdisciplinary team's contributions to the prevention of delirium. For example, trained volunteers and family members can play roles in daily orientation, therapeutic recreation activities, and feeding assistance. Physical rehabilitation experts and nurses can assist with mobilization and the incorporation of daily exercises to prevent functional decline. Dietitians can help to maximize appropriate caloric intake and oral hydration in acutely ill patients. Consultant pharmacists, chaplains, and social workers also may provide specialized expertise to address patient care issues pertinent to individuals at risk for delirium.

Proactive geriatric consultation has been demonstrated to reduce the risk of delirium posthip fracture by 40% in a randomized controlled trial. The targeted multicomponent consultation strategy focused on 10 domains, namely, adequate brain oxygen delivery, fluid/electrolyte balance, pain management, reduction in psychoactive medications, bowel/bladder function, nutrition, early mobilization, prevention of postoperative complications, appropriate environmental stimuli, and treatment of delirium (**Table 47-6**). The recommendations were carried out with good adherence (77%) and provided a feasible and effective approach to address a leading complication of hip fracture surgery.

TABLE 47-6 PREVENTIVE INTERVENTIONS AFTER HIP FRACTURE

RISK FACTOR	INTERVENTION
Hypoxia	• Supplemental oxygen • Raise systolic blood pressure • Transfusion to hematocrit > 30%
Fluid/electrolyte imbalance	• Restore serum sodium, potassium, glucose • Treat fluid overload or dehydration
Pain	• Around-the-clock acetaminophen • Low-dose morphine, oxycodone for breakthrough pain
Psychoactive medications	• Minimize benzodiazepines, anticholinergics, antihistamines • Eliminate drug interactions and redundancies
Bowel/bladder dysfunction	• Treat constipation • Discontinue urinary catheter by postoperative day 2, screen for retention or incontinence
Poor nutrition	• Provide dentures, assistance • Supplements or enteral nutrition
Immobilization	• Early mobilization (out of bed postoperative day 1) • Physical therapy
Postoperative complications	• Monitor and treat for: Myocardial ischemia Atrial arrhythmias Pneumonia Pulmonary embolus Urinary tract infection
Sensory deprivation	• Use glasses and hearing aids • Provide clock and calendar • Provide radio and soft lighting
Treatment of agitation	• Diagnostic work-up • Reassurance, family presence, sitter • If pharmacologic management necessary, use haloperidol

Adapted with permission from Marcantonio ER, Flacker JM, Wright RJ, et al. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc. 2001;49:516.

At least 13 studies have examined primary prevention with nonpharmacologic multicomponent approaches to delirium in controlled trials with prospective sampling frameworks and validated delirium assessments. These studies have applied multifactorial interventions or educational strategies targeted toward health care professionals, staff, and families, and have demonstrated reductions in delirium rates, health care–associated costs, and/or duration. Multifactorial interventions consisted of staff education strategies combined with the administration of individually tailored treatment and management of patients with delirium, sometimes with proactive geriatric consultation. Educational interventions sought to increase awareness and knowledge of delirium among medical staff, in hopes of improving assessment, prevention, and management strategies of patients with delirium. One controlled trial found that home rehabilitation after acute hospitalization in the older adults was associated with lower risk of delirium, and greater patient satisfaction, when compared with the hospital setting. Taken together, results from controlled trials suggest that 30% to 50% of cases of delirium may be preventable and that prevention strategies should begin early during hospitalization.

On a larger scale, preventive efforts for delirium will require system-wide changes and large-scale shifts in local and national policies and approaches to care. Recommended changes include routine cognitive and functional assessments on admission of all older patients; monitoring mental status as a “vital sign”; education of physicians and

nurses to improve recognition and heighten awareness of the clinical implications; enhanced geriatric physician and nursing expertise at the bedside; incentives to change practice patterns that lead to delirium (eg, immobilization, use of sleep medications, bladder catheters, and physical restraints); and creation of systems that enhance high-quality geriatric care (eg, geriatric expertise, case management, clinical pathways, and quality monitoring for delirium). Implementing these changes will not only impact on delirium, but also result in high-quality hospital care more generally.

MANAGEMENT

Drugs

The recommended management approach for all delirious patients begins with nonpharmacologic strategies (see "Nonpharmacologic Management" and "Nonpharmacologic Sleep Protocol" later in this chapter), which usually result in successful symptom amelioration. In selected cases, such strategies must be supplemented with a pharmacologic approach, usually reserved for patients in whom delirium symptoms would result in interruption of needed medical therapies (eg, mechanical ventilation, central lines) or may endanger the safety of the patient or other persons. However, prescribing any drug requires balancing the benefits of delirium management against the potential for adverse medication effects because sedative drugs may prolong delirium and worsen clinical outcomes. Sometimes the decision to prescribe may be influenced by other members of the clinical team, the family, or caregivers. All interested parties should understand that the choice of almost any medication may further cloud the patient's mental status, prolong delirium symptoms, and obscure efforts to monitor the course of the mental status change. Consequently, any drug chosen should be initiated at the lowest starting dose for the shortest time possible.

Antipsychotics

When required, antipsychotics are the preferred agents of treatment, with haloperidol being the agent in most widespread use, whose effectiveness has been established in a randomized clinical trial. Haloperidol is available in parenteral form and is associated with less postural blood pressure changes and fewer anticholinergic side effects compared with thioridazine; however, high-potency antipsychotics such as haloperidol are associated with a higher rate of extrapyramidal side effects and acute dystonias. The intravenous route should be reserved for use in monitored settings due to the risk of torsades and sudden death. Parenteral administration is required in cases where rapid onset of action is required with short duration of action, whereas oral or intramuscular use is associated with a more optimal duration of action. The recommended starting dose is 0.25 to 0.5 mg of haloperidol orally or parenterally. The dose may be repeated every 30 minutes after the vital signs have been rechecked and until sedation has been reached. The clinical end point should be an awake but manageable patient, a goal that can be achieved by following the general geriatric prescribing principle, "start low and go slow." Most older patients naïve to prior treatment with a neuroleptic should require a total loading dose of no more than 3 to 5 mg of haloperidol. A subsequent maintenance dose consisting of one-half of the loading dose should be administered in divided doses over the next 24 hours, with doses tapered over the ensuing 48 hours as the agitation resolves.

Other Pharmacologic Approaches

Benzodiazepines (eg, lorazepam) are not recommended as first-line agents in the treatment of delirium because of their increased propensity to cause oversedation and to exacerbate acute mental status changes. However, they remain the treatment of choice for delirium caused by seizures and alcohol- and medication-related withdrawal syndromes. While other drugs have been advocated for use in treatment of delirium, evaluation of their use has resulted in discrepant findings, and there is no consensus recommendation for their general use. These drugs include the newer atypical antipsychotic agents, procholinergic agents (such as donepezil), serotonin receptor antagonists (such as trazodone), α_2-agonists (clonidine), and sedatives (such as dexmedetomidine). The atypical antipsychotic drugs (such as risperidone, olanzapine, and quetiapine) have the potential for fewer sedative and extrapyramidal effects. There is some evidence, however, that treatment with antipsychotic drugs may prolong delirium and result in poor clinical outcomes; thus, the current recommendation is that their use be restricted to patients with severe agitation that poses a threat to their safety. Moreover, official warnings have been issued regarding the increased mortality associated with use of atypical antipsychotics in dementia patients.

Nonpharmacologic Management

Nonpharmacologic approaches are the mainstays of treatment for every delirious patient. These approaches include strategies for reorientation and behavioral intervention, such as ensuring the presence of family members, use of sitters, and transferring a disruptive patient to a private room or closer to the nurse's station for increased supervision. Orienting influences such as calendars, clocks, and the day's schedule should be prominently displayed, along with familiar personal objects from the patient's home environment (eg, photographs and religious artifacts). Personal contact and communication are critical to reinforce patient awareness and encourage patient participation as much as possible. Communication should incorporate repeated reorientation strategies, clear instructions, and frequent eye contact. Correction of sensory impairments (ie, vision and hearing) should be maximized as applicable for individual patients by encouraging the use of eyeglasses and hearing aids during the hospital stay. Mobility and independence should be promoted; physical restraints should be avoided because they lead to decreased mobility, increased agitation, and greater risk of injury and worsening delirium. Patient involvement in self-care and decision making should also be encouraged. Other environmental interventions include limiting room and staff changes and providing a quiet patient care setting with low-level lighting at night. An environment with decreased noise allowing for an uninterrupted period for sleep at night is of crucial importance in the management of delirium. This may require unit-wide changes in the coordination and scheduling of nursing and medical procedures, including medication dispensing, vital sign recording, and administration of intravenous medications and other treatments. Hospital-wide changes may be needed to ensure a low level of noise at night, including minimizing hallway noise, overhead paging, and staff conversations.

Nonpharmacologic Sleep Protocol

Nonpharmacologic approaches for relaxation and sleep can be effective for management of agitation in delirious patients and for prevention of delirium through minimization of psychoactive medications. The nonpharmacologic sleep protocol includes three components: (1) a glass of warm milk or herbal tea, (2) relaxation music or tapes, and (3) back massage. This protocol was demonstrated to be feasible and effective. Use of the protocol reduced the use of sleeping medications from 54% to 31% ($p < 0.002$) in a hospital environment.

SPECIAL ISSUES

Patient Preference and Decision Making

In a condition characterized by acute fluctuations in attention and decision-making capacity, delirium presents formidable challenges to the ethical care of afflicted patients (see Chapters 12 and 61). Recent research has highlighted the importance of determining and appropriately documenting cognitive impairment prior to initiating nonemergent treatments. Cognitive assessments in patients with suspected delirium help to ensure that patients can be involved in decision making wherever possible and that appropriate surrogate decision makers (eg, family members or caregivers) are involved in representing a patient's wishes and understanding the risks and benefits of procedures and treatments. Because the patient may exhibit periods of lucidity in delirium, there may be times during which the decision-making and informed consent process can and must involve the patient. Following resolution of an acute delirium episode, the clinician should be cognizant of ongoing subclinical manifestations of delirium, or partial forms of delirium, which may be important for considerations of both the long-term management and decision-making capacity of the patient.

Nursing Home Setting

The patient population in nursing homes can be divided into two distinct groups: postacute patients who receive short-term rehabilitative care in nursing homes after an acute hospitalization, and long-term care patients who reside in nursing homes long term as a result of severe cognitive and functional impairments. Both are high-risk groups for delirium, though the epidemiology differs between the two populations.

For the postacute population, persistent delirium after an acute hospitalization is the major issue. A recent study demonstrated that 16% of new admissions to postacute care met full CAM criteria for delirium, while another 50% demonstrated signs of subsyndromal (partial) delirium. Patients with delirium on admission to postacute care experience more complications such as falls, have higher rehospitalization rates, and higher mortality. Delirium among postacute patients is also persistent—of those admitted with delirium, over 50% are still delirious 1 month later. Persistence of delirium prevents functional recovery in the postacute setting; only those patients whose delirium

cleared within 2 weeks of admission recovered to their prehospitalization functional status. Persistent delirium is also associated with higher mortality.

The long-term care population represents a high-risk group for delirium, with a high prevalence of dementia and functional impairments. In these individuals it is incident, rather than prevalent delirium, which is the primary concern. Large-scale epidemiologic studies of delirium in these patients have not been performed, but data from the minimum data set suggest that incident delirium is common in this population, and frequently heralds the onset of an acute illness that results in hospitalization and/or death.

Interventions for delirium in the nursing homes are challenging. First, because of the high prevalence of dementia in both postacute and long-term care populations, case identification can be challenging. This is compounded in the postacute population by a lack of knowledge of the patient's baseline cognitive state. Poor nursing staffing ratios, high turnover, and competing concerns make attention to delirium challenging in this setting. Nonetheless, these patients represent among the most vulnerable of all elders, and further attention to delirium in this setting is warranted. Adaptations of the HELP delirium prevention strategies are currently under way in the nursing home setting.

Palliative and End-of-Life Care

Management of delirium at the end of life poses particular challenges. Because delirium occurs in more than 80% of patients at the end of life, it is considered nearly inevitable in the terminal stages by most hospice care providers and may serve as a herald of approaching death. Establishing the goals of care with the patient and family is a crucial step, including discussions about the potential causes of the delirium, intensity of medical evaluations considered appropriate, and the need for titration between alertness and adequate control of pain and agitation. For example, some patients may wish to preserve their ability to communicate as long as possible, while others may focus on comfort perhaps at the expense of alertness. Physicians must be cognizant that even in the terminal phase, many causes of delirium are potentially reversible, and may be amenable to interventions (eg, medication adjustments, treatment of dehydration, hypoglycemia, or hypoxia) that may improve comfort and quality of life. However, the burdens of evaluation (eg, invasive testing) or treatment (eg, reduction in narcotic dose) may not be consistent with the goals for care. In all cases, symptom management should begin immediately, while evaluation is under way. Nonpharmacologic approaches should be instituted in all patients, with pharmacologic approaches for selected cases. Haloperidol remains the first-line therapy for delirium in terminally ill patients. In end-of-life care, there is a lower threshold for the use of sedative agents. Sedation may be indicated as an additional therapy for management of severe agitated delirium in the terminally ill patient, which can cause considerable distress for the patient and family. Because sedation poses the risks of decreased meaningful interaction with family, increased confusion, and respiratory depression, this choice should be made in conjunction with the family according to the goals for care. If sedation is indicated, an agent that is short acting and easily titrated to effect is recommended. Lorazepam (starting dose 0.5–1.0 mg PO, IV, or SQ) is the recommended agent of choice.

FURTHER READING

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Chapter 48

Falls

Stephen R. Lord

Learning Objectives

- To be aware of the extent of the problem and consequences of falls in older people
- To appreciate the broad range of risk factors for falls, and in particular, the risk factors that are amenable to correction through fall prevention initiatives
- To be aware of appropriate fall risk screens and assessments for community, hospital, and residential aged care settings
- To have knowledge of effective single and multifaceted interventions for preventing falls and the appropriate populations for which appropriate interventions should be targeted

Key Clinical Points

1. **Falls are common in older people and frequently have serious consequences including fractures, significant fear of falling, reduced mobility and dependency, and need for institutional care.**
2. **A broad range of risk factors for falls have been documented. Key among these are factors directly or indirectly influencing balance control and gait stability.**
3. **Evidence-based screens and assessments are available for community, hospital, and residential aged care settings.**
4. **Single intervention strategies shown to successfully prevent falls include exercise, enhanced podiatry, occupational therapy interventions, psychotropic medication withdrawal, cognitive behavioral therapy, expedited cataract extraction, provision of single lens glasses for regular multifocal glasses wearers, cardiac pacing for carotid sinus hypersensitivity and vitamin D supplementation in people with low levels of vitamin D.**
5. **Tailored multifaceted and multifactorial interventions are the most effective interventions for preventing falls in high-risk populations including residential aged care facility (RACF) residents.**

EPIDEMIOLOGY OF FALLS AND FALL-RELATED INJURIES IN OLDER PEOPLE

A fall is "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level." Prospective studies undertaken in community settings have reported fall incidence rates of 32% to 40% in people aged 65 or more, and fall rates of 40% to 50% in people beyond the age of 75. Prospective studies in residential aged care facilities (RACFs) report fall incidence rates between 30% and 56%. Falls also occur frequently when people are in hospital, with incidence rates ranging between 2% in general hospitals and 27% in acute hospital geriatric wards.

Fall-related injuries can be severe and lead to a decline in the quality of life of an older person. Around 37% to 56% of all falls lead to minor injuries, while 10% to 15% of falls cause major injuries. Falls are the leading cause of injury-related hospitalizations in persons aged 65 and older, and account for 14% of emergency admissions and 4% of all hospital admissions in this age group. Falls that do not result in physical injuries can also have serious consequences including significant fear of falling, which can lead to reduced mobility and frailty through the

avoidance of daily activities. Furthermore, falls constitute a key predisposing factor for older people requiring institutional care.

RISK FACTORS OF FALLS

Many sociodemographic, medical, neuropsychological, and sensorimotor factors are strongly related with falls. As a result of age-related changes, disease, or adverse medication effects, sensorimotor and balance systems may become impaired and predispose to falls (**Figure 48-1**). **Table 48-1** summarizes the findings of many of these studies and rates each risk factor according to the strength of published evidence.

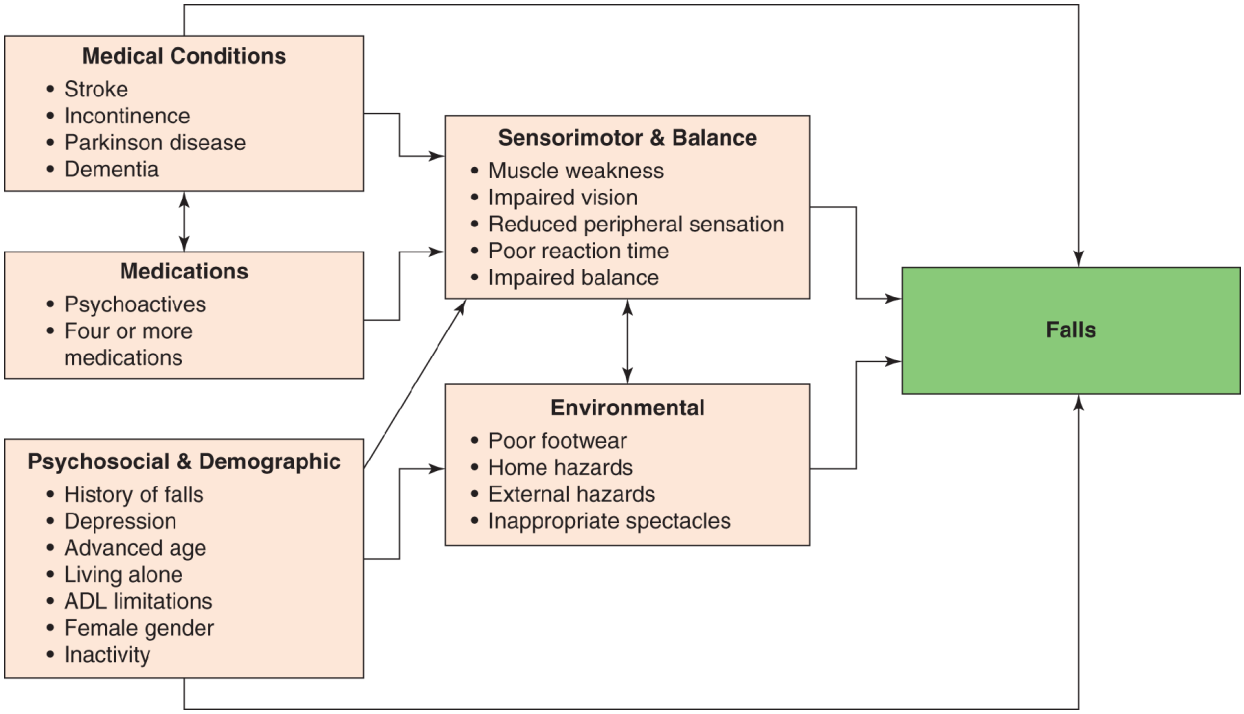


FIGURE 48-1. Risk factors of falling in older adults. ADL, activities of daily living.

TABLE 48-1 RISK FACTORS FOR FALLS

DOMAIN	RISK FACTOR	ASSOCIATION
Psychosocial and demographic factors	Advanced age	***
	Female gender	**
	Living alone	**
	History of falls	***
	Inactivity	**
	ADL limitations	***
	Alcohol consumption	–
Medical factors	Stroke	***
	Parkinson disease	***
	Abnormal neurologic signs	**
	Incontinence	**
	Acute illness	**
	Vestibular disorders	–
	Arthritis	**
	Foot problems	**

	Dizziness	**
	Orthostatic hypotension	*
Medication factors	Psychoactive medication use	***
	Antihypertensive use	*
	NSAIDs	–
	Use of 4+ medications	***
Balance and mobility factors	Impaired stability when standing	**
	Impaired stability when leaning and reaching	***
	Inadequate responses to external perturbations	*
		**
	Slow voluntary stepping	**
	Impaired gait and mobility	**
	Impaired ability in standing up	**
	Impaired ability with transfers	
Sensory and neuromuscular factors	Visual acuity	**
	Visual contrast sensitivity	***
	Visual field loss	**
	Reduced peripheral sensation	***
	Reduced vestibular function	*
	Muscle weakness	***
	Poor reaction time	***
Neuropsychological factors	Impaired cognition	***
	Depression	***
	Fear of falling	***
Environmental factors	Poor footwear	*
	Inappropriate spectacles	*
	Home hazards	–
	External hazards	–

***, strong evidence (consistently found in high-quality studies); **, moderate evidence (usually but not always found); *, weak evidence (occasionally but not usually found); –, little or no evidence (not found in published studies despite research to examine the issue).
ADL, activities of daily living; NSAIDs, nonsteroidal anti-inflammatory drugs.

Psychosocial and Demographic Risk Factors

Falls are associated with increased age and female gender in community-living older people. The difference in fall rates between men and women has been attributed to reduced muscle strength and more frequent use of psychotropic medications. Additionally, older women are also more likely to sustain fall-related fractures as a result of a higher prevalence of osteoporosis. However in hospitals and institutions, fall incidence is similar for men and women, or even higher for men. The finding that living alone is a risk factor for falls is most likely confounded by gender and increased age, in that older women comprise the majority of the very old people.

As outlined in the intervention section later, physical activity can improve strength, balance, and functional abilities in older people and can prevent falls. However, being more physically active does not always prevent falls, which is probably because the more physically active older person takes part in activities which increase exposure to fall risk situations. Clearly, this risk should be balanced against other benefits of exercise including increased physical functioning and independence.

The most surprising finding regarding associations between sociodemographic factors and falls is that alcohol consumption has not been shown to be a fall risk factor. Despite examining the issue, no significant associations have been found between alcohol use and falls in several large cohort studies. The lack of a positive association between alcohol use and falls may be due to response and selection biases, in that heavy alcohol consumers are likely to

underreport their drinking levels or simply decline participation in research studies. However, despite the lack of an association between current alcohol use and falls, there is strong evidence that long-term high alcohol intake can lead to multiple medical problems including osteoporosis, cerebellar atrophy, and peripheral neuropathy.

Medical Factors

Many diseases and associated impairments have been identified as risk factors of falling, mainly through impairing neuropsychological function and balance control. Major conditions include stroke, Parkinson disease, cognitive impairment, depression, dizziness, urinary incontinence, and arthritis. These conditions increase the risk of falls in both community and institutional settings, although the importance of some of these such as incontinence and impaired cognition are of greater important in institutions. Vitamin D insufficiency has been associated with a range of physiologic and neuropsychological impairments that predispose older people to falls. Increased risk of falls as a result of vitamin D deficiency has been found especially in those living in residential aged care settings, older men, and older people at increased risk of hip fracture. On the other hand, certain conditions commonly thought to be strong risk factors for falls, such as vestibular disorders and orthostatic hypotension, have not been found to be strong risk factors in community-based research studies but may be important in clinical populations.

Medications

Both community and institutional studies have demonstrated a relationship between medication use and falls in older people, especially the use of multiple and psychoactive medications (benzodiazepines, antidepressants, and antipsychotics). These studies indicate that use of psychoactive medications leads to a two- to threefold increased risk of falling and a twofold increased risk of experiencing a hip fracture. Use of anti-inflammatory drugs, however, does not appear to be associated with increased risk of falls after controlling for the presence of arthritis. Results of studies into use of antihypertensive medications have been conflicting and have also highlighted the importance of examining drug classes rather than grouping all antihypertensive medications together. In fact, there is preliminary evidence that some classes of antihypertensive agents (ie, angiotensin system-blocking medications) may be protective against falls, but this requires further research before any firm conclusions can be drawn.

Balance, Mobility, and Gait Factors

The ability to rise from a chair, turn while walking, and ascend and descend stairs all require good balance control. Normal aging is associated with impairments in sensorimotor systems that contribute to balance, which in turn can impair ability to safely perform a range of functional tasks. Gait changes are also common with increasing age. Older adults tend to walk with slower speed, shorter step length, increased step time variability, wider step width, and a relatively increased proportion of time spent in the double-support phase. It is not clear whether these changes are due to physical limitations or an adaptive strategy for improved safety; however these spatiotemporal gait patterns are more common in fallers compared to nonfallers. Older adults at risk of falls are also less able to undertake transfers, and are less able to negotiate obstacles and recover from trips.

Sensory and Neuromuscular Factors

Good balance requires the complex integration of sensory information regarding the position of the body relative to the surroundings and the ability to generate appropriate motor responses to control body movement. Reduced balance and mobility in older people can result from impairments in sensory, motor, and central processing systems. Impairments may be the result of a specific pathology affecting a particular system, or a progressive age-related loss of function. Visual input provides a continually updated reference frame regarding the position and motion of body segments in relation to each other and the environment. Impaired vision—presence of visual conditions such as cataracts and glaucoma or impaired contrast sensitivity and depth perception—is a risk factor for falls and fractures as it increases the likelihood of misjudging obstacles in the environment. Sensory systems provide information about the nature of a balance perturbation under challenging conditions. Decreased lower limb muscle strength also has important ramifications for balance and falls in older people, and in large community-based studies, reduced knee extension strength has been shown to increase fall risk. Similarly in RACFs, knee extension and ankle dorsiflexor weakness have been found to be major risk factors for falling. Finally, adequate central processing and reaction time are necessary for voluntarily correcting a balance perturbation.

Neuropsychological Factors

Several recent studies have shown that walking is not an automated process and that increased cognitive resources are required for balance control in older age. For example, it has been shown that a significant percentage of older people in residential aged care are unable to answer a simple question while maintaining walking, with such people at increased risk of falls. Older people who fall also do poorly in tests of executive functioning and attention. Fear of falling and depression, both prevalent in older people, may have detrimental effects on several domains of life, including restricting activities of daily living and enjoyable pastimes, which may, then, lead to physical inactivity and social isolation.

Environmental Factors

It has been estimated that extrinsic factors are involved in 35% to 45% of falls that result in injuries, but prospective studies have not been able to demonstrate that hazards in the home are major risk factors of falls. However, the interaction between an older person's abilities and their exposure to environmental factors is clearly important. People with high physical abilities can withstand a bigger range of environmental challenges without falling, yet when faced with an extreme challenge, such as an icy footpath, may still fall. People with lower physical abilities can generally cope well in an environment that offers few challenges, such as in their own home, but in people with very poor abilities, falls may occur in relatively safe, hazard-free environments. In addition, the extent of a person's risk-taking behavior or exposure to fall risk situations also plays an important role in the interaction between an older person's abilities and their environment. There is evidence that environmental hazards play a greater role in falls that occur away from the home where about one-quarter to one-half of falls occurs. Falls occurring away from the home often involve stairs or slipping and tripping hazards, or temporary hazards that cannot be anticipated. In addition, environmental factors can play a role in whether a fall will lead to a serious injury. For example, a fall on stairs is associated with a twofold increase in risk of injury.

FALL RISK SCREENING AND ASSESSMENT

A range of tools for screening fall risk have been validated for use in older people in community, hospital, and nursing and residential care settings (**Table 48-2**). Fall risk screening provides an efficient means of identifying those people at greatest risk of falling who should have a comprehensive fall risk assessment performed. A simple, easy-to-administer screen is to ask older people about their history of falls in the past 12 months and assess their balance and mobility status. A number of studies have identified previous falls as one of the strongest predictors for falling again in the following year. It has therefore been suggested that health care practitioners should ask all older people about any falls they have experienced. Several balance assessment tools have been developed and validated for different population groups and settings.

TABLE 48-2 EXAMPLES OF VALIDATED FALL RISK SCREENING TOOLS

SETTING	SCREENING TOOL
Community	The Timed Up and Go Test (TUG) measures the time taken for a person to rise from a chair, walk 3 m at normal pace with their usual assistive device, turn, return to the chair, and sit down. The TUG has shown some predictive value in prospective and retrospective studies, and a time of 12 or more seconds to complete the tests indicates impaired functioning in community-living older people.
Emergency department	For older people presenting to the emergency department after a fall, two simple questions (fall in the past 12 mo, use of 6+ medications) identify people at increased risk of further falls.
Hospital	The St. Thomas risk assessment tool (STRATIFY) has been shown to have intermediate-to-high accuracy in discriminating fallers from nonfallers. This tool contains five clinical factors associated with falling with a simple scoring system. A positive score on ≥ 2 of the 5 items indicates an increased risk of falls. It has been suggested that clinical judgment to classify a patient as high risk for falls is equal to or even better than the use of screening tools in acute care.

Residential aged care facilities	The CaHFRiS Fall Screen comprises easily collectable measures and provides a simple way of quantifying the probability with which a care home resident will fall over a 6-mo period. The CaHFRiS items are: MMSE < 17, presence of impulsivity, reduced standing balance, requires a walking frame, a fall in the previous year, and use of antidepressants and/or hypnotics/anxiolytics.

MMSE, Mini Mental State Examination.

Assessment

People with a history of one or more falls in the past year and who perform poorly on a simple test of balance or gait should be assessed further in order to develop an individualized fall prevention care plan. Assessment tools provide detailed information on the underlying deficits contributing to overall risk and should be used to guide interventions. Assessing fall risk typically involves either the use of multifactorial assessment tools that cover a wide range of fall risk factors, or individual functional mobility assessments that focus on the physiologic and functional domains of postural stability, including vision, strength, coordination, balance, and gait. A range of comprehensive assessment tools have been developed for use in a range of settings—see www.safetyandquality.gov.au/our-work/falls-prevention/. The choice of tool depends on the time and equipment available and the level of ability of the older people being assessed.

FALL PREVENTION STRATEGIES

There is now strong evidence to support interventions for preventing falls in older people. Single intervention strategies shown to successfully reduce falls in randomized controlled trials include exercise, enhanced podiatry, occupational therapy interventions, psychotropic medication withdrawal, cognitive behavioral therapy, expedited cataract extraction, provision of single lens glasses for regular multifocal glasses wearers, and cardiac pacing for carotid sinus hypersensitivity. Multifactorial interventions, which target risk factors identified in a fall risk assessment, have also been shown to prevent falls in community, hospital, and residential aged care settings. For a full overview, please refer to systematic reviews from the Cochrane Collaboration and the “Further Reading” list.

Successful Single Fall Prevention Strategies

Exercise Exercise has a major role to play in preventing falls among older people and is recommended in evidence-based guidelines for fall prevention. Exercise covers a wide range of physical tasks (balance, strength, flexibility, etc) delivered in many formats, some of which result in bigger reductions in falls than others. A systematic review showed that greater effects are seen in programs that include medium- to high-intensity balance training and have a higher dose of exercise. The results from 44 randomized controlled trials indicated that people allocated to well-designed exercise programs had 42% fewer falls than those allocated to control programs. Four contrasting examples of effective exercise interventions for preventing falls that contain medium-high–intensity balance training are outlined in **Table 48-3**.

TABLE 48-3 EXAMPLES OF EFFECTIVE EXERCISE FALL PREVENTION STRATEGIES

EXERCISE	DESCRIPTION
Individually prescribed home exercise	Individually prescribed home exercise programs to be undertaken three times per week. Exercises include: standing with one foot directly in front of the other; walking placing one foot directly in front of the other; walking on the toes and walking on the heels; walking backward, sideways, and turning around; stepping over an object; bending and picking up an object; stair climbing in the home; rising from a sitting position to a standing one; knee squats, moderate-intensity strengthening exercises with ankle cuff weights, and a walking program.
LiFE program	Integration of balance and strength training into daily life activity. Rather than a prescribed set of exercises conducted several times a week, LiFE activities occur whenever the opportunity arises during the day. The strategies to improve balance include reducing base of support, moving to limits of sway, shifting weight from foot to foot, stepping over

	objects, and turning and changing direction.
Hybrid home-group program	Progressive group exercise programs with a supplementary home program. The exercise classes comprise balance-specific, individually tailored, and targeted training for dynamic balance, strength, bone, endurance, flexibility, gait, and functional skills. The home exercises comprise strength and balance training to be undertaken twice a week.
Tai Chi	Group exercise involving practiced controlled leaning movements, multidirectional weight shifting, awareness of body alignment, and multisegmental (arms, legs, and trunk) movement coordination with synchronized breathing.

Recently, several trials have examined the roles of exergames (performed on the Wii balance board, step mats, or using virtual reality technology). **Figure 48-2** shows a step mat exergame in which participants must make quick and accurate steps in response to target stimuli presented on a screen. Preliminary evidence indicates that exergame training can improve physical and cognitive factors associated with falls in older people and are equivalent to traditional exercise interventions in their effect on fall risk factors. Further research is required, however, to determine whether exergame training can prevent falls.

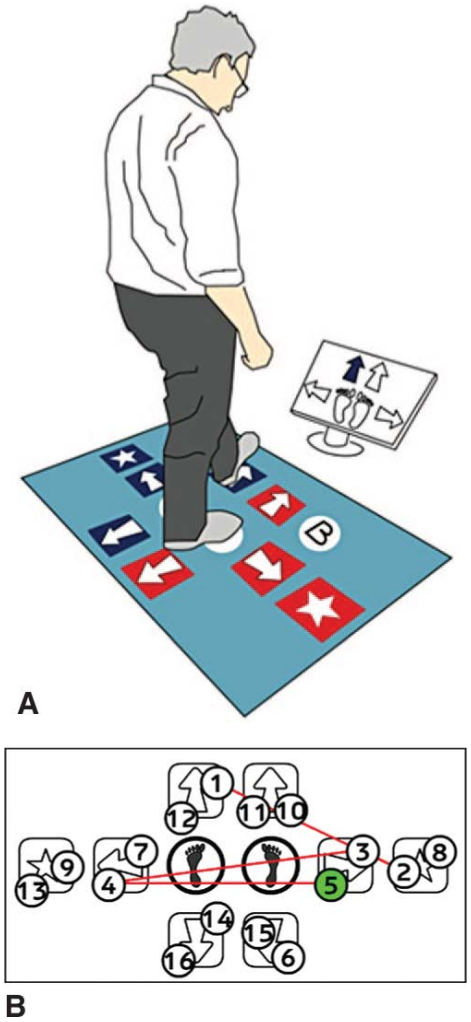


FIGURE 48-2. A step mat training intervention. Panel A shows a participant undertaking a choice stepping reaction time task: one of four arrows on the screen changes color and the participant is asked to step as quickly as possible onto the same location of the pad. Panel B shows the screen for a step version of a Trail Making Test in which participants must step on the panel corresponding to the highlighted number on the screen as quickly as possible.

Exercise as a single intervention in certain high-risk populations, however, may not be an effective fall prevention strategy. **Figure 48-3** presents a summary finding from a systematic review of 49 exercise randomized controlled trials for older people which indicates intervention effects are less marked in high fall risk groups compared with general populations of older people (see **Figure 48-3**). In recent trials, exercise programs have failed to prevent falls in long-

term stroke survivors or in frail older people, and a home-based exercise program actually significantly increased falls in older people recently discharged from hospitals by 43%. This area requires further investigation, but it seems that other interventions may be needed to prevent falls in high-risk people with these more complex conditions.

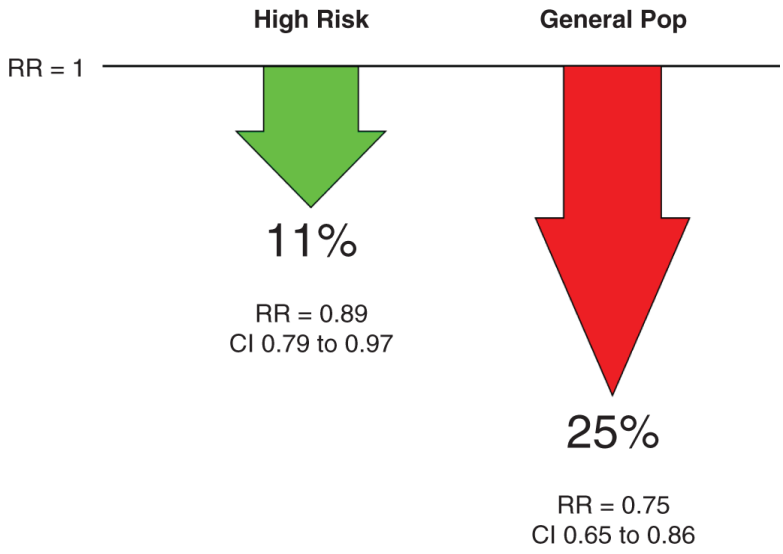


FIGURE 48-3. Meta-regression findings from a systematic review of 49 exercise interventions for older people. Intervention effects were less marked in the high fall risk groups than in general populations of older people. CI, confidence interval; RR, relative risk.

The effects on fall rates of acute hospital interventions that involve exercise alone are not known, but in subacute hospital settings with lengths of stay of at least 3 weeks, three randomized controlled trials (RCTs) have shown that intervention programs that include interventions to improve balance and mobility can prevent falls. The evidence for exercise programs in RACFs as a single intervention is also inconclusive. However, several multifaceted programs that have included exercise have shown positive effects in preventing falls. For example, an intervention program that involved staff training and feedback, information and education for residents, environmental adaptations, hip protectors, and twice-weekly exercise in groups of six to eight people delivered by exercise instructors reduced falls by 45%.

Visual interventions Two trials have examined the effects of expedited cataract surgery in reducing falls. The first examined the efficacy of cataract surgery in the first eye and showed that the fall rate in the operated group was significantly lower (a 34% reduction) than that observed in the control group. The second trial showed that cataract surgery for the second eye reduced falls by a similar amount (ie, 32%) in the operated group, but this reduction did not reach statistical significance.

In contrast, the evidence for updating glasses to ensure the use of correct prescription glasses is less clear. One RCT evaluated a vision improvement intervention in people with impaired vision and found that this intervention strategy did not significantly reduce the rate of falls. A second RCT that assessed vision and provided vision-related treatments if required, showed a significantly *increased* fall rate, by about 50%. A third RCT provided single lens distance glasses to community-dwelling older people at risk of falls who regularly used multifocal glasses outdoors. This visual intervention involved counseling as a core intervention component to demonstrate how bifocal glasses blur ground level hazards (**Figures 48-4** and **48-5**) and was effective in significantly reducing all falls (by 40%), outside falls, and injurious falls in the subgroup of people who regularly took part in outside activities. Some older people have impaired vision that cannot be corrected. A targeted home safety assessment and modification program designed for older people with low vision has been shown to reduce the rate of falls by 41% in people with severe visual impairment.

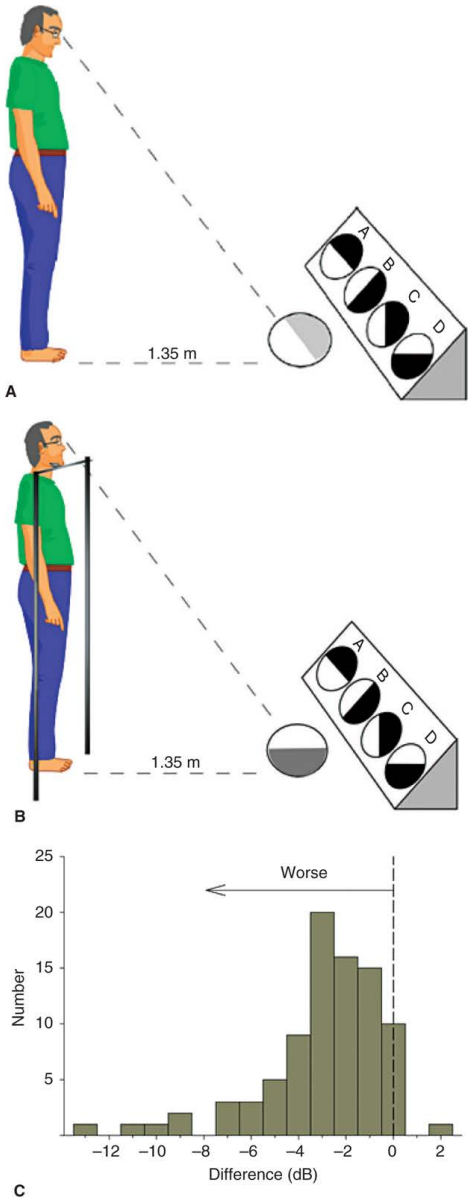


FIGURE 48-4. Contrast sensitivity assessments of edge stimuli (24 separate plates with reducing contrast edges) placed at floor level. In panel A, the participant views the edge stimulus through the upper lens of bifocal spectacles. In panel B, the participant is forced to view the edge stimulus through the lower lens. Participants are then shown the difference between their upper and lower lens contrast vision. For reference, panel C, shows differences between upper and lower lens edge contrast sensitivity scores for 87 regular multifocal glasses wearers.



FIGURE 48-5. Simulated view of a street scene used in counseling to demonstrate how bifocal glasses blur ground level hazards such as pavement misalignments.

Medication management Gradual withdrawal of psychoactive medications has shown a large reduction in falls (66%) in a placebo-controlled trial of 93 people aged greater than or equal to 65 living in the community and regularly taking these medications. However, about half of the intervention group participants who had successfully withdrawn from medications resumed their medications within a month of the trial completion, which emphasizes how difficult it is for older people to stop using psychoactive medications.

The effectiveness of an educational medicine review program delivered in general (primary care) practice has also been evaluated in a randomized controlled trial which provided face-to-face education to 20 family physicians (provision of prescribing information and feedback, medication risk assessment, facilitation of medication review, and financial incentives) as the intervention. Intervention participants had improved medication regimens, and were taking significantly fewer nonsteroidal anti-inflammatory drugs (NSAIDs), with trends for reduced benzodiazepine and thiazide diuretics use. At 12 months, intervention participants reported 39% fewer falls, 46% fewer injuries, and 54% fewer injuries requiring medical attention.

Medication review as a single intervention for fall prevention has also been implemented successfully in RACFs and found to reduce falls by 38%. Two other studies have reviewed "culprit" medications as part of a multifactorial falls intervention in residential aged care, and showed significant reductions in recurrent fallers. In hospital patients, medications have also been reviewed as part of an effective multifactorial fall prevention interventions.

Vitamin D supplementation may prevent falls via improvements in muscle strength and balance. However, findings regarding the effect of a vitamin D supplementation on the prevention of falls in older adults have been contradictory. A recent Cochrane review concluded that vitamin D does not reduce rate of falls or risk of falling in community-dwelling older adults, but that supplementation appeared effective in reducing falls when administered to those with lower vitamin D. The benefit may depend on providing a sufficiently high dose; a daily intake of 700 to 1000 IU supplemental vitamin D. Greater benefits may also result from the use of vitamin D_3 instead of vitamin D_2.

Home safety interventions Home safety interventions are effective in high-risk groups and when delivered by an occupational therapist. A meta-analysis showed that intensive interventions carried out by occupational therapists can reduce fall risk by 21% overall and by 39% for high-risk groups. These interventions included a comprehensive evaluation process of hazard identification and adequate follow-up and support for adaptations and modifications, while involving the older person in priority setting. The effectiveness of home safety interventions appears to depend on safe mobility advice and subsequent behavioral change rather than purely on environmental modification as successful interventions have had an impact on outdoor as well as indoor falls.

Feet and footwear One RCT has evaluated the efficacy of a multifaceted podiatry intervention on preventing falls in community-dwelling older people with disabling foot pain. This intervention consisted of the provision of foot orthoses, advice on footwear, a voucher for new safe footwear, a home-based program of foot and ankle exercises, a fall prevention education booklet, and routine podiatry care for 12 months. Compared with a control group who received routine podiatry care, there was a significant 36% reduction in falls in the enhanced podiatry group. The enhanced podiatry group also showed improvements in ankle strength, ankle flexibility, and standing and leaning balance.

Psychological interventions There is limited evidence on psychological interventions in relation to fall prevention. In one study involving 540 community-dwelling older people with fear of falling, cognitive behavioral therapy reduced the proportion of people who suffered recurrent falls by 62%. Other psychological conditions, such as depression, anxiety, and sleep disorders, have been identified as risk factors for falls. There is good evidence that cognitive behavioral therapy is an effective treatment of these conditions in older people, but this approach has not been investigated in relation to fall prevention.

Cardiovascular interventions Not all falls are caused directly by gait and balance problems. Individuals presenting with recurrent falls and no obvious balance or mobility impairment can benefit from a specialist assessment and specific diagnostic investigations. Three studies have evaluated the efficacy of implantation of pacemakers as a fall prevention strategy for people with cardioinhibitory carotid sinus hypersensitivity—an abnormal hemodynamic response to massage of the carotid sinus that is characterised clinically by unexplained dizziness and/or syncope. Overall these studies indicate that pacemakers are effective in reducing drop attacks and syncope and reducing the frequency of falls.

Multifactorial Fall Prevention Strategies

Multifactorial interventions involve identifying a range of risk factors associated with falls and interventions based on the identified risk profile. Common strategies in multifactorial prevention programs are medication adjustment, home safety modifications, exercise programs, and education. Overall, it appears that multifactorial interventions are most effective in reducing falls if the interventions are provided directly, but are less effective if the interventions rely on referral to routine service providers.

A number of trials have also targeted their interventions toward older people seeking health care. For example, one UK-based trial used a structured, interdisciplinary falls assessment and subsequent tailored intervention for older people presenting to the emergency department. This intervention, which involved medical management and home safety interventions, reduced the risk of falling by 61%. Another study specifically targeted older people who called an emergency ambulance because of a fall but were not taken to hospital. The intervention, consisting of referral to community fall prevention services, reduced falls by 55%. A third targeted older people discharged from hospital and found that a home safety and educational intervention reduced falls by 36% in older people discharged from hospital who reported a fall in the previous year.

Residents of RACFs have a high prevalence of physical frailty and cognitive impairment, and in this setting, single approaches to intervention have not been shown to be effective. In contrast, multifactorial interventions provided by multidisciplinary teams with appropriate staff education have been shown to significantly reduce falls. Some of these trials have included comprehensive geriatric assessments of each patient whereas others have used specific fall risk assessments. Multifactorial interventions successful at reducing falls in hospital inpatients include different combinations of supervised exercise and balance training, education, medication review, vitamin D with calcium supplementation, environmental review, walking aids, and provision of hip protectors.

CONCLUSION

Many randomized controlled trials have shown that falls in older people can be prevented. These have built on large epidemiologic studies that have identified risk factors for falls amenable to intervention and validated assessments that can identify individuals at high risk of falls. A variety of single-intervention strategies have been shown to successfully reduce falls, including exercise containing medium-high–intensity balance training, enhanced podiatry, home safety interventions, medication review, expedited cataract extraction, cardiac pacing for people having carotid sinus hypersensitivity, and vitamin D supplementation in people with low levels of vitamin D. Tailored multifaceted and multifactorial interventions are particularly effective in preventing falls in high-risk populations including RACF

residents. The translation of research findings into clinical practice remains a challenge. A combination of population health initiatives for lowering fall risk in the general population of older people combined with targeted interventions for those at increased risk is required to realize fall reductions at the population level.

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Chapter 49

Sleep Disorders

Armand Ryden, Cathy Alessi

Learning Objectives

- Recognize sleep disorders that are most common or particularly important in the care of older adults.
- Identify key differences in the presentation and recognition of common sleep disorders in older compared to younger adults.
- Describe evidence-based treatment for sleep disorders in older adults, including insomnia, obstructive sleep apnea, and other common conditions.
- Summarize important issues in the management of sleep disturbance in special populations of older adults, such as those with dementia and those living in institutional settings.

Key Clinical Points

1. **Poor sleep is common in older adults, and is more closely associated with comorbidities than with chronological age.**
2. **Many important health outcomes are associated with poor sleep in older adults, including cognitive decline, increased medication use, and higher health care utilization.**
3. **Insomnia is common in older adults, and many of the pharmacologic therapies are relatively contraindicated in this population. Cognitive behavioral therapy for insomnia has a strong evidence base for safe and effective treatment of insomnia in older adults.**
4. **In older adults, obstructive sleep apnea (OSA) is less likely to present with classic signs and symptoms, and has been linked with important health outcomes including hypertension, cardiovascular disease, diabetes, and cognitive impairment. Continuous positive airway pressure (CPAP) for the treatment of OSA can be successful in older adults, including those with mild to moderate dementia.**
5. **Rapid eye movement (REM) behavior disorder (RBD), which is characterized by dream enactment and lack of normal muscle atonia during REM sleep, can be comorbid with and even the precursor to neurodegenerative disorders such as Parkinson disease, multiple system atrophy, and Lewy body dementia.**
6. **Sleep-wake cycle disruption is common in nursing home patients and may be improved by behavioral interventions such as exposure to bright light and maintenance of a regular day-night cycle.**

INTRODUCTION

Problems with sleep are frequently encountered in older adults. More than two-thirds of older people with multiple comorbidities report sleep problems. These problems commonly include difficulty falling asleep, difficulty staying asleep, or sleepiness during the day. This chapter will explore the epidemiology, pathophysiology, clinical presentation, diagnosis, and management of sleep disorders commonly encountered in older adults.

SLEEP AND AGING

Sleep is a reversible behavioral state that is characterized by a decreased responsiveness to the environment and stereotypical changes in the electroencephalogram (EEG). Each sleep period involves a progression of sleep stages on a cycle that averages 90 minutes. There are two major sleep states: rapid eye movement (REM) and nonrapid eye movement (NREM) sleep. REM sleep is characterized by having brain activity that is more similar to wake, REMs, and a complete loss of skeletal muscle tone. When people are awaken from REM sleep they usually report vivid dreaming. NREM sleep is divided into three stages; N1, N2, and N3 (slow wave sleep). As sleep progresses from N1 through N3 patients become more difficult to arouse, hence N1 sleep is considered light sleep, while N3 sleep is considered deep sleep. As people age there is a reduction in sleep efficiency, which is the amount of time actually asleep divided by time spent in bed (**Figure 49-1**). Furthermore, the amount of N3 sleep decreases with age starting in early adulthood. The reduction in N3 sleep with age is more prominent in men. Whether there are changes in REM sleep with aging is less clear. Objective measures of sleepiness have also shown that, compared to younger adults, older adults are sleepier during the day.

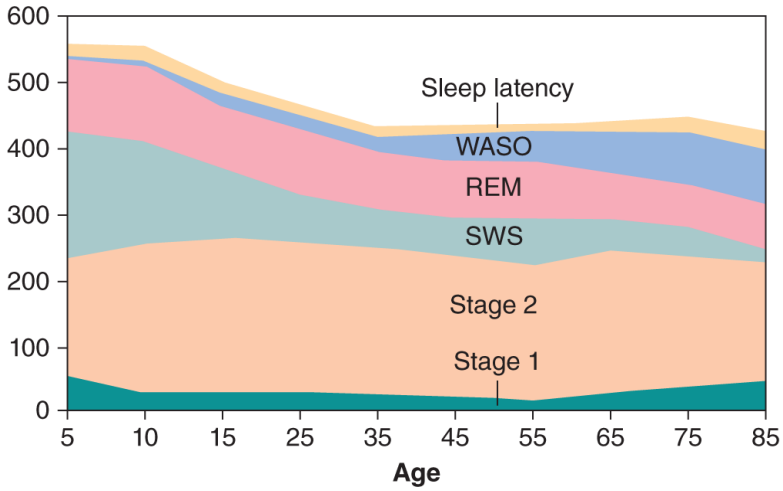


FIGURE 49-1. Change in sleep stages with age. Time spent in wake after sleep onset (WASO) increases significantly while time spent in slow wave sleep (SWS) decreases with age. (From Krieger MH, Roth T, Dement WC, eds. *Principles and Practices of Sleep Medicine*. 5th ed. St. Louis, MO: Elsevier Saunders; 2011, Figure 2-8.)

Although it is somewhat controversial, many experts believe that the age-related changes in sleep are due to a decreased ability to sleep rather than a decreased need to sleep. When older poor sleepers and good sleepers are compared, poor sleepers have worse health-related quality of life, increased medication use, and greater health care utilization. Many of the illnesses associated with aging can disrupt sleep, which may inhibit the normal progression through sleep stages. Thus, chronological age itself may not be the greatest predictor of sleep quality. Several lines of evidence have suggested that lower sleep efficiency and higher amount of wake after sleep onset are associated with more cognitive decline compared to those in whom sleep is well preserved. Since N3 sleep is associated with growth hormone secretion, the reduction in N3 sleep with aging may be partly responsible for the decrease in growth hormone in older men. Given the link between insufficient and fragmented sleep on quality of life and health outcomes, there is a need for awareness, evaluation, and treatment of sleep disorders that commonly affect older adults.

SLEEP-DISORDERED BREATHING

Definition

Sleep-disordered breathing (SDB) is characterized by disturbed respiration during sleep arising from repetitive events of complete (ie, apnea) or partial (ie, hypopnea) cessation of airflow lasting at least 10 seconds. This is classified as OSA when the events are due to an obstructed airway, which is determined by the persistence of respiratory effort. On the other hand, if there is concomitant cessation of breathing effort, the disorder is classified as central sleep apnea

(CSA) because there is a momentary defect in the central control of breathing (**Figure 49-2**). OSA is by far the most common sleep-related breathing disorder; however, there is often overlap between the two clinical syndromes. CSA can be associated with several different clinical conditions. Heart failure is the most commonly recognized cause of CSA and is often characterized by Cheyne-Stokes respiration, which is periodic cycling between hypoventilation and hyperventilation (**Figure 49-3**). Other common causes of CSA include cerebrovascular accidents, opioid use, and hypoventilation syndromes. The severity of SDB is generally determined by the apnea hypopnea index (AHI), which is the number of apneas and hypopneas per hour of sleep. SDB can be diagnosed when the AHI is greater than 15, or when it is greater than 5 with significant symptoms or related comorbidities. An AHI greater than 30 is generally considered to indicate severe SDB.

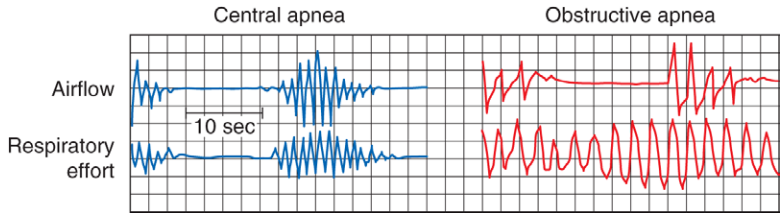


FIGURE 49-2. Obstructive versus central sleep apnea. (From Krieger MH, Roth T, Dement WC, eds. *Principles and Practices of Sleep Medicine*. 5th ed. St. Louis, MO: Elsevier Saunders; 2011, Figure 100-1.)

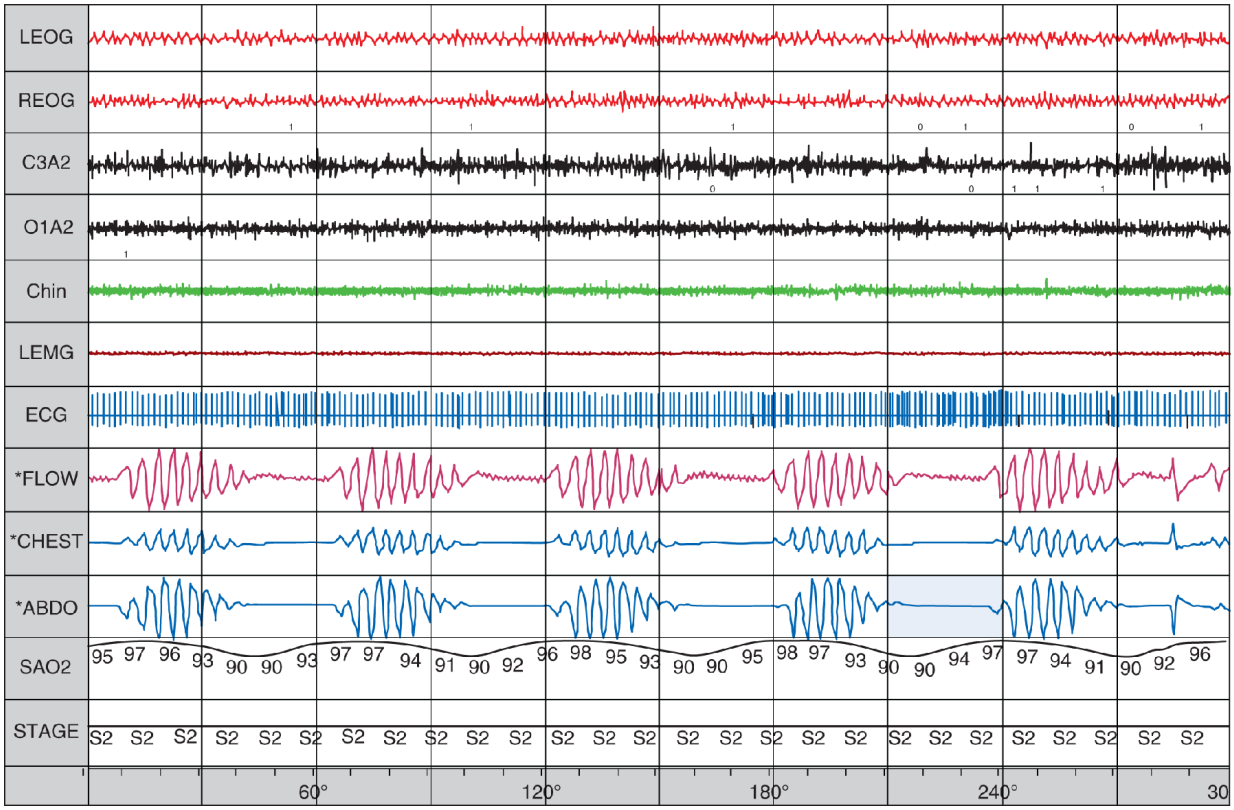


FIGURE 49-3. This figure represents central sleep apnea with a Cheyne-Stokes breathing pattern. During the periods of apnea there is no chest or abdominal effort. (From Javaheri S, Randernath WJ. Opioid-induced central sleep apnea: mechanisms and therapies. *Sleep Med Clin*. 2014;9(1):49–56.)

The consequences of respiratory events during sleep include arousals from sleep, intrathoracic pressure swings, and cyclical drops in the blood oxygen level. This ultimately leads to sleep fragmentation and nocturnal hypoxemia, which may lead to significant health consequences.

Epidemiology

Many of the risk factors for OSA increase with age (**Table 49-1**). Estimates of the prevalence of OSA have varied widely and are dependent on the populations studied. Prior work estimated the prevalence of moderate to severe SDB

to be 4% for women and 9% for men aged 30 to 60. However, with the current rise in obesity more patients are now at risk for OSA. A more recent update from a cohort between 2007 and 2010 has estimated moderate to severe SDB to occur in 6% of women and 13% of men. Evidence suggests that OSA is underdiagnosed in the general population, particularly in women. If the rate of obesity and overweight continues to increase the rates of SDB will also increase. Less is known about the epidemiology of SDB in an older population; however most studies have shown that the risk of OSA increases with increasing age until the age of 70 at which time there is a plateau (**Figure 49-4**). Furthermore, premenopausal status appears to protect against OSA meaning that the gender discrepancy between men and women narrows in the older population. OSA may be more severe in African-American and Asian populations compared to the Caucasian population.

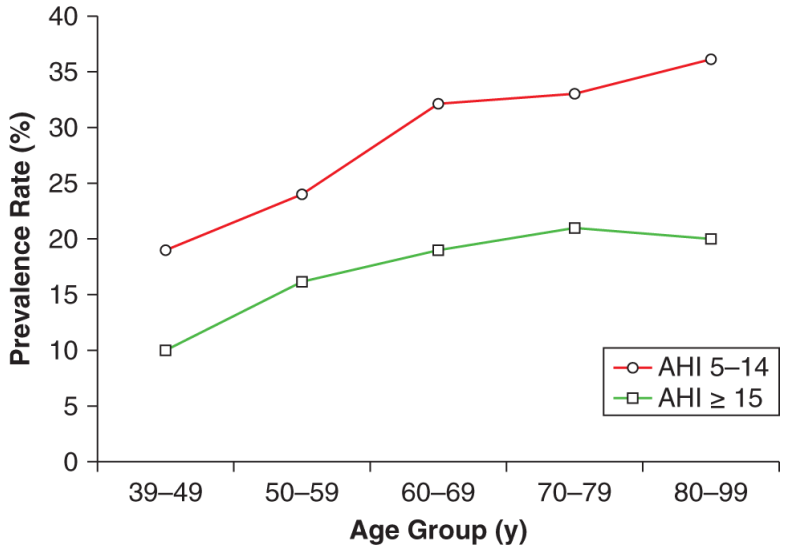


FIGURE 49-4. Association of obstructive sleep apnea (OSA) with age. Mild obstructive sleep apnea is shown in red while moderate to severe obstructive sleep apnea is shown in green. (From Norman D, Loredo JS. Obstructive sleep apnea in older adults. *Clin Geriatr Med*. 2008;24(1):151–164.)

TABLE 49-1 POTENTIAL AGE-DEPENDENT RISK FACTORS IN SLEEP-DISORDERED BREATHING

Increased body mass index (central obesity)
Decreased muscle tension
Changes in airway anatomy
Increased airway collapsibility
Decreased thyroid function
Decreased lung volume

It is estimated that upwards of 50% of patients with stable heart failure have some form of SDB. The majority of these patients have a form of CSA, however many have OSA or a combination of the two disorders. It has also become increasingly recognized that patients with end-stage renal disease have a very high prevalence of SDB as well. Other conditions associated with CSA include stroke, neurodegenerative diseases, respiratory disorders leading to hypoventilation, and chronic pain requiring opiates. Since the conditions that contribute to CSA are more common in older adults, the prevalence of CSA is much higher in older compared to younger adults.

Pathophysiology

There are three types of SDB events: central, obstructive, and mixed. Central events result from a failure of the respiratory control center to send a signal to breathe. This often occurs because of an abnormal sensitivity of the respiratory controller, which can lead to oscillations between hyperventilation and hypoventilation. Obstructive events occur from anatomic obstruction of the upper airway despite respiratory effort. The major factor that governs the presence of obstructive events is an anatomically narrow airway; however, other mechanisms such as failure of

adequate upper airway neuromuscular activation are thought to play a role. Features that govern the size of the upper airway include excess adiposity, craniofacial structure, excessive tonsilar and peritonsilar soft tissue, and lower lung volumes. Mixed events are a combination of central and obstructive components.

The most significant immediate consequence of OSA is excessive daytime sleepiness and the risk of motor vehicle accidents. Significant epidemiologic associations of OSA with adverse cardiovascular and metabolic consequences have been reported. The association between SDB and these comorbidities is likely multifactorial. SDB results in sleep fragmentation, which has been shown to increase sympathetic nervous system activation, increase nocturnal cortisol levels, and interfere with insulin sensitivity. The potential downstream effects of these neurohumoral changes include the development of hypertension and diabetes. Furthermore, the cyclic deoxygenation and reoxygenation that occurs with OSA leads to endothelial cell injury and inflammatory changes, which predispose to coronary and cerebral vascular disease (**Figure 49-5**). The intrathoracic pressure changes associated with increasing respiratory effort against a closed airway can lead to esophageal reflux as well as potentially deleterious hemodynamic effects in heart failure.

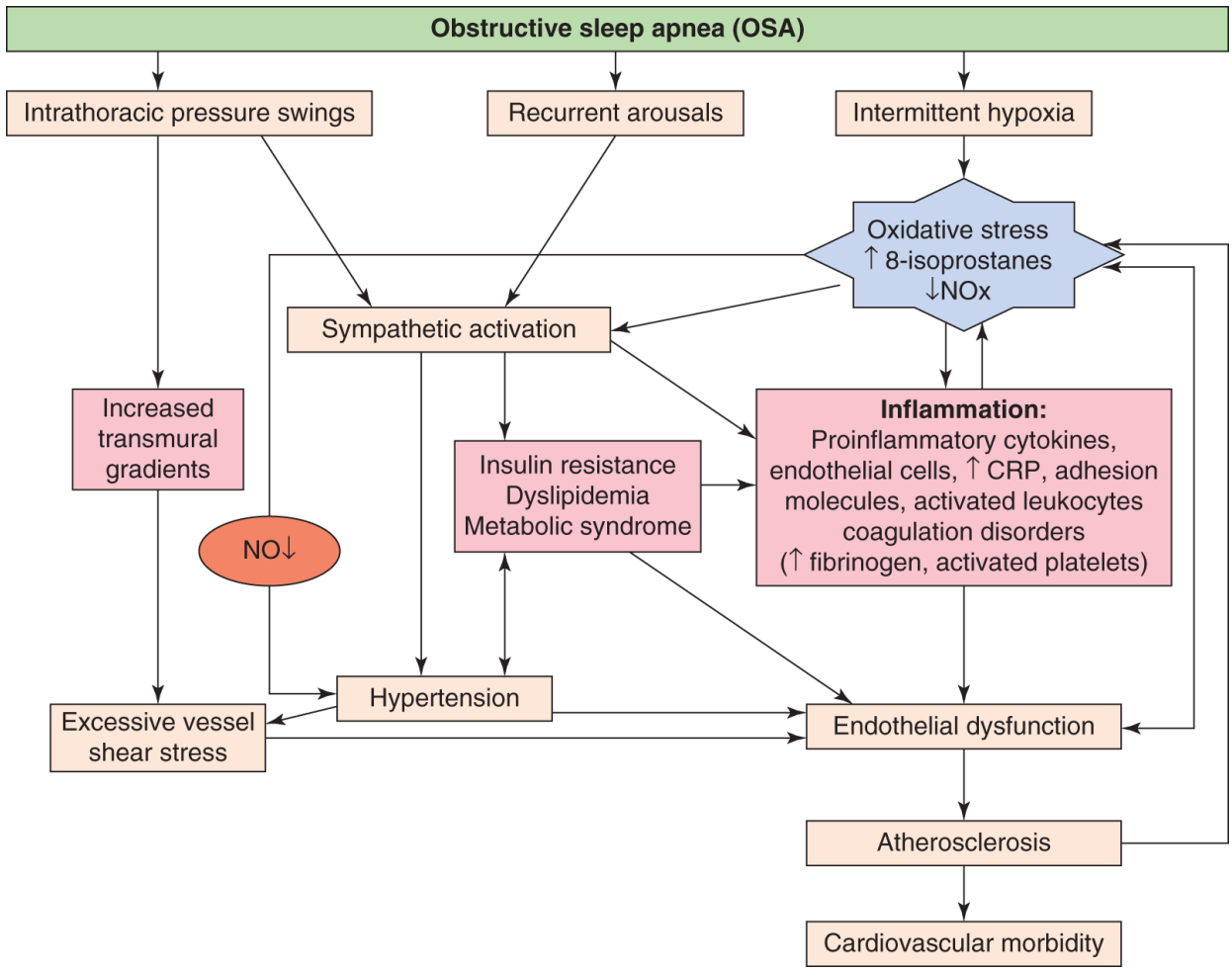


FIGURE 49-5. Model explaining why obstructive sleep apnea (OSA) might be associated with increased cardiovascular risk. (From Juillian-Desayes I, Joyeux-Faure M, Tamisier R, et al. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. *Sleep Med Rev*. 2015;21:23–38.)

Clinical Presentation

The major symptoms of SDB include excessive daytime sleepiness and nocturnal snoring. The patient may present to the clinic complaining of sleepiness or at the request of a loved one with the complaint of snoring. The paradigmatic patient with SDB is an obese male with nocturnal snoring, witnessed apneas, frequent nocturnal awakenings, and excessive daytime sleepiness. However, these associations are less predictive in an older population. Other important symptoms of SDB include nocturia, insomnia, morning headaches, nocturnal confusion, and daytime impairments in mood and cognition. Sleepiness can be assessed with a standardized measure such as the Epworth Sleepiness Scale. It is often helpful to obtain corroborating information from a bed partner regarding snoring, witnessed apneas as well as

additional features that may point to a comorbid sleep disorder. Snoring is indicative of a partially collapsed airway and is a useful predictor of the presence of OSA or future development of the condition. The lack of classic symptoms and findings of OSA should not preclude further evaluation for SDB.

Physical features that predict increased risk of OSA include an elevated body mass index (BMI), a large neck circumference, and a crowded upper airway. In older adults, an elevated BMI has less predictive value of the likelihood of OSA. In clinic the airway can be assessed using a modified Mallampati score known as the Friedman classification, with positions III and IV conferring a high risk for OSA (**Figure 49-6**). In general, the less posterior oropharynx that can be visualized confers a greater risk of SDB. Neck circumference greater than 17 inches in men and 16 inches in women is another predictor for SDB on physical examination. However, the predictive value of neck circumference is not as great in older patients.

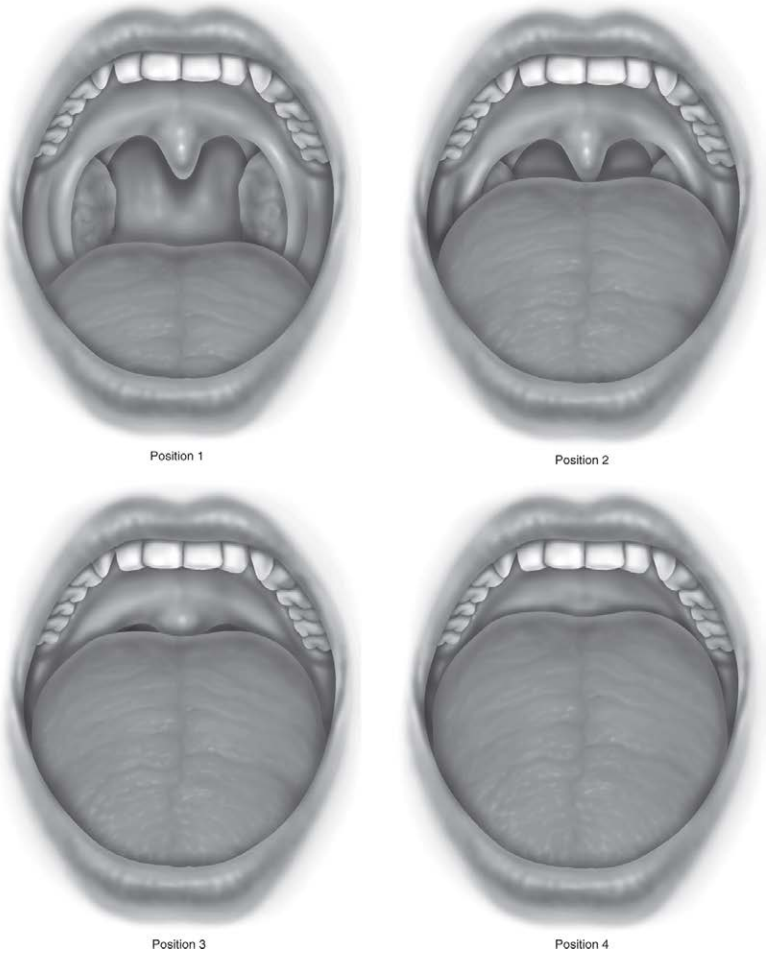


FIGURE 49-6. Friedman palate position. Positions 3 and 4 are associated with increased risk of obstructive sleep apnea (OSA). (From Friedman M, Ibrahim H, Bass L. Clinical staging for sleep-disordered breathing. *Otolaryngol Head Neck Surg*. 2002;127:13–21.)

The presence of disturbed sleep in a patient with congestive heart failure may be indicative of SDB. A high percentage of patients with heart failure have OSA, CSA with Cheyne-Stokes respiration, or a combination of the two conditions. It can be difficult to tease apart symptoms of heart failure such as orthopnea from those of SDB. Opioid medication use is a risk factor for another form of CSA, which should be considered when patients on opioids present with sleep complaints.

Evaluation

Patients suspected of having SDB should be referred for sleep testing. An attended in-laboratory polysomnography (PSG) is considered the gold standard test for SDB. This involves traveling to a sleep laboratory to spend the night. The test involves the use of EEG, electromyogram (EMG), and electrooculogram (EOG) leads to determine presence and stage of sleep. There is measurement of airflow with a nasal pressure transducer as well as an oronasal thermistor. Respiratory effort is measured using chest and abdominal belts; and occasionally with an esophageal pressure monitor or accessory muscle EMG. An alternative approach to the diagnosis of SDB uses out-of-center testing. The patient

takes the sleep testing equipment home and puts it on before bed. These tests are not generally able to measure sleep directly. Most of these tests measure airflow, effort, and pulse oximetry. Out-of-center sleep testing is only recommended for patients with a high pretest probability of having SDB who do not have significant cardiopulmonary comorbidities.

The advantages of an attended full-channel PSG include a higher reliability of the data, the ability to carefully define AHI by measuring sleep directly, and the simultaneous assessment for alternative sleep diagnoses to SDB. The advantages of out-of-center sleep testing include lower cost, the convenience for patients to sleep at home, and increased access to sleep testing. In populations at high risk for OSA, studies have shown that out-of-center sleep testing leads to similar patient outcomes compared to in-laboratory PSG. Due to cost issues third-party payers are increasingly pressuring practitioners to move toward out-of-center sleep testing. However, out-of-sleep center testing may be difficult for some older patients due to the need for the patient or caregiver to independently place the sensors and the contraindication for use when conditions that may lead to CSA are present. It must also be emphasized that out-of-center sleep testing does not rule out SDB, but a positive test confirms SDB. An out-of-center sleep test may be negative simply because the patient did not sleep during the test or due to technically inadequate data.

Management

The first-line treatment for SDB is positive airway pressure therapy. The most basic of these therapies is CPAP, which has been available since the early 1980s. CPAP is a device that delivers a constant positive pressure in order to splint the airway open preventing collapse. To apply this pressure an air-tight interface goes in the nose, over the nose, or over the nose and mouth, and then connects to the CPAP machine via a hose. Traditionally, the amount of air pressure (usually between 5 and 20 cm H_2O) is manually determined in the sleep laboratory with the sleep technologist adjusting the pressure to eliminate respiratory events and snoring. There is evidence that patients who have mild to moderate dementia are able to tolerate CPAP therapy and such a condition is not a contraindication to CPAP initiation.

Autotitrating CPAP (APAP) is now available, in which the machine adjusts the pressure based on events and flow characteristics using internal algorithms that are proprietary to the device manufacturers. APAP can be used to determine a fixed CPAP pressure or can be used as the primary modality of therapy. APAP has small advantages of questionable clinical significance for adherence to therapy in all-comers. Individual patients, however, particularly those with very different CPAP needs depending on body position or sleep stage, may find APAP to be more comfortable than fixed CPAP. The main advantage of APAP is the ability to determine, or provide, a therapeutic pressure without requiring a resource-intensive in-laboratory PSG.

CPAP is usually 100% effective in eliminating obstructive apneas and hypopneas. However, long-term adherence is the major limiting factor to this treatment modality. Estimates are that at the end of a year only 50% of patients are adherent to CPAP therapy. Factors that may improve CPAP adherence include early follow-up, education and setting of expectations, humidification, attention to interface comfort, expiratory pressure relief, possible early use of hypnotics, and desensitization to therapy. Each of these interventions has small but important impacts in individual patient acceptance to therapy. Bilevel airway pressure has sometimes been used for patients who have difficulty tolerating therapy due to difficulty exhaling against pressure.

Positive airway pressure therapy has to be individualized in patients who have CSA. Many patients who have Cheyne-Stokes respiration will respond to a combination of CPAP and/or supplemental oxygen. Likewise, the majority of patients with obesity-hypoventilation syndrome respond to CPAP alone. However, many patients require more advanced ventilatory modalities to eliminate CSA. Regardless of the particular mode, these advanced devices involve applying bilevel pressure with a back-up respiratory rate. The amount of pressure support given during a certain breath can be controlled by sophisticated proprietary algorithms in order to achieve specific desired clinical effects.

Dental devices that move the jaw forward (mandibular advancement or mandibular repositioning devices) are a treatment alternative to positive airway pressure in OSA. The principal behind such therapy is that when the lower jaw moves forward the tongue is also pulled forward, thus opening up the airway. These devices are generally thought to be more effective in mild to moderate OSA rather than severe OSA. However, the severity of OSA may not necessarily predict response to mandibular advancement therapy in all patients. In general, mandibular advancement therapy does not reduce the residual AHI to as great of an extent as positive airway pressure therapy. However, recent comparative effectiveness studies suggest equivalence for major outcomes likely due to the fact that adherence rates tend to be higher for mandibular advancement therapy. Side effects include temporomandibular joint pain and occlusion abnormalities. One of the major limiting factors to mandibular advancement therapy, particularly in older adults, is that teeth are generally required to anchor the device in place. However, more specialized devices can sometimes be

fabricated for edentulous patients. Tongue repositioning/retaining devices can be used in patients who lack their native teeth. However, these devices have been less extensively studied and are less likely to be effective.

Other therapies have been utilized in OSA. One of these therapies is expiratory positive airway pressure (EPAP) provided through nasal valves. This therapy consists of nasal valves that adhere to the nares via adhesive, which makes it more difficult to breathe out than breathe in. This causes pressure build up that helps stent the airway open, as well as causing an increase in lung volume that may prevent obstructive respiratory events. This therapy is less well validated but may be used as a salvage therapy or in mild cases. Another therapy that is available with limited evidence involves the application of negative pressure to the mouth to reposition the soft palate and tongue out of the airway.

One therapeutic modality that is on the horizon is hypoglossal nerve stimulation. This involves an implanted box with a lead that goes to the respiratory muscles to sense the onset of inspiration and a lead that goes to the hypoglossal nerve that causes tongue contraction to open the airway with inspiration. A recent randomized trial found promising results in a highly selected group of patients with a BMI less than 32 kg/m^2 who could not tolerate CPAP therapy. In this group there was a significant reduction in AHI. However, there were not many older adults included in this study.

Surgery is also an alternative therapy for SDB. There are multiple surgical techniques that are available to otolaryngologists for the treatment of SDB. The most common of which is the uvulopalatopharyngoplasty (UPPP). This procedure has variable success rates depending on anatomic factors and the degree of obesity. Furthermore, even after successful therapy SDB may reoccur due to growth of scar tissue.

A more aggressive surgical approach is a maxillary mandibular advancement. In this approach both the maxilla and mandible are cut and advanced forward. This surgery requires the patient's jaw to be wired shut for several weeks. Although this is the most effective surgery for SDB, many patients opt to not undergo such an extensive procedure.

Other behavioral changes that the patients with SDB can implement to help treat the syndrome include weight loss, sleeping on the side, and the avoidance of alcohol and other sedatives. In particular, positional techniques to encourage sleeping on the side may be beneficial when SDB occurs primarily in the supine position.

It is becoming increasingly recognized that while positive airway pressure therapy eliminates SDB more effectively than other interventions it is essentially ineffective in a subset of patients who cannot tolerate its use. The use of multiple modalities of therapy, with each having a modest effect on AHI, may be able to achieve adequate control of SDB in those who cannot tolerate CPAP.

Pharmacologic therapy There are limited pharmacologic agents available for SDB and none that are approved for this indication. However, occasionally patients who are successfully treated for SDB with CPAP will have residual excessive daytime sleepiness. Modafinil and armodafinil, central nervous system stimulants, have Food and Drug Administration (FDA) approval for the treatment of residual excessive daytime sleepiness in treated OSA. Acetazolamide has an unclear role in some CSA syndromes. Ventilatory stimulants such has progesterone have been tried unsuccessfully in obesity hypoventilation syndrome.

Prevention

There is no specific disease prevention strategy for SDB. Addressing factors that contribute the subsequent development of SDB contributes to prevention. Since elevated BMI is the most potent risk factor for the development of OSA, weight loss and lack of weight gain are the most important preventative measures for OSA. Preventing decompensation of heart failure may be a way to prevent the development of heart failure–related CSA.

Patient Preference

Patient preference is clearly a key factor in determining the therapy of choice. CPAP and mandibular advancement devices can both be difficult to tolerate due to the need for equipment use and potential discomfort. The health benefit of treating minimally symptomatic SDB in older patients is unclear. Therefore, it is reasonable to withhold SDB treatment if the patient declines treatment and they have minimal symptoms. In patients who are sleepy and drive, it is more imperative to encourage SDB therapy. Also, in sleepy older patients with SDB the treatment may have a greater beneficial impact on the prevention of SDB-related comorbidities and improvement in quality of life.

Comorbidity

SDB is associated with significant mental and physical comorbidities. Given the association between obesity and SDB, many of the comorbidities of obesity and SDB overlap. However, there are several lines of evidence suggesting an independent relationship between SDB and the development of hypertension, atrial arrhythmias, heart failure, coronary

artery disease, cerebrovascular accidents, and diabetes mellitus. Most of these relationships have been elucidated from observational population studies and basic science investigations. Direct evidence that treatment of SDB can reverse some of these comorbidities is more limited. However, treatment of OSA does result in modest improvement in blood pressure among hypertensive patients. In addition, treatment of OSA after cardioversion for atrial arrhythmias such as atrial fibrillation has been found to increase the likelihood of staying in sinus rhythm. Other investigations have been limited by sample size and poor adherence to positive airway pressure therapy. Treatment of CSA using CPAP was studied almost a decade ago in the CANPAP trial. There was no evidence of a survival advantage to treating heart failure–related CSA with CPAP. However, CPAP did not universally suppress CSA in that study. In fact, subsequent post-hoc analysis of data from the CANPAP trial showed that there was a mortality benefit in the subset of patients in whom the CSA was suppressed. Currently, there are ongoing randomized controlled multicenter trials looking at mortality outcomes in bilevel devices, which are better able to eliminate CSA in heart failure.

Insomnia is an important comorbidity of SDB. In fact, SDB itself may contribute to insomnia by disrupting sleep architecture and even preventing stable sleep onset due to OSA respiratory events. Sometimes insomnia improves with the treatment of SDB. However, insomnia may be exacerbated by the invasiveness of positive airway pressure or mandibular advancement. For a successful treatment outcome both disorders must be addressed. SDB and other mental illnesses such as anxiety, depression, and posttraumatic stress are frequently present in the same patient. Once again, the SDB may exacerbate some of the symptoms of these mental illnesses, and these illnesses may present barriers to acceptance of therapy.

RESTLESS LEGS SYNDROME AND PERIODIC LIMB MOVEMENT DISORDER

Definition

Restless legs syndrome (RLS) is characterized by the urge to move one’s legs. Most often patients with RLS have uncomfortable sensations in their legs, and sometimes arms, which lead to this urge. The other defining features of RLS are that the symptoms are improved with movement, worsen with relaxation, and occur later in the day. RLS can also affect and may even be limited to the arms. There is no objective test that defines RLS.

Periodic leg movements in sleep (PLMS) are characterized by cyclic movements of the lower limbs during sleep. These consist of stereotyped movements that typically involve the flexion of the big toe with partial flexion of the ankle, knee, and sometimes hip. PLMS last between 0.5 seconds and 10 seconds with a period between movements of 5 to 90 seconds (**Figure 49-7**). At least four movements in a row must occur to count as PLMS. Periodic limb movement disorder (PLMD) can be diagnosed if there are at least 15 PLMS per hour, the PLMS cause sleep disturbance and the symptoms are not better explained by another sleep disorder or a medical illness. Since PLMS are often seen in RLS (80%–90%), REM behavior disorder (70%), and narcolepsy (45%–65%), PLMD can only be diagnosed in the absence of these sleep disorders. A sleep study is required to define PLMS and thus diagnose PLMD.

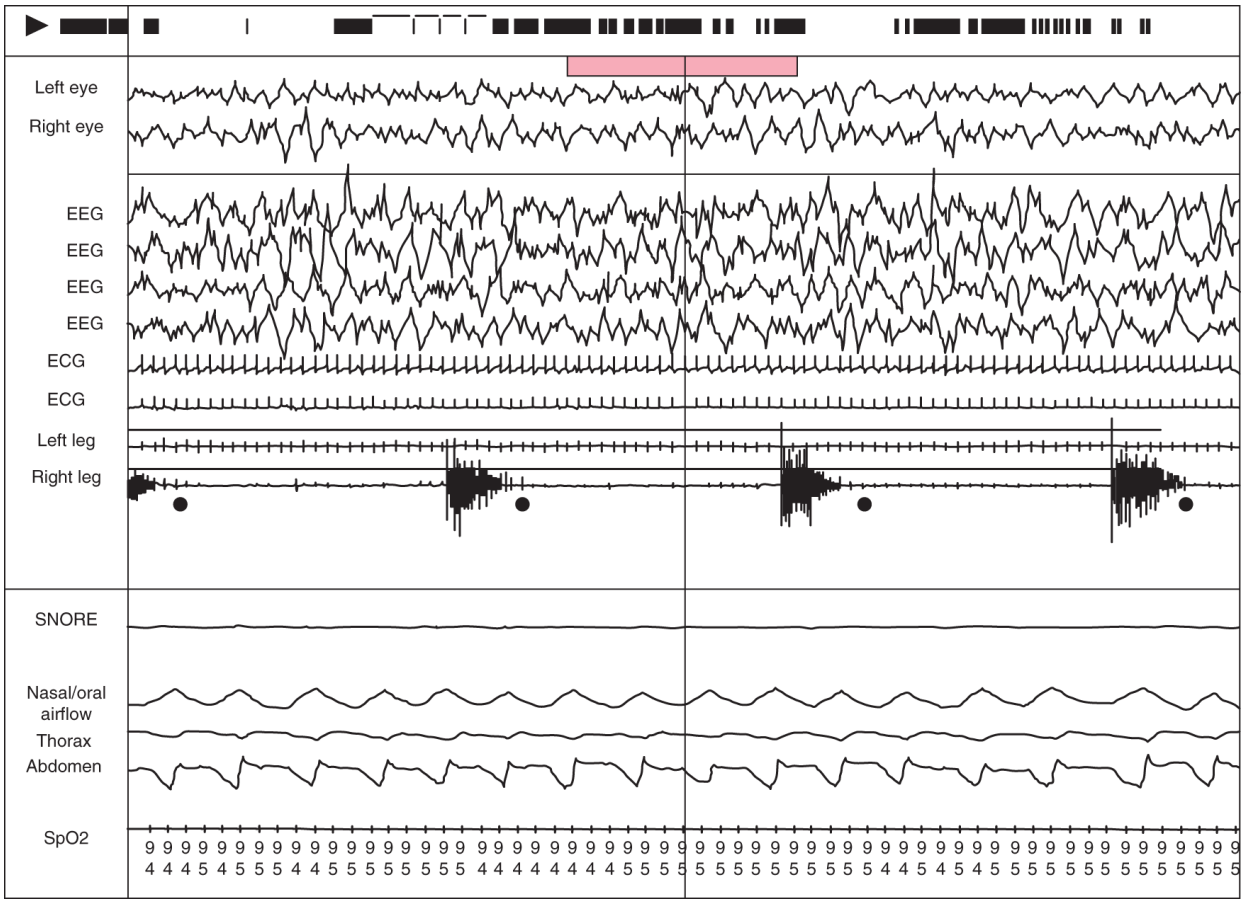


FIGURE 49-7. Periodic leg movements in sleep (PLMS) seen on polysomnography (PSG). (From Avidan AY. Sleep disorders in the older patient. *Prim Care*. 2005;32(2):563–586.)

Epidemiology

The prevalence of RLS has been estimated to be between 5% and 10%, making it a very commonly encountered disorder in the outpatient setting. Prevalence increases with age in most populations up to 60 to 70 years. RLS is 1.5 to 2 times more common in women than in men. Iron deficiency and family history increase the odds of developing RLS. The prevalence of RLS is two to five times greater in patients with chronic renal failure. Taking antihistamines and most antidepressants are risk factors for the development of RLS. RLS severity correlates with a reduced health-related quality of life when comorbid with other conditions. Large population studies have found associations between RLS and cardiovascular disease.

The exact prevalence of PLMD is not known. PLMS increases in frequency with age. Up to 45% of older people have PLMS, often of unknown clinical consequence. The existence of comorbidities with aging makes a clear-cut diagnosis of PLMD difficult. Having a family history of RLS may make PLMD more likely.

Pathophysiology

RLS and PLMS are often thought of as sharing a similar pathophysiology, with RLS being a sensory manifestation and PLMS a motor manifestation. The exact mechanisms of RLS and PLMS are not exactly known. There appears to be a defect in the homeostatic regulation of iron that then leads to a dysfunction in the dopamine system.

Clinical Presentation

RLS may present with complaints of specific RLS symptoms or simply with a primary complaint of insomnia. The most classic presentation is of a creepy crawly sensation that is predominately in the lower calf and gets better with walking. It is worse at night and with rest. Sometimes RLS symptoms involve the upper extremities as well. By definition the symptoms occur while awake. In patients who are not able to describe symptoms due to significant dementia or aphasia the patients may be seen rubbing or massaging the legs or may present with increased motor activity at night. Since 80% to 90% of patients with RLS have PLMS the observation of kicking during sleep makes

the diagnosis of RLS more likely. One of the difficult issues clinically is distinguishing RLS symptoms from peripheral neuropathy. The nighttime onset of symptoms and relief of symptoms with movement help distinguish the two conditions. For patients with both conditions present, determining the contribution of RLS over neuropathy remains challenging.

PLMD may present with a patient or bed partner complaint of kicking at night. The patient may simply present with complaints of disturbed sleep, insomnia, and/or excessive daytime sleepiness. Since PLMS are so common in older adults, significant clinical sleep disturbance and/or daytime sleepiness are required to make the diagnosis. The symptom of waking up kicking has to be distinguished from hypnic jerks or sleep starts—total body jerking often with a sensation of falling that occur at sleep onset. Hypnic jerks are very common and generally not pathologic.

Evaluation

The diagnosis of RLS can be based on clinical criteria alone. A PSG is sometimes helpful to rule out other sleep disorders, particularly SDB which may be comorbid or on the differential diagnosis for the patient's sleep disturbance. Presence of PLMS on PSG is suggestive of RLS but neither rules in nor rules out RLS.

A sleep study with limb electrode measurement is required for the diagnosis of PLMD because this is the only way for PLMS to be accurately measured. Furthermore, since PLMD is a diagnosis of exclusion other sleep disorders must be ruled out at the same time.

Patients with RLS or PLMD should have a serum ferritin measured to rule out any degree of iron deficiency leading to these conditions.

Management

Pharmacologic management The treatment options for RLS and PLMD are similar. However, whether to initiate treatment for PLMD is more controversial. For either condition the decision to treat needs to be individualized, based on the severity of symptoms and the impact on quality of life.

Patients should receive iron supplementation if the serum ferritin is less than 50 to 70 ng/dL. This entails a much more aggressive iron replacement strategy than is typically used in patients without RLS.

The first-line specific pharmacologic treatment is an evening dose of a long-acting dopamine agonist (either pramipexole or ropinirole) 1 to 2 hours prior to bedtime (**Table 49-2**). Carbidopa-levodopa can be used in patients for as-needed dosing when symptoms are infrequent. The major drawback to the use of dopamine agents is a phenomenon called augmentation. Augmentation is a worsening of RLS manifested by: the onset of RLS symptoms earlier in the day, and/or increased intensity of RLS symptoms, and/or spread of symptoms to the upper extremities and trunk when these areas were previously unaffected. Augmentation is much more frequent with carbidopa-levodopa, which is why this agent is reserved for use when symptoms are infrequent. Estimates of augmentation on the long-acting dopamine agonists have ranged between 2% and 15% per year. The risk of augmentation is higher with higher doses and longer duration of therapy. Augmentation can sometimes be managed by giving an additional dose of dopamine agonist earlier in the day, switching to a different dopamine agonist or switching to a different class of medication. Other important side effects of dopamine agonists include daytime sleepiness, sleep attacks, and behavioral disinhibition.

TABLE 49-2 PHARMACOLOGIC TREATMENT OF PLMS/RLS

CLASS	GENERIC	BRAND	DOSE
Dopaminergic agents	Ropinirole	Requip	0.25–4 mg
	Pramipexole	Mirapex	0.125–2 mg
	Carbidopa/levodopa[a]	Sinemet	25/100–25/200 mg
α2δ calcium channel ligands	Gabapentin encarbil	Horizant	600–1200 mg
	Gabapentin[a]	Neurontin	100–1800 mg
	Pregabalin[a]	Lyrica	300 mg
Benzodiazepines	Clonazepam[a]	Klonopin	0.25–2 mg
	Temazepam[a]	Restoril	15–30 mg
Opiate agents	Codeine[a]	Tylenol #3/#4	30–60 mg (codeine)

[a]

	Tramadol	Ultram	50–100 mg
	Oxycodone[a]	Roxycodone	5–15 mg
	Hydrocodone[a]	Vicodin	5–15 mg
	Methadone[a]		5–10 mg

[a]Off-label.

The other agents that have good evidence for RLS therapy are the α2δ calcium channel ligands, which include gabapentin, gabapentin enacarbil, and pregabalin. Only gabapentin enacarbil is FDA approved for RLS treatment. These agents may be particularly useful when the patient also has peripheral neuropathy. A recent randomized controlled trial showed that pregabalin was as efficacious as pramipexole, with a lower rate of augmentation. Major adverse effects from these medications can include drowsiness, dizziness, and suicidal ideation.

Other medications that can be used for the treatment of RLS include benzodiazepines and opiates. Benzodiazepines have a long history of use for intermittent RLS; however, the evidence base for this practice is limited. Low-dose opiates including methadone can be used for treatment of refractory RLS. Clearly, benzodiazepines and opiates can have adverse cognitive effects in older patients and should be used with caution.

Nonpharmacologic therapy Behavioral strategies that can be used for RLS include moderate exercise, pneumatic compression, massage, hot showers, and leg stretching. Avoidance of possible triggers for RLS should also be recommended. These include sleep deprivation, caffeine, and alcohol use. Also, most antidepressants are known to elicit or provoke RLS symptoms. However, bupropion is less frequently associated with RLS and therefore a switch from a selective serotonin reuptake inhibitor (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) to bupropion when RLS symptoms are present could be considered.

Prevention

There is no specific prevention for RLS. Adherence to a healthy lifestyle may be beneficial. This includes moderate exercise, a regular sleep schedule, and limiting caffeine and alcohol intake.

Patient Preference

The focus of RLS management is symptom relief. The medications used for the treatment of RLS may have important side effects. Therefore, therapy is determined by the balance between symptom control and side effects, in addition to patient input and preferences.

Comorbidities

Frequently encountered comorbidities of RLS include Parkinson disease, chronic kidney disease, iron deficiency anemia, and peripheral neuropathy. It is essential to address both the underlying disease process and the RLS symptoms at the same time.

REM SLEEP BEHAVIOR DISORDER

Definition

REM sleep behavior disorder (RBD) is defined as recurrent complex movements or vocalizations during sleep characterized by dream enactment. Normally during REM sleep, there is complete loss of skeletal muscle tone (ie, atonia). However, in RBD there is REM sleep without atonia, which is required for the diagnosis of RBD, in addition to dream enactment behavior.

Epidemiology

RBD is a male-predominant syndrome, which usually occurs after the age of 50. The exact prevalence of RBD is not known; however, it is estimated to be from 0.4% to 0.8%. RBD is more common in certain neurologic disorders such as Parkinson disease, multiple system atrophy, and Lewy body dementia.

Pathophysiology

There is an association between neurodegenerative disorders and RBD, particularly synucleinopathies. The synucleinopathies result from a pathologic lesion of aggregates of insoluble α-synuclein protein. These aggregates are linked to degradation of specific brain regions and clinical symptoms. The most important clinical diagnoses of synucleinopathies are Parkinson disease, dementia with Lewy bodies, and multiple system atrophy. The α-synuclein protein aggregates can be found in the brain areas responsible for producing active atonia during REM sleep. Up to 90% of patients who present with RBD develop another synucleinopathy disorder over the course of a 10- to 15-year follow-up (**Figure 49-8**).

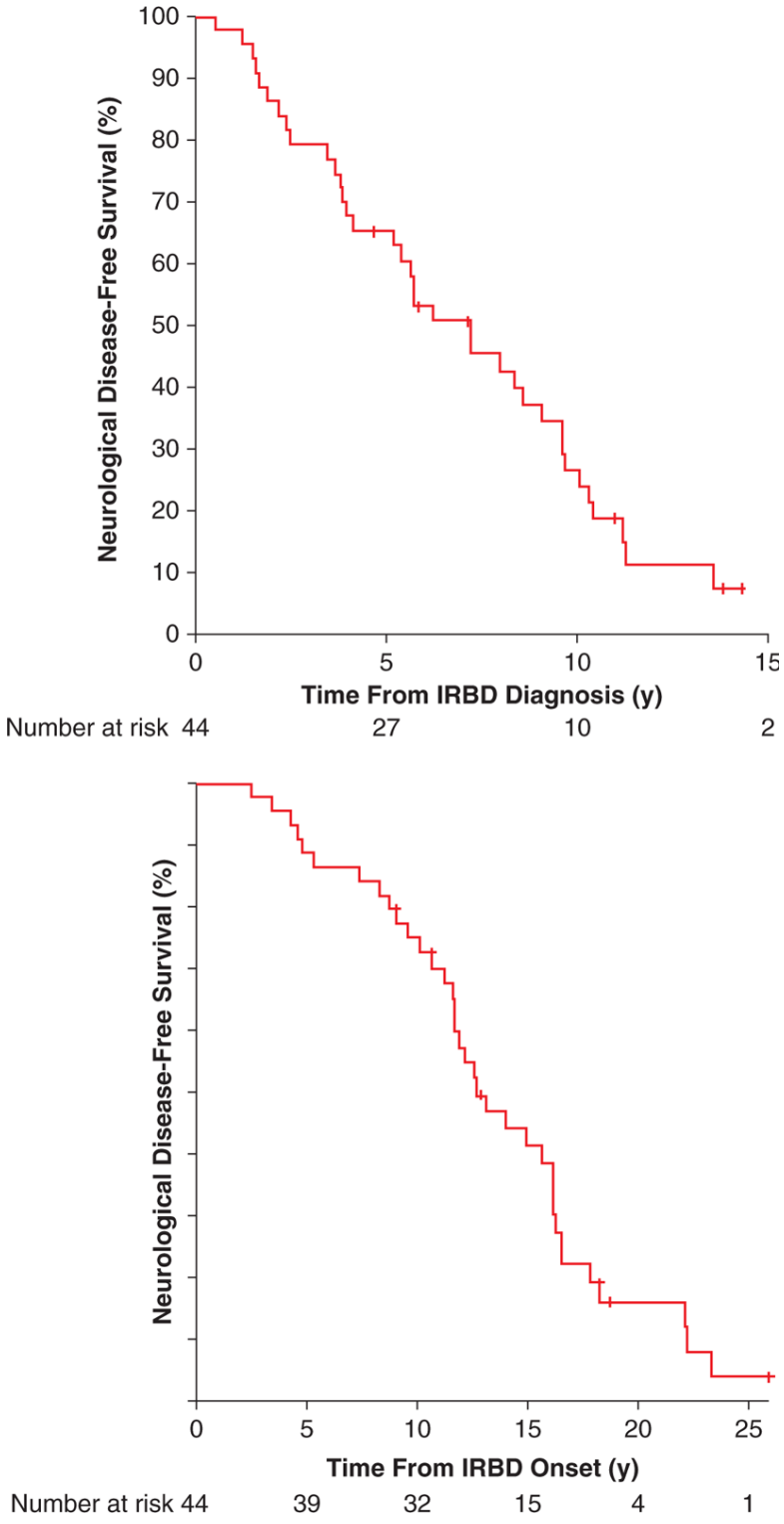


FIGURE 49-8. Relationship between the diagnosis of idiopathic REM behavior disorder (IRBD) and the development of a neurodegenerative

disorder. (From Iranzo A, Tolosa E, Gelpi E, et al. Neurodegenerative disease status and post-mortem pathology in idiopathic rapid-eye-movement sleep behaviour disorder: an observational cohort study. *Lancet Neurol*. 2013;12(5):443–453.)

RBD is also strongly linked with narcolepsy, which may be a different form of REM sleep motor-behavior control. The RBD may be worsened by the use of SSRIs to treat cataplexy. Other neurologic disorders have been associated with RBD including cerebrovascular disease, multiple sclerosis, Guillain-Barre syndrome, normal pressure hydrocephalus, Tourette syndrome, and autism.

Clinical Presentation

RBD will often present with sleep-related injury that results from the enactment of unpleasant violent dreams. The dreams that are acted out are often more violent and thus the behaviors are violent. It is rare for patients with RBD to walk. Patients are usually not able to leave the room they are in because their eyes are closed and thus are inattentive to the environment. Because RBD occurs during REM sleep, it usually appears at least 90 minutes after sleep onset and is more likely to occur later in the sleep period. Often RBD is the first manifestation of a Parkinson disease or dementia with Lewy bodies, but may also present later in patients with these disorders.

Evaluation

The evaluation of RBD includes a neurologic and sleep history. The history should focus on common associated conditions such as Parkinson disease and associated dementia. The presence of vivid dream enactment makes RBD more likely than other parasomnias. A predilection for events to occur later in the sleep period also makes RBD more likely. A detailed neurologic examination can elucidate a comorbid neurodegenerative disorder. It may be difficult to distinguish RBD symptoms from those of other parasomnias, nocturnal seizures, and nightmares of posttraumatic stress disorder (PTSD). SDB can cause RBD-like symptoms, which typically resolve with effective SDB therapy.

An attended in-laboratory PSG is the gold standard for diagnosing RBD. Actual acting out of dreams in REM sleep during the sleep study is fairly convincing for RBD. However, often patients will not have RBD behavior events during PSG. In this case, a 30-second epoch of REM sleep during the sleep study in which over 50% of the epoch has increased muscle tone is consistent with RBD. The majority of patients with RBD will also have PLMS on their PSG.

Managegement

Pharmacologic management There are no currently FDA-approved therapies for RBD. Clonazepam at low doses has been successfully used to treat RBD symptoms. As with any benzodiazepines, caution needs to be exercised in older patients with this drug. The other therapy that has been used with success is melatonin at 3- to 6-mg doses, which is generally well tolerated in older people. It is possible that since REM sleep occurs later in the night that the extended-release melatonin may be more effective. The major drawback to melatonin is that it is not an FDA-regulated pharmaceutical. Therefore, quality and strength may not be as tightly regulated. Also, insurance will usually not cover the expense of this therapy.

Nonpharmacologic therapy Ensuring that the patient sleeps in a safe environment and that others are not in danger is of paramount importance in RBD. The patient should consider sleeping separately from their bed partner for that person’s safety. Sharp furniture and other sharp objects should be removed from the patient’s bedroom. Likewise any weapons should not be freely accessible. If falling out of bed has been an issue, moving the mattress to the floor can be considered. Some patients have gone so far as to sleep in sleeping bags to prevent injuring themselves.

Well-recognized precipitating factors for RBD symptoms include the use of SSRIs, venlafaxine, mirtazapine, and other antidepressants except for bupropion. Hence, tapering off these medications or switching to bupropion should be considered. Any sort of comorbid SDB disorder should be aggressively treated, which may help with RBD symptoms.

Prevention

There are no known preventative measures for RBD.

Patient Preference

Since the treatment of RBD is symptom based, patient preferences often dictate the intensity and type of therapy. Many patients may opt for melatonin therapy given that its side effect profile appears to be favorable to clonazepam. The desire for the patient to know the ramifications of an RBD diagnosis as a predictor of development of a future

neurodegenerative disorder needs to be carefully elucidated.

Comorbidities

As discussed previously presence of RBD strongly predicts the subsequent development of a synucleinopathy such as Parkinson disease, multiple system atrophy, and dementia with Lewy bodies. Often RBD is the first manifestation of one of these disorders. Therefore, RBD will eventually coexist with one of these neurodegenerative disorders in most patients. RBD can also present in patients with narcolepsy. There are some cases in which RBD and NREM parasomnias coexist as well.

OTHER PARASOMNIAS

Other parasomnias occur in NREM sleep, which include sleep walking, confusional arousals, and sleep terrors. These disorders are much more common in children and young adults, and generally do not first present in old age. The distinguishing features of these conditions are that they predominantly occur in the first part of the night and the patients are difficult to arouse and do not have recollection of the event or associated dream imagery. One aspect of these NREM parasomnias relevant to older adults is that nonbenzodiazepine hypnotics can be associated with very complex sleep behaviors such as sleep cooking, sleep eating, and sleep driving. This is a rare but possibly dangerous side effect of these medications.

CIRCADIAN RHYTHM DISORDERS

Definition

Circadian rhythms refer to the 24-hour biological rhythms that control functions such as hormone secretion, core body temperature, and the sleep-wake cycle. The endogenous circadian rhythms originate in the suprachiasmatic nucleus (SCN), which is the internal circadian pacemaker. The SCN synchronizes itself using other internal rhythms from hormone secretion patterns and external signals, the most potent of which is light. The sleep-wake cycle is driven by melatonin secretion and body temperature, which are both governed by the SCN. However, external light can disrupt this cycle.

Circadian rhythm disorders are a chronic or recurrent pattern of sleep-wake rhythm disruption due to a misalignment between the patient's endogenous circadian rhythm and their desired or required sleep-wake cycle. For this to be considered a disorder it must cause bothersome insomnia symptoms and/or excessive sleepiness. For instance, a retired person who is not bothered by going to bed at 8 PM and waking up at 4 AM does not have a disorder.

Delayed sleep-wake phase disorder is a delay in the phase of the endogenous major sleep episode with respect to the desired major sleep episode such that the patient complains of an inability to fall asleep and difficulty waking up at the desired time.

Advanced sleep-wake phase disorder is an advance in the phase of the endogenous major sleep episode with respect to the desired major sleep episode such that the patient complains of difficulty staying awake until the desired bedtime, with an inability to remain asleep until the desired awakening time.

Irregular sleep-wake rhythm disorder is characterized by a lack of a clearly defined circadian rhythm characterized by insomnia at night and excessive sleep during the day. This disorder is often associated with neurodegenerative diseases and is likely common in the nursing home setting (**Figure 49-9**).

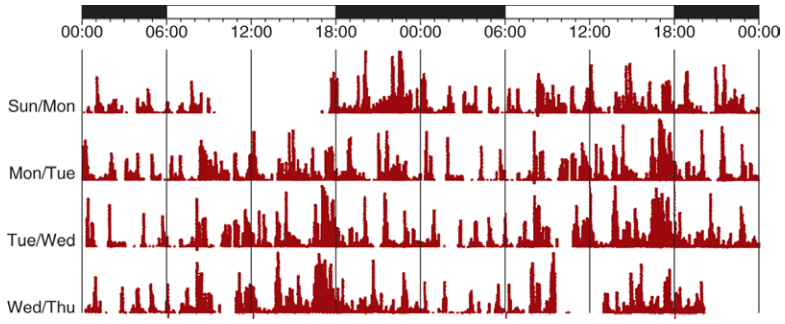


FIGURE 49-9. Actigraphy of a patient with irregular sleep-wake disorder. The red lines indicate bouts of movement and activity. In this patient there is not a set time when there is activity versus inactivity. (From Kryger MH, Avidan AY, Berry RB, eds. *Atlas of Clinical Sleep Medicine*. 2nd ed. Philadelphia, PA: Elsevier; 2014, Figure 9.1-7.)

Non–24-hour sleep-wake rhythm disorder usually occurs from a lack of the ability to entrain their circadian rhythm to light due to complete blindness. The natural circadian rhythm is typically longer than 24 hours. Thus each subsequent day, the patient will go to bed and wake up a little later. This leads to episodes of insomnia and hypersomnia (**Figure 49-10**).

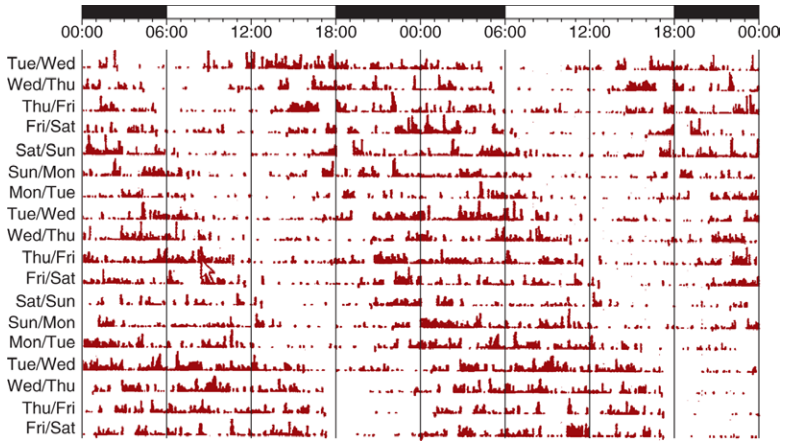


FIGURE 49-10. Actigraphy of a patient with non–24-hour sleep-wake rhythm disorder. Because the internal circadian rhythm is longer than 24 hours, each night the patient goes to bed later and wakes up later causing a drift in the sleep period over time. (From Kryger MH, Avidan AY, Berry RB, eds. *Atlas of Clinical Sleep Medicine*. 2nd ed. Philadelphia, PA: Elsevier; 2014, Figure 9.1-6.)

Epidemiology

Delayed sleep-wake phase disorder is more common among adolescents and young adults; however familial patterns and psychiatric disorders are risk factors for development of delayed sleep-wake phase disorder in later life.

The prevalence of advanced sleep-wake disorder is not fully known and is thought to comprise 1% of a middle-aged population. Advanced age appears to be a risk factor, given that aging is associated with the development of morningness tendencies. However, older patients may be more tolerant of these changes in endogenous circadian rhythm.

Irregular sleep-wake rhythm disorder is commonly seen in older adults with neurodegenerative disorders such as Alzheimer disease, Parkinson disease, and Huntington disease.

Pathophysiology

Possible causes of advanced sleep-wake phase disorder include a loss of the ability for the circadian clock to phase delay, a tendency to abnormally phase advance to entraining stimuli or a shorter endogenous circadian pacemaker. The latter of these has been shown to underlie the pathophysiology in select familial patients with circadian clock gene mutations.

There are several factors that may cause irregular circadian rhythms with aging. These may include (1) degeneration of the SCN with age, (2) a blunting of melatonin secretion at night, (3) decreased sensitivity to entraining cues, and (4) less availability to cues such as bright light. Furthermore, neurodegenerative disorders may result in

physical disruption of circadian rhythm pathways. Irregular sleep patterns prevent the normal sequence of progression through sleep stages.

Clinical Presentation

Patients with delayed sleep phase disorder present with sleepiness in the morning and an inability to sleep in the evening. Patients with advanced sleep phase disorder present with sleepiness in the evening, and an inability to sleep in the early morning. These patients will essentially present with insomnia complaints. However, an ability to sleep when the patient aligns their sleep-wake cycle with their endogenous circadian rhythm will be indicative of a circadian rhythm disorder rather than insomnia. Patients with advanced sleep phase syndrome may develop a self-imposed sleep deprivation from trying to adhere to a "normal schedule" but will wake up too early. A strong familial pattern may also suggest a circadian disorder.

Patients with irregular sleep-wake rhythm disorder will present with poorly consolidated sleep. Caregivers of patients with dementia may complain of nighttime wandering and agitation. In fact, sundowning may be a phenotype of a circadian rhythm disturbance. Patients will generally sleep for less than 4 hours at a time, and will have many short periods of sleep and wake throughout the day and night.

Evaluation

The key component in evaluating patients with suspected circadian rhythm disturbances is a comprehensive sleep history. Sleep logs for 1 to 2 weeks are helpful in establishing the diagnosis of a circadian disorder. Wrist actigraphy (a device with an accelerometer) can also be useful, particularly in patients who cannot fill out sleep logs, or for those in whom the accuracy of the sleep logs is doubtful. Newer actigraphy monitors that have a light sensor can also give the clinician a sense of the patient's light exposure. Polysomnography is only indicated when other sleep disorders are suspected.

Management

The primary management for circadian rhythm disorders involves the use of appropriately timed bright light therapy. Appropriately timed melatonin can be used as an alternative to, or in conjunction with, bright light therapy. However, there is less evidence for this approach. There are commercially available light boxes, or where feasible, natural sunlight can be used. In general, exposure to bright light in the morning will advance the circadian rhythm, while exposure in the evening will cause a delay in rhythm. Patients with advanced sleep-wake phase disorder should wear sunglasses in the morning and spend late afternoons outdoors without sunglasses.

For irregular sleep-wake rhythm disorder a strong routine with natural light and increased activity during the day and darkness with decreased noise at night may be helpful. Tasimelteon is a newly released melatonin agonist for the MT1 and MT2 receptors with greater affinity for the MT2 receptor. This agent is only approved for non–24-hour sleep-wake rhythm disorder.

INSOMNIA

Definition

Insomnia is defined as the inability to fall asleep, the inability to stay asleep, or waking up earlier than desired. In order to have a clinical diagnosis of insomnia the patient must have an adequate sleep opportunity and adequate sleep environment. The sleep disturbance must also have an impact on their quality of life such as fatigue, impaired cognitive performance, mood disturbance, daytime sleepiness, behavioral problems, reduced motivation, proneness for errors, or concerns about sleep. Insomnia is categorized as chronic if it persists more than 3 months and short term if it has lasted fewer than 3 months. The most recent International Classification of Sleep Disorders no longer emphasizes previously distinguished insomnia subtypes or insomnia due to mental or medical disorders. This is because it is increasingly recognized that even when insomnia is related to another condition, treatment of the comorbid condition often does not cure the insomnia. Furthermore, individual patients often have an overlap across insomnia subtypes.

Epidemiology

Insomnia is a highly prevalent sleep disorder, affecting up to 10% of young adults; however it increases to about 30%

in those greater than 65 years. Transient insomnia may affect up to 30% to 40% of the population. The prevalence of insomnia is much higher in older adults, which is likely due to age-related reductions in sleep efficiency and the accrual of comorbidities that are associated with insomnia. A recent meta-analysis of epidemiologic studies shows that the relative risk of insomnia in women compared with men increases with age.

Comorbid psychiatric conditions increase the likelihood of developing chronic insomnia. Depression is perhaps the most common and strongly associated mental illness with insomnia. Anxiety is also a risk factor for developing insomnia; as is being a caregiver for an ill family member, with up to 40% of caregivers reporting taking sleep aids for insomnia.

A wide variety of medical problems are associated with insomnia. Epidemiologic evidence shows a greater prevalence of insomnia in hypertension, heart disease, arthritis, lung disease, gastrointestinal reflux, stroke, and neurodegenerative disorders, to only name a few. Symptoms of medical illnesses that can disrupt sleep include pain, paresthesias, cough, dyspnea, reflux, and nocturia.

Many medications can impair sleep or change sleep architecture. If stimulating medications (eg, caffeine, sympathomimetics, bronchodilators, activating psychiatric medications) are taken too near to bedtime, sleep can be disturbed (**Table 49-3**).

TABLE 49-3 EFFECT OF COMMON DRUGS TAKEN BY OLDER ADULTS

SEDATING	ALERTING
Hypnotics	Alcohol/nicotine
Antihypertensives	CNS stimulants
Antihistamines	Thyroid hormones
Antpsychotics	Bronchodilators
Antidepressants	Corticosteroids
	β-Blockers
	Calcium channel blockers

Late-life insomnia is often a long-lasting problem. One study showed that a third of older patients had persistent severe insomnia symptoms at 4-year follow-up. Among women older than 85 years, more than 80% reported sleeping difficulties, with many using over-the-counter (OTC) sleeping medications. Several epidemiologic studies have linked sleep disturbances with worse health-related quality of life, nursing home placement, and even death.

Pathophysiology

The causes of insomnia are often multifaceted. One popular theoretical model for insomnia posits that there are predisposing factors, precipitating factors, and perpetuating factors. Predisposing factors are a vulnerability to insomnia and may include anxiety, depression, or hyperarousal. Precipitating factors are triggers for insomnia such as loss of a spouse, retirement, moving to a new home, or any other sort of stressor. Perpetuating factors are maladaptive habits or beliefs that the patient has acquired to deal with the insomnia such as spending long periods in bed or taking naps.

As noted earlier, insomnia in older adults is often comorbid with medical or psychiatric illnesses. The symptoms such as pain, dyspnea, or nocturia may be so significant that these become the primary driving factors behind the sleep disturbance.

Clinical Presentation

Patients with insomnia may present to their primary care provider with specific complaints about either not being able to fall asleep or stay asleep. However, many patients do not talk to their doctors about their sleep complaints. Instead, the presence of insomnia may be revealed by eliciting self-medication with OTC or alternative sedatives.

A careful sleep history and evaluation should be conducted in patients with insomnia in order to assess whether there are comorbid sleep disorders, such as SDB, underlying the sleep disturbance.

Evaluation

PSG and other sleep studies are not necessary in the evaluation of insomnia; however, they should be obtained if a

comorbid sleep condition is suspected. Sleep diaries with daily entries over 1 to 2 weeks can be very helpful in determining the severity of the insomnia as well as identifying possible perpetuating factors such as irregular bedtimes or late-night caffeine (**Table 49-4**). This may help the patient gain more insight into their sleep problem. Wrist actigraphy in conjunction with a sleep diary can be used to obtain a more objective measure of the patient's overall sleep-wake pattern. This device is particularly helpful when accuracy of the sleep diary is questionable or when sleep-wake misperception is suspected.

TABLE 49-4 SAMPLE SLEEP DIARY

NAME:_____					DATE: _____TO_____		
	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
1. Bedtime							
2. Time taken to fall asleep (after lights off)							
3. Number of nighttime awakenings							
4. Wake-up time							
5. Time out of bed (morning)							
6. Total sleep time (night only)							
7. Total wake time (night only)							
8. Nap time (if any)							
9. Medication (time/dosage)							
10. Alcohol (time/dosage)							
11. How was your sleep last night?[a]							
12. How tired were you in the morning?[b]							

[a]1 = excellent to 5 = very poor; [b]1 = not tired to 5 = very tired.

Management

Behavioral and nonpharmacologic interventions appear to have better long-term efficacy with fewer side effects than pharmacologic interventions. Therefore, behavioral interventions are preferred for the treatment of insomnia, particularly in older patients. However, access to highly skilled professionals trained in such interventions may be limited in some health care systems.

Pharmacologic management Most pharmacotherapy for insomnia is designed and approved for the treatment of transient sleep disturbances. Pharmacotherapy can be considered when insomnia is triggered by an acute event or when chronic insomnia persists despite behavioral insomnia treatment. Sedative-hypnotics have been associated with adverse side effects in older adults, such as falls, cognitive slowing, and fractures. Therefore, if a sedative-hypnotic is used in older individuals, the smallest dose of an agent with the least risk of adverse events should be chosen for the shortest duration necessary. In general, short-acting drugs should be used for patients who have trouble falling asleep while intermediate-acting drugs should be used when patients have trouble staying asleep (**Table 49-5**).

TABLE 49-5 PRESCRIPTION MEDICATIONS COMMONLY USED FOR INSOMNIA IN OLDER ADULTS

CLASS, MEDICATION	STARTING DOSE (MG)	USUAL DOSE (MG)	HALF-LIFE (H)	COMMENTS

Intermediate-acting benzodiazepine				
Temazepam	7.5	7.5–30	8.8	Psychomotor impairment, increased risk of falls
Short-acting nonbenzodiazepines				
Eszopiclone	1	1–2	6	Reportedly effective for long-term use in selected individuals; may be associated with unpleasant taste, headache; avoid administration with high-fat meal
Zaleplon	5	5–10	1 (reportedly unchanged in older adults)	Reportedly little daytime carryover, tolerance, or rebound insomnia
Zolpidem	5	5	1.5–4.5 (3 in older adults, 10 in hepatic cirrhosis)	Reportedly little daytime carryover, tolerance, or rebound insomnia
Melatonin receptor agonist				
Ramelteon	8	8	1.5 (2.6 in older adults)	Dizziness, myalgia, headache, other adverse events reported; no significant rebound insomnia or withdrawal with discontinuation
Sedating antidepressants				
Doxepin	3	3–6	15.3 (doxepin); 31 (metabolite)	Somnolence/sedation, nausea, and upper respiratory tract infection reported; antagonizes central H_1 receptors (antihistamine); active metabolite; should not be taken within 3 h of a meal
Mirtazapine	7.5	7.5–45	31–39 in older adults; 13–34 in younger adults; mean = 21	Increased appetite, weight gain, headache, dizziness, daytime carryover; used for insomnia with depression
Trazodone	25–50	25–150	Reportedly 6 ± 2; prolonged in older adults and obese individuals	Moderate orthostatic effects; administration after food minimizes sedation and postural hypotension; used for insomnia with depression

Benzodiazepines have had a long history of being used for insomnia. These drugs bind nonselectively to the γ-aminobutyric acid benzodiazepine (GABA-A) receptor subunits. The overall effects of these drugs are to induce anxiolysis, sedation, and amnesia. Temazepam, lorazepam, and estazolam are intermediate-acting agents that are most commonly used for insomnia, while triazolam is a shorter-acting agent that is sometimes used for insomnia. Due to next-day effects, the longer-acting agents, flurazepam and quazepam, should not be used in older adults. Benzodiazepines do decrease the time to fall asleep by about 10 minutes on average and the number of awakenings, thereby increasing the total sleep time by 30 to 60 minutes during the nighttime. The side effects associated with this class of medications include confusion, falls, rebound insomnia, tolerance, and withdrawal symptoms on discontinuation. These agents are all Beer criteria–listed medications as potentially inappropriate for use in geriatric patients.

Nonbenzodiazepine-benzodiazepine receptor agonists (NBRAs [ie, nonbenzodiazepines such as eszopiclone, zolpidem, and zaleplon]) are structurally unrelated to benzodiazepines but bind selectively to the GABA-A receptors. They generally produce sedation and amnestic effects without the anxiolytic properties. These agents likely have similar efficacy to benzodiazepines but with a somewhat better side effect profile, in part due to their relatively short duration of action. In healthy older adults without comorbidities, NBRAs are relatively well tolerated. Zolpidem and zaleplon should only be taken immediately before bed because of their rapid onset of action. Eszopiclone has a longer

duration of action than the other NRBAs, and is better for sleep maintenance but may cause drowsiness in the morning. There is also an extended-release form of zolpidem that can be used for sleep maintenance insomnia. Guidelines only recommend these medications for use in short-term insomnia. Concerns remain regarding the risks of falls, confusion, and fracture in older adults, particularly in those with frailty. The emergence of complex sleep-related behaviors such as sleep driving and sleep eating has been seen with zolpidem, which may be class side effect with these agents.

Melatonin receptor agonists (eg, ramelteon) are approved for insomnia. Rather than activating GABA receptors, ramelteon is selective for the MT1/MT2 melatonin receptors. Ramelteon has been shown to reduce total sleep latency and increase sleep time in older adults, with fewer side effects. Somnolence, dizziness, headache, and fatigue can be side effects of this agent. The major downside of ramelteon is that its lack of amnestic properties makes it somewhat less effective for subjective improvement in sleep.

Other agents are available for treatment of insomnia. The tricyclic antidepressant doxepin has recently been developed for insomnia in a low-dose formulation (3–6 mg). For comparison, the usual antidepressant dose of doxepin is 100 to 300 mg per day. At these low dosages doxepin selectively antagonizes H_1 receptors, which is believed to have sleep-promoting effects. The duration of action for doxepin makes it more attractive for problems with sleep maintenance rather than sleep onset. The use of low doses of other sedating antidepressants such as trazodone and mirtazapine at bedtime is common. However, there is limited evidence to support this practice. In fact, a study in the use of trazodone for nondepressed patients showed that there was short-term benefit, which dissipated after 2 weeks. Thus, the benefits may be very small compared to the potential for side effects. However, if there is comorbid depression it should be treated, and sedating antidepressants may be a good choice as primary or adjunctive therapy.

Although sedating antipsychotics are sometimes used to treat insomnia, there is scant evidence demonstrating their efficacy, and these medications can have significant adverse events, including increased mortality particularly in older adults with dementia. Guidelines suggest that sedating antipsychotics should not routinely be used in the management of insomnia in older adults without coexisting serious psychiatric conditions that warrant use of these agents.

Almost half of all older adults report the use of nonprescription OTC sleeping agents. Common nonprescription agents include sedating antihistamines, acetaminophen, alcohol, melatonin, and herbal products. The sedating antihistamines (eg, diphenhydramine) are the most common ingredients in these OTC drugs marketed for sleep. Diphenhydramine is sedating through its potent anticholinergic effect, and tolerance to its sedating effect develops rapidly. The long half-life of diphenhydramine may result in next-day sedation. Patients may also experience dry mouth, urinary retention, delirium, decreased cognition, constipation, and increased ocular pressure. For these reasons, diphenhydramine should not be used as a primary treatment for insomnia in older patients. Many patients may use alcohol to self-medicate for insomnia; however, it can interfere with sleep in the later evening and worsen sleep difficulties.

Other supplements are available OTC, such as melatonin and valerian. One drawback of these supplements is the lack of standardization and oversight of traditional pharmaceuticals. There is evidence that melatonin improves time to fall asleep and sleep efficiency in older adults. However, the results of studies have been mixed. Valerian is a herbal product marketed for insomnia due to its mild sedative properties. Some valerian preparations contain multiple botanicals, which may increase the chance of side effects. A recent systematic review on the efficacy for valerian for insomnia was inconclusive. Kava, another herbal product marketed for insomnia, has a significant risk of adverse events, including hepatotoxicity, and is not recommended.

Behavioral and other nonpharmacologic interventions Behavioral treatment of insomnia is the safest, and perhaps, the most effective therapy for insomnia in older adults. This modality of therapy has also proven effective in patients with comorbid conditions. Effective behavioral interventions for insomnia go beyond sleep hygiene, which is not generally effective when used alone for chronic insomnia. Several randomized trials and systematic reviews provide strong evidence for cognitive behavioral therapy for insomnia (CBT-I). CBT-I usually combines sleep hygiene, stimulus control, sleep restriction, and cognitive therapy, each of which will be discussed in greater detail below. CBT-I has reliably been shown to produce improved sleep efficiency, decreased nighttime wakefulness, and greater satisfaction with sleep. In at least two randomized trials with older adults comparing CBT-I with a prescription sedative-hypnotic agent, participants reported better improvement in sleep and more satisfaction with the CBT-I therapy. One feature that permeates studies comparing CBT-I to pharmacologic therapy is that the improvements with CBT-I are more sustained. One of the major downsides to CBT-I is the limited access to practitioners who are trained in this specific therapy, but efforts are underway in some health care systems to increase access. Also, CBT-I requires significant buy-in from the patient. New delivery models that involve the use of the internet, nonspecialist providers,

and telehealth-based CBT-I have yielded promising preliminary results.

Sleep hygiene is education on a list of general guidelines to maintain a healthy sleep-wake routine. When a sleep history is performed behaviors that contribute to disruptive sleep should be ascertained. Examples of these behaviors include sleeping with the television on, or excessive caffeine consumption. The patient should be educated on some of their behaviors that constitute poor sleep hygiene (**Table 49-6**).

TABLE 49-6 SLEEP HYGIENE RULES FOR OLDER ADULTS

Check effect of medication on sleep and wakefulness.
Avoid caffeine, alcohol, and cigarettes after lunch.
Limit liquids in the evening.
Keep a regular bedtime-waketime schedule.
Avoid naps or limit to 1 nap a day, no longer than 30 min.
Spend time outdoors (without sunglasses), particularly in the late afternoon or early evening.
Exercise—but limit exercise immediately before bedtime.

Stimulus-control therapy is designed to break the negative associations patients have with their sleep environment, which have come about from maladaptive behaviors. Patients are instructed to not have any other in-bed activities aside from sleep or sex, and to only go to bed when tired enough to fall asleep. They should unwind prior to going to bed and should not watch an alarm clock. If the patient cannot fall asleep within approximately 20 minutes they should get out of bed and do a relaxing activity and only return to bed when able to fall asleep. For a regular pattern to develop the patient needs to avoid napping and should get out of bed the same time each day. Daytime sleepiness may increase early in this therapy (**Table 49-7**).

TABLE 49-7 INSTRUCTIONS FOR STIMULUS-CONTROL THERAPY FOR OLDER ADULTS

1. Patient should only go to bed when tired or sleepy.
2. If unable to fall asleep within 20 min, patient should get out of bed (and bedroom if possible). While out of bed, do something quiet and relaxing.
3. Patient should only return to bed when sleepy.
4. If unable to fall asleep within 20 min, patient should again get out of bed.
5. Behavior is repeated until patient can fall asleep within a few minutes.
6. Patient should get up at the same time each morning (even if only a few hours of sleep).
7. Naps should be avoided.

Sleep-restriction therapy was developed from the observation that many patients with insomnia spend a large amount of time in bed unsuccessfully attempting to sleep. This unsuccessful attempt at sleep causes anxiety and frustration which then can lead to the negative associations around the sleep environment. Sleep-restriction therapy is guided by the patient's sleep diary. The amount of time the patient actually sleeps is calculated and the patient is only allowed to spend that amount of time plus around 15 minutes in bed each night for the following week. Since the amount of sleep will be less this will lead to some sleep deprivation, which then may allow the patient to subsequently fall asleep more quickly and have more consolidated sleep. Once the patient is spending at least 85% of their time asleep the time in bed is increased gradually until the patient is getting adequate sleep (**Table 49-8**).

TABLE 49-8 INSTRUCTIONS FOR SLEEP RESTRICTION THERAPY FOR OLDER ADULTS

1. Calculate the average amount of time in bed per night reported by patient.
2. Patient is only allowed to stay in bed for this amount of time plus 15 min.
3. Patient must get up at the same time each day.
4. Daytime napping should be strictly avoided.
5. When sleep efficiency has reached 80% to 85%, patient can go to bed 15 min earlier.

6. This procedure should be repeated until patient can sleep for 8 h (or period needed for a good night's sleep).

Cognitive therapy in CBT-I addresses the maladaptive thoughts or dysfunctional beliefs patients have about their sleep. This is essential to be addressed to ensure adherence to the behavioral aspects of the therapy. Other components of CBT-I may include various relaxation techniques and scheduled worry time. Image rehearsal therapy may be helpful with patients who have trouble sleeping from nightmares related to PTSD.

There are several small studies that have found a beneficial effect of bright light, either from natural sunlight or light boxes, on the sleep of older adults. The reported effects of light on insomnia are more variable than those reported for circadian rhythm disorders. Evening light exposure may be useful for those who go to sleep and wake up too early (ie, advanced sleep phase), while morning exposure may be useful in patients who stay up and sleep in late (ie, delayed sleep phase).

There is less evidence to support other behavioral interventions, but individual patients may find them useful. For example, bathing before sleep can enhance sleep quality in some older individuals, which is likely related to changes in body temperature. A moderate exercise program can improve sleep in healthy sedentary older adults. However, strenuous exercise should not be done close to bedtime because this may interfere with sleep. Some studies have shown a beneficial effect of Tai Chi on symptoms of insomnia.

SLEEP IN INSTITUTIONALIZED OLDER ADULTS AND NEURODEGENERATIVE DISORDERS

Sleep in older adults living in nursing homes is well known to be disturbed particularly in patients with neurodegenerative disorders. The prevalence of disturbed sleep in neurodegenerative disorders may be due to damaged brain structures responsible for regulation of sleep and circadian rhythms. Furthermore, a lack of exposure to light and alerting activities during the day can contribute to poor sleep at night. At the extremes, some patients may not spend a full hour fully awake or fully asleep in a 24-hour period. This lack of consolidated sleep prevents the normal sequence through various sleep stages and results in light nonrestorative sleep. In noninstitutionalized patients with significant dementia, progressive disturbances in the sleep-wake cycle often reach a point where nighttime behaviors become a significant stressor for caregivers. In fact, frequent nocturnal wandering and confusion is a leading cause of institutionalization.

The presence of dementia and other neurodegenerative disorders may impact therapy for sleep disorders. Severe dementia may impair the ability of patients to use CPAP for SDB, however studies have shown that CPAP can be successfully used in mild to moderate dementia. Treatment of SDB in these patients can actually improve cognitive function. Furthermore, dementia can impact appropriateness of CBT for insomnia, where patients may not be able to participate. Insomnia behavioral treatment programs that involve the caregiver have been used in patients with dementia. Most pharmacologic therapies for insomnia are relatively contraindicated in those with significant dementia. However, there are behavioral interventions that may be helpful in nursing home patients (**Table 49-9**). There is mixed evidence for use of melatonin for insomnia or circadian rhythm disturbances in dementia, however bright light may be beneficial. However, the most beneficial timing of bright light therapy in dementia is not clearly known.

TABLE 49-9 SLEEP HYGIENE RULES FOR NURSING HOME PATIENTS

Limit the amount of time in bed, particularly during the day.
Limit naps to 1 h once a day, early in the afternoon.
Keep regular sleep-wake schedule (if possible similar to prior home routine).
Keep regular meal schedule (if possible patients should not eat in bed).
Avoid caffeinated beverages and food.
Limit nighttime noise.
Ensure that patient rooms are as dark as possible during the night.
Ensure that patient environment is brightly lit during the day.
Encourage exercise appropriate for each patient.
Match roommates on sleep-wake behavior.

Assess patients for possible sleep problems and initiate specific treatment.

Check medications for sedating/alerting effects.

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Chapter 50

Dizziness

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Learning Objectives

- Understand the epidemiology and pathophysiologic mechanisms that contribute to chronic dizziness in older persons.
- Describe different presentation types of dizziness.
- Describe key elements of history and physical examination needed to create a differential diagnosis.
- Identify and describe the evaluation and management of common causes of dizziness.
- Discuss the role of vestibular rehabilitation in the management of chronic dizziness.

Key Clinical Points

1. **Dizziness is associated with increased fear of falling, worsening of depressive symptoms, and functional disability.**
2. **Dizziness is often classified in four types: vertigo, dysequilibrium, presyncope, and other nonspecific sensations such as whirling and floating. A fifth category, "mixed dizziness"—combinations of these four types—is the most common type of dizziness reported by older persons.**
3. **Chronic dizziness should be considered a geriatric syndrome, as it involves multiple factors or diseases affecting multiple systems.**
4. **A careful history and clinical examination are required to evaluate dizziness.**
5. **Expensive tests, such as neuroimaging, electronystagmography (ENG), and computerized posturography, are often not needed in the evaluation of dizziness.**
6. **Multifactorial interventions can help in either alleviating dizziness or decreasing the disabilities associated with dizziness.**

DEFINITION

Dizziness is a broad term used to describe various abnormal sensations arising from perceptions of the body's relationship to space or of unsteadiness. Dizziness has been arbitrarily defined on the basis of duration as acute (present for < 2 months) or chronic (present for > 2 months). The differential diagnosis of acute dizziness is similar in younger and older persons, and management of acute dizziness is not qualitatively different in older persons as compared to younger adults, with the possible exception that recovery may be more prolonged in older adults. This chapter focuses on chronic dizziness.

EPIDEMIOLOGY

The prevalence of dizziness ranges from 4% to 30% in persons aged 65 or older, and more commonly is reported by women than men. In one study of persons aged 65 and older, the likelihood of reporting dizziness increased by 10%

for every 5 years of increasing age.

Chronic dizziness is associated with a number of comorbid conditions, including falls, functional disability, orthostatic hypotension, syncope, and strokes. In older persons, chronic dizziness can cause substantial adverse effects on a person's quality of life. In one prospective study of older persons with dizziness, after 2 years of follow-up, older persons with dizziness were more likely to become disabled than were those who were not, although mortality was no different. In another study, 197 older persons with chronic dizziness reported poor health-related quality of life, most notably in relation to limitations in the physical and emotional dimensions. Chronic dizziness is also associated with fear of falling, worsening depressive symptoms and self-rated health, and decreased participation in social activities.

PATHOPHYSIOLOGY

Dizziness is a sensation of postural instability or imbalance. Causes of dizziness can be difficult to diagnose, specifically in older persons, in whom it often represents dysfunction in more than one body system. Maintenance of balance and equilibrium is complex, achieved by integration of sensory information obtained from vestibular, proprioceptive, visual, and auditory systems by the cerebral cortex and cerebellum, leading to appropriate balance-maintaining responses. Abnormal function in any one or a combination of these systems may result in imbalance and the sensation of dizziness.

The vestibular system maintains spatial orientation at rest and during acceleration. Elements of the vestibular system and its connecting pathways include the semicircular canals, utricle, saccule, vestibular nerve, vestibular nuclei, vestibulospinal tracts, and vestibulocerebellar pathways. Diseases affecting this system and producing dizziness include Ménière disease, benign paroxysmal positional vertigo, recurrent vestibulopathy, labyrinthitis/vestibular neuronitis, acoustic neuroma, and drug toxicity (especially aminoglycosides). Age-related changes have also been reported in the sensory (hair) cells in the semicircular canals, saccule, and utricle.

The proprioceptive system consists of mechanoreceptors in the joints, peripheral nerves, and posterior columns, and multiple central nervous system (CNS) connections. Proprioception contributes to equilibrium by providing information about changes in body position, and helping mediate the body's response to position change. Common disorders include peripheral neuropathy associated with diseases such as diabetes or vitamin B_{12} deficiency and cervical degenerative disorders. The few data on age-related changes in proprioception have been conflicting; one study reports a substantial decline in joint position sense with aging, while another found no major changes.

Vision provides important information about spatial orientation, and is particularly important when vestibular and/or proprioceptive function is impaired. Common ocular diseases include cataracts, macular degeneration, and glaucoma. Age-related visual changes include decrease in visual acuity, dark adaptation, contrast sensitivity, and accommodation. Hearing also provides spatial clues, but to a lesser extent than vision. Impairment in hearing, common in older persons, may be secondary to age-related changes, or to disease processes.

The cerebral cortex and cerebellum, along with their synaptic networks, integrate information and supply the musculoskeletal system with information for appropriate responses. Because of multiple and complex connections, essentially any central nervous system disorder can lead to imbalance which may manifest as dizziness.

PRESENTATION

Dizziness is described using many names, including vertigo, light-headedness, dysequilibrium, giddiness, wooziness, and spinning. The sensation of dizziness is commonly categorized as vertigo, dysequilibrium, presyncope, and other. In addition to these four types, another category, mixed dizziness, is a combination of two or more of the above types. Mixed dizziness is the most common type of dizziness reported by older persons.

Vertigo

Vertigo refers to a sensation of spinning, in which the individual perceives movements of the environment in relation to the body (objective vertigo) or vice versa (subjective vertigo). Vertigo is often assumed to result from disorders of the vestibular system and its connecting pathways, although other causes of dizziness, such as cervical disorders may present as vertigo as well.

Dysequilibrium

Dysequilibrium refers to feelings of unsteadiness or imbalance, primarily involving the lower extremities or trunk rather than the head. The person often expresses the feeling that he/she is about to fall. Dysequilibrium results mostly from disorders of the proprioceptive system, musculoskeletal weakness, or cerebellar disease.

Presyncope

Presyncope is a feeling of light-headedness or impending faintness or the sensation that one is about to pass out. Presyncope usually results from hypoperfusion of the brain; cardiovascular causes (including vasovagal disorders) are common causes in older persons.

Other and Multifactorial

Often the sensation does not fit any of the above three types. The patient may describe “whirling,” “tilting,” “floating,” and other nonspecific sensations. Furthermore, the correlation between sensations and organ systems is not as consistent among older persons as in younger persons. Thus, the sensation reported does not have diagnostic specificity in older patients.

In addition, although dizziness may be a symptom of one or more discrete diseases, multifactorial etiologies of dizziness are common in older persons. Chronic dizziness is associated with risk factors such as angina, myocardial infarction, arthritis, diabetes, stroke, syncope, anxiety, depressive symptoms, impaired hearing, and polypharmacy. In a population-based study of community-dwelling older persons, the factors that were independently associated with dizziness included anxiety, depressive symptoms, impaired hearing, the use of five or more medications, postural hypotension, impaired balance, and a past history of myocardial infarction. Almost 70% of patients with five or more of the above risk factors reported dizziness, whereas only 10% of patients with none of these factors reported dizziness. These findings suggest that chronic dizziness, at least in a subset of older persons, may be a geriatric syndrome, which is the result of the accumulated effect of multiple coexisting risk factors and diseases.

As presented in the following section, dizziness may be the presenting complaint of a discrete disease or the result of multiple contributing factors.

CLASSIFICATION

Discrete Diseases Causing Dizziness

Vestibular disorders Vestibular diseases have been reported in anywhere from 4% to 71% of older persons with dizziness. The most common vestibular disorders causing chronic dizziness in older persons are Ménière disease, benign paroxysmal positional vertigo, recurrent vestibulopathy, the effects of ototoxic medications, and acoustic neuroma.

Ménière Disease Ménière disease, also called endolymphatic hydrops, is reported in 2% to 8% of older patients with dizziness. It is a debilitating disorder of the inner ear, consisting of a triad of recurrent episodic vertigo, tinnitus, and fluctuating sensorineural hearing loss. A sensation of fullness in the inner ear is common. Episodes of true vertigo usually last for 1 to 24 hours. The patient may complain of nausea, vomiting, and headaches during the episodes. The exact cause is unknown, but the pathology is characterized by excess endolymph within the cochlea and vestibular labyrinth. The disease is unilateral in a majority of patients; men and women are affected equally. In a 14-year follow-up study, the episodes of vertigo disappeared in 50% of patients and improved in 28%, while hearing in the affected side was absent in 48% and impaired in 21% of the patients.

Benign Paroxysmal Positional Vertigo (BPPV) has been reported to be the cause of dizziness in 4% to 34% of cases. In this condition, patients report sudden-onset, episodic vertigo, often associated with nausea and/or vomiting, precipitated by changes in the position of the head, such as rolling over in bed, getting in and out of bed, or bending forward to pick something up. It is classically accompanied by rotational nystagmus. In most cases, the etiology is unknown, although some patients have a history of head injury or viral neurolabyrinthitis. BPPV results from freely moving particulate matter within the semicircular canal. These particles most likely are dislodged otoconia, which are tiny calciferous granules that make up part of the receptor mechanism in the otolithic apparatus. The particles are most commonly present in posterior semicircular canal, but can also be found in anterior and/or horizontal semicircular canals. It is postulated that movement of these free-floating particles cause alteration in the endolymphatic pressure,

resulting in episodes of vertigo and nystagmus. In one study, researchers reported that otoconia undergo age-related degenerative changes, which may lead to their dislodgment from the utriculus. A definitive diagnosis of BPPV can be made by the Dix-Hallpike test, described under “Evaluation” later in this chapter.

Recurrent Vestibulopathy is an idiopathic disorder characterized by recurring episodes of vertigo without auditory or neurologic symptoms or signs. The vertigo usually lasts from 5 minutes to 24 hours. It is differentiated from Ménière disease by the absence of auditory symptoms. Over 8.5 years of follow-up, and a spontaneous recovery was reported in 62% of patients. The diagnosis was changed to Ménière disease or BPPV in 14% and 8% of patients, respectively.

Acoustic Neuroma Acoustic neuroma, also known as cerebellopontine angle tumor, is a benign tumor of the eighth cranial nerve, and is reported in 1% to 3% of older persons with dizziness. Clinical features include tinnitus and progressive unilateral sensorineural hearing loss, particularly for the higher frequencies. Patients complain more often of a feeling of unsteadiness rather than of true vertigo. Patients with large tumors may also have occipital headache, diplopia, paresthesias in trigeminal or facial nerve distribution, and/or ataxic gait.

Central nervous system disorders The frequency of cerebrovascular disease ranges from 4% to 70% among older persons with dizziness. Patients with transient ischemic attack (TIA) or stroke involving vertebrobasilar distribution commonly present with dizziness, along with diplopia or dysarthria, numbness, or weakness. Dizziness rarely is a presenting symptom in patients with anterior or posterior cerebral artery ischemia or with internal carotid artery disease. The patient may complain of either a rotatory or nonrotatory dizziness, along with other neurologic symptoms and signs. A number of specific stroke syndromes present with dizziness, including cerebellar infarction and posterior lateral medullary artery infarction, also known as Wallenberg syndrome.

Other central nervous disorder causes of dizziness include Parkinson disease and basilar artery migraine. The latter is rare in older persons.

Psychiatric disorders Anxiety, depression, obsessive-compulsive disorder, panic disorder, and other psychiatric conditions are among the most common causes of chronic dizziness in young adults. In older persons as well, psychiatric conditions are often associated with dizziness. Common psychiatric conditions causing or contributing to dizziness in older persons include depressive and anxiety disorders. Recent studies show that depressive symptoms are associated with symptoms of dizziness, while conversely, persons who have chronic dizziness are at increased risk of depression, indicating a reciprocal relationship between dizziness and depressive symptoms among older persons.

Cervical disorders Disorders of the cervical spine as a cause of dizziness in older persons have been reported in the range of 0% to 57%. Patients with cervical dizziness usually present with vague light-headedness or vertigo, associated with turning of the head. Both vascular and proprioceptive mechanisms have been proposed to explain cervical dizziness.

Obstruction of the vertebral arteries is thought to be the most common vascular mechanism of cervical dizziness. One hypothesis suggests that in the presence of atheromatous narrowing of one vertebral artery, rotation of the head may cause sufficient obstruction of the contralateral vertebral artery to produce ischemia of the brain stem. Another hypothesis suggests that turning the head or neck results in compression of the adjacent vertebral artery by a strategic osteoarthritic spur, causing a transient disruption of the blood flow.

Degenerative changes in the cervical spine may cause dizziness because of impairment of the cervical proprioceptive mechanoreceptors. These receptors provide information for postural control via the vestibulospinal tract. The patient may present with decreased range of motion and radicular pain in the neck upon movement, as well as dizziness.

Systemic Causes

Hypothyroidism, anemia, electrolyte imbalance, hypertension, coronary artery disease, congestive heart failure, and diabetes mellitus are commonly found in patients with dizziness, although the frequency of dizziness as a symptom of each is low. Studies have found an independent association between dizziness and a history of hypertension, angina, myocardial infarction, and diabetes mellitus. Systemic disorders may contribute to instability or dizziness by affecting the sensory, central, or effector components. These systemic disorders may also cause decreased cerebral perfusion, fatigue, or confusion, each of which may subsequently lead to a sensation of instability or dizziness.

Orthostatic Hypotension

Orthostatic hypotension is a primary or contributing cause in 2% to 15% of older persons with dizziness. There is a long list of causes of orthostatic hypotension (see Chapter 51). Although there is no consensus on the definition of orthostatic hypotension in older adults, commonly noted criteria include a 20 mm Hg drop in systolic blood pressure, a 10 mm Hg drop in diastolic blood pressure, or typical symptoms associated with any drop in blood pressure after standing from a supine or sitting position. Another entity reported is postural dizziness, in which patients complain of dizziness on standing from a supine position but have no drop in blood pressure. In these studies, a subset of patients who have orthostatic blood pressure changes do not complain of dizziness, suggesting that orthostatic changes in blood pressure may be asymptomatic, while, conversely, all dizziness with postural changes may not be caused by a drop in blood pressure. Vestibular dysfunction is thought to account for the postural dizziness not accompanied by postural blood pressure drops.

Postprandial hypotension Another important entity to consider in older persons is postprandial hypotension, defined as a decrease in systolic blood pressure of 20 mm Hg or more in a sitting or standing posture within 1 to 2 hours of eating a meal; dizziness often is a symptom. In one study, the effects of postprandial hypotension and orthostatic hypotension were found to be additive but not synergistic, suggesting that the two entities have different pathophysiologic mechanisms.

Medications Contributing to Dizziness

Many classes of drugs can cause or contribute to dizziness. Common examples include antihypertensives, antiarrhythmic agents, anticonvulsants, antidepressants, anxiolytics, antibiotics (aminoglycosides, macrolides, and vancomycin analogs), antihistamines, nonsteroidal anti-inflammatory agents, and over-the-counter cold and sleep preparations. These agents cause dizziness through different mechanisms. Antihypertensive agents can cause dizziness simply by lowering blood pressure to a level at which symptoms occur. Calcium channel blockers, nitrates, and hydralazine are common offenders. Loop diuretics, such as furosemide can cause dizziness by ototoxicity and/or volume depletion. Antiarrhythmics, anticonvulsants, and anxiolytics are responsible for dizziness through their direct effects on the central nervous system. Tricyclic antidepressants, antihistamines, and cold preparations cause dizziness via their sedating anticholinergic properties. Antibiotics (eg, aminoglycosides, macrolides, and vancomycin analogs), nonsteroidal anti-inflammatory agents, and loop diuretics cause dizziness through ototoxicity, especially in the presence of impaired renal function, which decreases their clearance. The aminoglycosides are especially hazardous because of their toxicity to both the kidney and the vestibular system.

Apart from risks conferred by specific toxicity of drugs, studies have also reported an association between dizziness and the number of medications taken, independent of the effect of comorbid diseases.

EVALUATION

Evaluation of dizziness can be a complex and challenging task for clinicians. The differential diagnosis is broad, and the literature offers no evidence-based clinical practice guidelines. Optimal care requires the identification and treatment of the condition or combination of conditions causing dizziness when possible. If treatable conditions cannot be found, then the objective becomes maximum symptomatic improvement of dizziness. Based on these objectives and on the available evidence, a stepwise approach is recommended for the evaluation of chronic dizziness, proceeding from careful history and physical examination to screening laboratory tests. A targeted battery of more elaborate and expensive tests is indicated only when routine evaluation suggests a specific disease entity and the results of these tests are likely to influence the management. For the majority of older persons in whom a routine evaluation does not suggest a single discrete cause, the clinician should try to focus on identifying various factors (**Table 50-1**) that might be contributing to dizziness, some of which are likely to be modifiable. When etiology is multifactorial, identifying and treating one or more contributing factors may improve, if not eliminate the dizziness.

TABLE 50-1 POSSIBLE CONTRIBUTORS TO CHRONIC DIZZINESS

CONTRIBUTOR	HISTORY	EXAMINATION	POSSIBLE CAUSES	POTENTIAL INTERVENTIONS
Vision	Use of bifocals or trifocals	Abnormalities in near/distant acuity;	Cataract; glaucoma; macular degeneration;	Appropriate refraction; consider avoiding

		contrast sensitivity; depth perception	perceptual difficulties with glasses	bifocals or trifocals when walking; drugs for glaucoma; surgery; good lighting without glare
Hearing	Deafness in one or both ears; difficulty hearing in social situations	Abnormal findings with Rinne test, Weber test, Whisper test, or audiometry	Presbycusis; otosclerosis	Hearing aid; surgery (for otosclerosis); hearing rehabilitation; listening devices
Vestibulocochlear system	True vertigo, worse in dark or with specific head positions; tinnitus; history of aminoglycosides, furosemide, aspirin use; ear surgery; ear or mastoid infections	Nystagmus (horizontal or rotary nystagmus suggests a peripheral vestibular disorder; vertical nystagmus suggests a central disorder); decreased neck range of motion; decreased hearing; abnormal Hallpike maneuver; abnormal vestibular testing	Drug toxicity; previous infections, tumor (eg, acoustic neuroma); previous surgery; vascular (eg, brainstem infarct); benign positional vertigo; Ménière disease	Avoid toxic drugs and long-term vestibular suppressants; remove earwax; vestibular rehabilitation; surgery
Peripheral nerves	Worse in dark or on uneven surfaces or inclines	Decreased neck range of motion; signs of radiculopathy or myelopathy; clumsiness with fine motor tasks; mild spastic gait; increased tone	Spondylosis; degenerative or inflammatory arthritis	Treatment of underlying disease; cervical or balance exercises; appropriate assistive device; consider surgery in selected cases
Cerebral hypoperfusion	Presyncope; near fainting	Postural hypotension; signs of underlying disease	See causes for syncope in Chapter 51; cardiovascular and pulmonary diseases; anemia	Treatment of underlying disease
Postprandial hypotension	Symptoms within 1 h of eating	Hypotension after meals	Postprandial hypotension	Small meals; avoid exertion after meals; avoid hypotensive drugs near meals; have caffeine with meals
Postural hypotension	Near fainting—worse when getting up, walking, exercising; complaints consistent with predisposing diseases; may be asymptomatic; history of predisposing drugs	Blood pressure and heart rate; signs of predisposing diseases	Drugs, volume/salt depletion; deconditioning; Parkinson syndrome; diabetes; autonomic dysfunction	Treatment of salt and water repletion; reconditioning exercises; ankle pumps or hand clenching; slow rising; elevate head of bed; graduated stockings; lowest effective dosage of essential contributing drugs
Cardiac dysfunction	Variable, depending on specific etiology	Cardiac auscultation, ECG, echocardiography	Cardiac arrhythmias, valvular lesions, myocardial ischemia, myxoma, hypertrophic cardiomyopathy	Variable, depending on specific etiology
Brain stem	Any sensation (eg, vertigo, near fainting,	Findings may be transient or fixed; ataxia	Transient ischemic attack; brain stem	Low-dose aspirin; assistive device if ataxic

	wooziness); transient neurologic symptoms (eg, slurred speech, visual change, one-sided weakness); symptoms on looking up		infarct; vertebrobasilar insufficiency	
Metabolic diseases	Symptoms of underlying disease	Signs of underlying disease	Any metabolic disease, (eg, thyroid disorders, diabetes)	Treatment of underlying disease
Medications Past	Vestibulocochlear symptoms (see above)	See above under vestibulocochlear system	See above under vestibulocochlear system	See above under vestibulocochlear system
Current	Confusion; fatigue; weakness; dizziness often vague, may be constant	May have postural hypotension	Specific: nitrates, β-blockers, antidepressants, antipsychotics, anticholinergics; vestibular depressants, benzodiazepines, others General: total number and dose of all drugs	Eliminate, substitute, or reduce specific offending drugs if possible; reduce all other drugs to lowest effective dose possible; remember over-the-counter drugs
Depression, anxiety	Constant dizziness; multiple somatic complaints; poor concentration; positive results on anxiety or depression screening; vegetative complaints (sleep, appetite)	See Chapter 71	Depression, anxiety	Thorough consideration of risks and benefits of antidepressant drug; counseling

Adapted from Beers MH, Berkow R, eds. The Merck Manual of Geriatrics. 3rd ed. Whitehouse Station, NJ: Merck Research Laboratories; 2000:181. *Copyright 2000 by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.*

History

Patients should be asked to describe the feelings of dizziness in their own words, supplemented by directed questions. Older patients often describe a vague sensation, such as “whirling,” or “giddiness,” or a combination of sensations. Before physicians ask leading questions, patients should be encouraged to describe symptoms in their own words. In one retrospective chart review study of 310 older patients, charts documenting patients’ dizziness symptoms in their own words were more likely to have a clinical diagnosis, compared to charts without such documentation. Narrowing the differential diagnosis can often occur following a careful history. Determining whether the attacks are episodic or continuous may help in identifying a specific disease. For example, patients with Ménière disease or BPPV will usually have episodic dizziness, the latter precipitated by specific movements, while psychogenic dizziness is usually continuous. Frequency and duration of dizziness also should be determined. Episodic dizziness lasting less than 1 minute suggests BPPV, episodes lasting 5 to 120 minutes suggest TIA or migraine, while episodes longer than 120 minutes suggest Ménière disease or recurrent vestibulopathy. One should also ask about any precipitating factors of dizziness, such as missing a meal, drinking alcohol, taking a medication, standing from a lying position, rolling over in bed, changing the position of the head or neck (such as looking up or from side to side), bending forward to pick something up, micturition, or defecation. Any relationship between the onset of dizziness and meals should be sought, because postprandial hypotension is common, especially in frail older persons. The patient should also be asked about any symptoms associated with dizziness. For example, patients with Ménière disease often will complain of tinnitus, fullness in ear, and fluctuating hearing loss. Patients with vertebrobasilar involvement may complain of double vision, dysarthria, or sudden blackouts. Patients with cervical arthritis may also complain of associated neck pain on movement. The clinician should also ask about comorbid conditions, such as anemia, cardiac diseases, or diabetes which may contribute to dizziness. One should look for symptoms suggestive of depression or anxiety disorders; use of screening instruments can be helpful. Finally, all medications, including over-the-counter, should be reviewed as

potential contributors to dizziness.

Physical Examination

The clinician should do a focused physical examination (see **Table 50-1**), keeping in mind the complex pathophysiology and broad differential diagnosis of dizziness. The examiner should look for spontaneous nystagmus on cranial nerve testing. The nystagmus is vertical in central lesions and horizontal or rotatory in peripheral lesions. The nystagmus of central lesions is not suppressed by visual fixation; in peripheral lesions, nystagmus can be suppressed by visual fixation. One should also test for near and distant vision. The ear examination should include both a hearing test (Whisper test or audioscope) and an otoscopic examination to rule out cerumen impaction or structural abnormalities. Blood pressure and heart rate should be assessed upright after at least 5 minutes of lying quietly to rule out orthostatic hypotension. One should examine the neck for local tenderness and restriction in the range of movement, which can result from cervical arthritis. One should also consider that the patient might voluntarily restrict the range of neck movement in order to minimize dizziness secondary to vestibular dysfunction; such patients may respond well to vestibular rehabilitation.

A neurologic examination should include cranial nerves, the motor and sensory systems, and gait and balance. In the cranial nerve examination, one should look for diplopia, dysarthria, or facial paresthesia to rule out vertebrobasilar involvement. An absence of corneal reflex suggests acoustic neuroma, especially if accompanied by unilateral hearing loss, tinnitus, and cerebellar signs. The presence of cogwheel rigidity and bradykinesia is suggestive of parkinsonism. Although most of the abnormalities detected in the balance examination are not specific, the presence of a positive Romberg sign with the eyes closed is suggestive of an abnormality of proprioception and/or the vestibular system. A wide-based stance, a worsening of the gait with the eyes closed, and an improvement in gait with minimal handheld assistance of the examiner, in combination, suggest a proprioceptive deficit.

In addition to the history and physical examination, clinicians can also perform certain provocative tests at the bedside or in the office which may help in detecting abnormalities of the vestibular system.

Provocative Tests

These tests include the Dix-Hallpike maneuver, head thrust, postheadshake, and stepping tests. The Dix-Hallpike test establishes the diagnosis of BPPV (**Figure 50-1**). In this test, the patient is asked to sit on an examination table with the head rotated 45 degrees to one side. The patient is then asked to fix his/her vision upon the examiner's forehead. The examiner, while holding the patient's head firmly in the same position, moves the patient from a seated to a supine position with the head hanging below the edge of the table. If the ipsilateral ear is affected then this maneuver will result in vertigo and nystagmus. If present, the direction, latency, and duration of nystagmus, and duration of vertigo should be noted. The diagnostic criteria for BPPV are (1) vertigo accompanied by a rotatory nystagmus; (2) a latency of 1 to 5 seconds between the completion of the maneuver and the onset of vertigo and nystagmus; (3) paroxysmal nature of the vertigo and nystagmus (lasting for 10–20 seconds); and (4) fatigability, that is, a decrease in the intensity of the vertigo and nystagmus with repeated testing. In a US emergency department study, the authors reported that Dix-Hallpike test is underused to rule out BPPV in patients presenting with complain of dizziness.

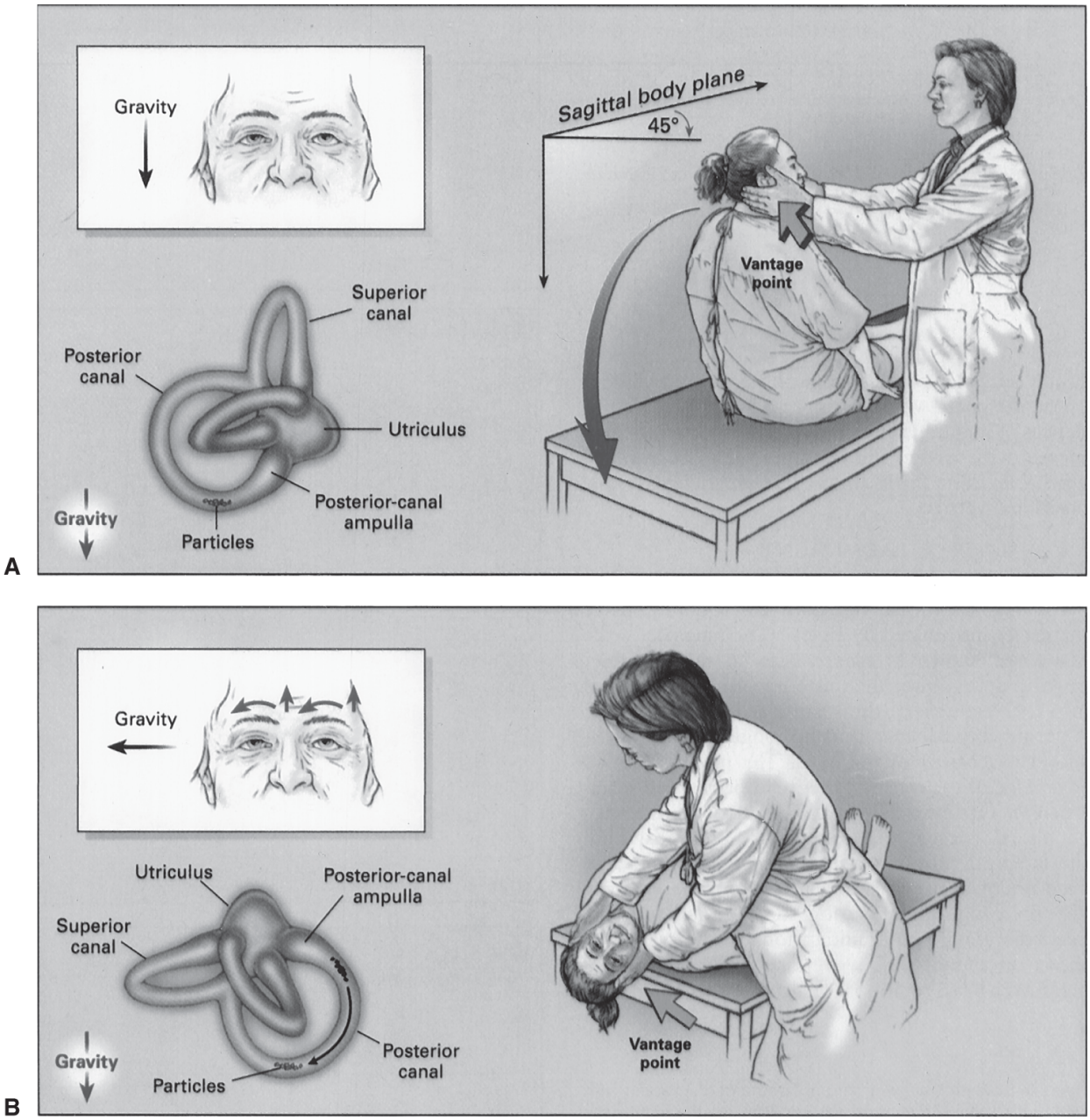


FIGURE 50-1. Dix-Hallpike test. (From Furman JM, Cass SP. Benign paroxysmal positional vertigo. *N Engl J Med*. 1999;341:1590. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

The head thrust and postheadshake tests can help in determining if the vestibuloocular reflex (VOR) is intact. The VOR helps maintain visual stability during head movement. It functions according to the information relayed by the vestibular nucleus to the sixth cranial nerve nucleus in the pons, as well as to the third and fourth cranial nerve nuclei in the midbrain through the median longitudinal fasciculus. The head thrust test requires the patient to fix vision on the examiner's nose, while the head is quickly turned approximately 10 degrees to the left or right. If the VOR is intact, the eyes will stay fixed to the target. But in patients with a vestibular defect, the eyes move with the head away from the target before a corrective saccade back to it. For instance, head thrusts to the left in patients with left-sided vestibular lesions will cause a slipping away of the pupils from the target, followed by a corrective movement; head thrusts to the right will produce a normal visual response.

Using Frenzel lenses to eliminate fixation of vision, the postheadshake test calls for the head to be rotated for approximately 10 seconds, either passively by the examiner or actively by the patient at a frequency of approximately 2 Hz in the horizontal plane, after which the examiner checks for nystagmus. If there is a unilateral peripheral vestibular lesion, a horizontal nystagmus will result; the fast phase will usually beat away from the side of the lesion. With central lesions, the nystagmus may be vertical.

Unterberger originally introduced the stepping test, later modified by Fukuda. A positive stepping test suggests a

lesion in the vestibular or vestibulospinal system. In this test, the patient stands at the center of a circle that is divided into sections, with lines intersecting at 30-degree angles. Blindfolded, the patient is asked to stretch out both arms at 90 degrees to the body and then to flex and raise high one knee and then the other, and to continue stepping in place at a normal walking speed for a total of 50 or 100 steps. The blindfolded patient marches and the examiner watches for deviation from the straight line. If there is a unilateral vestibular lesion or acoustic neuroma, a gradual rotation of the body (more than 30 degrees) toward the affected side will occur.

These tests are more useful in detecting unilateral than bilateral vestibular dysfunction. Upon finding any abnormalities, one can proceed with specialized vestibular function, tests such as ENG and the rotational chair test, described under "Laboratory Tests." Clinicians must be aware that compensatory mechanisms may mask a vestibular deficit when these tests are used in patients with long-standing vestibular loss. There are no data addressing the specificity or sensitivity of these tests in older persons.

Laboratory Tests

There is no standardized approach for laboratory testing for patients with chronic dizziness. However, a modest baseline battery of tests should be done in all older persons with chronic dizziness to rule out common modifiable contributors to dizziness. Thus, a hematocrit, basic metabolic panel, thyroid function tests, and vitamin B_{12} levels should be done in all patients to rule out anemia, diabetes, azotemia, hypothyroidism, and vitamin B_{12} deficiency.

Further testing should be tailored to the situation. Audiometry should be done in patients with a history of fluctuating or gradual hearing loss. An audiogram will reveal sensorineural loss in both Ménière disease and acoustic neuroma; the hearing loss will be greater in lower frequencies in Ménière disease and in higher frequencies in acoustic neuroma, often unilaterally. Presbycusis usually results in bilateral high-frequency hearing loss. An electrocardiogram is indicated if there is a suspicion of myocardial infarction or cardiac arrhythmia. Holter or event monitoring or tilt table testing is indicated only in selected patients with unexplained syncope (see Chapter 51).

In patients with a suspicion of cervical osteoarthritis, imaging of the cervical spine can be considered, but the frequency of false positives is great. Neuroimaging is needed when a stroke or cerebellopontine tumor is suspected. Magnetic resonance imaging (MRI) is preferred over computed tomography scans because of its greater sensitivity, particularly for lesions in the brain stem. Routine MRI is unlikely to reveal specific causes of dizziness. In one study of MRI in patients with dizziness, there were no significant differences in structural abnormalities found in the brain or neck in patients with and without dizziness. Doppler studies or a magnetic resonance angiogram (MRA) may be needed to detect vertebrobasilar insufficiency.

Abnormalities of the peripheral vestibular system can be evaluated by performing special tests, such as ENG including caloric testing, a rotational chair test, and computerized posturography. These tests can help confirm history and physical examination data. However, abnormalities are common in older persons without dizziness, so a positive test is often neither specific nor diagnostic.

In ENG, movements of the eyes (nystagmus) are recorded in the form of tracings with the help of electrodes placed around the eyes. These electrodes record changes in scalp potential produced by the corneal-retinal potential in response to visual and vestibular stimuli, which can be either spontaneous or provoked by caloric stimuli of warm and cold water in the external ear canal. In caloric testing, each ear is stimulated first with warm (111°F [44°C]) and then with cold water (86°F [30°C]), each instilled over 30 seconds. When vestibular function is normal, the temperature change will result in nystagmus, but there will be decreased or no response in an ear on the side of peripheral vestibular disorder. The caloric test assesses the symmetry of vestibular function, and is useful in detecting unilateral vestibular lesions. However, patients with bilateral vestibular loss or patients in whom caloric testing cannot be performed should undergo rotational chair testing.

A rotational chair test, in addition to quantifying the extent of lesions in patients with bilateral peripheral vestibular loss, also helps reveal the degree of peripheral or central vestibular dysfunction. In this test, the patient is seated on a chair in a dark room, and eye movements are recorded when the chair is rotated at different frequencies.

Computerized posturography evaluates the ability of the patient to maintain balance in response to individual or combinations of visual, vestibular, or proprioceptive stimuli while standing on a platform that can be perturbed in three dimensions. This test may be helpful in providing additional confirmatory data when there is a suspicion of peripheral vestibular pathology, but ENG and rotational chair testing are equivocal. In addition, computerized posturography may be the only positive test in the case of central vestibular and extravestibular CNS pathology. Posturography also may be helpful in determining which patients with dizziness are likely to benefit from vestibular rehabilitation.

MANAGEMENT

Clinicians often feel frustrated in managing patients with dizziness. As discussed in the previous section, the goal should be to identify and treat modifiable factors either causing (single condition causing) or contributing to (multiple conditions contributing) dizziness. In many patients with chronic dizziness, a single specific diagnosis may be elusive in the presence of multiple factors contributing to dizziness. In these patients, instead of focusing on a single diagnosis-oriented approach, one should try to identify and treat as many of these contributing or causative factors as possible, recognizing that some may not be modifiable. The result of such an approach usually is a decrease in the disability associated with dizziness.

Systemic disorders such as anemia, metabolic derangements, vitamin B_{12} deficiency, and thyroid abnormalities should be corrected. Correction of vision and hearing deficits is very important. Anxiety and depression should be treated, recognizing the dilemma that most antidepressants also cause dizziness. Medications potentially contributing to dizziness, including over-the-counter medicines, should be identified and either withdrawn or reduced. Stopping a potentially offending medication is preferable to adding new ones.

Pharmacologic Therapy

Drugs commonly used as vestibular suppressants include antihistamines (eg, meclizine), anticholinergic agents (eg, scopolamine), and benzodiazepines (eg, diazepam). Vestibular suppressants are more effective when used for acute episodes of dizziness than for chronic dizziness. Many vestibular suppressants themselves may cause dizziness. Scopolamine should not be used in older persons because of its anticholinergic side effects. Meclizine, a weak antihistaminic agent, is usually given in doses of 12.5 to 25 mg up to three times daily, as needed. These medications should be used only temporarily, as their prolonged use may compromise central and peripheral adaptation, and thus, paradoxically, prolong the dizziness. Benzodiazepines may at times be indicated as a long-term vestibular suppressant in persons with severe unilateral lesions who are not surgical candidates. In one study, selective serotonin reuptake inhibitors were found to be effective in treating chronic dizziness associated with anxiety.

Vestibular Rehabilitation

Vestibular rehabilitation can play an important role in managing patients with peripheral or central vestibular causes of dizziness by enhancing the adaptation of the vestibular system. Vestibular rehabilitation has been shown to improve symptoms, postural instability, and dizziness-related handicap in patients with chronic dizziness. Vestibular rehabilitation consists of exercises combining movements of eyes, head, and body designed to stimulate the vestibular system. At first, these exercises may worsen the dizziness, but with continued practice and gradual increase in the frequency, these exercises can improve dizziness, probably through central adaptation and habituation. These exercises also may help patients alleviate anxiety and fears in performing various activities. Improvement is usually seen after 6 to 8 weeks of vestibular rehabilitation. Patients should perform these exercises initially under the supervision of a trained specialist, such as a physical therapist, and later independently at home.

In patients with cervical dizziness, physical therapy can substantially decrease the frequency and severity of dizziness and neck pain, and can improve postural stability. Some patients may benefit from cervical collars or cervical traction.

Patients suffering from BPPV can be treated by performing one of four bedside maneuvers: Epley canalith repositioning procedure, Brandt and Daroff exercises, Semont maneuver, and Li maneuver. Epley canalith repositioning procedure (**Figure 50-2**) is performed to move free-floating particles from the posterior semicircular canal into the utricle of the labyrinth by the effects of gravity, thereby eliminating turbulence and fluctuation of the endolymphatic pressure in the semicircular canals. In this five-position procedure, the patient is asked to sit on a table and a vibrator is applied to the ipsilateral mastoid process. Next, the patient is made to lie down supine on the examining table with the head rotated 45 degrees toward the affected ear and hanging below the edge of the table, similar to the Dix-Hallpike test. This position will induce vertigo. Once the vertigo subsides, the head is rotated 45 degrees to the opposite side, which may induce vertigo again. Then the head and body are rotated further in the same direction until the head is facing downward. Subsequently, while holding the head in the same position, the patient sits up. Finally, the head is turned forward with the chin down by about 20 degrees. The examiner holds the head in each of these positions for approximately 10 to 15 seconds or until the vertigo subsides. The patient should be told not to lie flat for the next 24 to 48 hours. Alternatively, a cervical collar can be used to prevent loose particles from sliding back

to the posterior semicircular canals. There are no data to support these recommendations. These maneuvers can be performed without using the vibrator, although the results are said to be not as good. This maneuver can be repeated at weekly intervals until vertigo ceases and the Dix-Hallpike test is negative.

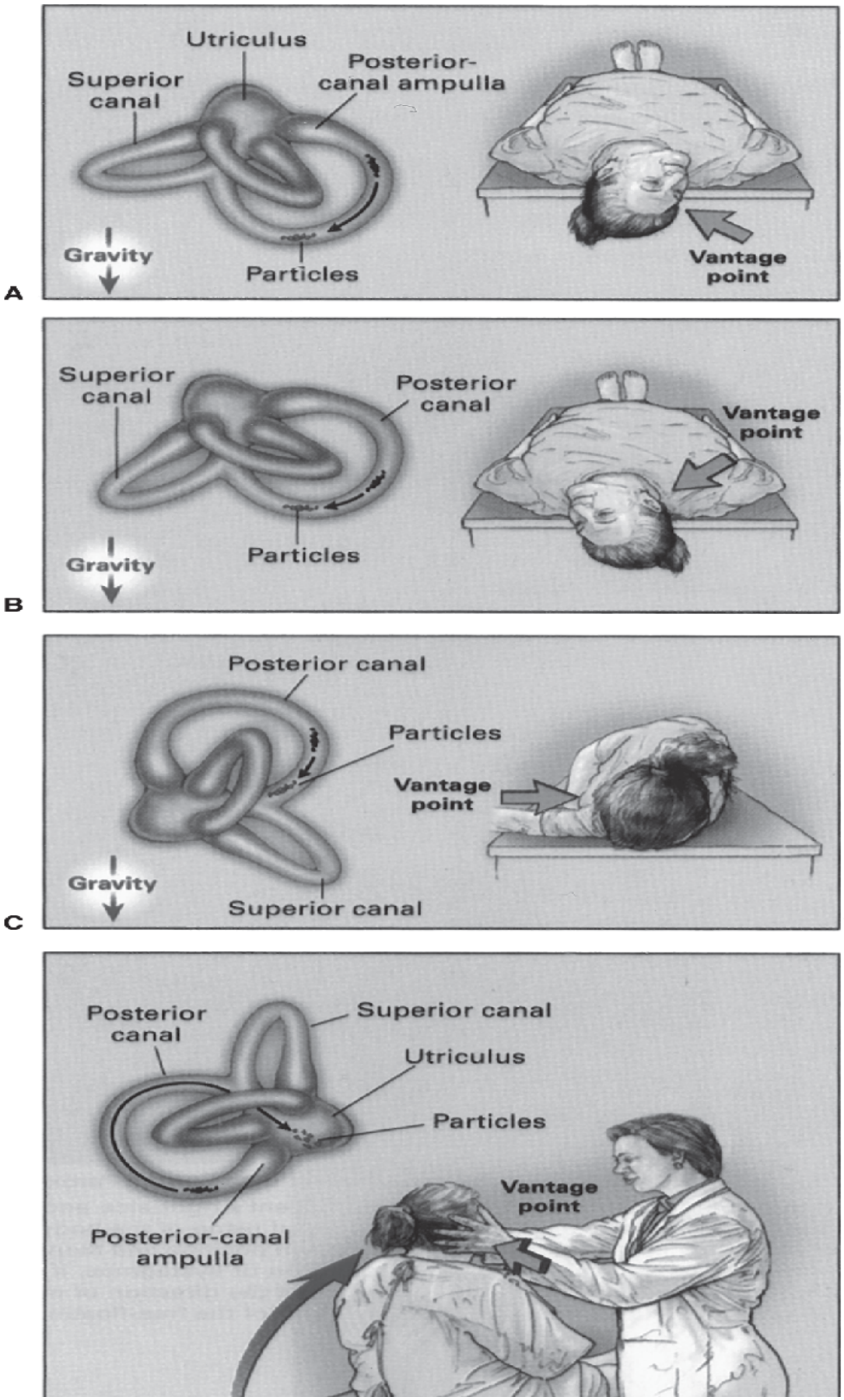




FIGURE 50-2. Epley canalith repositioning procedure. (From Furman JM, Cass SP. Benign paroxysmal positional vertigo. *N Engl J Med*. 1999;341:1590. Copyright © 1999 Massachusetts Medical Society. All rights reserved.)

Brandt and Daroff exercises can be used in patients who cannot keep their heads upright for 24 to 48 hours, as recommended in Epley maneuver. The patient can do the exercises at home without the presence of a supervising health professional. These exercises probably work by habituation. The patient is asked to sit on the edge of the bed with eyes closed and to rotate the head horizontally by approximately 45 degrees. The patient then lies down on the side opposite to the direction of head rotation and waits for at least 30 seconds or until the vertigo has resolved. The movement is then repeated in the opposite direction. Patients can repeat these exercises every 3 hours; exercises can be stopped 2 to 3 days after symptoms abate. Improvement usually occurs after 1 to 2 weeks of exercises.

In Semont maneuver, the patient sits on the edge of the treatment table. The clinician rapidly moves the patient to lying on the involved side with the head rotated 45 degrees toward the uninvolved side. While maintaining the head-on-trunk position, the clinician swings the patient from lying on the involved side to lying on the uninvolved side. The head then is gently tapped on the treatment table. Each position is maintained for 1.5 minutes. The procedure is repeated three times. In a double-blind randomized trial, the authors concluded that Semont maneuver is easy and safe to use in the treatment of posterior semicircular canal BPPV.

Li repositioning maneuvers consist of three different series of movements that have been developed to manage BPPV of posterior, anterior, or horizontal semicircular canals.

There is also a device called DizzyFIX, which is approved by US Food and Drug Administration for treatment at home by patients suffering from posterior semicircular canal BPPV. This device is a visual representation of semicircular canals and is worn on the head. This device guides the patient in performing particle repositioning maneuvers and provides visual feedback during the maneuver.

Surgery

Surgery is reserved for a small group of patients who fail pharmacologic or vestibular rehabilitation, or who have cerebellopontine angle tumors. Patients with uncontrolled Ménière disease can have a transmastoid labyrinthectomy, or partial vestibular neurectomy, or endolymphatic sac decompression. Very rarely, patients with benign paroxysmal positional vertigo who do not respond to repeated canalith repositioning procedures may benefit from disabling of the semicircular canal either by singular neurectomy or by occluding the posterior semicircular canal.

PATIENT EDUCATION

Patient education plays a very important role in the management of chronic dizziness. Understanding the basic pathophysiology of dizziness often alleviates associated anxiety. Education also helps patients to modify activities appropriately, thus encouraging patients to cope actively with their dizziness. While most patients need to be advised to be more active, some should be told to avoid looking up or bending down if these motions precipitate cervical dizziness attacks. Home modifications to reduce neck extension can include storing commonly used items on lower shelves. When orthostatic hypotension is present, patients should be instructed to rise slowly from a supine or sitting position. They should also flex their hands and feet a few times before standing and should never try to walk while feeling dizzy. They should avoid over-the-counter medications, such as sleeping pills and cold and allergy medicine, and should keep well hydrated.

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Chapter 51

Syncope

R. A. Kenny, Conal Cunningham

Learning Objectives

- Understand the presentation of syncope and that syncope can mimic falls.
- Describe the common subtypes and differential diagnosis of syncope.
- Discuss risk stratification and how risk stratification drives management.
- Detail pathophysiology of common syncope subtypes in older patients and their management.
- Discuss the challenges for recognition and management of syncope in the oldest old such as frailty, unwitnessed events, medications, and cognitive impairment.

Key Clinical Points

1. **Syncope is a common symptom throughout life; however, presentation is more frequent as people age and in the context of comorbidity and multiple medications.**
2. **Cardiac causes of syncope become more common with advanced aging.**
3. **Etiology in the older patient is often multifactorial.**
4. **Presentation in the older patient may result in patients presenting with falls rather than transient loss of consciousness (T-LOC).**
5. **Age-related physiologic changes including altered baroreflex sensitivity may result in coexistent supine hypertension coupled with hypotensive syndromes.**
6. **The prevalence of hypotensive and bradyarrhythmic syndromes increases due to age-related physiologic changes and/or cardiovascular medications.**
7. **Modification of cardiovascular and psychotropic medications is often needed to address syncope in older patients.**
8. **Additional challenges in the older patient include frailty, unwitnessed events, polypharmacy, cognitive impairment, and coexistence of multiple causes of syncope.**

DEFINITION

Syncope is a transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion, and is characterized by rapid onset, short duration, and spontaneous complete recovery. T-LOC is a term that encompasses all disorders characterized by self-limited loss of consciousness, irrespective of mechanism. By including the mechanism of unconsciousness, that is transient global cerebral hypoperfusion, the current syncope definition excludes other causes of T-LOC such as epileptic seizures and concussion as well as certain common syncope mimics such as psychogenic pseudosyncope.

EPIDEMIOLOGY

Syncope is a common symptom, experienced by up to 30% of healthy adults at least once in their lifetime. Syncope accounts for 3% of emergency department visits and 1% of medical admissions to a general hospital. Syncope is the seventh most common reason for emergency admission of patients over 65 years. The cumulative incidence of syncope in long-term care facilites is close to 23% over a 10-year period with an annual incidence of 6% and recurrence rate of 30%, over 2 years. The age of first faint, a commonly used term for syncope, is less than 25 years in 60% of persons, but 10% to 15% of individuals have their first faint after age 65.

Syncope due to a cardiac cause is associated with higher mortality rates irrespective of age. In patients with a noncardiac or unknown cause of syncope, older age, a history of congestive cardiac failure, and male sex are important prognostic factors of mortality. It remains undetermined whether syncope is directly associated with mortality or is merely a marker of more severe underlying disease. **Figure 51-1** details the age-related difference in prevalence of benign vasovagal syncope compared to other causes of syncope.

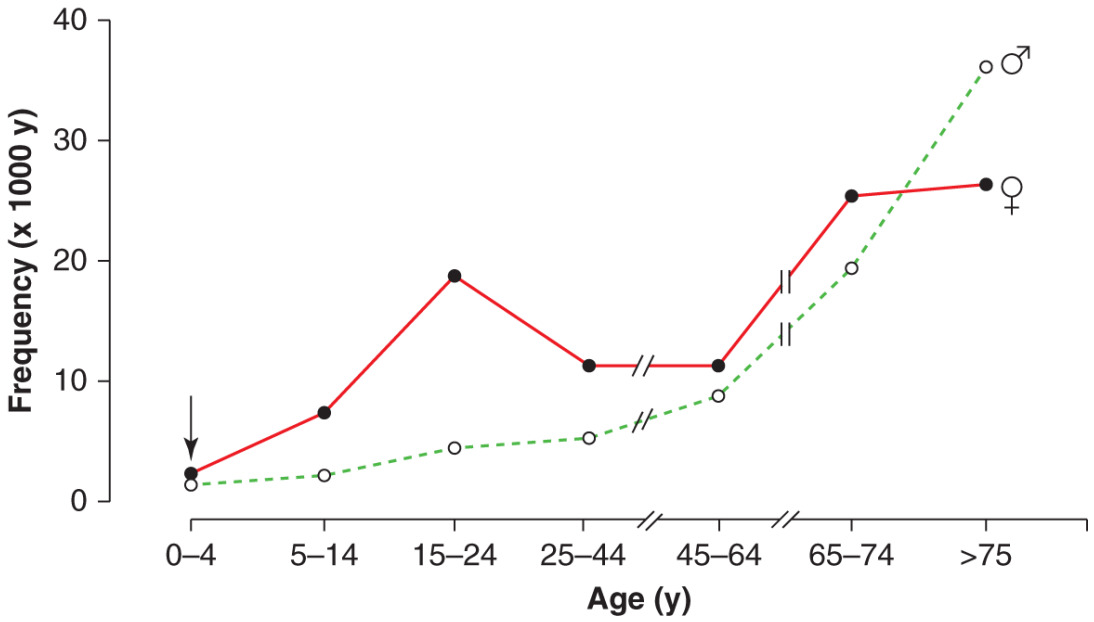


FIGURE 51-1. Frequency of the complaint fainting as reason for encounter in general practice in the Netherlands. Data are obtained from the general practitioners' transition project. It concerns an analysis of 93,297 patient-years. The arrow around 1 year is to indicate that a small peak occurs between 6-18 months. (From Wieling W, Ganzeboom KS, Krediet CT, Grundmeijer HG, Wilde AA, van Dijk JG. Initial diagnostic strategy in the case of transient losses of consciousness: the importance of the medical history. *Nederlands tijdschrift voor geneeskunde*. 2003;147(18):849–854.)

The Irish Longitudinal Study on Ageing (TILDA [www.tilda.ie]) is a population-based study of adults 50 years and over that incorporated questions on syncope and falls in addition to a broad spectrum of health, social and economic questions. A number of community-dwelling adults, mean age 62, range 50 to 106 years, were asked whether they experienced fainting in their youth, throughout their life, or over the past 12 months. A total of 23.6% had one or more episodes in the previous 12 months of which 4.4% were syncope and 19.2% were falls (**Table 51-1**). Although the prevalence of syncope rose with age, the increase in falls was much more remarkable, in particular the increase in nonaccidental or unexplained falls was most striking. Unwitnessed syncope most commonly presents as nonaccidental or unexplained falls, supporting the rising prevalence of atypical syncope wth advancing years.

TABLE 51-1 PREVALENCE OF SYNCOPE AND FALLS IN A POPULATION STUDY (*n* = 8572)—THE IRISH LONGITUDINAL STUDY OF AGEING (TILDA)

PREVIOUS YEAR %	50–64 Y	65–74 Y	75+ Y	TOTAL
Syncope	4.1	4.7	4.8	4.4
Falls	17.5	19.5	24.4	19.2
Nonaccidental/unexplained falls	7.6	9.4	11.6	8.9

The General Practitioners' Transition Project in the Netherlands demonstrated that the age distribution of patients presenting to their general practioner with syncope shows a peak in females at 15 years and a second peak in older patients (see **Figure 51-1**). The Framingham Offspring study similarly demonstrates a bimodal peak of first syncope in mid-teens and the second occurring over 70 years.

The true prevalence of syncope is underestimated due to the pheonomen of amnesia for T-LOC. Amnesia has been reported in patients with vasovagal syncope (VVS) and carotid sinus syndrome (CSS), but is likely to be present in all causes of syncope. The overlap between syncope and falls also leads to underreporting.

PATHOPHYSIOLOGY

The temporary cessation of cerebral function that causes syncope results from transient and sudden reduction of blood flow to parts of the brain (brainstem reticular activating system) responsible for consciousness. The predisposition to vasovagal syncope starts early and lasts for decades. Other causes of syncope are uncommon in young adults, but much more common as people age.

Regardless of the etiology, the underlying mechanism responsible for syncope is a drop in cerebral oxygen delivery below the threshold for consciousness. Cerebral oxygen delivery, in turn, depends on both cerebral blood flow and oxygen content. Any combination of chronic or acute processes that lowers cerebral oxygen delivery below the "consciousness" threshold may cause syncope. Age-related physiologic impairments in heart rate (HR), blood pressure (BP), cerebral blood flow, and blood volume control, in combination with comorbid conditions and concurrent medications account for the increased incidence of syncope in the older person. Blunted baroreflex sensitivity manifests as a reduction in the heart rate response to hypotensive stimuli. Older adults are prone to reduced blood volume due to excessive salt wasting by the kidneys as a result of a decline in plasma renin and aldosterone, a rise in atrial natriuretic peptide and concurrent diuretic therapy. Low blood volume together with age-related diastolic dysfunction, leading to low cardiac output coupled with inadequate heart rate responses to stress, increases susceptibility to orthostatic hypotension (OH) and VVS. Cerebral autoregulation which maintains a constant cerebral circulation over a wide range of blood pressure changes is altered in the presence of hypertension and possibly by aging—the latter is still controversial. In general it is agreed that sudden mild to moderate declines in blood pressure can markedly affect cerebral blood flow and render an older person particularly susceptible to presyncope and syncope. Syncope may thus result either from a single process that markedly and abruptly decreases cerebral oxygen delivery or from the accumulated effect of multiple processes, each of which contributes to reduced oxygen delivery.

Causes of Syncope in Older People

Reflex syncope and OH are the most frequent causes of syncope in all age groups and clinical settings and responsible for the majority of episodes in younger patients. However, cardiac causes of syncope, structural and arrhythmic, become more common in older patients and are responsible for one-third of syncope in patients attending the emergency room and chest pain unit. The prevalence of unexplained syncope varies according to diagnostic facilities and age from 9% to 41%. In the older patient, history may be less reliable and multiple causes of syncope may also be present (**Table 51-2**). Multimorbidity and polypharmacy are more common in older patients with syncope and can add to the complexity of identifying an attributable cause of events (**Tables 51-2** and **51-3**).

TABLE 51-2 CAUSES OF SYNCOPE

Reflex syncopal syndromes

- Vasovagal faint (common faint)
- Carotid sinus syncope
- Situational faint
  - Acute hemorrhage
  - Cough, sneeze
  - Gastrointestinal stimulation (swallow, defecation, visceral pain)
  - Micturition (postmicturition)
  - Postexercise

Pain, anxiety

- Glossopharyngeal and trigeminal neuralgia

Orthostatic

- Aging
- Antihypertensives
- Autonomic failure

  Primary autonomic failure syndromes (eg, pure autonomic failure, multiple system atrophy, Parkinson disease with autonomic failure)

  Secondary autonomic failure syndromes (eg, diabetic neuropathy, amyloid neuropathy)
- Medications (see **Table 51-3**)
- Volume depletion

  Hemorrhage, diarrhea, Addison disease, diuretics, febrile illness, hot weather

Cardiac arrhythmias

- Sinus node dysfunction (including bradycardia/tachycardia syndrome)
- Atrioventricular conduction system disease
- Paroxysmal supraventricular and ventricular tachycardias
- Implanted device (pacemaker, ICD) malfunction
- Drug-induced proarrhythmias

Structural cardiac or cardiopulmonary disease

- Cardiac valvular disease
- Acute myocardial infarction/ischemia
- Obstructive cardiomyopathy
- Atrial myxoma
- Acute aortic dissection
- Pericardial disease/tamponade
- Pulmonary embolus/pulmonary hypertension

Cerebrovascular

- Vascular steal syndromes

Multifactorial

TABLE 51-3 DRUGS THAT CAN CAUSE OR CONTRIBUTE TO SYNCOPE

DRUG	MECHANISM
Diuretics	Volume depletion
Vasodilators Angiotensin-converting enzyme inhibitors Calcium channel blockers Hydralazine Nitrates α-Adrenergic blockers Prazosin	Reduction in systemic vascular resistance and venodilation
Other antihypertensive drugs α-Methyldopa Clonidine	Centrally acting antihypertensives

Guanethidine Hexamethonium Labetalol Mecamylamine Phenoxybenzamine β-Blockers	
Drugs associated with torsades de pointes Amiodarone Disopyramide Encainide Flecainide Quinidine Procainamide Sotalol	Ventricular tachycardia associated with a prolonged QT interval
Digoxin	Cardiac arrhythmias
Psychoactive drugs Tricyclic antidepressants Phenothiazines Monamine oxidase inhibitors Barbiturates	Central nervous effects causing hypotension; cardiac arrhythmias
Alcohol	Central nervous system effects causing hypotension; cardiac arrhythmias

Multifactorial Etiology

Previously up to 40% of patients with recurrent syncope remained undiagnosed despite extensive investigations, particularly among older patients who have limited cognitive impairment and for whom a witnessed account of events is often unavailable. More recently, diagnostic yield for all ages has improved with application of clinical guidelines. The high frequency of unidentified causes in clinical studies may occur because patients failed to recall important diagnostic details, because of the stringent diagnostic criteria used in clinical studies or, probably most often, because the syncopal episode resulted from a combination of chronic and acute factors rather than from a single obvious disease process. Indeed, a multifactorial etiology likely explains the majority of cases of syncope in older persons who are predisposed because of multiple chronic diseases and medication effects superimposed on the age-related physiologic changes described earlier. Common factors that, in combination may predispose to, or precipitate, syncope include anemia, chronic lung disease, congestive heart failure, and dehydration. Medications that may contribute to, or cause, syncope are listed in **Table 51-3**.

Individual Causes of Syncope

Common causes of syncope are listed in **Table 51-2**. The most frequent individual causes of syncope in older patients are neurally mediated syndromes including CSS, orthostatic hypotension, and postprandial hypotension as well as arrhythmias including both tachyarrhythmias and bradyarrhythmias. These disease processes are described in the next section. Disorders that may be confused with syncope and which may, or may not, be associated with loss of consciousness are listed in **Table 51-4**.

TABLE 51-4 DIFFERENTIAL DIAGNOSIS OF SYNCOPE IN THE OLDER PERSON

CONDITIONS WITH LOC/PARTIAL LOC[a]	CONDITIONS WITHOUT LOC
• Epilepsy	• Cataplexy
• Metabolic disorders including hypoglycemia, hypoxia,	• Drop attacks

hyperventilation with hypocapnia • Vertebrobasilar TIA[b]	• Falls • TIA (anterior circulation)
• Intoxication (alcohol, medication overdose—sedatives/analgesics)	

[a]LOC, loss of consciousness.
[b]TIA, transient ischemic attack.

PRESENTATION

Presentation in this age group is challenging, and recognition is often the first step to optimizing management and care of these patients. To start with, syncope in the older patient is underrecognized, particularly in acute care settings because the presentation is frequently atypical. The older patient is less likely to have a warning or prodrome prior to syncope, commonly has amnesia for loss of consciousness, and frequently experiences an unwitnessed event, thus presenting with a fall rather than T-LOC. These events are typically described as nonaccidental (not a trip or slip) or unexplained falls. Therefore, history alone cannot be relied upon when assessing the older patient. Injurious events such as fractures and head injuries are also more common, further emphasizing the importance of thorough early investigations and diagnosis.

The underlying mechanism of syncope is transient cerebral hypoperfusion. In some forms of syncope there may be a premonitory period in which various symptoms (eg, light-headedness, nausea, sweating, weakness, and visual disturbances) offer warning of an impending syncopal event. Often, however, loss of consciousness occurs without warning or recall of warning. Recovery from syncope is usually accompanied by almost immediate restoration of appropriate behavior and orientation. Amnesia for loss of consciousness occurs in many older individuals, especially in those with cognitive impairment. The postrecovery period may be associated with fatigue of varying duration. In young patients, nausea, blurred vision, and sweating predict noncardiac syncope, only dyspnea predits cardiac syncope in older patients.

Syncope and falls are often considered two separate entities with different etiologies. Recent evidence suggests, however, that these conditions may not always be distinctly separate. In older adults, determining whether patients who have fallen have had a syncopal event can be difficult. At least half of syncopal episodes are unwitnessed and older patients may have amnesia for loss of consciousness. Amnesia for loss of consciousness has been observed in 30% of patients with CSS who present with falls and a quarter of all patients with CSS irrespective of presentation. Emerging evidence suggests a high incidence of falls in addition to traditional syncopal symptoms in older patients with sick sinus syndrome and atrioventricular conduction disorders. Thus, syncope and falls may be indistinguishable and may, in some cases, be manifestations of similar pathophysiologic processes.

EVALUATION

The initial step in the evaluation of syncope is to consider whether there is a specific cardiac or neurologic etiology or whether the etiology is likely multifactorial. The starting point for the evaluation of syncope is a careful history and physical examination. A witness account of events is important to ascertain when possible. Three key questions should be addressed during the initial evaluation: (1) Is loss of consciousness attributable to syncope?, (2) Is heart disease present or absent?, and (3) Are there important clinical features in the history and physical examination, which suggest the etiology?

Differentiating true syncope from other “nonsyncopal” conditions associated with real or apparent loss of consciousness is generally the first diagnostic challenge and influences the subsequent diagnostic strategy. A strategy for differentiating true and nonsyncope is outlined in **Figures 51-2 and 51-3**. The presence of heart disease is an independent predictor of a cardiac cause of syncope, with a sensitivity of 95% and a specificity of 45%.

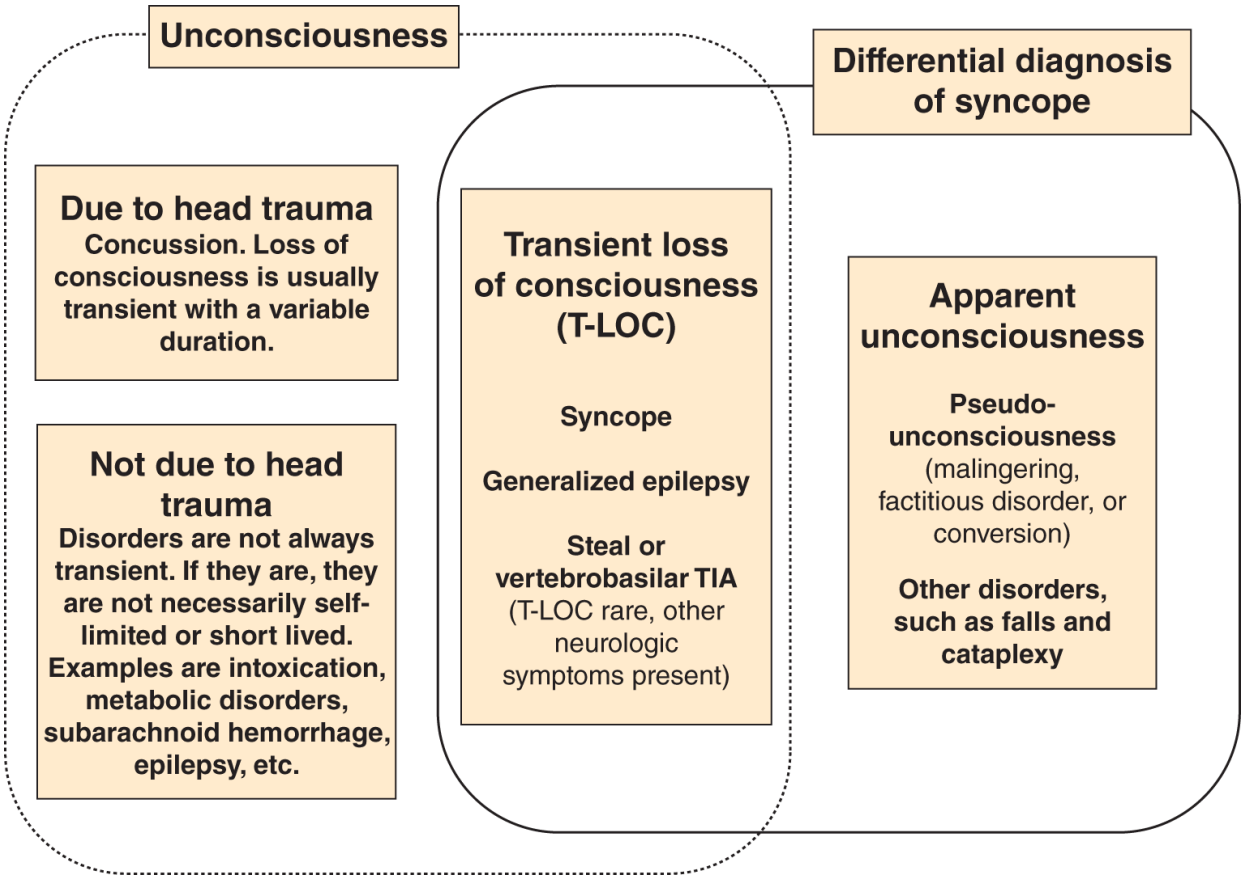


FIGURE 51-2. Syncope in relation to real and apparent loss of consciousness.

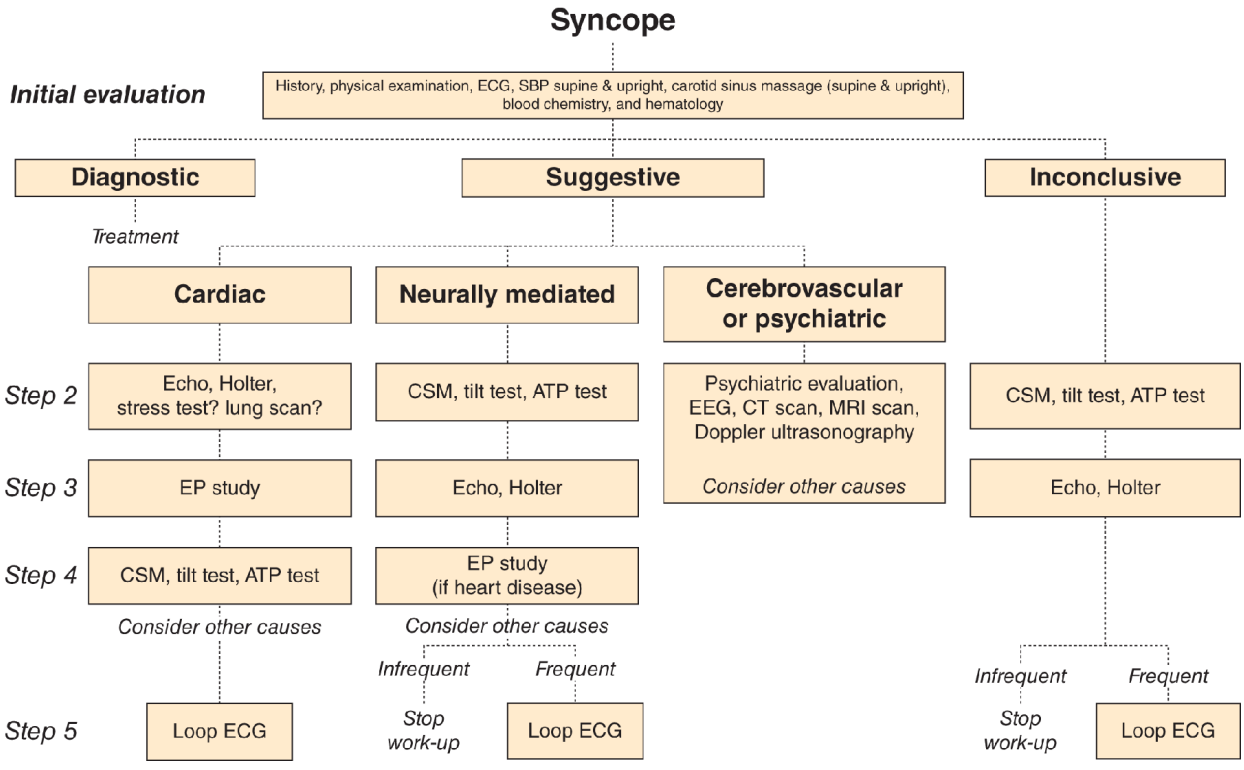


FIGURE 51-3. An approach to the evaluation of syncope for all age groups. ATP test, adenosine provocation test; CSM, carotid sinus massage; CT, computed tomography; Echo, echocardiogram; ECG, electrocardiogram; EEG, electroencephalogram; EP study, electrophysiologic study; MRI, magnetic resonance imaging; SBP, systolic blood pressure.

Patients frequently complain of dizziness alone or as a prodrome to syncope and unexplained falls. Four categories of dizzy symptoms—vertigo, dysequilibrium, light-headedness, and others have been recognized. These symptom

categories have neither the sensitivity nor specificity in older, as in younger, patients. Dizziness, however, may more likely be attributable to a cardiovascular diagnosis if associated with pallor, syncope, prolonged standing, palpitations, or the need to lie down or sit down when symptoms occur.

Initial evaluation may lead to a diagnosis based on symptoms, signs, or electrocardiogram (ECG) findings. Under such circumstances, no further evaluation is needed and treatment, if any, can be planned. More commonly, the initial evaluation leads to a suspected diagnosis (see **Figure 51-3**), which needs to be confirmed by directed testing. If a diagnosis is confirmed by specific testing, treatment may be initiated. On the other hand, if the diagnosis is not confirmed, then patients are considered to have unexplained syncope and should be evaluated following a strategy such as that outlined in **Figure 51-3**. It is important to attribute a diagnosis, if possible, rather than assume that an abnormality known to produce syncope or hypotensive symptoms is the cause. In order to attribute a diagnosis, patients should have symptom reproduction during investigation and preferably alleviation of symptoms with specific intervention. It is not uncommon for more than one predisposing disorder to coexist in older patients, rendering a precise diagnosis difficult. In older persons treatment of possible causes without clear verification of attributable diagnosis may often be the only option.

An important consideration in patients with unexplained syncope is the presence of structural heart disease or an abnormal ECG. These findings are associated with a higher risk of arrhythmias and a higher mortality at 1 year. In these patients, cardiac evaluation consisting of echocardiography, stress testing, and tests for arrhythmia detection such as prolonged electrocardiographic and loop monitoring or electrophysiologic study are recommended. The most alarming ECG sign in a patient with syncope is probably alternating complete left and right bundle branch block, or alternating right bundle branch block with left anterior or posterior fascicular block, suggesting trifascicular conduction system disease and intermittent or impending high-degree atrioventricular (AV) block. Patients with bifascicular block (right bundle branch block plus left anterior or left posterior fascicular block, or left bundle branch block) are also at high risk of developing high-degree AV block. A significant problem in the evaluation of syncope and bifascicular block is the transient nature of high-degree AV block and, therefore, the long periods required to document it by ECG.

In patients without structural heart disease and a normal ECG, evaluation for neurally mediated syncope should be considered. The tests for neurally mediated syncope consist of tilt testing and carotid sinus massage.

The majority of older patients with syncope are likely to have a multifactorial etiology and thus both predisposing and precipitating causes should be sought in the history, examination, and laboratory evaluation, particularly if the initial evaluation does not suggest an obvious single cause.

The presentation, evaluation, and management of other common etiologies of syncope are presented in the following sections. These etiologies may occur as the sole cause of a syncopal episode or as one of multiple contributing causes.

ORTHOSTATIC HYPOTENSION

Pathophysiology

Orthostatic or postural hypotension (OH) is arbitrarily defined as either a 20 mm Hg fall in systolic blood pressure or a 10 mm Hg fall in diastolic blood pressure on assuming an upright posture from a supine position. OH implies abnormal blood pressure homeostasis and is a frequent observation with advancing age. Prevalence of postural hypotension varies between 4% and 33% among community-living older persons depending on the methodology used. Higher prevalence and larger falls in systolic blood pressure have been reported with increasing age and often signify general physical frailty. Prevalence of OH in the older-aged community-dwelling adults is 30% and increases to more than 50% in hospitalized geriatric patients making its diagnosis highly relevant. OH is an important cause of syncope, accounting for 14% of all diagnosed cases in a large series. In a tertiary referral clinic dealing with unexplained syncope, dizziness and falls, 32% of patients over age 65 had orthostatic hypotension as a possible attributable cause of symptoms.

A recent population-based study which employed beat-to-beat measurement of orthostatic blood pressure demonstrated a significant age gradient for abnormalities in orthostatic blood pressure such that in 7% of 50- to 55-year-olds, systolic and diastolic blood pressure failed to stabilize by 2 minutes after standing compared with 41% of those 80 years old and older. Failure of stabilization was associated with falls, depression, and global cognitive impairment.

Aging

The heart rate and blood pressure responses to orthostasis occur in three phases: (1) an initial heart rate rise and blood pressure drop, (2) an early phase of stabilization, and (3) a phase of prolonged stabilization. All three phases are influenced by aging. The maximum rise in heart rate and the ratio between the maximum and the minimum heart rate in the initial phase decline with age, implying a relatively fixed heart rate irrespective of posture. Despite a blunted heart rate response, blood pressure and cardiac output are adequately maintained on standing in active, healthy, well-hydrated, and normotensive older persons because of decreased vasodilatation and reduced venous pooling during the initial phases and increased peripheral vascular resistance after prolonged standing. However, in older persons with hypertension, cardiovascular disease or receiving vasoactive drugs, these circulatory compensatory adjustments to orthostatic stress are disturbed, rendering them vulnerable to develop postural hypotension. More recent research suggests that the velocity of the initial orthostatc heart rate response at 10 and 20 seconds predicts mortality and morbidity.

This age-related gradient may reflect autonomic dysfunction, increased arterial stiffness, and muscle pump defects. Traditionally, OH is defined as a reduction in systolic BP of at least 20 mm Hg or in diastolic BP of at least 10 mm Hg within 3 minutes of standing. Orthostatic intolerance (OI) refers to symptoms and signs with upright posture due to circulatory abnormality. Syndromes of OI that may cause syncope include initial OH where symptoms of light-headedness/dizziness or visual disturbance are experienced seconds after standing; classic OH where dizziness, presyncope, fatigue, weakness, palpitations, visual and hearing disturbances are experienced; delayed OH where there is a prolonged prodrome frequently followed by rapid syncope; delayed OH and reflex syncope where a prolonged prodrome is always followed by syncope; reflex syncope triggered by standing where there is classic prodrome and triggers always followed by syncope; and postural orthostatic tachycardia syndrome where there is symptomatic HR increase and instability of BP without syncope. Many older patients with OH also have postprandial hypotension. Causes of OH include volume depletion or disturbance of the autonomic nervous system resulting in failure in vasoconstrictor compensatory mechanisms induced by upright posture.

Hypertension

Hypertension further increases the risk of hypotension by impairing baroreflex sensitivity and reducing ventricular compliance. Hypertension increases the risk of cerebral ischemia from sudden declines in blood pressure. Older persons with hypertension are more vulnerable to cerebral ischemic symptoms even with modest and short-term postural hypotension, because the threshold for cerebral autoregulation is altered by prolonged elevation of blood pressure. In addition, antihypertensive agents may impair cardiovascular reflexes and further increase the risk of orthostatic hypotension.

Medications

Drugs (see **Table 51-3**) are important causes of OH. Ideally establishing a causal relationship between a drug and OH requires identification of the culprit medicine, abolition of symptoms by withdrawal of the drug, and rechallenge with the drug to reproduce symptoms and signs. Rechallenge is often omitted in clinical practice in view of the potential serious consequences. In the presence of polypharmacy, which is common in the older person, it becomes difficult to identify a single culprit drug because of the synergistic effect of different drugs and drug interactions. Thus all drugs should be considered as possible contributors to orthostasis.

Other Conditions

A number of nonneurogenic conditions are also associated with postural hypotension. These conditions include myocarditis, atrial myxoma, aortic stenosis, constrictive pericarditis, hemorrhage, diarrhea, vomiting, ileostomy, burns, hemodialysis, salt-loosing nephropathy, diabetes insipidus, adrenal insufficiency, fever, and extensive varicose veins. Volume depletion for any reason is often a common sole, or contributing, cause of postural hypotension, and, in turn, syncope.

Primary Autonomic Failure Syndromes

Three distinct clinical entities—namely pure autonomic failure (PAF), multiple system atrophy (MSA) or Shy-Drager syndrome (SDS), and autonomic failure associated with idiopathic Parkinson disease (IPD)—are associated with orthostatic hypotension. PAF, the least common condition and a relatively benign entity, was previously known as

idiopathic orthostatic hypotension. This condition presents with orthostatic hypotension, defective sweating, erectile dysfunction, and bowel disturbances. No other neurologic deficits are evident and resting plasma norepinephrine levels are low. MSA is the most common among these syndromes and has the poorest prognosis. Clinical manifestations include features of dysautonomia and motor disturbances due to striatonigral degeneration, cerebellar atrophy, or pyramidal lesions. Additional neurologic deficits include muscle atrophy, distal sensorimotor neuropathy, pupillary abnormalities, restriction of ocular movements, disturbances in rhythm and control of breathing, life-threatening laryngeal stridor, and bladder disturbances. Psychiatric manifestations and cognitive defects are usually absent. Resting plasma norepinephrine levels are usually within the normal range, but fail to rise on standing or tilting.

The prevalence of orthostatic hypotension in Parkinson disease rises with advancing years and with the number of medications prescribed. Cognitive impairment, in particular abnormal attention and executive function, is more common in Parkinson disease with orthostatic hypotension suggesting a possible causal association with hypotension including watershed hypoperfusion and infarction. Orthostatic hypotension in Parkinson disease can be due to autonomic failure and/or side effects of antiparkinsonian medications.

Secondary Autonomic Dysfunction

Autonomic nervous system involvement is seen in several systemic diseases. A large number of neurologic disorders are also complicated by autonomic dysfunction which may involve several organs leading to a variety of symptoms in addition to orthostatic hypotension including anhidrosis, constipation, diarrhea, erectile dysfunction, urinary retention, urinary incontinence, stridor, apneic episodes, and Horner syndrome. Among the most serious and prevalent conditions associated with an orthostasis due to autonomic dysfunction are diabetes, multiple sclerosis, brainstem lesions, compressive and noncompressive spinal cord lesions, demyelinating polyneuropathies (Guillain-Barre syndrome), chronic renal failure, chronic liver disease, and connective tissue disorders.

Presentation

The clinical manifestations of orthostatic hypotension are due to hypoperfusion of the brain and other organs. Depending on the degree of fall in blood pressure and cerebral hypoperfusion, symptoms can vary from dizziness to syncope associated with a variety of visual defects, from blurred vision to blackout. Other reported ischemic symptoms of orthostatic hypotension are nonspecific lethargy and weakness, suboccipital and paravertebral muscle pain, low backache, calf claudication, and angina. Several precipitating factors for orthostatic hypotension have been identified including speed of positional change, prolonged recumbency, warm environment, raised intrathoracic pressure (coughing, defecation, micturition, physical exertion), and vasoactive drugs.

Evaluation

The diagnosis of orthostatic hypotension involves a demonstration of a postural fall in blood pressure after active standing. Reproducibility of orthostatic hypotension depends on the time of measurement and on autonomic function. The diagnosis may be missed on casual measurement during the afternoon. The procedure should be repeated during the morning after first maintaining supine posture for at least 10 minutes. Sphygmomanometer measurement will detect hypotension which is sustained. Phasic blood pressure measurements are more sensitive for detection of transient falls in blood pressure. Where possible these methods should be employed. Active standing is more appropriate than head-up tilt because the former more readily represents the physiologic α-adrenergic–mediated vasodilation due to calf muscle activation. Once a diagnosis of postural hypotension is made, the evaluation involves identifying the cause or causes of orthostasis mentioned earlier.

Management

The goal of therapy for symptomatic orthostatic hypotension is to improve cerebral perfusion. There are several nonpharmacologic interventions that should be tried in the first instance. These interventions include patient education regarding avoidance of precipitating factors for low blood pressure, maintaining adequate volume status, and application of graduated pressure from an abdominal support garment or from stockings (**Table 51-5**). Medications known to contribute to postural hypotension should be eliminated or reduced. There are reports to suggest benefit from implantation of cardiac pacemakers, in a small number of patients, by increasing heart rate during postural change. However, the benefits of tachypacing on cardiac output in patients with maximal vasodilatation are short lived, probably because venous pooling and vasodilation dominate. A large number of drugs have been used to raise blood

pressure in orthostatic hypotension, including fludrocortisone, midodrine, ephedrine, desmopressin (DDAVP), octeotride, erythropoeitin, and nonsteroidal anti-inflammatory agents. Fludrocortisone (9α-fluorohydrocortisone), in a dose of 0.1 to 0.2 mg, causes volume expansion, reduces natriuresis, and sensitizes α-adrenoceptors to norepinephrine. In older people, the drug can be poorly tolerated in high doses and for long periods. Adverse effects include hypertension, cardiac failure, depression, edema, and hypokalemia. Midodrine is a directly acting sympathomimetic vasoconstrictor of resistance vessels. Treatment is started at a dose of 2.5 mg three times daily and requires gradual titration to a maximum dose of 30 mg/day. Adverse effects include hypertension, pilomotor erection, gastrointestinal symptoms, and central nervous system toxicity. Side effects are usually controlled by dose reduction. Midodrine can be used in combination with low-dose fludrocortisone with good effect. DDAVP has potent antidiuretic and mild pressor effects. Intranasal doses of 5 to 40 μg at bedtime are useful. The main side effects are hyponatremia and water retention. This agent can also be combined with fludrocortisone with synergistic effect. The drug treatment for orthostatic hypotension in older persons requires frequent monitoring for supine hypertension, electrolyte imbalance, and congestive heart failure. One option for treating supine hypertension which is most prominent at night is to apply a nitroglycerine patch after going to bed, remove it in the morning, and take midrodrine with or without fludrocortisone 20 minutes before rising. This is effective provided that the older person remains in bed throughout the night. Nocturia is therefore an important consideration. In order to identify these coexistent diurnal BP variations of supine hypertension and morning orthostasis, 24-hour ambulatory BP monitoring is the preferred investigation. Postprandial hypotension, due to splanchnic vascular pooling often coexists with orthostatic hypotension in older patients.

TABLE 51-5 MANAGEMENT OF ORTHOSTATIC HYPOTENSION IN OLDER PERSONS

Identify and treat correctable causes
Reduce or eliminate drugs causing orthostatic hypotension (see **Table 51-3**)
Avoid situations that may exacerbate orthostatic hypotension
Standing motionless
Prolonged recumbency
Large meals
Hot weather
Hot showers
Straining at stool or with voiding
Isometric exercise
Ingesting alcohol
Hyperventilation
Dehydration
Wear waist-high custom-fitted elastic stockings and an abdominal binder
Participate in physical conditioning exercises
Controlled postural exercises using the tilt table
Avoid diuretics and eat salt-containing fluids (unless congestive heart failure is present)
Drug therapy
Caffeine
Fludrocortisone
Midodrine
Desmopressin
Erythropoietin

VASOVAGAL SYNCOPE

Pathophysiology

The normal physiologic responses to orthostasis, as described earlier, are an increase in heart rate, rise in peripheral vascular resistance (increase in diastolic blood pressure), and minimal decline in systolic blood pressure, to maintain an adequate cardiac output. In patients with vasovagal syncope, these responses to prolonged orthostasis are paradoxical. The precise sequence of events leading to vasovagal syncope is not fully understood. The possible mechanism involves a sudden fall in venous return to the heart, rapid fall in ventricular volume, and virtual collapse of the ventricle due to vigorous ventricular contraction. The net result of these events is stimulation of ventricular mechanoreceptors and activation of Bezold-Jarisch reflex leading to peripheral vasodilatation (hypotension) and bradycardia. Several neurotransmitters, including serotonin, endorphins, and arginine vasopressin, play an important role in the pathogenesis of vasovagal syncope possibly by central sympathetic inhibition, although their exact role is not yet well understood.

Healthy older persons are not as prone to vasovagal syncope as younger adults. Due to an age-related decline in baroreceptor sensitivity, the paradoxical responses to orthostasis (as in vasovagal syncope) are possibly less marked in older persons. However hypertension, atherosclerotic cerebrovascular disease, cardiovascular medications, and impaired baroreflex sensitivity can cause inappropriate autonomic responses during prolonged orthostasis (in which blood pressure and heart decline steadily over time) and render older persons susceptible to vasovagal syncope. Diuretic or age-related contraction of blood volume further increases the risk of vasovagal syncope.

Presentation

The hallmark of vasovagal syncope is hypotension and/or bradycardia sufficiently profound to produce cerebral ischemia and loss of neural function. Vasovagal syncope has been classified into cardioinhibitory (bradycardia), vasodepressor (hypotension), and mixed (both) subtypes depending on the blood pressure and heart rate response. In most patients, the manifestations occur in three distinct phases: a prodrome or aura, loss of consciousness, and postsyncopal phase. A precipitating factor or situation is identifiable in most patients. Common precipitating factors include extreme emotional stress, anxiety, mental anguish, trauma, physical pain or anticipation of physical pain (eg, anticipation of phlebotomy), warm environment, air travel, and prolonged standing. The commonest triggers in older individuals are prolonged standing and vasodilator medication. Some patients experience symptoms in specific situations such as micturition, defecation, and coughing. Prodromal symptoms include extreme fatigue, weakness, diaphoresis, nausea, visual defects, visual and auditory hallucinations, dizziness, vertigo, headache, abdominal discomfort, dysarthria, and paresthesias. The duration of prodrome varies greatly from seconds to several minutes, during which time some patients are able to take actions such as lying down to avoid an episode. Older patients may have poor awareness or recall for prodromal symptoms. The syncopal period is usually brief during which some patients develop involuntary movements—usually myoclonic jerks but tonic-clonic movements also occur. Thus, vasovagal syncope may masquerade as a seizure. Recovery is usually rapid but older patients can experience protracted symptoms such as confusion, disorientation, nausea, headache, dizziness, and a general sense of ill health.

Evaluation

Several methods have evolved to determine an individual's susceptibility to vasovagal syncope such as Valsalva maneuvres, hyperventilation, ocular compression, and immersion of the face in cold water. However these methods are poorly reproducible and lack correlation with clinical events. Using the strong orthostatic stimulus of head-upright tilting and maximal venous pooling, vasovagal syncope can be reproduced in a susceptible individual. Head-up tilting as a diagnostic tool was first reported in 1986 and since then validity of this technique in identifying susceptibility to neurocardiogenic syncope has been established. Subjects are tilted head up for 40 minutes at 70 degrees. Heart rate and blood pressure are measured continuously through out the test. A test is diagnostic or positive if symptoms are reproduced with a decline in blood pressure of greater than 50 mm Hg or less than 90 mm Hg. This may be in addition to significant heart rate slowing. As with CSS, the hemodynamic responses are classified as vasodepressor, cardioinhibitory, or mixed. The cardioinhibitory response is defined as asystole in excess of 3 seconds or heart rate slowing to less than 40 beats/min for a minimum of 10 seconds. Orthostatic hypotension, vasovagal syncope, and carotid sinus hypersensitivity (CSH) may overlap particularly in older patients.

The sensitivity of head-up tilting can be further improved by provocative agents that accentuate the physiologic events leading to vasovagal syncope. One agent is intravenous isoproterenol, which enhances myocardial contractility by stimulating β-adrenoreceptors. Isoproterenol is infused, prior to head-up tilting, at a dose of 1 μg/min and gradually increased to a maximum dose of 3 μg/min to achieve a heart rate increase of 25%. Although the sensitivity of head-up tilt testing improves by about 15%, the specificity is reduced. In addition, as a result of the decline in β-receptor

sensitivity with age, isoproterenol is less well tolerated, less diagnostic, and has a much higher incidence of side effects. The other agent that can be used as a provocative agent and is better tolerated in older persons is sublingual nitroglycerin, which, by reducing venous return due to vasodilatation can enhance the vasovagal reaction in susceptible individuals. Nitroglycerin provocation during head-up tilt testing is thus preferable to other provocative tests in older patients. The duration of testing is less, cannulation is not required, and the sensitivity and specificity are better than for isoproterenol.

Because syncopal episodes are intermittent, external loop recording will not capture events unless they occur approximately every 2 to 3 weeks. Implantable loop recorders can aid diagnosis by tracking brady- or tachyarrhythmias causing less frequently occuring syncope. To date no implantable blood pressure monitors are available with the exception of intracardiac monitors that are not recommended for diagnosis of a benign condition such as vasovagal syncope.

Management

Avoidance of precipitating factors and preventative actions such as lying down during prodromal symptoms, have great value in preventing episodes of vasovagal syncope. Withdrawal or modification of culprit medications is often the only necessary intervention in older persons. Doses and frequency of antihypertensive medications can be tailored by information from 24-hour ambulatory monitoring. Older patients with hypertension who develop syncope—either orthostatic or vasovagal—while taking antihypertensive drugs, present a difficult therapeutic dilemma and should be treated on an individual basis.

Many patients experience symptoms without warning, necessitating drug therapy. A number of drugs are reported to be useful in alleviating symptoms. Fludrocortisone (100–200 μg/day) works by its volume-expanding effect. Recent reports suggest that serotonin antagonists such as fluoxetine (20 mg/day) and sertraline hydrochloride (25 mg/day) are also effective although further trials are necessary to validate these findings. Midodrine acts by reducing peripheral venous pooling and thereby improving cardiac output and can be used either alone or in combination with fludrocortisone but with the caution. Elastic support hose, relaxation techniques (biofeedback), and conditioning using repeated head-up tilt as therapy have been adjuvant therapies. Permanent cardiac pacing is beneficial in some patients who have recurrent syncope due to cardioinhibitory responses.

POSTPRANDIAL HYPOTENSION

The effect of meals on the cardiovascular system was appreciated from postprandial exaggeration of angina that was demonstrated objectively by deterioration of exercise tolerance following food ingestion. Postprandial reductions in blood pressure manifesting as syncope and dizziness were subsequently reported, leading to extensive investigation of this phenomenon. In healthy older subjects, systolic blood pressure falls by 11 to 16 mm Hg, and heart rate rises by 5 to 7 beats/min 60 minutes after meals of varying compositions and energy content. However the change in diastolic blood pressure is not as consistent. In older persons with hypertension, orthostatic hypotension and autonomic failure, the postprandial blood pressure fall is much greater and without the corresponding rise in heart rate. These responses are accentuated if the energy and simple carbohydrate content of the meal is high. In the majority of fit as well as frail older persons, most postprandial hypotensive episodes go unnoticed. When systematically evaluated, postprandial hypotension was found in over one-third of nursing home residents. Postprandial physiologic changes include increased splanchnic and superior mesenteric artery blood flow at the expense of peripheral circulation and a rise in plasma insulin levels without corresponding rises in sympathetic nervous system activity. Vasodilator effects of insulin and other gut peptides, including neurotensin and vasoactive intestinal peptide (VIP) contribute to hypotension. The clinical significance of a fall in blood pressure after meals is difficult to quantify. However, postprandial hypotension is causally related to recurrent syncope and falls in older persons. A reduction in simple carbohydrate content of food, its replacement with complex carbohydrates or high protein, high fat, and frequent small meals are effective interventions for postprandial hypotension. Drinking 500 mL of water is also effective. Drugs useful in the treatment of postprandial hypotension include fludrocortisone and indomethacin, octreotide, and caffeine. Given orally along with food, caffeine prevents hypotensive symptoms in fit as well as frail older persons but should preferably be given in the mornings as tolerance develops if it is taken throughout the day.

CAROTID SINUS SYNDROME AND CAROTID SINUS HYPERSENSITIVITY

Pathophysiology

Carotid sinus syndrome is an important but frequently overlooked cause of syncope and presyncope in older persons. Episodic bradycardia and/or hypotension resulting from exaggerated baroreceptor-mediated reflexes or CSH characterize the syndrome. The syndrome is diagnosed in persons with otherwise unexplained recurrent syncope who have CSH. The latter is considered present if carotid sinus massage produces asystole exceeding 3 seconds (cardioinhibitory), or a fall in systolic blood pressure exceeding 50 mm Hg in the absence of cardioinhibition (vasodepressor) or a combination of the two (mixed).

Epidemiology

Up to 30% of the healthy older population have carotid sinus hypersensitivity. The prevalence is higher in the presence of coronary artery disease or hypertension. Abnormal responses to carotid sinus massage are more likely to be observed in individuals with coronary artery disease and in those on vasoactive drugs known to influence carotid sinus reflex sensitivity such as digoxin, β-blockers, and α-methyldopa. Other hypotensive disorders such as vasovagal syncope and orthostatic hypotension coexist in one-third of patients with carotid sinus hypersensitivity. In centers that routinely perform carotid sinus massage in all older patients with syncope, carotid sinus syndrome is the attributable cause of syncope in 30%. This frequency needs to be interpreted within the context that these referral centers evaluate a preselected group of patients who have a higher likelihood of carotid sinus syndrome than the general population of older persons with syncope. The prevalence in all older persons with syncope is unknown.

Carotid sinus syndrome is virtually unknown before the age of 50; its incidence increases with age thereafter. Males are more commonly affected than females and the majority have either coronary artery disease or hypertension. Carotid sinus syndrome is associated with appreciable morbidity. Approximately half of patients sustain an injury, including a fracture, during symptomatic episodes. In a prospective study of falls in nursing home residents, a threefold increase in the fracture rate in those with CSH was observed. Indeed, CSH can be considered as a modifiable risk factor for fractures of the femoral neck. Carotid sinus syndrome is not associated with an increased risk of death. The mortality rate in patients with the syndrome is similar to that of patients with unexplained syncope and the general population matched for age and sex. Mortality rates are similar for the three subtypes of the syndrome.

The natural history of CSH has not been well investigated. In one study, the majority (90%) of persons with abnormal hemodynamic responses but without syncopal symptoms, remained symptom free during a follow-up over 19 + 16 months while half of those who presented with syncope had symptom recurrence. More recent neuropathologic research suggests that CSH is associated with neurodegenerative pathology at the cardiovascular centre in the brain stem.

Presentation

The syncopal symptoms are usually precipitated by mechanical stimulation of the carotid sinus such as head turning, tight neckwear, neck pathology, and by vagal stimuli such as prolonged standing. Other recognized triggers for symptoms are the postprandial state, straining, looking or stretching upwards, exertion, defecation, and micturition. In a significant number of patients no triggering event can be identified. Abnormal response to carotid sinus massage (see below) may not always be reproducible, necessitating repetition of the procedure if the diagnosis is strongly suspected.

Evaluation

Carotid sinus massage Carotid sinus reflex sensitivity is assessed by measuring heart rate and blood pressure responses to carotid sinus massage. Cardioinhibition and vasodepression are more common on the right side. In patients with cardioinhibitory carotid sinus syndrome, over 70% have a positive response to right-sided carotid sinus massage either alone or in combination with left-sided carotid sinus massage. There is no fixed relationship between the degree of heart rate slowing and the degree of fall in blood pressure.

Carotid sinus massage is a crude and unquantifiable technique and is prone to intra- as well as interobserver variation. More scientific diagnostic methods using neck chamber suction or drug-induced changes in blood pressure can be used for carotid baroreceptor activation, but are not validated for routine clinical use. The recommended duration of carotid sinus massage is from 5 to 10 seconds. The maximum fall in heart rate usually occurs within 5 seconds of the onset of massage.

Complications resulting from carotid sinus massage include cardiac arrhythmias and neurologic sequelae. Fatal

arrhythmias are extremely uncommon and have generally only occurred in patients with underlying heart disease undergoing therapeutic rather than diagnostic massage. Digoxin toxicity has been implicated in most cases of ventricular fibrillation. Neurologic complications result from either occlusion of, or embolization from, the carotid artery. Several authors have reported cases of hemiplegia following carotid sinus stimulation, often in the absence of hemodynamic changes. Complications from carotid sinus massage however are uncommon. In a prospective series of 1000 consecutive cases, no patient had cardiac complications and 1% had transient neurologic symptoms that resolved. Persistent neurologic complications were uncommon, occurring in 0.04%. Carotid sinus massage should not be performed in patients who have had a recent cerebrovascular event or myocardial infarction (MI).

Symptom reproduction during carotid sinus massage is preferable for a diagnosis of carotid sinus syndrome. Symptom reproduction may not be possible for older patients with amnesia for loss of consciousness. Spontaneous symptoms usually occur in the upright position. It may thus be worth repeating the procedure, with the patient upright on a tilt table, even after demonstrating a positive response when supine. This reproduction of symptoms aids in attributing the episodes to CSH, especially in patients with unexplained falls who deny loss of consciousness. In one-third of patients a diagnostic response is only achieved during upright carotid sinus massage.

Management

No treatment is necessary in persons with asymptomatic carotid sinus hypersensitivity. There is no consensus, however, on the timing of therapeutic intervention in the presence of symptoms. Considering the high rate of injury in symptomatic episodes in older persons as well as the low recurrence rate of symptoms, it is prudent to treat all patients with a history of two or more symptomatic episodes. The need for intervention in those individuals with a solitary event should be assessed on an individual basis, taking into consideration the severity of the event and the patient's comorbidity.

Treatment strategies in the past included carotid sinus denervation achieved either surgically or by radioablation. Both procedures have largely been abandoned. Dual-chamber cardiac pacing is the treatment of choice in patients with symptomatic cardioinhibitory carotid sinus syndrome. Atrial pacing is contraindicated in view of the high prevalence of both sinoatrial and atrioventricular block in patients with carotid sinus hypersensitivity. Ventricular pacing abolishes cardioinhibition but fails to alleviate symptoms in a significant number of patients because of aggravation of a coexisting vasodepressor response or the development of pacemaker-induced hypotension, referred to as the pacemaker syndrome. The latter occurs when ventriculoatrial conduction is intact as is the case for up to 80% of patients with the syndrome. Atrioventricular sequential pacing (dual chamber) is thus the treatment of choice and because this maintains atrioventricular synchrony, there is no risk of pacemaker syndrome. With appropriate pacing, syncope is abolished in 85% to 90% of patients with cardioinhibition.

In a report of cardiac pacing in older fallers (mean age of 74) who had cardioinhibitory carotid sinus hypersensitivity, falls during 1 year of follow-up were reduced by two-thirds in patients who received dual-chamber systems. Syncopal episodes were reduced by half. Over half of the patients in the aforementioned series had gait abnormalities and three-quarters had balance abnormalities which would render individuals more susceptible to falls under hemodynamic circumstances, thus further suggesting the multifactorial nature of many falls and syncopal episodes.

Treatment of vasodepressor carotid sinus syndrome is less successful due to poor understanding of its pathophysiology. Ephedrine has been reported to be useful, but long-term use is limited by side effects. Dihydroergotamine is effective but poorly tolerated. Fludrocortisone, a mineralocorticoid widely used in the treatment of orthostatic hypotension, is used in the treatment of vasodepressor carotid sinus syndrome with good results but its use is limited in the longer term by adverse effects. A recent small randomized controlled trial suggests good benefit with midodrine (an α-agonist). Surgical denervation of the carotid artery may be a valid treatment option in refractory situations.

CARDIAC SYNCOPE

One-third of cases of syncope in the older patient are caused by cardiac disorders (**Figure 51-4**). There is a higher morbidity and mortality associated with cardiac syncope. Cardiac syncope is characterized by little or no prodrome, occurrence when supine or during exercise and association with palpitations or chest pain. However, the older patient may not recall these symptoms. Heart disease is an independent predictor of cardiac syncope—sensitivity 95% and specificity 45%. The prevalence of cardiac disease, including structural heart disease and arrhythmias, rises

dramatically with age. Cardiac syncope should be considered when the surface ECG is abnormal or left ventricular systolic dysfunction is present.

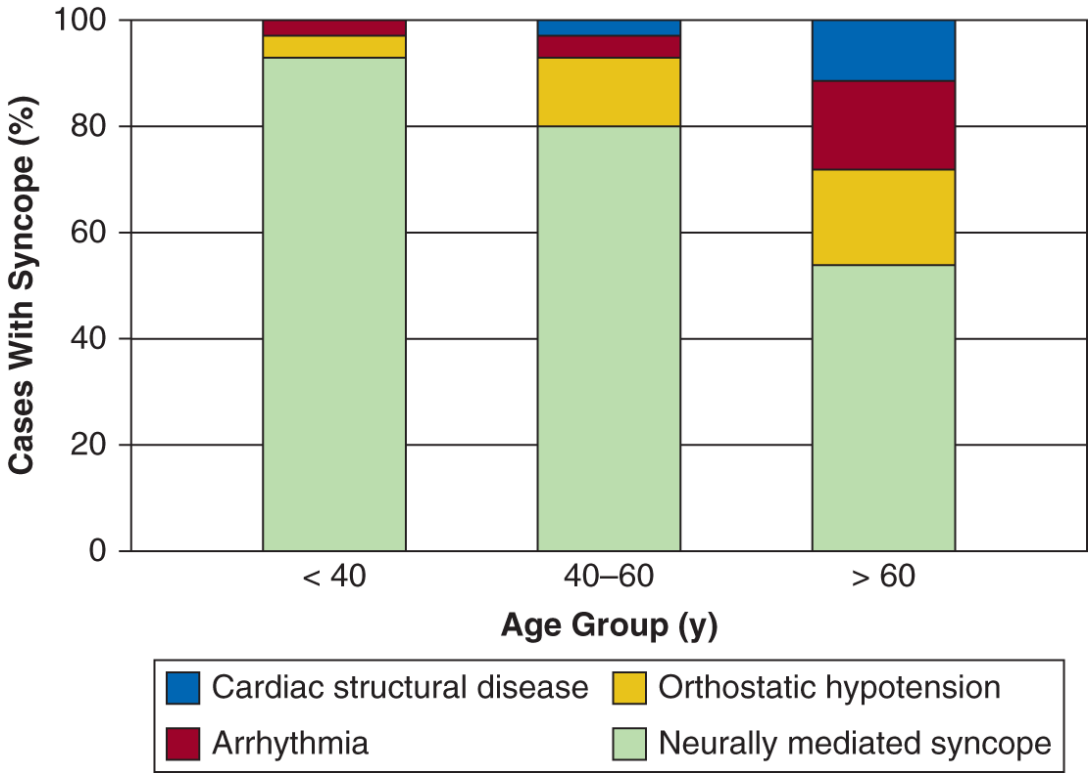


FIGURE 51-4. Causes of syncope by age. (From Parry SW, Tan MP. An approach to the evaluation and management of syncope in adults. *BMJ*. 2010;340:c880.)

Investigation

The gold standard for the diagnosis of cardiac syncope is symptom rhythm correlation—that is, contemporaneous HR and rhythm recording during syncope. Cardiac monitoring may also identify diagnostic abnormalities, such as asystole in excess of 3 seconds and rapid supraventricular (SVT) or ventricular tachycardia (VT). The absence of an arrhythmia during a recorded syncopal event excludes arrhythmia as a cause unless the patient has a dual diagnosis. In patients over 40 years with recurrent unexplained syncope who do not have structural heart disease or abnormal ECG, the attributable cause of syncope is bradycardia in over 50%.

Cardiac Monitoring

Prompt hospital admission or intensive monitoring is recommended when cardiac disease is present in the setting of syncope (**Table 51-6**). Although telemetry or in-patient monitoring is indicated if the patient is at high risk of a life-threatening arrhythmia based on the ECG abnormalities detailed in **Table 51-6**, the diagnostic yield from telemetry is low—16% in one series.

TABLE 51-6 TASK FORCE FOR THE DIAGNOSIS AND MANAGEMENT OF SYNCOPE OF THE EUROPEAN SOCIETY OF CARDIOLOGY

RECOMMENDATIONS	CLASS[a]	LEVEL[b]
Syncope due to cardiac arrhythmias must receive treatment appropriate to the cause	I	B
Cardiac pacing		
• Pacing is indicated in patients with sinus node disease in whom syncope is demonstrated to be due to sinus arrest (symptom—ECG correlation) without a correctable cause	I	C
• Pacing is indicated in sinus node disease patients with syncope and abnormal CSNRT	I	C

• Pacing is indicated in sinus node disease patients with syncope and asymptomatic pauses ≥ 3 s (with the possible exceptions of young trained persons, during sleep and in medicated patients)	I	C
• Pacing is indicated in patients with syncope and second-degree Mobitz II advance or complete AV block	I	B
• Pacing is indicated in patients with syncope, BGBB, and positive EPS	I	B
• Pacing should be considered in patients with unexplained syncope and BBB	IIa	C
• Pacing many be indicated in patients with unexplained syncope and sinus node disease with persistent sinus bradycardia itself asymptomatic	IIb	C
• Pacing is not indicated in patients with unexplained syncope without evidence of any conduction disturbance	III	C
Catheter ablation		
• Catheter ablation is indicated in patients with symptom—arrhythmia ECG correlation in both SVT and VT in the absence of structural heart disease (with exception of atrial fibrillation)	I	C
• Catheter ablation may be indicated in patients with syncope due to the onset of rapid atrial fibrillation	IIb	C
Antiarrhythmic drug therapy		
• Antiarrhythmic drug therapy, including rate control drugs, is indicated in patients with syncope due to onset of rapid atrial fibrillation	I	C
• Drug therapy should be considered in patients with symptom—arrhythmia ECG correlation in both SVT and VT with catheter ablation cannot be undertaken or had failed	IIa	C
Implantable cardioverter defibrillator		
• ICD is indicated in patients with documented VT and structural heart disease		
• ICD is indicated when sustained monomorphic VT is induced at EPS in patients with previous myocardial infarction		
• ICD should be considered in patients with documented VT and inherited cardiomyopathies or channelopathies		

[a]Class of recommendation.

[b]Level of evidence.

AV, atrioventricular; BBB, bundle branch block; CSNRT, corrected sinus node recovery time; ECG, electrocardiogram; EPS, electrophysiologic study; ICD, implantable cardioverter defibrillator; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Diagnostic yield from Holter monitoring is only 1% to 2% in unselected populations. Incidental arrhythmias are much more common in older persons, for example, atrial fibrillation occurs in one in five men over 80 years. External loop recorders have a higher diagnostic yield in older patients; however, some older patients may have difficulty operating the devices, therefore automated arrhythmia detection is preferred. Normal ambulatory ECG (Holter or external loop or otherwise) in the absence of symptoms does not exclude a causal arrhythmia and monitoring for longer intervals is imperative to capture rhythm during symptoms. Diagnostic rates are much higher in older patients using the implantable loop recorder (ILR)—up to 50% in patients with syncope and unexplained falls. Early insertion of ILRs in the older person is important to consider in view of the disproportionately high number of cardiac causes of syncope in this group. This approach is also more cost-effective. Difficulties with ILRs include inability to activate the device, particularly if patients have cognitive impairment, however, automated recordings and remote monitoring have much improved diagnostic yield.

Echocardiography

Echocardiography (echo) should be performed in syncope patients in whom a structural abnormality is suspected. The prevalence of structural cardiac abnormalities increases with age. The test is of most benefit in older patients with aortic stenosis and to evaluate ejection fraction. Cardiac arrhythmias are evident in up to 50% of patients with an

ejection fraction of less than 40%.

Ambulatory BP Monitoring

Patterns of blood pressure behavior including postprandial hypotension, hypotension after medication ingestion, orthostatic and exercise-induced hypotension, and supine systolic hypertension can be readily identified by this investigation. Modification of timing of meals and medications is guided by BP patterns.

Exercise Stress Testing

Exercise stress testing is indicated to investigate cardiac disease and in patients who present with exercise-induced syncope. It is not always possible in older patients who may alternatively require angiography to investigate cardiac status.

Electrophysiologic Study

Electrophysiologic study is indicated in the older nonfrail patient with syncope when a cardiac arrhythmia is suspected. Diagnosis is based on confirmation of an inducible arrhythmia or conduction disturbance. The benefit is dependent on pretest probability based on the presence of organic heart disease or an abnormal ECG.

Electrophysiologic study has the advantage of providing both diagnosis and treatment in the same session (transcatheter ablation). It is most effective for identification of sinus node dysfunction in the presence of significant sinus bradycardia of 50 beats/min or less, prediction of impending high-degree AV block in patients with bifascicular block, inducible monomorphic VT (in patients with previous MI), and inducible SVT with hypotension in patients with palpitations.

Management

Management of cardiac syncope is dependent on specific cardiac diagnosis as outlined in **Table 51-6**.

CHALLENGES IN THE OLDER PATIENT

Frailty

Because people are living longer, frailty and prefrailty are more commonly encountered in clinical practice. Frailty is associated with a reduction in the ability to respond to stressors and an increased vulnerability to adverse outcomes. There is no consensus on how best to operationalise or define frailty but two types of definitions have emerged as the most commonly used constructs: The Cumulative Burden Index as proposed where frailty is defined as an accumulation of health conditions and deficits and the “Biological Syndrome Model” as proposed by Fried (see Chapter 46). A person is deemed to be frail if they present with three or more of poor grip strength, slow walking speed, low levels of physical activity, exhaustion, and unintentional weight loss. Frailty is a predictor of falls, hospitalization, disability, and death.

Unwitnessed Events

In the older adult a witness account may not be available for falls or syncopal events in up to 40% of patients.

Polypharmacy

Polypharmacy is more common with advancing age. Some of the most frequently prescribed syncope-related medications used in combination are are antihypertensives, antianginals, antihistamines, antipsychotics, tricyclic antidepressants, and diuretics. These medications cause bradycardia, QT interval prolongation, orthostatic hypotension, and vasovagal syncope. Drug interactions can also cause syncope particularly in the older patient with multiple comorbidity and polypharmacy. A temporal association between onset or change of medication and symptoms may be evident although progression of age-related physiologic changes may cause syncope even with long-standing established medications.

The TILDA study reported an increased risk and frequency of syncope with use of tricyclic antidepressants. The side effect most frequently reported is hypotension, but bradycardia and tachycardia have also been reported.

Cognition

Cognitive impairment rises with age—20% of people over 80 have established dementia rising to 40% over 90 years. Cognitive impairment is characterized by memory problems, attention difficulties, and executive dysfunction—hence compliance with cardiac monitoring systems may be compromised.

Cognitive impairment is particularly high in older patients with CSH. Likewise, patients with some subtypes of dementia such as Lewy body dementia and Alzheimer dementia have a higher prevalence of syncope, OH, and CSH. Establishing a causal relationship between symptoms and arrhythmia or hypotension is particularly difficult in these patients—given that the history is not reliable and events are often unwitnessed. There is emerging evidence that low blood pressure may cause or exaggerate cognitive dysfunction, possibly because cerebral hypoperfusion is associated with cerebral damage via small vessel arteriosclerosis and cerebral amyloid angiopathy, as well as exaggerated white matter disease.

Dual Diagnosis

In the older patient multiple causes of syncope may be present including cardiac (bradyarrhythmias, SVT tachyarrythmias, ventricular tachyarrhythmias, long QT) and reflex syncope or autonomic impairment (see **Table 51-2**). Attribution of cause in the context of multiple abnormalities is not always possible and treatment of all possible causes is recommended. In one series of patients with syncope, mean age 67 ± 18, 23% had a dual diagnosis. The principal predictors of dual diagnosis were advanced age and treatment with α-receptor blockers and benzodiazepines. The most frequent dual diagnoses were OH and vasovagal syncope—2.8% had a triple diagnosis, and these were the oldest old.

Focal Neurology With Syncope

Transient ischemic attacks (TIAs) or stroke and syncope are considered mutually exclusive presentations. However, one recent series reported that 5.7% of syncope patients experienced focal neurologic events at the time of syncope or presyncope. Awareness of this phenomenon is important to prevent misdiagnosis of stroke and inappropriate increase of antihypertensive medications, which would further exacerbate hypotensive symptoms.

SUMMARY

The prevalence of syncope rises with age and is challenging because of atypical presentation, overlap with falls, and poor recall of events. Older patients are less likely to have a prodrome, may have amnesia for loss of consciousness, and may have unwitnessed events. Cardiac causes and dual pathology are more common and compliance with newer monitoring technologies is inadequate. Consequently, morbidity and mortality are higher than in younger patients. A high index of suspicion for cardiovascular causes of falls and dual pathology will increase diagnosis and early intervention.

Syncope is a common symptom in older adults due to age-related neurohumoral and physiologic changes plus chronic diseases and medications that reduce cerebral oxygen delivery through multiple mechanisms. Common individual causes of syncope encountered by the geriatrician are orthostatic hypotension, carotid sinus syndrome, vasovagal syncope, postprandial syncope, sinus node disease, atrioventricular block, and ventricular tachycardia. Algorithms for the assessment of syncope are similar to those for young adults, but the prevalence of ischemic and hypertensive disorders and cardiac conduction disease is higher in older adults and the etiology is more often multifactorial. A systematic approach to syncope is needed with the goal being to identify either a single likely cause or multiple treatable contributing factors. Management is then based on removing or reducing the predisposing or precipitating factors through various combinations of medication adjustments, behavioral strategies, and more invasive interventions in select cases such as cardiac pacing, cardiac stenting, and intracardiac defibrillators. It is often not possible to clearly attribute a cause of syncope in older persons who frequently have more than one possible cause and pragmatic management of each potential etiology is recommended.

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Chapter 52

Pressure Ulcers

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Learning Objectives

- Identify the four pathophysiologic factors of pressure ulcer development.
- Describe the six pressure ulcer classifications according to the National Pressure Ulcer Advisory Panel's (NPUAP's) guidelines.
- Outline the process for pressure ulcer risk screening and risk assessment.
- Describe the essential strategies for a successful pressure ulcer prevention program.
- Describe the standard of care for full-thickness pressure ulcers.

Key Clinical Points

1. **Pressure ulcers are caused by mechanical force compressing tissues between the bony skeleton and external surfaces occluding capillaries and lymphatics with resultant ischemia and buildup of metabolic cellular waste products, release of oxygen free radicals from reperfusion injury, and cellular apoptosis from cell deformation.**
2. **Prevention includes screening for risk followed by risk assessment using standardized risk assessment tools to determine individual-specific risk and implementing targeted prevention interventions based on identified risk factors.**
3. **Scheduled repositioning programs, use of reactive and active support surfaces, assessment and management of nutrition, and use of prophylactic dressings are key prevention strategies.**
4. **Adequate, timely, and complete debridement of necrotic tissue, identification and treatment of infection and management of biofilm development, and providing a moist wound environment are the key tenets of appropriate pressure ulcer care.**
5. **Medical record documentation must include pressure ulcer risk status, prevention strategies, pressure ulcer assessment (size, stage, location, and description of wound bed minimally), treatment plan and evaluation of treatment success.**
6. **Partial-thickness pressure ulcers (stage 2) should heal within 60 days maximum; full-thickness pressure ulcers (stage 3/4/unstageable) should demonstrate improvement in overall ulcer status every 2 to 4 weeks.**

DEFINITION

Pressure ulcers are areas of local tissue trauma, usually developing where soft tissues are compressed between bony prominences and any external surface for prolonged time periods. A pressure ulcer is a sign of local tissue necrosis. Pressure ulcers are most commonly found over bony prominences subjected to external pressure. The most common locations are sacrum, ischial tuberosities, trochanters, and heels with sacral and heel sites most frequent. Pressure exerts the greatest force at the bony tissue interface; therefore, there may be significant muscle and subcutaneous fat

tissue destruction underneath intact skin. Other terms for pressure ulcers include pressure injury, bedsore or decubitus ulcer, both of which imply development only in those confined to bed. Since the major causative factor is pressure, and because pressure ulcers occur in positions other than just lying down, pressure ulcer is the preferred term.

EPIDEMIOLOGY

Pressure ulcers occur in all health care settings. Among hospitalized older patients, the prevalence of pressure ulcers in acute care units has declined by 1% to 2% over the last decade with a median estimate of 6.3%. Most (75%) present with stage 1 or stage 2 ulcers. The incidence during hospitalization ranges between 2.8% over 4 days and 9% over 5 days. Critical care settings present increased risk with pressure ulcer prevalence rates reported at 13% and incidence rates reported between 12% and 17%. There are some evidence of improvement in pressure ulcer incidence. The National Database of Nursing Quality Indicators (NDNQI) is the national project established by the American Nurses Association in 1998 to monitor quality indicators in hospitalized patients that are nursing sensitive. In 2000, the NDNQI added hospital-acquired pressure ulcers (HAPUs) as one of the patient safety and quality-of-care indicators to monitor in participant hospitals. Hospital sites in 2011 included 1721 hospitals in 50 states. Participating institutions collect data by medical record abstraction and direct skin assessments and enter it into a secure website. Comparing HAPU data from 2010 (first and second quarter) to 2004 (quarter 2 and 3) and 2006 (quarter 4) to 2007 (quarter 1) shows a decrease in stages 1 to 4 and unstageable pressure ulcers with a rate of 3.8% in 2010 compared to 6.4% in both 2004 and 2006 to 2007.

Pressure ulcers generally occur within the first 2 weeks of hospitalization (the first 5 days in critical care units), and of those patients with an ulcer, more than half develop them after admission. A new area of concern for pressure ulcer development is related to use of medical devices. Medical devices have been associated with 34% of the pressure ulcers that develop in acute care settings. Medical device pressure ulcer prevalence in acute care is estimated from 8.3% to 9.7% with incidence reported as 5.4%. Epidemiologic data now also separate the suspected deep tissue injury (DTI) pressure ulcer classification with acute care incidence rates of DTI estimated to be 0.5% to 9%.

Pressure ulcers represent a significant health concern for those in nursing homes, rehabilitation systems, and for special populations. The incidence of new lesions varies widely by clinical situation: the highest rates are found among orthopedic populations (9%–19% incidence) and quadriplegics (33%–60% incidence). In nursing homes, prevalence estimates vary from 8.6% to 32.2%. Reported prevalence rates are higher among nursing home residents transferred to the hospital. Prevalence in high-risk residents has been estimated to range from 9.6% to 16.8%. Incidence is similarly diverse with estimates ranging from 3.4% to 4.7% for stage 2 to 4 ulcers and higher incidence when stage 1 ulcers are included (range 5.2%–13.6%). Incidence among terminally ill nursing home residents is reported much higher, 37.5%. Approximately 10% of persons admitted to nursing homes have a pressure ulcer.

There is some evidence of health disparities related to pressure ulcer development. African Americans demonstrate a higher incidence of pressure ulcers and more severe pressure ulcers compared to Caucasians in nursing homes with incidence rates reported as 0.56 per person-year compared to 0.35 per person-year for Caucasians. Incidence of stage 2 to 4 pressure ulcers are nearly two times higher among African Americans than Caucasians. Further, pressure ulcer–associated mortality is higher among blacks than whites. Hispanic and non-Hispanic blacks have a higher prevalence of pressure ulcers than non-Hispanic whites (7.6%, 9.7%, and 12.1%, respectively).

Rehabilitation facilities present special concerns related to pressure ulcer development, because patients in these facilities have conditions that limit mobility, such as spinal cord injury (SCI), traumatic brain injury, cerebral vascular accident, burns, multiple trauma, or a chronic neurologic disorder. Prevalence rates range from 12% to 25%. Individuals with SCI are at higher risk for pressure ulcer development, with incidence rates reported at 20% for those undergoing spinal surgery, increasing to 30% to 40% over 1-year time. Prevalence of pressure ulcers in persons with SCI is also high with reports of 33% to 40% during acute rehabilitation and for those living in the community, with recurrence rates up to 40% after an ulcer heals. In the community, the prevalence of pressure ulcers is 6% to 9% in home health care settings, and 1.6% in outpatient clinic settings. In the home health setting, 20% of the pressure ulcers develop in the first week after admission, and the incidence increases 10% each week through week 4. Of those who develop a pressure ulcer, 50% develop the ulcer within 24 days after admission to home health services.

MORBIDITY ASSOCIATED WITH PRESSURE ULCERS

Pressure ulcers can lead to pain and disfigurement. Of those persons with pressure ulcers who are able to report pain, across nursing homes, home health, and hospital settings, 87% report pain with dressing changes, 84% report pain at rest, and 42% report pain at rest and during dressing changes. Further, 18% of those persons reporting dressing change wound pain report pain at the highest level (eg, "excruciating"). Yet, only 6% of those persons reporting pressure ulcer pain receive any medication for pain. There is some evidence that a higher proportion of persons with stage 3 or 4 ulcers report ulcer pain compared to those persons with stage 2 ulcers and they report more severe pain than those with stage 2 pressure ulcers.

Septicemia is the most severe complication from pressure ulcers. The incidence of bacteremia from pressure ulcers is approximately 1.7 per 10,000 hospital discharges. When the pressure ulcer is the source of bacteremia, overall mortality is 48%. Further, septicemia is reported in 40% of pressure ulcer–associated deaths. Clinicians should be aware that transient bacteremia occurs after pressure ulcer debridement in as many as 50% of patients. Other infectious complications of pressure ulcers include wound infection, cellulitis, and osteomyelitis. Infected pressure ulcers are one of the most common infections found in skilled nursing facilities, and are reported in 6% of residents. Of note, pressure ulcers are typically colonized with greater than or equal to 10^5 organisms/mL of normal skin flora. Although greater than or equal to 10^5 organisms/mL of normal skin flora can cause local infection in intact skin and impair wound healing in flaps and skin grafts, chronic wounds such as pressure ulcers may bear microbial growth at this level for prolonged periods without noticeable clinical manifestations of infection and with evidence of healing. Among patients with nonhealing or worsening pressure ulcers, 26% of ulcers have underlying bone pathology consistent with osteomyelitis, 88% are colonized with *Pseudomonas aeruginosa* species, and 34% with *Providencia* species. The presence of either *P aeruginosa* or *Providencia* species should not be considered typical colonization. Infected pressure ulcers also can serve as reservoirs for infections with antibiotic-resistant bacteria. Methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in infected pressure ulcers has been reported as high as 59%. Bacterial biofilms are known to cause chronic inflammation that contributes to the molecular pathology that is present in nonhealing full-thickness pressure ulcers. Approximately 60% of chronic wounds contain biofilms, which may explain the state of chronic inflammation and impaired healing that occurs in many pressure ulcers. The presence of bacterial colonization in pressure ulcers has been suggested to elevate proinflammatory cytokines such as interleukin 1 and tumor necrosis factor which in turn, increases the level of matrix metalloproteinases (MMPs), decreases the level of inhibitors in tissue against the MMPs, and decreases the production of growth factors and fibroblast activity.

Prolonged hospitalization, slow recovery from comorbid conditions, and increased death rates are consistently observed in older individuals who develop pressure ulcers in both hospitals and nursing homes. Hospital-acquired pressure ulcer development is associated with higher in-hospital mortality (11.2%), mortality 30 days after discharge (15.3%), and longer hospital stays (11.6 ± 10.1 days for those with HAPU vs 4.9 ± 5.2 days for those without).

In addition, failure of an ulcer to heal or improve has been associated with a higher rate of death in nursing home residents. Nursing home residents whose pressure ulcer healed within 6 months show a lower mortality rate (11% vs 64%) than residents with ulcers that did not heal within 6 months. It is unclear how pressure ulcers lead to death. The link between pressure ulcers and mortality may be related to an unidentified causal pathway, to pressure ulcers as a marker for coexisting morbidity in frail, sick patients, or to the association between fatal sepsis and pressure ulcers as cause of death. Whatever the link, pressure ulcers are reported as a cause of death among 114,000 persons per year (age-adjusted mortality rate of 3.8 per 100,000 population).

Pressure ulcers are a quality issue for all areas of health care. Pressure ulcer incidence and severity are used as markers of quality care by regulators in long-term care facilities, home care agencies, and acute care hospitals. The Joint Commission estimates that 2.5 million patients in acute care hospitals are treated for pressure ulcers each year and this number is likely to increase as the population ages. Unlike facility-specific conditions (such as surgical site infection or ventilator-associated pneumonia), pressure ulcers present across all care settings and patients, especially among geriatric populations.

Pressure ulcers are costly. Annual costs were estimated at $10.5 to $17.8 billion for 2010. The cost for managing a single full-thickness pressure ulcer is as much as $70,000. One study reports the average hospital-associated costs for managing one full-thickness stage 4 ulcer and related complications for one hospital admission at $129,248 and costs for managing a community-acquired stage 4 ulcer over an average of four hospital admissions at $124,327. The Centers for Medicare and Medicaid Services (CMS) reports the cost of treating a pressure ulcer in acute care (as a secondary diagnosis) is $43,180.00 per hospital stay. Contributing cost factors include increased length of stay due to pressure ulcer complications such as pain, infection, high-tech support surfaces, and decreased functional ability. The Agency for Healthcare Research and Quality (AHRQ) reported that pressure ulcer–related hospitalizations ranged from 13 to 14 days and cost $16,755 to $20,430 compared to the average stay of 5 days and costs approximately $10,000.

Health care utilization and costs of caring for persons with SCI who experience the complication of a severe (stage 3/4) pressure ulcer are high (in excess of $100,000 annually). As a result, pressure ulcers remain on the national agenda for improving quality. This emphasis on pressure ulcers across the spectrum of health care settings highlights the importance of the condition for clinicians. Pressure ulcers have also received attention in the courtroom. Organizations have been prosecuted for negligence related to pressure ulcer care and development, and, in a landmark case, one health care facility operator was found guilty of manslaughter for a resident's death related to improper care for her pressure ulcers.

PATHOPHYSIOLOGY

Pressure ulcers are the result of mechanical injury to the skin and underlying tissues. The primary external factors involved in pressure ulcer development include pressure (stress), shear, and friction. More recently deformation (strain), heat, re-perfusion injury, and impaired lymphatic function have been considered as additional primary forces involved in pressure damage. Four hypotheses for the pathophysiology behind pressure ulcer development include the following:

1. Ischemia caused by capillary occlusion
2. Impairment in lymphatic flow with increase in metabolic waste products
3. Reperfusion injury (damage that occurs because of the inflammatory response that occurs when blood flow resumes to the ischemic tissues)
4. Deformation of tissue cells

Pressure (stress) and deformation (strain) are involved in all four pressure ulcer development hypotheses. Pressure is the perpendicular force or load exerted on a specific area, causing ischemia and hypoxia of the tissues. The gravitational pull on the skeleton causes loading and deformation of the soft tissue between the bony prominence and external support surface. High-pressure areas in the supine position are the occiput, sacrum, and heels. In the sitting position, the ischial tuberosities exert the highest pressure, and the trochanters are affected in the side-lying position. The mechanical physical forces of shear which is force applied against a surface as it moves or slides in an opposite but parallel direction stretching tissues and displacing blood vessels laterally and deformation which stretches and pulls cells are also key factors in pressure ulcer development. Friction, which is the resistance to motion or rubbing of one object or surface against another in a parallel direction, and moisture which macerates tissues and increases the coefficient of friction between surfaces are major forces in superficial damage over bony prominences, abrading the epidermal surface, and increasing the risk for infection. As the amount of soft tissue available for compression decreases, the pressure gradient increases, thus, most pressure ulcers occur over bony prominences where there is less tissue for compression and the pressure gradient within the vascular network is altered.

The changes in the vascular network allow an increase in the interstitial fluid pressure, which exceeds the venous flow. This results in an additional increase in the pressure and impedes arteriolar circulation. The capillary vessels collapse and thrombosis occurs. Increased capillary arteriole pressure leads to fluid loss through the capillaries, tissue edema, and subsequent autolysis. Lymphatic flow is decreased, allowing further tissue edema, and contributing to the tissue necrosis.

Pressure, over time, occludes blood and lymphatic circulation, causing deficient tissue nutrition and accumulation of waste products, as a result of ischemia. If pressure is relieved before a critical time period is reached, a normal compensatory mechanism, reactive hyperemia, restores tissue nutrition and compensates for compromised circulation. If pressure is not relieved, the blood vessels collapse and thrombose. The tissues are deprived of oxygen, nutrients, and waste removal. In the absence of oxygen, cells use anaerobic pathways for metabolism and produce toxic by-products. The toxic by-products lead to tissue acidosis, increased cell membrane permeability, edema, and eventual cell death.

Deformation of tissues is a key factor in the damage seen in DTI and full-thickness pressure ulcers and may be the force that initiates cell death. Tissues are deformed due to the bone's compression of the soft tissue against the external surface. How the tissues are deformed depends on the tissues (ie, size and shape of the different tissue layers), the mechanical properties of the involved tissues (eg, stiffness, strength), and the magnitude and distribution of the external mechanical force applied to the tissues. The tissues' ability to withstand deformation can change with time due to aging, lifestyle changes, injury, or disease. The sustained mechanical deformation damages cells directly and also obstructs blood flow. In fact it is likely that tissue deformation is the major underlying factor in muscle damage.

Several investigators have examined the reaction of cells to deformation. Observing single muscle cells has demonstrated that deformations exceeding 80% have consistently ruptured cell membranes, causing immediate and irreversible damage. Observations of an entire muscle have demonstrated similar findings; 2 hours of sustained deformation at strains higher than 50% inflicted irreversible damage to muscle tissue. As with hypoxia and ischemia, muscle tissue is more sensitive to deformation forces and irreversible damage may be present at the muscle layer without such damage occurring in the skin or subcutaneous layers. The cell death and local tissue necrosis change the geometry and characteristics of the tissues, which further increases the deformation force exacerbating the pressure injury. Heat accumulation or increased skin temperature intensifies the effects of ischemia and hypoxia on tissues. Increased skin temperature causes an increase in metabolic rate, which increases the need for oxygen in the tissues.

When prolonged pressure is finally relieved, the damage does not end. As the vascular network is relieved of pressure, the tissues are reperfused and reoxygenated. The sudden entry of oxygen into previously ischemic tissues releases oxygen-free radicals known as *superoxide anions*, *hydroxyl radicals*, and *hydrogen peroxide*, all of which induce new endothelial damage and decrease microvascular integrity causing postischemic or reperfusion injury.

These cellular changes result in inflammation and edema *locally* at the site of injury. The inflammatory changes exist in the tissues before any damage is fully visible on the skin surface. This is the *nonvisible spectrum of pressure-induced tissue damage*, the preclinical stage of disease in the physiology cascade leading to frank ulceration. These inflammatory changes with tissue edema can occur from 3 to 10 days before visible skin breakdown.

PRESENTATION AND DETECTION

Detection of Pressure-Induced Tissue Damage

Detection of prestage 1, or preclinical, pressure-induced tissue damage is important because early intervention may prevent decline to more severe pressure damage. There are several nonvisual methods of detecting pressure damage currently being explored for use in clinical practice: ultrasound, thermography, spectroscopy, and surface electrical capacitance. Of these, ultrasound, thermography, and surface electrical capacitance show promise for use clinically.

High-resolution ultrasound is a noninvasive method of visualizing skin and soft tissues that provides echogenic images of skin and deeper tissues. Over 50% of ultrasound images obtained from nursing home residents indicated abnormal findings with tissue edema present compared to ultrasound images obtained from healthy volunteers. Nearly 80% of those with abnormal ultrasound images did not have documentation of erythema suggesting that ultrasound technology can detect tissue damage before clinical signs occur. Advantages of ultrasound technology for detecting early pressure ulcer development include (1) reproducibility, (2) noninvasiveness, and (3) objective and quantitative data on tissue damage below skin surface. However, ultrasound equipment is large and expensive, requires skilled technicians to obtain useful images, and requires trained providers to interpret images.

Thermography, the measurement of skin surface temperature and with some equipment, temperatures of tissues below the skin surface may provide a method for detecting nonvisual pressure damage. Both increased and decreased skin temperature (compared to adjacent normal tissue) is associated with stage 1 pressure ulcers in rehabilitation patients with pressure-induced erythema. Skin temperature variability also differentiates between nursing home residents at high and low risk for pressure ulcer development and between those residents who do and do not develop pressure ulcers. In a study of nursing home residents using a handheld thermistor to measure skin surface temperature, temperatures for sacral and buttocks sites with erythema or stage 1 pressure ulcers were significantly higher than for normal skin. Skin surface temperature was responsive to visual changes in the skin, with higher temperatures associated with any change in the skin, deterioration or improvement. Further, a decrease in skin surface temperature by 4°F predicted stage 1 pressure ulcers that were visible on the skin the following week. One disadvantage to using temperature for detecting nonvisual pressure damage is determination of the normal or baseline temperature for the individual and the specific anatomic site (all studies looked at determining a baseline skin temperature for an individual and specific anatomic site).

Measurement of the water content of the skin and underlying tissue can be accomplished using surface electrical capacitance devices. These devices detect and measure water or edema as the initial inflammatory response of injured tissues *below* the stratum corneum. Using dielectric parameters, high-frequency, low-power electromagnetic waves of 300 MHz or less are transmitted via a device that is manually placed on the skin. In the skin, the induced electrical field interacts with water molecules closest to the probe and displays subepidermal moisture (SEM) values. At the cellular level, SEM indirectly measures the action potential of sodium and potassium across cell membranes. When

cells are injured such as occurs with early pressure-induced tissue damage, cellular permeability increases and the action potential across the cell membrane is decreased allowing quick/high electrical charges to pass through the tissues (eg, SEM increases). Devices to measure SEM are small, portable, handheld dermal phase meters, which require light skin touch with readings available within 3 to 8 seconds. In nursing home residents, critical care patients, veterans with SCI, and persons with dark skin tones SEM has detected inflammatory changes in the tissues, identifying prestage 1, stage 1, and DTI pressure ulcers on the sacrum and heels. In nursing home residents SEM was higher (eg, increased edema and inflammation) when residents exhibited no visible skin damage at the time but a stage 1 or more severe pressure ulcer was visible on the skin 1 week later. SEM identified 26% and 30% of the stage 1 pressure ulcers the following week. For populations at high risk or as a method of screening and monitoring specific populations SEM use holds great promise and appears the most clinically practical of the measures being examined for early detection.

Presentation

The first clinical sign of pressure ulcer formation, blanchable erythema, presents as discoloration of a patch or flat, nonraised area of the skin larger than 1 cm. This discoloration presents as redness or erythema that varies in intensity from pink to bright red in light-skinned patients. In dark-skinned patients, the discoloration appears as deeper normal ethnic pigmentation; a purple or blue-gray hue to the skin. Other characteristics include slight edema and increased temperature of the area. The beginning clinical indicators of pressure ulceration all relate to the signs of inflammation in the tissues. This beginning stage of damage is transient if the pressure is relieved. If pressure is not relieved, the damage can progress. One method of monitoring existing erythema for progression of tissue damage is to test capillary refill every 8 hours. When capillary refill is not present, it indicates an increase in tissue damage.

Nonblanchable erythema involves more severe damage to underlying tissues and is commonly the first stage of pressure ulceration (stage 1 pressure ulcer). The color of the skin is more intense. It varies from dark red to purple or cyanotic in both light- and dark-skinned patients. Dark-skinned patients exhibit deepening of normal skin color, a purple or gray hue to the skin, and changes in skin texture, with induration and an orange-peel appearance. Skin temperature is cool compared with healthy tissues, and the area may feel indurated. This stage of tissue destruction is also reversible, although tissues may take 1 to 3 weeks to return to normal.

The result of further deterioration in the tissues is evidenced as the epidermis is disrupted with subepidermal blisters, crusts, or scaling present (stage 2 pressure ulcer). If properly treated, the situation may resolve in 2 to 4 weeks. The early pressure ulcer is superficial, with indistinct margins and a red, shiny base, and reflects continued tissue insult and progressive injury. It is usually surrounded by erythema. If not dealt with aggressively, the lesion may progress to a chronic, deep ulcer. Superficial ulcers also may begin at the skin surface as the result of friction and moisture on the skin, the effects of both are increased with pressure. While superficial ulcers may progress to deeper ulcers, many deep ulcers do not originate at the skin surface; they begin at the bony prominence and soft tissue interface, and spread to involve the skin structures.

The chronic, deep, full-thickness ulcer usually has a dusky red wound base and does not bleed easily. It is surrounded by blanchable or nonblanchable erythema or deepening of normal skin tone in persons with dark skin tones, induration, and warmth. Undermining, or pocketing, and tunneling may be present with a large necrotic cavity. Eschar formation may be a result of larger vessel damage below skin surface from shearing forces. Eschar is the formation of an acellular dehydrated compressed area of necrosis, usually surrounded by an outer rind of blanchable erythema. Eschar formation indicates a full-thickness loss of skin.

ASSESSMENT

Assessment involves screening for risk of developing pressure ulcers, assessment of the severity of the tissue damage (staging), and evaluation of ulcer healing over the course of treatment.

Risk Screening and Risk Assessment

Pressure ulcer development is related to multiple factors, with immobility or severely restricted mobility being the most important risk factor for all populations and a necessary condition for the development of pressure ulcers. A study of geriatric patients, who were monitored for movements using devices on the bed, showed that individuals with more than 50 movements a night did not develop pressure ulcers compared to 90% of individuals with 20 or fewer spontaneous body movements at night who developed a pressure ulcer.

Incontinence, malnutrition, impaired mental status, and altered sensation or response to pain and discomfort are all risk factors with strong relationships to pressure ulcer development in prospective studies. Fecal incontinence has a more powerful relationship to pressure ulcer development than urinary incontinence. Certain risk factors can be easily identified and used to quickly screen individuals in order to place them immediately on a general prevention program. Screening is particularly useful for acute care hospitals and specific populations. Screening factors range from individual factors such as age to factors that are more related to procedures or medical conditions such as emergent admission to the hospital or prolonged surgical time. Some factors that might be used as a screen for pressure ulcer risk include the following:

- Demographic characteristics: African-American race, and advanced age (over 75 years).
- Individuals of all ages who have limited mobility or for whom movement is not possible without staff or caregiver assistance including persons who are unable to move due to sedation.
- Persons admitted to the hospital from a nursing home. These individuals are already frail as they require nursing home care and are acutely ill.
- Persons admitted to the critical care unit from the emergency department.
- Persons over 65 years admitted to the acute care hospital who are scheduled for a surgical procedure anticipated to be 4 hours or longer.
- Patients who experience intraoperative hypotensive episodes.
- Older patients admitted to the hospital from the community who were found down for a prolonged time.
- Patients undergoing special therapy, for example, oncology patients admitted for bone marrow transplant or with graft-versus-host disease.
- Patients with hospital transport times more than 1 hour.
- Patients readmitted to a nursing home from the hospital.
- All persons who have had a previous pressure ulcer and especially persons with SCI or dysfunction with prior pressure ulcers.
- Patients admitted with any diagnosis affecting skin integrity (besides obvious open wounds this includes gangrene, nutritional deficiencies, diabetes, and anemia).
- Patients admitted with system failure including paralysis, senility, respiratory failure, acute renal failure, cerebral vascular accident, and congestive heart failure.
- Patients admitted with infection: sepsis, osteomyelitis, pneumonia, bacterial infections, and urinary tract infections.
- Intensive care unit patients with sepsis, surgery times more than or equal to 8 hours, or long-term vasopressor therapy (consider at high risk).

For practitioners to intervene cost-effectively, a method of screening for risk of developing pressure ulcers is necessary followed by more specific risk assessment to develop individualized prevention strategies. Use of a risk assessment tool is a mechanism to identify those persons at risk of developing pressure ulcers in multiple health care settings and for developing care plans that reflect specific risk. Risk assessment is recommended in all clinical practice guidelines for pressure ulcers. The purpose in identifying patients at risk for pressure ulcer development is to allow for appropriate use of resources for prevention.

The use of a risk assessment tool allows targeting of interventions to specific risk factors for individual patients. There is, however, limited evidence to support a direct link between use of risk assessment tools and decreased incidence of pressure ulcers. Multifaceted prevention interventions that have included use of risk assessment tools have shown decreased pressure ulcer incidence levels from 13% to 23% preintervention to 2% to 5% postintervention. The outcome, however, cannot be solely attributed to use of risk assessment tools. Use of risk assessment tools is linked to increased documentation of prevention interventions and is better than use of clinical judgment alone, particularly for those at moderate risk. While there is no study that provides definitive evidence linking risk assessment directly with pressure ulcer prevention, there is a relationship between conducting risk assessment and initiating preventive interventions leading to decreased pressure ulcer incidence.

Pressure ulcer risk assessment should be performed on admission to the health care setting and at periodic intervals thereafter. In acute care hospitals, risk assessment should be repeated every 48 hours. Those persons admitted to intensive or critical care units should have risk assessment conducted on admission and if determined at risk, daily thereafter. In home health settings, risk assessment should be conducted weekly for the first 4 weeks with every other week reassessments thereafter depending on patient condition and frequency of home visits. Nursing home residents

should be reassessed for pressure ulcer risk status weekly for the first 4 weeks following admission followed by quarterly assessments.

The most commonly used risk assessment tools are the Norton Scale and the Braden Scale for predicting pressure sore risk. The Norton Scale is the oldest risk assessment instrument. Developed in 1961, it consists of five subscales: physical condition, mental state, activity, mobility, and incontinence. Each parameter is rated on a scale of 1 to 4, with the sum of the ratings for all five parameters yielding a total score, ranging from 5 to 20. Lower scores indicate increased risk, with a score of or below 16 indicating "onset of risk" and scores 12 and below indicating high risk for pressure ulcer formation. A systematic review and meta-analysis of risk assessment tools found sensitivity of 0.75, specificity of 0.68, area under the receiver operating curve 0.74, and relative risk 3.69 (confidence interval [CI] 2.64–5.16) for the Norton tool using a cutoff score of 14 for indicating risk status. The Braden Scale was developed in 1987 and is composed of six subscales: sensory perception, moisture, activity, mobility, nutrition, and friction and shear. All subscales are rated from 1 to 4, except for friction and shear, which is rated from 1 to 3. The subscales may be summed for a total score, with a range from 6 to 23. Lower scores indicate lower function and higher risk for developing a pressure ulcer. The cutoff score for hospitalized adults is considered to be 16, with scores of 16 and below indicating at-risk status. In older patients, some have found cutoff scores of 17 or 18 to be better predictors of risk status. Levels of risk are based on the predictive value of a positive test. Scores of 15 to 16 indicate mild risk, with a 50% to 60% chance of developing a stage 1 pressure ulcer; scores of 12 to 14 indicate moderate risk, with a 65% to 90% chance of developing a stage 1 or 2 lesion; and scores below 12 indicate high risk, with a 90% to 100% chance of developing a stage 2 or deeper pressure ulcer. A systematic review and meta-analysis of risk assessment tools found sensitivity of 0.74, specificity of 0.68, area under the receiver operating curve 0.77, and relative risk 4.26 (CI 3.27–5.55) for the Braden Scale using a cutoff score of 18 for indicating risk status.

Specific prevention strategies should be targeted to risk factors identified in individual patients. In those persons in whom prevention is not successful, the continued monitoring of risk status may prevent further tissue trauma at the wound site and development of additional wound sites.

Assessment of Pressure Ulcer Stage

Pressure ulcers are commonly classified using grading or staging systems based on the observable depth of tissue destruction. The stage is determined on initial assessment by noting the deepest layer of tissue involved. The ulcer is not restaged unless deeper layers of tissue become exposed. The initial method of classifying pressure ulcers was a pathology-based classification system intended to simplify communication for health-care professionals, provide a mechanism for identification of pressure ulcers, and suggest a broad guide for determining whether operative care was needed. Each grade of pressure ulceration was defined by the anatomic limit of soft tissue damage that could be observed. The numeric classification system suggested an orderly evolution of pressure ulceration, however, pressure ulcers do not heal or deteriorate in a linear fashion.

The most commonly used staging system is the NPUAP's system describing six classifications of pressure ulcers. The NPUAP staging system was updated in 2014 in conjunction with the European Pressure Ulcer Advisory Panel (EPUAP) and again in 2016. **Table 52-1** presents the definitions for pressure ulcer stages.

TABLE 52-1 NATIONAL PRESSURE ULCER ADVISORY PANEL, 2016 PRESSURE ULCER STAGING CLASSIFICATIONS

PRESSURE ULCER STAGE	DEFINITION AND CLINICAL DESCRIPTION
Stage 1	Intact skin with a localized area of non-blanchable erythema, which may appear differently in darkly pigmented skin. Presence of blanchable erythema or changes in sensation, temperature, or firmness may precede visual changes. Color changes do not include purple or maroon discoloration; these may indicate deep tissue pressure injury.
Stage 2	Partial-thickness loss of skin with exposed dermis. The wound bed is viable, pink or red, moist, and may also present as an intact or ruptured serum-filled blister. Adipose (fat) is not visible and deeper tissues are not visible. Granulation tissue, slough and eschar are not present. These injuries commonly result from adverse microclimate and shear in the skin over the pelvis and shear in the heel. This stage should not be used to describe moisture associated skin damage (MASD) including incontinence associated dermatitis (IAD), intertriginous dermatitis (ITD), medical adhesive related skin injury (MARSI), or traumatic wounds (skin tears, burns, abrasions).

Stage 3	Full-thickness loss of skin, in which adipose (fat) is visible in the ulcer and granulation tissue and epibole (rolled wound edges) are often present. Slough and/or eschar may be visible. The depth of tissue damage varies by anatomical location; areas of significant adiposity can develop deep wounds. Undermining and tunneling may occur. Fascia, muscle, tendon, ligament, cartilage and/or bone are not exposed. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.
Stage 4	Full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage or bone in the ulcer. Slough and/or eschar may be visible. Epibole (rolled edges), undermining and/or tunneling often occur. Depth varies by anatomical location. If slough or eschar obscures the extent of tissue loss this is an Unstageable Pressure Injury.
Unstageable	Full-thickness skin and tissue loss in which the extent of tissue damage within the ulcer cannot be confirmed because it is obscured by slough or eschar. If slough or eschar is removed, a stage 3 or stage 4 pressure injury will be revealed. Stable eschar (i.e. dry, adherent, intact without erythema or fluctuance) on an ischemic limb or the heel(s) should not be removed.
Suspected deep tissue injury	Intact or non-intact skin with localized area of persistent non-blanchable deep red, maroon, purple discoloration or epidermal separation revealing a dark wound bed or blood filled blister. Pain and temperature change often precede skin color changes. Discoloration may appear differently in darkly pigmented skin. This injury results from intense and/or prolonged pressure and shear forces at the bone-muscle interface. The wound may evolve rapidly to reveal the actual extent of tissue injury, or may resolve without tissue loss. If necrotic tissue, subcutaneous tissue, granulation tissue, fascia, muscle or other underlying structures are visible, this indicates a full thickness pressure injury (Unstageable, stage 3 or stage 4). Do not use DTPI to describe vascular, traumatic, neuropathic, or dermatologic conditions.

Assessment of Pressure Ulcer Healing

Routine pressure ulcer assessment is the base for maintaining and evaluating the therapeutic plan of care. Initial assessment and follow-along assessments at regular intervals to monitor progress are necessary to determine the effectiveness of the treatment plan. Assessment of ulcer status should be performed weekly and whenever a significant change is noted in the wound. Assessment should not be confused with monitoring the ulcer at each dressing change. Monitoring can be performed by less skilled caregivers; however, assessment should be performed on a routine basis by trained clinicians. At a minimum, the ulcer should be assessed for location, depth and stage, size, and wound bed description such as necrotic tissue, exudate, wound edges for undermining and tunneling, and presence or absence of granulation and epithelialization.

There are two research-based pressure ulcer assessment tools for evaluating wound status and healing, the Bates-Jensen Wound Assessment Tool (BWAT) (**Figure 52-1**) and the NPUAP's Pressure Ulcer Scale for Healing tool (PUSH) (**Figure 52-2**). Clinical practice guidelines, expert panels, and federal nursing home guidelines recommend standardized assessment of pressure ulcers, and many groups recommend use of a standardized tool for pressure ulcer assessment. One prospective study showed improved pressure ulcer healing outcomes (36% of stage 3 and 4 ulcers during 12 weeks with an average healing time of 62 days) when the BWAT was used for standardized pressure ulcer assessment and interventions were tied to the assessment.

The PUSH tool incorporates surface area measurements, exudate amount, and surface appearance. The clinician measures the size of the wound, using length and width to calculate surface area and chooses the appropriate size category of 10 categories. Exudate is evaluated as none (0), light (1), moderate (2), and heavy (3). Tissue type is rated as closed (0), epithelial tissue (1), granulation tissue (2), slough (3), and necrotic tissue (4). Each of the three items is scored, then the three subscores can be summed for a total score. The PUSH tool offers a quick assessment to predict healing outcomes, but assessment of additional wound characteristics may still be needed in order to develop a treatment plan for the pressure ulcer.

The BWAT, developed in 1990 and revised in 2001, evaluates 13 wound characteristics using a five-point numerical rating scale, and rates them from best (scored as 1) to worst (scored as 5) possible (see **Figure 52-1**). Characteristics include size, depth, edges, undermining or pockets, necrotic tissue type and amount, exudate type and amount, surrounding skin color, peripheral tissue edema and induration, granulation tissue, and epithelialization.

Similar to the PUSH tool, once characteristics have been scored, they can be summed for a total score (range 13–65). The total score differentiates between early pressure ulcers (stage 1 and 2) and stage 3 and 4 ulcers with mean total scores of 23 versus 32, respectively. A 1-week improvement in the total score demonstrates a positive predictive value of 65% (sensitivity 61%; specificity 52%) for achieving 50% wound healing within a 6-week time period. The BWAT has been incorporated in a variety of electronic medical records. Both the PUSH tool scores and the BWAT tool scores are highly correlated, and use is based on provider and institutional preference.

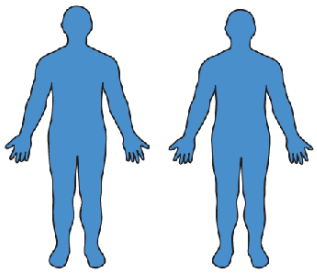
BATES-JENSEN WOUND ASSESSMENT TOOL NAME

Complete the rating sheet to assess wound status. Evaluate each item by picking the response that best describes the wound and entering the score in the item score column for the appropriate date. If the wound has healed/resolved, score items 1, 2, 3, & 4 as = 0.

Location: Anatomic site. Circle, identify right **(R)** or left **(L)** and use **"X"** to mark site on body diagrams:

___ Sacrum & coccyx
___ Trochanter
___ Ischial tuberosity
___ Lateral ankle
___ Medial ankle
___ Heel

Other Site



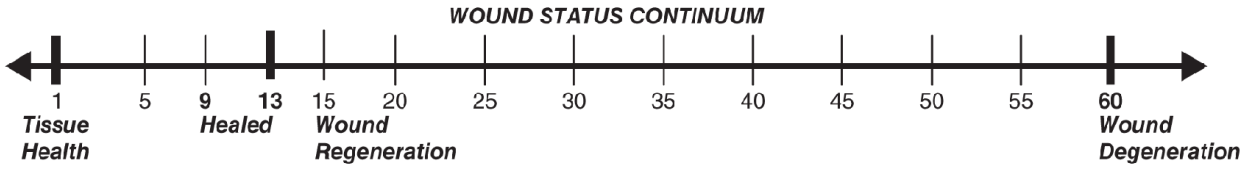
Shape: Overall wound pattern; assess by observing perimeter and depth.
Circle and date appropriate description:

___ Irregular
___ Round/oval
___ Square/rectangle
___ Linear or elongated
___ Bowl/boat
___ Butterfly

Other Shape

Item	Assessment	Date Score	Date Score	Date Score
1. Size*	*0 = Healed, resolved wound 1 = Length × width < 4 sq cm 2 = Length × width 4–< 16 sq cm 3 =Length × width 16.1–< 36 sq cm 4 = Length × width 36.1–< 80 sq cm 5 = Length × width > 80 sq cm			
2. Depth*	*0 = Healed, resolved wound 1 = Nonblanchable erythema on intact skin 2 = Partial thickness skin loss involving epidermis &/or dermis 3 = Full thickness skin loss involving damage or necrosis of subcutaneous tissue; may extend down to but not through underlying fascia; &/or mixed partial & full thickness &/or tissue layers obscured by granulation tissue 4 = Obscured by necrosis 5 = Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures			
3. Edges*	*0 = Healed, resolved wound 1 = Indistinct, diffuse, none clearly visible 2 = Distinct, outline clearly visible, attached, even with wound base 3 = Well-defined, not attached to wound base 4 = Well-defined, not attached to base, rolled under, thickened 5 = Well-defined, fibrotic, scarred, or hyperkeratotic			
4. Under-mining*	*0 = Healed, resolved wound 1 = None present 2 = Undermining < 2 cm in any area 3 = Undermining 2–4 cm involving < 50% wound margins 4 = Undermining 2–4 cm involving > 50% wound margins 5 = Undermining > 4 cm or tunneling in any area			
5. Necrotic Tissue Type	1 = None visible 2 = White/grey nonviable tissue &/or nonadherent yellow slough 3 = Loosely adherent yellow slough 4 = Adherent, soft, black eschar 5 = Firmly adherent, hard, black eschar			
6. Necrotic Tissue Amount	1 = None visible 2 = < 25% of wound bed covered 3 = 25% to 50% of wound covered 4 = > 50% and < 75% of wound covered 5 = 75% to 100% of wound covered			
7. Exudate Type	1 = None 2 = Bloody 3 = Serosanguineous: thin, watery, pale red/pink 4 = Serous: thin, watery, clear 5 = Purulent: thin or thick, opaque, tan/yellow, with or without odor			

Item	Assessment	Date Score	Date Score	Date Score
8. Exudate Amount	1 = None, dry wound 2 = Scant, wound moist but no observable exudate 3 = Small 4 = Moderate 5 = Large			
9. Skin Color Surrounding Wound	1 = Pink or normal for ethnic group 2 = Bright red &/or blanches to touch 3 = White or grey pallor or hypopigmented 4 = Dark red or purple &/or nonblanchable 5 = Black or hyperpigmented			
10. Peripheral Tissue Edema	1 = No swelling or edema 2 = Nonpitting edema extends < 4 cm around wound 3 = Nonpitting edema extends > 4 cm around wound 4 = Pitting edema extends < 4 cm around wound 5 = Crepitus and/or pitting edema extends > 4 cm around wound			
11. Peripheral Tissue Induration	1 = None present 2 = Induration, < 2 cm around wound 3 = Induration 2–4 cm extending < 50% around wound 4 = Induration 2–4 cm extending > 50% around wound 5 = Induration > 4 cm in any area around wound			
12. Granulation Tissue	1 = Skin intact or partial thickness wound 2 = Bright, beefy red; 75% to 100% of wound filled &/or tissue overgrowth 3 = Bright, beefy red; < 75% & > 25% of wound filled 4 = Pink, &/or dull, dusky red &/or fills 25% of wound 5 = No granulation tissue present			
13. Epithelialization	1 = 100% wound covered, surface intact 2 = 75% to < 100% wound covered &/or epithelial tissue extends > 0.5 cm into wound bed 3 = 50% to < 75% wound covered &/or epithelial tissue extends to < 0.5 cm into wound bed 4 = 25% to < 50% wound covered 5 = < 25% wound covered			
	TOTAL SCORE			
	SIGNATURE			



Plot the total score on the Wound Status Continuum by putting an "**X**" on the line and the date beneath the line.
Plot multiple scores with their dates to see-at-a-glance regeneration or degeneration of the wound.

2001Barbara Bates-Jensen

FIGURE 52-1. Bates-Jensen Wound Assessment Tool.

PUSH Tool 3.0

Patient Name:_____ Patient ID#:_____

Ulcer Location: _____ Date:_____

DIRECTIONS:
Observe and measure the pressure ulcer. Categorize the ulcer with respect to surface area, exudate, and type of wound tissue. Record a subscore for each of these ulcer characteristics. Add the subscores to obtain the total score. A comparison of total scores measured over time provides an indication of the improvement or deterioration in pressure ulcer healing.

Length	**0** 0 cm^2	**1** < 0.3 cm^2	**2** 0.3–0.6 cm^2	**3** 0.7–1.0 cm^2	**4** 1.1–2.0 cm^2	**5** 2.1–3.0 cm^2	
× Width		**6** 3.1–4.0 cm^2	**7** 4.1–8.0 cm^2	**8** 8.1–12.0 cm^2	**9** 12.1–24.0 cm^2	**10** > 24 cm^2	**Subscore**
Exudate Amount	**0** None	**1** Light	**2** Moderate	**3** Heavy			**Subscore**
Tissue Type	**0** Closed	**1** Epithelial Tissue	**2** Granulation Tissue	**3** Slough	**4** Necrotic Tissue		**Subscore**
							Total Score

Length × Width: Measure the greatest length (head to toe) and the greatest width (side to side) using a centimeter ruler. Multiply these two measurements (length × width) to obtain an estimate of surface area in square centimeters (cm^2). Caveat: Do not guess! Always use a centimeter ruler and always use the same method each time the ulcer is measured.

Exudate Amount: Estimate the amount of exudate (drainage) present after removal of the dressing and before applying any topical agent to the ulcer. Estimate the exudate (drainage) as none, light, moderate, or heavy.

Tissue Type: This refers to the types of tissue that are present in the wound (ulcer) bed. Score as a "4" if there is any necrotic tissue present. Score as a "3" if there is any amount of slough present and necrotic tissue is absent. Score as a "2" if the wound is clean and contains granulation tissue. A superficial wound that is reepithelializing is scored as a "1." When the wound is closed, score as a "0."

4 - Necrotic Tissue (Eschar): black, brown, or tan tissue that adheres firmly to the wound bed or ulcer edges and may be either firmer or softer than surrounding skin.
3 - Slough: yellow or white tissue that adheres to the ulcer bed in strings or thick clumps, or is mucinous.
2 - Granulation Tissue: pink or beefy red tissue with a shiny, moist, granular appearance.
1 - Epithelial Tissue: for superficial ulcers, new pink or shiny tissue (skin) that grows in from the edges or as islands on the ulcer surface.
0 - Closed/Resurfaced: the wound is completely covered with epithelium (new skin).

Version 3.0: 9/15/98
©National Pressure Ulcer Advisory Panel

FIGURE 52-2. National Pressure Ulcer Advisory Panel Pressure Ulcer Scale for Healing tool. (© National Pressure Ulcer Advisory Panel.)

In general, pressure ulcer healing is accelerated during the initial 3 months after development with 31% of stage 3 and 23% of stage 4 ulcers healing within that time frame. In both partial- and full-thickness pressure ulcers, reduction in size after 1 to 2 weeks of therapy has been shown to be predictive of healing outcomes. Clinical practice guidelines suggest pressure ulcers should show evidence of improvement within 2 to 4 weeks after initiating appropriate treatment, and if no improvement is evident, the treatment plan should be reevaluated. Improvement rates for stage 3 and 4 ulcers are slower than stage 2 ulcers with 75% of stage 2 wounds healing in 60 days, while only 17% of stage 3 or 4 ulcers heal in the same time period.

MANAGEMENT

Local Treatment

Pressure ulcer management includes debridement of necrotic tissue, management of infection and biofilms, adequate wound cleansing, and application of appropriate topical therapy. Wound debridement is necessary to reduce the necrotic tissue burden, decrease risk for infection, and promote granulation tissue formation. Benefits of debridement also may include removal of senescent fibroblasts and nonmigratory hyperproliferative epithelium, and stimulation of blood-borne growth factor production. Debridement is not indicated for dry eschar presenting on the heel or when the pressure ulcer presents on an ischemic limb.

Five methods of debridement (eg, surgical or sharp, mechanical, autolytic, enzymatic, biosurgical) are available. Choice of debridement method is based on clinician preference and availability rather than specific evidence. Clinical practice guidelines on pressure ulcer treatment recommend wound debridement with surgical or sharp debridement for extensive necrosis or when obtaining a clean wound bed quickly is important and more conservative methods (autolytic and enzymatic) for those in long-term care or home care environments. Adequate wound debridement is essential to wound bed preparation and healing. Initial debridement with additional debridement at intervals is often necessary to maintain a biofilm-free wound bed and support healing.

Sharp debridement involves use of a scalpel, scissors, or other sharp instruments to remove nonviable tissue. It is the most rapid form of debridement, and it is indicated over other methods for removing thick, adherent, and/or large amounts of nonviable tissue and when advancing cellulitis or signs of sepsis are present. Health care professionals who use sharp debridement must demonstrate their competency in sharp wound debridement skills and meet licensing requirements. One multicenter, randomized, controlled trial comparing the effects of topical growth factor versus placebo on healing noted that independent of treatment effects, centers that used sharp debridement more frequently experienced better healing rates than those that used sharp debridement less frequently. Sharp debridement is rapid, but is also considered nonselective as viable tissues may be inadvertently removed along with necrotic tissue.

Mechanical debridement involves the use of wet-to-dry dressings, whirlpool, lavage, or wound irrigation. Wet-to-dry gauze dressings continue to be used for debridement, despite the significant disadvantages of increased time/labor for application/removal of the dressings, removing viable tissue as well as nonviable tissue, and pain. This method of debridement should be used cautiously, as it can traumatize new granulation tissue and epithelial tissue, and adequate analgesia should be administered when this method is employed. It is not recommended in clinical practice guidelines.

Enzymatic debridement involves applying a concentrated, commercially prepared enzyme to the surface of the necrotic tissue, in the expectation that it will aggressively degrade necrosis by digesting devitalized tissue. The main enzyme ointment available in the United States is collagenase. Some of the effects noticed with enzymatic agents have been attributed to autolysis. Enzymatic ointments have yielded consistently positive results for their efficacy in wound debridement. Debridement with enzymatic ointments is faster than with autolysis, and more conservative than sharp debridement.

Autolytic debridement is the process of using the body's own mechanisms to remove nonviable tissue. Maintaining a moist wound environment allows collection of fluid at the wound site, which allows enzymes within the wound fluid to digest necrotic tissue. Autolytic debridement typically involves adequate wound cleansing to wash out the partially degraded nonviable tissue. It is more effective than wet-to-dry gauze dressings, as it selectively removes only the necrotic tissue and therefore protects healthy tissues. Autolytic debridement may be slower to achieve a clean ulcer bed than other methods.

Biosurgery is the fifth method of debridement. Biosurgery is the application of maggots (disinfected fly larvae, *Phaenicia sericata*) to the wound typically at a density of 5 to 8/cm^2. Comparative controlled studies evaluating the use of maggot therapy for pressure ulcer debridement have shown a higher proportion of complete debridement in maggot-treated wounds versus standard debridement therapy (80% vs 48%, respectively). Biosurgery may not be acceptable to all patients, and may not be available in all areas.

Pressure ulcers are the result of ischemia and as such, they are more susceptible to infection. Stage 3, 4, and unstageable pressure ulcers should be evaluated for infection. One difference in dealing with infection in chronic wounds such as pressure ulcers compared to acute wounds is the assessment and treatment of bacterial biofilms. Biofilms are the critical colonization of microorganisms on the wound bed that develop support structures that protect the bacteria. Biofilms cause chronic inflammation and have enhanced resistance to endogenous antibodies and phagocytic cells and exogenous antibiotics and antimicrobial solutions. Approximately 60% of chronic wounds contain bacterial biofilms, and this may be the underlying pathology preventing wounds like pressure ulcers from healing. Biofilm presence in pressure ulcers should be suspected when any of the following exist:

- Lack of signs of healing for 2 weeks *with* appropriate care
- Friable granulation tissue
- Odor
- Increased pain, heat, exudate, or necrotic tissue
- Change in exudate character
- Pocketing or tunneling in the wound bed

Bacterial burden of the pressure ulcer should be determined by tissue biopsy or quantitative swab technique (do not swab necrotic tissue or exudate, rotate end of swab over 1 cm^2 area for 5 seconds with sufficient force to cause tissue fluid expression). Use of antiseptic solutions for a course of therapy may be beneficial in reducing and/or preventing bacterial biofilms and supporting granulation tissue development and wound healing.

The best method of preventing biofilm development is adequate, timely, and complete debridement of necrotic tissue followed by appropriate topical therapy.

Pressure ulcer cleansing at each dressing change is recommended in clinical practice guidelines on pressure ulcer treatment. However, there is evidence that antiseptic solutions such as 5% mafenide acetate (Sulfamylon solution), 10% povidone with 1% free iodine (Betadine), 0.25% sodium hypochlorite ("half strength" Dakin solution), 3% hydrogen peroxide, and 0.25% acetic acid have varying effects on wound healing parameters as well as antimicrobial management in an animal wound model yet, how this affects human wounds is unclear.

Use of antiseptic and antimicrobial solutions for cleansing *clean* pressure ulcers is not indicated based on in vitro studies of the toxicity of topical wound cleansers. Findings from in vitro studies have not been confirmed in human wounds. Use of antiseptic and antimicrobial solutions for cleansing pressure ulcers with *necrotic* debris should be employed thoughtfully with attention to the solution chosen, the characteristics of the microorganisms present in the wound, and duration of use (eg, course of therapy for 2 weeks with evaluation for continuation at that time).

In general, if an ulcer contains necrotic debris or is infected, then antimicrobial activity is more important than cellular toxicity. The chemical and mechanical trauma of wound cleansing should be balanced by the dirtiness of the wound. For wounds with large amounts of debris, more vigorous mechanical force and stronger solutions may be used, while for clean wounds, less force and physiologic solutions such as normal saline should be used.

Topical therapy for pressure ulcers should be provided using moist wound healing dressings. Randomized controlled trials as well as several comparative studies provide compelling support for use of moist wound healing dressings instead of any form of dry gauze dressings (eg, wet-to-dry gauze, dry gauze dressing, or impregnated gauze dressing) for pressure ulcers. Moist wound healing allows wounds to re-epithelialize up to 40% faster than wounds left open to air. Controlled trials suggest that the use of semiocclusive dressings such as transparent films and hydrocolloid dressings improves healing of stage 2 pressure ulcers. These dressings are changed every 3 to 5 days, which allows wound fluid to gather underneath the dressing, facilitating epithelial migration. Moderate evidence exists to specifically support use of hydrocolloid dressings for pressure ulcer care in stage 3/4 pressure ulcers. One multicenter, randomized trial demonstrated faster healing in stage 3/4 pressure ulcers when treated sequentially with calcium alginate dressings followed by hydrocolloid dressings versus nonsequentially with hydrocolloid dressings. However, the relative merits of different categories of moisture retentive dressings versus another remain unclear. **Table 52-2** presents general characteristics of moisture retentive dressing categories.

TABLE 52-2 ■ GENERAL CHARACTERISTICS OF MOISTURE RETENTIVE DRESSING CATEGORIES

DRESSING CATEGORY	DEFINITION	USES	NOTES
Composite Dressings	Combine one dressing group with another to address wound characteristics. For example, gauze/foam and transparent film dressing properties, hydrocolloid, and alginates, etc.	Absorbent (depends on combination of dressings used in the composite) Wicks away excess moisture Nonadherent to wound bed Use depends on the combination of dressings used in the composite	• Some may be difficult to apply • If nonadherent to wound bed then requires secondary dressing to hold in place • Can be confusing to caregivers as combines various dressing category properties
Transparent Film Dressings	Polyurethane and polyethylene membrane	Appropriate for partial-thickness wounds	• May reinjure area on removal • Nonabsorbent so can lead to wound

	film coated with a layer of acrylic hypoallergenic adhesive. Moisture vapor transmission rates (MVTR) vary	Promotes epithelialization Semipermeable Bacterial barrier Autolysis Wound visible Protects against friction Self adhesive	edge maceration • Tendency to remove prematurely • Indicated for minimal exudate, does not absorb drainage • Not indicated for moderate-to-heavy exudate
Hydrocolloids Regular or thin wafers, paste, granules	Gelatin, pectin, carboxymethylcellulose in a polyisobutylene adhesive base with a polyurethane or film backing	Absorbs low-to-moderate wound fluid Autolysis Thermal insulation Bacterial barrier Reduces pain Translucent to opaque Easy to apply Controls odor (until dressing removed) Impermeable to semipermeable	• Not indicated for heavy exudate, limited absorbent abilities when used alone • Use with other products increases absorbent abilities • Odor on removal • Regular wafers are opaque, thin wafers allow some wound visualization • Edges may melt down and stick to linens • Some difficult to remove • Possible sensitivity to adhesive backing • Use with close supervision on immunosuppressed and diabetic patients, extensive burns, infected lesions
Hydrogels Sheets, wafers Amorphous gels Impregnated gauze	May or may not be supported by a fabric net, high water content, varying amounts of gel-forming material (glycerin, copolymer, water, propylene glycol, humectant)	Absorbs low-to-moderate drainage Autolysis Nonadhesive, may have adhesive borders Semipermeable or impermeable depending on backing Thermal insulation Reduces pain Conformable Carrier for topical medication	• Can dry out • May macerate surrounding tissues • Requires secondary dressing or tape to keep in place • Does not cause reinjury upon removal • Cooling effect can help relieve wound pain • Candidiasis may present from inappropriate usage
Wound Fillers (Exudate Absorbers) Beads, flakes Pastes, powders	Consists of copolymer starch, dextranomer beads or hydrocolloid paste that swell on contact with wound fluid to form gel, dextranomers, polysaccharides, starch, natural polymers, and colloidal particles	Moisture retentive Absorptive (moderate to large) Useful to fill cavities, pockets, undermining Can be used with topical medications	• Nonadhesive • Requires a secondary dressing to hold in place • May have burning sensation on application • May have odor • Some require mixing • Some require wound irrigation for nontraumatic removal
Alginates Ropes, pads, wafers	Calcium-sodium salts of alginic acid (naturally occuring polymer in seaweed)	Absorptive (moderate to large) Useful to fill cavities, pockets, undermining Moisture retentive Can use with topical medications or on infected wounds	• Nonadherent, requires secondary dressing to hold in place • Hemostatic properties • May require wound irrigation for removal • No reinjury on removal

		Reduces pain Thermal insulation	• May dry out, should not be used on wounds with low exudate
Foams Wafers (thick or thin), pillows, composite dressings with thin film covers, available with surfactant impregnated or charcoal layer	Inert material that is hydrophilic and nonadherent, modified polyurethane foam	Absorptive (moderate to large) Autolysis Can be used with topical medications and on infected wounds Conformable Thermal insulation	• Nonadhesive unless used with composite dressing • Requires tape or secondary dressing to hold in place • Nontraumatic removal • Opaque • Waterproof, inert
Hydrofibers Pads, wafers, ropes	Soft nonwoven pad or ribbon dressings made from sodium carboxymethyl-cellulose fibers, similar absorbent material used in hydrocolloid dressings	Absorptive (moderate to large) Autolysis Thermal insulation Reduces pain	• Nonadherent, requires secondary dressing to hold in place • Hemostatic properties • May require wound irrigation for removal • No reinjury on removal

Evidence supporting use of advanced wound therapy in pressure ulcers is unclear. There is some evidence supporting use of negative pressure wound therapy (NPWT) in large stage 3 and 4 nonhealing pressure ulcers with poor granulation tissue or excess exudate. Several clinical practice guidelines and panels have recommended use of NPWT with large stage 3 and 4 pressure ulcers that have failed to improve with standard care with moist wound healing. A case series of 10 patients with stage 4 pressure ulcers treated with NPWT showed greater than 50% average reduction in wound volume and depth (55% and 61%, respectively) over 4 weeks. Some have suggested that NPWT use should result in pressure ulcer improvement within a 2-week time period with further use questionable if improvement is not evident. Use of skin and tissue substitutes has not been examined specific to pressure ulcers but may be of benefit in certain populations with full-thickness ulcers.

Surgery

Surgical treatment of pressure ulcers includes primary closure, a variety of approaches to skin grafts and myocutaneous flaps, and removal of underlying bony prominences. In patients with large infected pressure ulcers, more aggressive procedures such as amputation and hemicorporectomy are sometimes required. Surgical complication rates (including dehiscence, infection, necrosis, and hematoma) for both younger paraplegic patients and nonparaplegic elders are as high as 50%, and pressure ulcer recurrence at the same site has been reported ranging from 30% to 70%. Thus, the long-term outcomes have not been ideal even though 70% to 80% of surgically treated pressure ulcers are healed upon discharge from the hospital. Further, while recurrence of pressure ulcers at the same site is lower for elders (40%) compared to younger paraplegic patients (more than 70%), 30% of elders develop new ulcer sites, and mortality in elders ranges from nearly 50% to 68%.

Thus, the benefits of surgical closure for pressure ulcer are uncertain. In addition to questions about the efficacy of surgical intervention, geriatric patients present with multiple chronic diseases and conditions that may make them less than ideal surgical candidates or affect rehabilitation efforts after surgery.

Drugs

Pharmacologic interventions for pressure ulcers focus on antibiotics and pain management. Antibiotics may be systemic or local. Clinicians should institute systemic antibiotics for patients exhibiting signs and symptoms of systemic infection such as sepsis or cellulitis with associated fever and an elevated white blood cell count. Systemic antibiotics should be initiated for osteomyelitis or for the prevention of bacterial endocarditis in persons with valvular heart disease and who require debridement of a pressure ulcer. Because of the high mortality of sepsis associated with pressure ulcers despite appropriate antibiotics, broad-spectrum coverage for aerobic gram-negative rods, gram-positive cocci, and anaerobes is indicated pending culture results in patients with suspected bacteremia. Ampicillin-sulbactam, imipenem, meropenem, ticarcillin-clavulanate, piperacillin-tazobactam, and a combination of clindamycin or metronidazole with ciprofloxacin, levofloxacin, or an aminoglycoside are appropriate choices for initial antibiotic therapy. Vancomycin may be required for MRSA.

Use of cadexomer iodine (not the same as povidone iodine) topical dressings has been shown to be effective for pressure ulcers colonized with MRSA. The most effective strategy for preventing infection and dealing with existing infection is adequate and full debridement of necrotic tissue followed by additional debridement to remove and prevent bacterial biofilm development. In patients with signs and symptoms of systemic infection and in those who are septic, the appropriate debridement method is surgical debridement.

Topical antibiotics are most appropriate for stage 3 or 4 ulcers when there is evidence of local infection such as erythema surrounding a clean nonnecrotic wound, failure to improve with adequate treatment, or friable granulation tissue. A 2-week trial of a broad- spectrum topical antibiotic can be considered for clean pressure ulcers that are not healing after 2 to 4 weeks of optimal management. Use of cadexomer iodine dressing or cleansing with hypochlorous acid solution may also be appropriate in this situation. On the other hand, clinicians should not use povidone-iodine, iodophor, sodium hypochlorite, hydrogen peroxide, or acetic acid as topical therapies on *clean* pressure ulcers. These antiseptic agents have been shown to be toxic to fibroblasts and to impair wound healing in in vitro laboratory studies, and how these solutions affect human wounds is unclear. There is no evidence for using prolonged silver release dressings in routine management of healing pressure ulcers.

There is limited evidence to guide clinicians on appropriate management of pressure ulcer–related pain. The pressure ulcer alone may not require routine pain medication, but medication prior to procedures is essential. Lower levels of pain may be manageable with appropriate wound dressing choice and topical wound analgesia. Nonpharmacologic techniques useful for noncyclic and cyclic wound pain associated with procedures (eg, debridement, dressing changes, repositioning) include use of distraction (eg, talking to the patient while performing the procedure), allowing the patient to call a “time-out” during the procedure, and allowing the patient to control and participate in the procedure.

Pressure ulcer–related pain can be minimized by keeping the pressure ulcer wound bed moist and covered. Use of hydrogels, hydrocolloids, alginates, polymeric membrane foams, and soft silicone dressings allows for less frequent dressing changes, and less trauma and pain on removal as they are nonadherent to the wound bed.

Pharmacologic strategies for wound pain include providing opioids and/or nonsteroidal anti-inflammatory drugs (NSAIDs) 30 minutes prior to the procedure and afterward, and administering topical anesthetics or topical opioids using hydrogels as a transport media. Two options have been successful for use in chronic wound pain, EMLA cream and diamorphine gel. EMLA cream (eutectic mixture of lidocaine 2.5% and prilocaine 2.5%) reduces debridement pain scores in chronic venous ulcers, and may have a vasoactive effect cutaneously. Use of EMLA cream in venous ulcers has been associated with a reduction in pain scores (measured on a 100-mm scale) of 20.6 mm. Low-dose topical morphine (diamorphine) has been used in several small, randomized, placebo-controlled studies to successfully control pressure ulcer–related pain.

Nutrition

Multiple studies have demonstrated a relationship between different markers of malnutrition (eg, serum albumin level, dietary protein intake, inability to feed self, and weight loss) and pressure ulcer formation. Other studies have demonstrated that the severity of the pressure ulcer is associated with the severity of the malnutrition. Malnutrition and/or weight loss has been associated with fourfold higher risk of pressure ulcer development. Although it seems intuitive, it has proven difficult to define a specific causal relationship between malnutrition and pressure ulcer development. Modest evidence exists to support providing oral nutritional supplements to persons at risk for pressure ulcers with relative reduction in pressure ulcer incidence of 25%. Moderately strong evidence exists that use of high-protein nutritional supplements (24%–25% protein) improves pressure ulcer healing. Providing 30 to 35 kcal/kg and 1.25 to 1.5 g/kg of calories and protein daily has been shown to significantly improve pressure ulcer healing. However, provision of nutritional supplementation by tube-feeding to persons with pressure ulcers has not achieved positive results.

No evidence exists for use of supplemental vitamins or minerals (eg, vitamin A, E, C, zinc) in persons with pressure ulcers with no coexisting specific vitamin/mineral deficiency to improve pressure ulcer healing. Moderate evidence exists to support use of high-calorie, high-protein nutritional supplements containing arginine to promote pressure ulcer healing in older adults in general (significant decrease in ulcer size at 8 weeks favoring supplement), older adults who do not have preexisting malnutrition (significant decrease in ulcer size and PUSH score over 8 weeks favoring supplement), and persons with SCI (10 vs 21 weeks to healing favoring supplement). Persons with pressure ulcers or at risk of developing pressure ulcers who also demonstrate malnutrition should have a standard nutritional assessment to identify deficits and nutrition support as indicated. A daily multivitamin and mineral supplement that

provides recommended daily allowances of vitamins and minerals is recommended for persons with suspected nutritional deficiencies.

PREVENTION

Pressure ulcer prevention involves scheduled turning and repositioning programs, use of support surfaces to reduce/relieve pressure, nutritional support (discussed earlier), and general skin care. Prevention interventions should be implemented for persons at risk for pressure ulcer development and those with existing pressure ulcers as part of the treatment plan.

Patients at risk for pressure ulcers that are unable to move independently should be placed on scheduled repositioning programs. The recommended time interval for full change of position or turning while in bed is every 2 hours, depending on the individual patient profile and the use of support surfaces. Pressure-reducing support surfaces (eg, foam, air, gel-filled mattress overlays, low-air-loss therapy devices) may reduce the frequency of repositioning required in some patients. One controlled clinical trial evaluating the effects of four different turn intervals in conjunction with standard hospital mattress versus a pressure reduction support surface found differences in pressure ulcer incidence. The four turn intervals evaluated were 2 hours on standard mattress (2 hours), 3 hours on standard mattress (3 hours), 4 hours on pressure-reducing surface (4 hours), 6 hours on pressure-reducing surface (6 hours) and a control group with usual care (no specified turning schedule). Over 4 weeks, 838 geriatric nursing home residents were evaluated. Although there was no difference in the incidence of stage 1 pressure ulcers or erythema, stage 2 pressure ulcer incidence was significantly decreased in the 4-hour group compared to all other groups (3% compared to 20%, no turns; 14.3%, 2 hours; 24.1%, 3 hours; and 15.9%, 6 hours). Others have shown similar findings related to use of a 4-hour repositioning program in conjunction with use of viscoelastic support surfaces.

Repositioning patients to avoid placing pressure on bony prominences, in particular the malleolus and trochanter is important. To avoid placing pressure on the trochanter and outer malleolus, position the patient at a 30-degree side-lying position (eg, 30-degree angle to the support surface) instead of the commonly used 90-degree side-lying position, which increases tissue compression over the trochanter and malleolus. Maintain the head of the bed at the lowest degree of elevation consistent with medical conditions, and limit the amount of time the head of the bed is elevated. This will decrease exposure of the sacral area to shearing and friction forces that may predispose to DTI. Use of footboards and pillows under the lower legs to prevent sliding and to maintain position, is also helpful in reducing shear effects on the skin when in bed.

There are techniques to make turning patients easier and less time consuming. Turning sheets, draw sheets, and pillows are essential for passive movement of patients in bed. Turning sheets are useful in repositioning the patient to a side-lying position, and draw sheets are used for pulling the patient up in bed and help to prevent dragging the patient's skin over the bed surface. Pillows should be used to position patients with minimal tissue compression between the medial knees, the medial malleolus, and the heels. Place pillows between the knees, between the ankles, under the heels as well as behind the back, and under the arms for comfort.

Use of real-time pressure mapping systems has been used to improve frequency of repositioning activities by caregivers. Pressure mapping systems may have a positive impact on pressure ulcer development because the duration and amount of pressure over specific bony prominences are displayed for caregivers allowing for more accurate offloading of bony prominences.

Similar approaches are useful for patients in chairs. Full-body change of position involves standing the patient and resitting them in the chair. Observation of the patient when sitting is also important, because patients who slide out of the chair are at high risk for shear or friction injury. Use of footstools and the foot pedals on wheelchairs and appropriate 90-degree flexion of the hip (may be achieved with pillows, special seat cushions, or orthotic devices) can help prevent chair sliding. Attention to proper alignment and posture is essential. Individuals at risk for pressure ulcer development should avoid uninterrupted sitting in chairs and should be repositioned every hour. The rationale behind the shorter time is extremely high pressure generated on the ischial tuberosities and sacrum in the seated position. When possible, individuals who are able should be taught to shift weight every 15 minutes while seated.

Repositioning for preventing pressure ulcers at the heel location involves completely offloading the heel using suspension devices or pillows. The goal is to keep the heels free of all pressure or "float" the heels. Elevating the lower leg and calf with pillows or suspension devices spreads the pressure to the lower legs and the heel is no longer subjected to pressure. Heel suspension devices are preferable for long-term use over pillows as it can be difficult for patients to keep their legs on pillows over longer time frames.

Reactive or active support surfaces should be initiated for beds and chairs of persons determined at risk for developing pressure ulcers. Reactive support surfaces are powered or nonpowered surfaces with the ability to only change load distribution properties in response to an applied load. Reactive surfaces are designed to reduce pressure ulcer development by deforming in response to loading with the goal of immersion and envelopment to reduce the deformation caused by pressure over the bony prominence. Active support surfaces are powered surfaces that produce alternating pressure through mechanical means and have the ability to change load distribution properties with or without an applied load. Active surfaces are designed to reduce pressure ulcer development by periodically shifting the areas of support on anatomic locations so that deformation is not sustained over one area. In general, active support surfaces are recommended for persons at higher risk for pressure ulcer development when frequent repositioning is not possible.

Use of support surfaces instead of standard hospital mattresses results in relative reduction in pressure ulcer incidence of 60%. Additionally, clinicians should advocate for use of support surfaces in the operating room to reduce postoperative pressure ulcer incidence. Use of reactive support surfaces such as mattress overlays (eg, foam, gel, or alternating air pads) or active surfaces such as low-air-loss therapy is appropriate for many patients at risk for pressure ulcers or with stage 1 or 2 pressure ulcers. However, for persons with existing pressure ulcers, use of air-fluidized therapy or low-air-loss therapy may improve healing rates. One retrospective, multisite, comparison study showed faster healing of existing pressure ulcers with air-fluidized therapy compared to both pressure reduction support surfaces and low-air-loss therapy (mean healing rate of 5.2 cm^2/week for the air-fluidized surface group compared to 1.5 cm^2/week for pressure reduction support surface group and 1.8 cm^2/week for low-air-loss therapy group). In addition, the odds of showing improvement in pressure ulcers are more than five times greater when air-fluidized therapy and 4-hour repositioning is implemented compared to alternating air mattresses and 2-hour repositioning in hospitals. Although air-fluidized therapy increased the odds of ulcer improvement, only 12% of hospitalized patients achieved healing of the largest pressure ulcer. In nursing home residents, a randomized, controlled trial suggests that pressure ulcer areas decrease three times faster when low-air-loss beds are used compared with conventional care. Additional controlled trials are needed to define the optimal repositioning schedules for patients on a variety of support surfaces.

Providing topical preparations or fabrics/linens (silk or noncotton blends) to eliminate or reduce the surface tension between the skin and the bed linen or support surface will assist in reducing friction-related injury. Use of appropriate techniques when moving patients so that skin is not dragged across linens will lessen friction-induced skin breakdown. Patients who exhibit voluntary or involuntary repetitive body movements (particularly of the heels or elbows) require stronger interventions. Use of a protective film, such as a transparent film dressing or a skin sealant; a protective dressing, such as a thin hydrocolloid; or protective padding will help to eliminate the surface contact of the area and decrease the friction between the skin and the linens. Even though heel, ankle, and elbow protectors do nothing to reduce or relieve pressure, they can be effective aids against friction. Posthip fracture patients are especially vulnerable to heel ulcers. Elevation of the heel off the bed surface is a useful preventive measure.

Use of prophylactic silicone foam dressings over bony prominences has demonstrated significantly decreased heel (3% vs 12% favoring dressing) and sacral (1% vs 5% favoring dressing) pressure ulcers among critical care patients with the number needed to treat of 10 to prevent any ulcer. Similar findings for preventing heel ulcers among residents in long-term care facilities by prophylactically applying a polyurethane foam hydrocellular dressing have been shown. Use of prophylactic silicone foam, hydrocolloid, foam, or silicone gel dressings around medical devices has also been shown to decrease pressure ulcer development related to medical devices including tracheostomy tubes, nasal intubation tubes, and nasal continuous positive airway pressure (CPAP) devices.

General skin care should include routine skin inspection, incontinence assessment and management, and skin hygiene interventions to maintain skin health. Routine skin inspection should occur daily with particular attention to bony prominences. Reddened areas should not be massaged. Massage can further impair the perfusion to the tissues. The skin should be evaluated for dryness and cracking, and use of moisturizers can be helpful. Attention should also be focused on gentle handling to prevent skin tears. Incontinence assessment and management with scheduled toileting or prompted voiding programs and for those unresponsive to these programs check and change schedules are important. Prompt cleansing after incontinent episodes with warm water and gentle cleansers and use of protective ointments and creams help maintain perineal skin health. **Table 52-3** presents general prevention interventions directed at risk factors for pressure ulcer development.

TABLE 52-3 ■ PRESSURE ULCER PREVENTION INTERVENTIONS

RISK FACTOR	PREVENTION INTERVENTONS
Immobility	Scheduled repositioning programs, use of pressure reduction/relief surfaces in bed and chairs.
Inactivity, limited mobility	Use of trapeze bars for self-movement in bed, encourage ambulation, rehabilitation as appropriate.
Decreased sensory perception	Scheduled repositioning programs, verbal reminders to move/reposition, use of pressure reduction/relief surfaces in bed and chairs.
Malnutrition	Nutritional assessment to determine deficits, nutritional supplementation (high protein), and daily multivitamin if indicated and appropriate to goals.
Excess moisture and incontinence	Scheduled toileting or prompted voiding programs if responsive, routine check and change programs with pads and adult briefs for persons who do not respond to scheduled toileting or prompted voiding, use of skin creams and ointments for protection from moisture.
Friction and shearing	Use of trapeze bars for those with upper body strength, turn sheets and draw sheets for moving in bed, use of cornstarch or lubricants to limit friction between surfaces, thin film or dressings, and pads over bony prominences subject to friction, use of footboards to help prevent sliding while in bed.
Dry skin	Use warm water, gentle cleansers, and limited force for cleansing when soiled and for routine bathing, lubricate and moisturize dry skin, inspect skin daily paying particular attention to bony prominences, avoid massage of reddened areas.

SPECIAL ISSUES

Some patients will benefit most from a palliative care approach. Palliative pressure ulcer care means that the goals are comfort and limiting the extent or impact of the pressure ulcer but without the intent of healing. Palliative care may be indicated for terminally ill patients such as those with end-stage cancer or in the terminal stages of other diseases. Institutionalized older adults with multiple comorbidities or older adults with severe functional decline may also benefit from palliative care. Palliative pressure ulcer care includes adequate debridement of necrotic tissue, identification and treatment of infection, provision of moist wound healing with management of exudate and odor, pain management, and prevention interventions. Prevention should still consist of use of reactive or active support surfaces and attention to scheduled repositioning, although time frames may be adjusted or lengthened to ease the burden on the patient. Providing pain medication 30 to 40 minutes prior to repositioning activity and use of positioning devices may help those with pain on movement.

SUMMARY

Pressure ulcers are chronic wounds and as such, require patience and diligence by clinicians. Some pressure ulcers never heal, and most require long periods of treatment with slow progress. Partial-thickness stage 2 pressure ulcers are more likely to heal than full-thickness stage 3 or 4 pressure ulcers. In fact, stage 2 pressure ulcers are 5.2 times more likely to heal in 6 months than stage 4 pressure ulcers. Among nursing home residents, up to 75% of stage 2 wounds heal within 60 days, while only 17% or fewer full-thickness pressure ulcers heal in the same time period. The best healing rate reported even after 6 months of treatment is 59%. Thus, identification of persons at risk for developing pressure ulcers and aggressive prevention interventions to actively avoid ulcer development are essential. Prevention includes screening for risk followed by risk assessment using standardized risk assessment tools to determine individual specific risk and implementing targeted prevention interventions based on identified risk factors. Scheduled repositioning programs, use of reactive and active support surfaces, assessment and management of nutrition, and use of prophylactic dressings are key prevention strategies. More research is needed to define optimal turning intervals for various support surfaces, to better elucidate the effect of nutrition interventions on both preventing pressure ulcers and healing pressure ulcers, and fully examine specific use of prophylactic dressings.

For those persons who do develop pressure ulcers, clinicians should provide appropriate treatment during early ulcer stages to capitalize on healing progress in the initial 3 months. Adequate, timely, and complete debridement of necrotic tissue, identification and treatment of infection and management of biofilm development, and providing a moist wound environment are the key tenets of appropriate pressure ulcer care. All preventive and therapeutic

interventions, and progress of the ulcer, should be carefully documented in the medical record. Unfortunately, no intervention or combination of interventions has demonstrated the ability to completely eliminate pressure ulcers. Thus, even as we develop more refined and specific screening, detection, and prevention interventions, it is likely we will continue to see pressure ulcers in all health care settings. The information presented in this chapter should provide a foundation for developing a successful approach to both those at risk for pressure ulcer development and those with existing pressure ulcers.

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Chapter 53

Incontinence

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Learning Objectives

- Identify different types of urinary incontinence based on clinical assessment.
- Describe initial management strategies for incontinence in the older adult, which involve soliciting patient preferences and goals for care.
- Determine when referral to a urologic or gynecologic specialist is indicated.

Key Clinical Points

1. **Incontinence in the older adult is often the result of potentially reversible and modifiable conditions.**
2. **Multicomponent interventions, including lifestyle and behavioral therapies, are effective first-line treatments for incontinence in the older adult.**
3. **Treatment of incontinence in the older adult, particularly drug therapy, should involve consideration of patient preferences and comorbid conditions.**

DEFINITION AND EPIDEMIOLOGY

Defined as the complaint of any involuntary leakage of urine, urinary incontinence is a common and bothersome condition in older adults. The prevalence of incontinence increases with age and with increasing frailty, and is 1.3 to 2.0 times greater in older women than in older men. Among community-dwelling older women, the prevalence of any urinary incontinence is approximately 35%; among older men, it is approximately 22%. The prevalence of daily urinary incontinence in older community-dwelling persons is approximately 12% for women and 5% for men. The prevalence approaches 60% among nursing home residents. Incontinence ranges in severity from occasional episodes of dribbling small amounts of urine to continuous urine leakage with concomitant fecal incontinence. In addition, many older people who do not “leak urine” still may have bothersome lower urinary tract symptoms such as urgency, frequency, and nocturia that require changes in lifestyle and/or the use of pads.

Physical health, psychological well-being, social status, and the costs of health care can all be adversely affected by incontinence. Urinary incontinence can be cured or greatly improved, especially in those who have adequate mobility and mental functioning. Even when not curable, incontinence can always be managed to allow for more patient comfort, make life easier for caregivers, and minimize costs of caring for the condition. Because many older patients are embarrassed to discuss their incontinence and may not be aware that treatment is available, it is essential for specific questions about incontinence to be included in periodic assessments and for incontinence to be noted as a problem (**Table 53-1**). This chapter briefly reviews the pathophysiology of urinary incontinence in older persons, provides detailed information on the evaluation and management of this condition, and briefly reviews fecal incontinence.

TABLE 53-1 ASKING ABOUT URINARY INCONTINENCE

Questions about incontinence should be open ended and phrased in language easily understood by the patient:
"Tell me about any problems you are having with your bladder."
"Tell me about any trouble you are having holding your urine (water)."
If the responses to the above questions are negative, following up with questions may be helpful:
"How often do you lose urine when you don't want to?"
"How often do you wear a pad or other protective device to prevent urinary accidents?"

Adapted from Fantyl JA, Newman DK, Colling J, et al. Urinary Incontinence in Adults: Acute and Chronic Management. Clinical Practice Guideline No. 2, 1996 Update. Rockville, MD: U.S. Dept of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1996. AHCPR publication 96–0682.

PATHOPHYSIOLOGY AND CLASSIFICATION

Continence requires effective functioning of the lower urinary tract, adequate cognitive and physical functioning, motivation, and an appropriate environment (**Table 53-2**). Anatomic and physiologic aspects of the lower urinary tract, as well as functional, psychological, and environmental factors, contribute to the pathophysiology of incontinence in older persons. Normal urination is a complex process; the neurophysiology of urination remains incompletely understood. Proper bladder filling and emptying are influenced by higher centers in the brain stem, cerebral cortex, and cerebellum. The brain stem facilitates urination and the cerebral cortex exerts a predominantly inhibitory influence. Additionally, the loss of the suprapontine inhibitory influences over the sacral micturition center from diseases such as stroke and Parkinson disease can produce incontinence in older patients. Even in the absence of specific, overt neurologic lesions, poor bladder control has been shown to be associated with inadequate activation of the orbitofrontal cortex and white matter hyperintensities (evidence of white matter wasting) in the right inferior frontal cortex. Disorders of the brain stem and lesions rostral to the lumbosacral spinal cord can interfere with the coordination of bladder contraction and urethral relaxation leading to detrusor-sphincter dyssynergia. Interruptions of the sacral innervation can cause impaired bladder contraction and problems with continence.

TABLE 53-2 ■ REQUIREMENTS FOR CONTINENCE

Effective lower urinary tract function
Storage
Bladder accommodation with increasing urine volumes while maintaining low pressure
Closed bladder outlet
Appropriate sensation of bladder fullness
Absence of involuntary bladder contractions
Emptying
Bladder capable of contraction
Lack of anatomic obstruction to urine flow
Coordinated lowering of outlet resistance with bladder contractions
Adequate mobility and dexterity to use toilet
Adequate cognitive function to recognize toileting needs
Motivation to be continent
Absence of environmental and iatrogenic barriers

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

At the most basic level, urination is governed by a reflex centered in the sacral micturition center. During normal bladder filling, afferent pathways (via somatic and autonomic nerves) carry information on bladder volume to the spinal cord. Motor output is adjusted accordingly (**Figure 53-1**). Sympathetic tone closes the bladder neck and inhibits parasympathetic tone (thus relaxing the dome of the bladder); somatic innervation maintains tone in the pelvic floor

musculature (including striated muscle around the urethra). Voluntary pelvic floor muscle contracture also leads to inhibition of parasympathetic tone. For bladder emptying, sympathetic and somatic tones diminish, and parasympathetic, cholinergically mediated impulses cause the bladder to contract. Normal urination is a dynamic process, requiring the coordination of several physiologic processes. Under normal circumstances, as the bladder fills, bladder pressure remains low ($\leq$ 15 cm H_2O). The bladder volume at first urge to void is variable, but generally occurs at between 150 and 350 mL; normal bladder capacity is 300 to 600 mL. When normal urination is initiated (usually every 3 to 4 hours during wakefulness), the detrusor contracts and detrusor pressure increases until it exceeds urethral resistance (which lowers immediately prior to bladder contraction). Urine flow occurs typically over less than 2 minutes. If at any time during bladder filling, total bladder pressure exceeds outlet resistance, urinary leakage occurs. Transmitted intra-abdominal pressure alone by coughing or sneezing may cause leakage in someone with low outlet resistance pressure or urethral sphincter weakness. Alternatively, the bladder can contract involuntarily and cause urinary leakage.

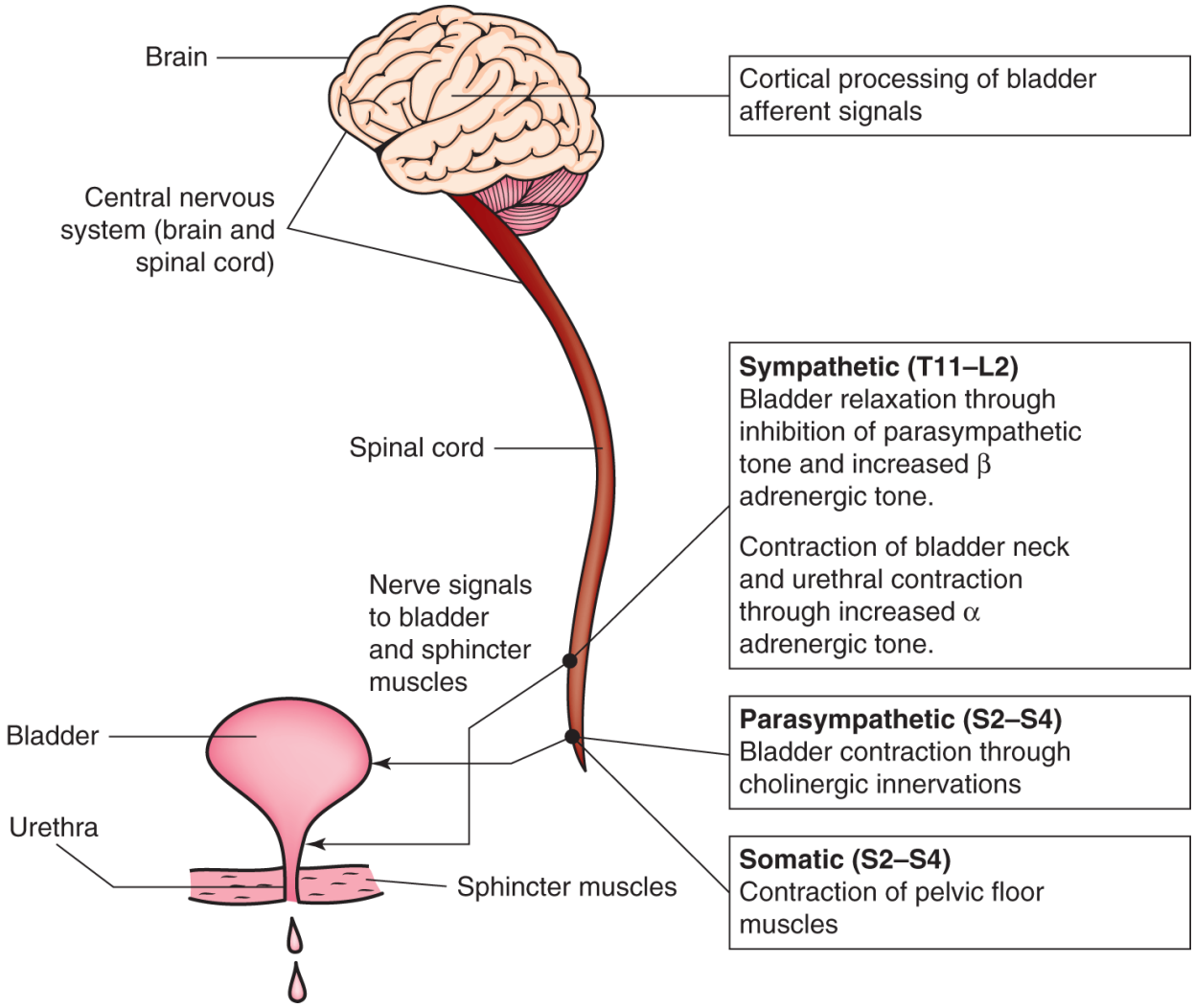


FIGURE 53-1. Central and peripheral nervous system involvement in micturition. (Adapted from http://www.niddk.nih.gov/health-information/health-topics/urologic-disease/nerve-disease-and-bladder-control/Pages/facts.aspx. Accessed May 18, 2016.)

Basic Causes

Urologic, neurologic, psychological, and functional factors may contribute to incontinence. As is the case for a number of other common geriatric problems, multiple disorders often interact to cause urinary incontinence. Determining the cause or causes facilitates proper management. Overall, aging is associated with increasing incontinence. The prevalence of stress incontinence likely does not increase in women with aging, while the prevalence of urge incontinence and mixed stress-urge incontinence do increase.

Several age-related changes can contribute to the development of urinary incontinence. In general, residual urine

volume following voiding is greater with increasing age. While a decline in functional bladder capacity has been associated with advanced age, this may be because of the higher prevalence of involuntary bladder contractions and detrusor overactivity in older persons. Involuntary bladder contractions are found in 40% to 75% of older incontinent patients, but also in 5% to 10% of older continent women and in up to one-third of older men with no or minimal urinary symptoms. Detrusor overactivity has been associated with specific anatomic findings (protrusion junctions and ultra-close abutment of detrusor muscle cells) on bladder biopsy and with evidence of cortical changes, which suggests impaired integration of bladder afferent signals. Demonstrated involuntary bladder contractions do not always indicate that an individual will have urge urinary incontinence, when this phenomenon combined with impaired mobility likely often results in frequent leakage in older functionally disabled patients. Aging in women is also associated with a decline in bladder outlet and urethral resistance pressure. While there is a recognition that laxity of pelvic structures associated with prior childbirths (either via vaginal deliveries or caesarean section) may result in a greater risk of future incontinence, the association between parity and incontinence is weak for women older than 65 years. Additionally, in older populations, poor vaginal support is more closely associated with obstructive urinary symptoms than with urinary leakage and urgency. Obesity, deconditioned muscles, and hysterectomy predispose women to future development of incontinence. Racial or ethnic characteristics are likely important; white women are more likely, as a group, to have stress urinary incontinence than women of other racial or ethnic groups.

Older men with prostatic enlargement may have decreased urine flow rates and detrusor muscle instability. Aging is also associated with higher rates of nocturia, which may in part be related to higher urine production at night. Many older individuals of both genders have impaired bladder contractility, often in combination with detrusor hyperactivity (a condition termed *detrusor hyperactivity with impaired contractility*, or DHIC). These individuals have evidence of widespread muscle degeneration on detrusor muscle biopsy.

Acute or Reversible Causes

The distinction between acute (or reversible) forms of incontinence and persistent (or established) incontinence is clinically important although not always distinct. *Acute incontinence* refers to those situations in which the incontinence is of sudden onset, usually related to an acute illness or an iatrogenic problem, and subsides once the illness or problem has been resolved. *Persistent incontinence* refers to incontinence that is unrelated to an acute illness and endures over time. Several of the reversible factors discussed below also can contribute to persistent forms of incontinence.

The potentially reversible causes of urinary incontinence are outlined in **Table 53-3**. These causes include impaired ability (or reduced willingness) to reach a toilet, conditions that affect the lower urinary tract, such as an infection, atrophic vaginitis, or surgical procedure, conditions that cause or contribute to polyuria, and iatrogenic factors. Because of urinary frequency and urgency, many older persons, especially those limited in mobility, carefully arrange their schedules (and may even limit social activities) in order to be close to a toilet. Thus, an acute illness can precipitate incontinence by disrupting this delicate balance. Hospitalization, with its attendant environmental barriers (such as catheters, tubes, lines, and bedside rails), and the delirium and immobility that often accompany acute illnesses in older patients can contribute to acute incontinence. Acute incontinence in these situations is likely to resolve with resolution of the underlying acute illness. In a substantial proportion of patients, incontinence may persist for several weeks after hospitalization and should be further evaluated.

TABLE 53-3 ■ REVERSIBLE CONDITIONS THAT CAUSE OR CONTRIBUTE TO URINARY INCONTINENCE IN OLDER PERSONS

CONDITION	MANAGEMENT
Conditions affecting the lower urinary tract	
Urinary tract infection (symptomatic with frequency, urgency, dysuria, etc)	Antimicrobial therapy (not for asymptomatic bacteriuria)
Atrophic vaginitis/urethritis	Topical estrogen
Postprostatectomy (incontinence will often resolve during first year)	Exercise-based behavioral interventions; avoid further surgical therapy during first year until it is clear condition will not resolve
Stool impaction	Disimpaction; appropriate use of stool softeners, bulk-forming agents, and laxatives if necessary; implement high fiber intake,

	adequate mobility, and fluid intake
Drug side effects (see **Table 53-4**)	Discontinue or change therapy if clinically appropriate. Dosage reduction or modification (eg, flexible scheduling of rapid-acting diuretics) may also help
Increased urine production	
Metabolic (hyperglycemia, hypercalcemia)	Better control of diabetes mellitus; therapy for hypercalcemia depends on underlying cause
Excess fluid intake	Reduction in intake of total fluids or diuretic fluids (eg, caffeinated or alcoholic beverages)
Volume overload	Diuretic therapy (may also increase risk of incontinence)
Venous insufficiency with edema	Peripheral compression stocking
	Leg elevation
	Sodium restriction
	Diuretic therapy (may also increase risk of incontinence)
Congestive heart failure	Medical therapy
Impaired ability or willingness to reach a toilet	Assistance and/or environmental modifications; prompted voiding, as appropriate
Delirium	Diagnosis and treatment of underlying cause(s) delirium (see Chapter 47)
Chronic illness, injury, or restraint that interferes with mobility	Regular toileting
	Use of toilet substitutes
	Environmental alterations (eg, bedside commode, urinal)
Psychological	Remove restraints if possible
	Appropriate pharmacologic and/or nonpharmacologic treatment

Fantyl JA, Newman DK, Colling J, et al. Urinary Incontinence in Adults: Acute and Chronic Management. Clinical Practice Guideline No. 2, 1996 Update. Rockville, MD: U.S. Dept of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1996. AHCPR publication 96–0682.

Fecal impaction is a common problem in both acutely and chronically ill older patients. Impaction may cause mechanical pressure on the bladder and outlet impingement that can interfere with adequate bladder emptying and cause reflex bladder contractions. Relief of a fecal impaction can lead to resolution of urinary, as well as fecal, incontinence. Urinary incontinence with a high postvoid residual should be considered in any patient who suddenly develops urinary incontinence. In addition to fecal impaction, causes of incontinence with a high postvoid residual in an older patient include immobility, anticholinergic, narcotic, calcium channel blocking, and β-adrenergic medications (**Table 53-4**). In addition, urinary retention may be an acute manifestation of an underlying process causing spinal cord compression or may occur after a stroke.

TABLE 53-4 ■ MEDICATIONS THAT CAN POTENTIALLY AFFECT CONTINENCE

TYPE OF MEDICATION	POTENTIAL EFFECTS ON CONTINENCE
Diuretics	Polyuria, frequency, urgency
Anticholinergics	Urinary retention, overflow incontinence, stool impaction
Psychotropics	
Antidepressants	Anticholinergic actions, sedation
Antipsychotics	Anticholinergic actions, sedation, immobility
Sedative-hypnotics	Sedation, delirium, immobility, urethral relaxation
Narcotic analgesics	Urinary retention, fecal impaction, sedation, delirium
α-Adrenergic blockers	Urethral relaxation

α-Adrenergic agonists	Urinary retention
Angiotensin-converting enzyme inhibitors	Cough precipitating stress incontinence
β-Adrenergic agonists	Rarely may contribute to urinary retention
Calcium channel blockers	May contribute to urinary retention
Alcohol	Polyuria, frequency, urgency, sedation, delirium, immobility
Caffeine	Polyuria, bladder irritation

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

Inflammation of the lower urinary tract may precipitate or exacerbate incontinence. Atrophic vaginitis and urethritis are common among older women, and can cause dysuria, urgency, and frequency that can contribute to incontinence. Physical signs include patchy erythema and increased vascularity of the labia minora and vaginal epithelium, petechiae and friability, and urethral erythema often with an inflamed caruncle (dark or bright red epithelium usually at the inferior aspect of the urethra). Topical estrogen therapy may be helpful in older women with these findings (discussed further later in chapter). Acute urinary tract infection also can precipitate or exacerbate incontinence. However, urine loss among older patients with *chronic* incontinence, especially frail nursing home residents, with otherwise asymptomatic bacteriuria (with or without pyuria) does not appear to improve with bacteriuria treatment. These patients, therefore, should not be treated with antibiotics because of the costs and risks unless the incontinence is new or acutely worsened.

Diuretics (especially rapid-acting loop diuretics) and conditions that cause polyuria, including hyperglycemia and hypercalcemia, can precipitate acute incontinence. Patients with volume-expanded states, such as those with congestive heart failure and lower extremity venous insufficiency, may have polyuria at night, which can contribute to nocturia and nocturnal incontinence. As is the case in many other conditions in geriatric patients, a wide variety of medications can play a role in the development of incontinence in older patients (see **Table 53-4**). Whether the incontinence is acute or persistent, the potential role of these medications in causing or contributing to a patient's incontinence should be considered. When feasible, stopping the medication, switching to an alternative, or modifying the dosage schedule can be beneficial and may be the only necessary treatment for incontinence. In addition to medications, drinking multiple caffeinated or alcoholic beverages can cause urinary frequency and urgency, which may precipitate incontinence.

Persistent Incontinence

Table 53-5 lists the clinical definitions and common causes of persistent urinary incontinence. These types can overlap with each other, and an individual patient may have more than one type simultaneously. Incontinence results from one or a combination of two basic abnormalities in lower genitourinary tract function:

TABLE 53-5 BASIC TYPES AND CAUSES OF PERSISTENT URINARY INCONTINENCE

TYPE	DEFINITION	COMMON CAUSES
Stress	Involuntary loss of urine (usually small amounts) with increases in intra-abdominal pressure (eg, cough, laugh, exercise)	Weakness of pelvic floor musculature and urethral hypermobility Bladder outlet or urethral sphincter weakness Postprostatectomy sphincter weakness
Urgency	Leakage of urine (variable but often larger volumes) because of inability to delay voiding after sensation of bladder fullness is perceived	Detrusor hyperactivity, isolated or associated with one or more of the following: Local genitourinary condition such as tumors, stones, diverticuli, or outflow obstruction Central nervous system disorders such as stroke, dementia, parkinsonism, spinal cord injury, multiple sclerosis
Mixed (stress & urgency)	Combination of above	

Functional	Urinary accidents associated with inability to toilet because of impairment of cognitive and/or physical functioning, psychological unwillingness, or environmental barriers	Severe dementia and other neurologic disorders Psychological factors such as depression and hostility
High postvoid residual (formerly referred to as "overflow")	Leakage of urine (usually small amounts) resulting from either mechanical forces on an overdistended bladder resulting in stress leakage or from other effects of urinary retention on bladder and sphincter function contributing to urge leakage	Anatomic obstruction by prostate, urethral stricture, severe cystocele Acontractile bladder associated with diabetes mellitus or spinal cord injury Neurogenic (detrusor-sphincter dyssynergy), associated with multiple sclerosis and other suprasacral spinal cord lesions Medication effect (see **Table 53-4**)

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

1. Failure to store urine, caused by a hyperactive or poorly compliant bladder or by diminished outflow resistance.
2. Failure to properly empty the bladder, caused by a poorly contractile bladder or by increased outflow resistance.

Stress incontinence is common in older women, especially in ambulatory clinic settings. The symptoms of stress incontinence are very specific: leakage coincident with increases in intra-abdominal pressure caused by coughing, sneezing, laughing, or exercising. Stress incontinence may be infrequent and involve very small amounts of urine. It may need no specific treatment in women who are not bothered by it; on the other hand, it may be so severe and/or bothersome that it renders the person housebound. Among women, it is most often associated with weakened supporting tissues, resulting in hypermobility of the bladder outlet and urethra and caused by lack of estrogen, obesity, previous vaginal deliveries, and/or surgery. Some women, generally those who have had previous lower urinary tract surgery, have intrinsic urethral weakness with failure of the urethra to coapt and prevent urine loss. These patients tend to have severe incontinence and may have constant wetting. Stress incontinence is unusual in men, and it mainly occurs following transurethral interventions for benign prostatic conditions or after surgical or radiation therapy for lower urinary tract malignancy when the anatomic sphincters are damaged.

Urgency incontinence can be caused by a variety of lower genitourinary and neurologic disorders (see **Table 53-5**). This type of incontinence is characterized by a sudden strong desire to void, accompanied by a fear of leakage, and followed by urine loss. The amount of urine lost is variable and largely dependent on sphincter function and the ability of the patient to abort a bladder contraction. Urgency incontinence, when it occurs along with urinary urgency, daytime urinary frequency, and nocturia, has been called "*wet* overactive bladder." Urgency incontinence is most often, but not always, associated with involuntary bladder contractions. Some patients have a poorly compliant bladder without involuntary contractions (eg, interstitial cystitis or following irradiation). A subgroup of older incontinent patients with detrusor hyperactivity also has impaired bladder contractility, emptying less than one-third of their bladder volume with involuntary contractions on urodynamic testing. These patients may be predisposed to significant urinary retention and may require training to learn to completely empty their bladder with voiding.

Experts now recommend *against* the use of the term "overflow incontinence" in favor of terms such as *acute* or *chronic urinary retention* and (either stress or urge) *incontinence with a high postvoid residual*. *Acute retention of urine* is "a painful, palpable, or percussable bladder, when the patient is unable to pass any urine"; and *chronic retention of urine* is where the patient has a "nonpainful bladder, which remains palpable or percussable after the patient has passed urine… (and) the patient may be incontinent." A high postvoid residual can result from anatomic or neurogenic obstruction to urinary outflow, a hypotonic or acontractile bladder, or both. The most common causes include prostatic enlargement, diabetic neuropathic bladder, and urethral stricture. Low spinal cord injury and anatomic obstruction in women (caused by pelvic prolapse and urethral distortion) are less common causes of overflow incontinence in older patients. Several types of drugs also can contribute to this type of persistent incontinence (see **Table 53-4**). Some patients with lesions rostral to the lumbosacral spinal cord lesions (such as multiple sclerosis) develop detrusor-sphincter dyssynergy and consequent urinary retention, which must be treated similarly to overflow incontinence; in some instances, a sphincterotomy is necessary.

Functional incontinence results when an older person is unwilling to attempt or unable to reach a toilet on time. Recognizing and removing these barriers to continence are critical. Factors such as inaccessible toilets and psychological disorders also can exacerbate other types of persistent incontinence. Patients with incontinence that

appears to be predominantly related to functional factors also may have abnormalities of the lower genitourinary tract, most commonly detrusor overactivity. In some patients, it can be very difficult to determine whether the functional factors or the genitourinary factors predominate without a trial of specific types of treatment.

Many older patients have more than one type of incontinence. Most common are combinations of urgency and stress incontinence (often called *mixed incontinence*) among older women and a combination of urge and functional incontinence among nursing home residents. In addition, many older patients have a syndrome of "overactive bladder," where urinary urgency is present sometimes with urinary symptoms such as frequency, and nocturia, and the patient may or may not be continent. These patients should be assessed and treated similar to patients with symptoms of urgency incontinence.

EVALUATION

Federal clinical practice guidelines, including an older guideline developed by the Agency for Health Care Policy and Research (now the Agency for Healthcare Research on Quality), and the surveyor guidance for nursing homes recommend a basic diagnostic evaluation. This evaluation includes a history (which can be enhanced by a bladder record), a physical examination, a urinalysis, and a postvoid residual determination (PVR). The PVR may not be needed in all older patients with incontinence and a reasonable approach may be to do this procedure only in patients at risk for urinary retention (see below). A number of other diagnostic studies are indicated in selected patients (**Table 53-6**). **Figure 53-2** summarizes the recommended diagnostic evaluation of incontinent older patients.

TABLE 53-6 COMPONENTS OF THE DIAGNOSTIC EVALUATION OF PERSISTENT URINARY INCONTINENCE[a]

All Patients
Focused history (a bladder record may be helpful in some patients)
Targeted physical examination
Urinalysis
Postvoid residual determination[b]
Selected Patients
Laboratory studies
Urine culture
Urine cytology
Blood glucose, calcium
Renal function tests
Renal and/or bladder ultrasound
Gynecologic evaluation
Urologic evaluation
Cystourethroscopy
Urodynamic tests
Simple
Observation of voiding
Standing cough test for stress incontinence
Simple (single channel) cystometry
Urine flowmetry (for men)
Complex
Multichannel cystometrogram
Pressure-flow study
Leak point pressure
Urethral pressure profilometry

	Sphincter electromyography
	Videourodynamics

[a]See also Table 53-7.

[b]The recommendation for a postvoid residual determination in all incontinent older patients is controversial (see text).

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

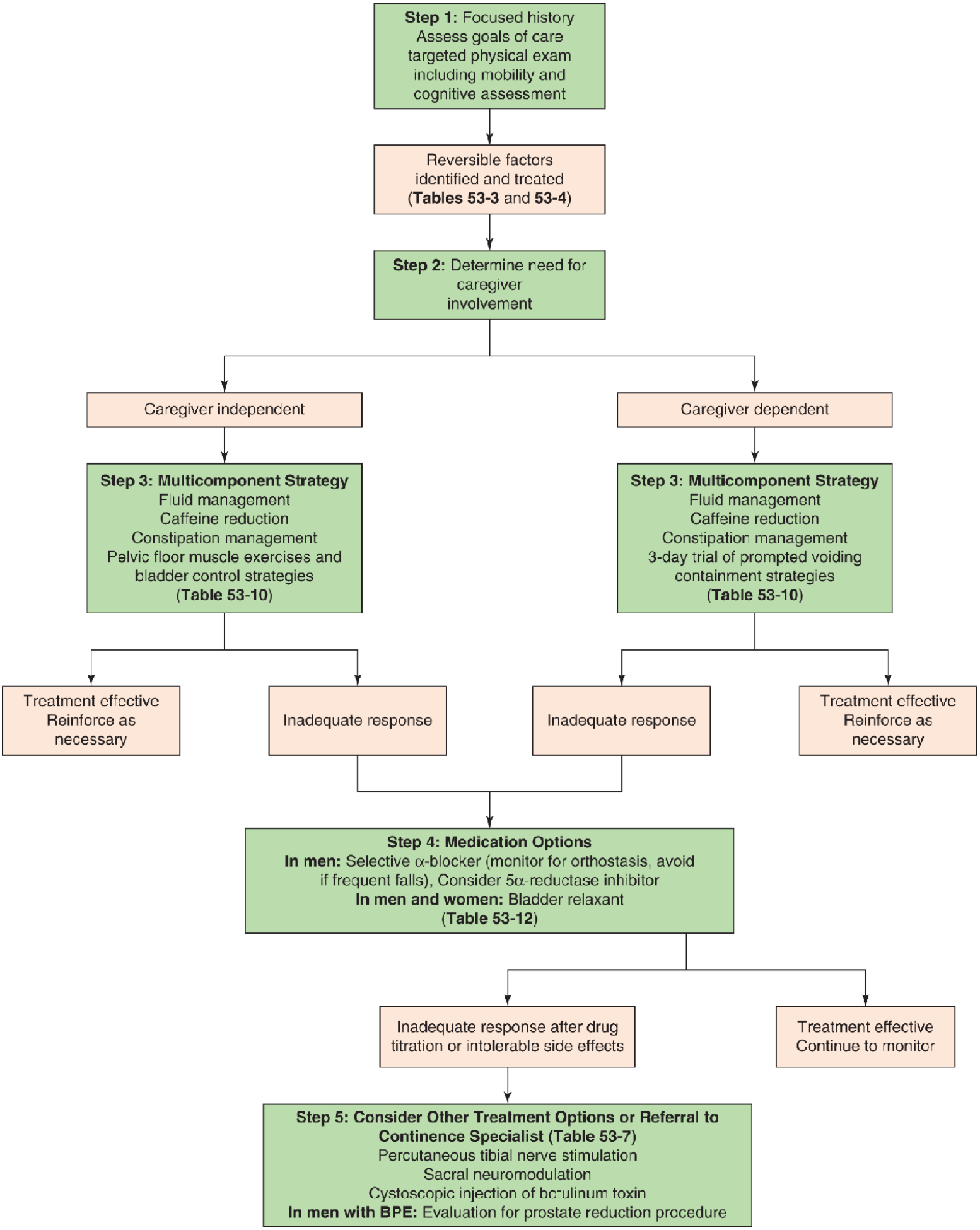

Step 1: Focused history
Assess goals of care
targeted physical exam
including mobility and
cognitive assessment
Reversible factors
identified and treated
(**Tables 53-3** and **53-4**)
Step 2: Determine need for
caregiver
involvement
Caregiver independent
Caregiver dependent
Step 3: Multicomponent Strategy
Fluid management
Caffeine reduction
Constipation management
Pelvic floor muscle exercises and
bladder control strategies
(**Table 53-10**)
Step 3: Multicomponent Strategy
Fluid management
Caffeine reduction
Constipation management
3-day trial of prompted voiding
containment strategies
(**Table 53-10**)
Treatment effective
Reinforce as
necessary
Inadequate response
Inadequate response
Treatment effective
Reinforce as
necessary
Step 4: Medication Options
In men: Selective α-blocker (monitor for orthostasis, avoid
if frequent falls), Consider 5α-reductase inhibitor
In men and women: Bladder relaxant
(**Table 53-12**)
Inadequate response after drug
titration or intolerable side effects
Treatment effective
Continue to monitor
**Step 5: Consider Other Treatment Options or Referral to
Continence Specialist (Table 53-7)**
Percutaneous tibial nerve stimulation
Sacral neuromodulation
Cystoscopic injection of botulinum toxin
In men with BPE: Evaluation for prostate reduction procedure

FIGURE 53-2. Summary of assessment of geriatric urinary incontinence. (See referenced tables and text for details.)

The objectives of the basic evaluation are threefold:

1. To identify potentially reversible conditions that might be contributing to the incontinence (see **Table 53-3**).
2. To identify conditions that require further diagnostic tests and/or referral for gynecologic or urologic evaluation.
3. To develop a management plan that may include referral for further evaluation or a therapeutic trial of behavioral and/or pharmacologic therapy.

In patients with the sudden onset of incontinence (especially when associated with an acute medical condition and/or hospitalization), the potentially reversible causes of acute incontinence (see **Table 53-3**) should be ruled out by a brief history, a physical examination, and basic laboratory studies including urinalysis, culture, and tests for serum glucose or calcium, if indicated.

The history should focus on the characteristics of the incontinence, on current medical problems and medications, and on the impact of the incontinence on the patient and caregivers. The incontinence should be characterized in terms of frequency, timing, and amount of leakage and symptoms of voiding difficulty including hesitancy, intermittent stream, and straining to void. Symptoms of urgency versus stress incontinence should be sought, recognizing that symptom history does not perfectly predict subtype of urinary incontinence. For those with nocturia or nocturnal incontinence, questions regarding sleep disturbance or snoring may herald the need for further evaluation for primary or coincident sleep dysfunction. Bladder records, such as the one shown in **Figure 53-3**, can be helpful in characterizing symptoms, as well as in following the response to treatment. The physical examination includes abdominal, rectal, and genital examinations, as well as an evaluation of lumbosacral innervation. The abdominal examination is insensitive for an elevated postvoid residual or chronic urinary retention, but gross bladder distention (eg, $\geq$ 500 mL) should be easily detected. In acute urinary retention, the distended bladder is a firm, midline mass that emanates from the pelvis and is dull to percussion. In gross distention with either acute or chronic retention, the superior margin of the bladder is often identifiable by either palpation or percussion.

Your Daily Bladder Diary

This diary will help you and your health care team figure out the causes of your bladder control trouble. The "sample" line shows you how to use the diary.

Your name: _____

Date: _____

Time	Drinks		Trips to the Bathroom		Accidental Leaks	Did you feel a strong urge to go?	What were you doing at the time?
	What kind?	*How much?*	*How many times?*	*How much urine? (circle one)*	*How much? (circle one)*	*Circle one*	*Sneezing, exercising having sex, lifting, etc*
Sample	Coffee	2 cups	✓✓	(sm) med lg	sm (med) lg	Yes (No)	Running
6-7 A.M.				sm med lg	sm med lg	Yes No	
7-8 A.M.				sm med lg	sm med lg	Yes No	
8-9 A.M.				sm med lg	sm med lg	Yes No	
9-10 A.M.				sm med lg	sm med lg	Yes No	
10-11 A.M.				sm med lg	sm med lg	Yes No	
11-12 noon				sm med lg	sm med lg	Yes No	

FIGURE 53-3. Example of a bladder record for ambulatory care settings. (From http://kidney.niddk.nih.gov/KUDiseases/pubs/diary/index.aspx. Accessed May 14, 2016.)

The pelvic examination in women includes inspection for significant prolapse, signs of inflammation suggestive of atrophic vaginitis, and a standing cough test to detect stress incontinence. The latter is best done when the patient has a comfortably full bladder, but not a strong sense of urgency. The patient should be positioned over a pad or towel against the perineum while standing next to a commode and then should be asked to cough forcefully three times. Leakage simultaneously with coughing documents stress incontinence; delayed leakage (eg, after 3 seconds) or the initiation of voiding generally indicates a cough-induced bladder contraction. The cough test for stress incontinence has excellent specificity and interrater reliability, but poor sensitivity.

Special attention during the examination should be given to mobility and mental status, because impairments may be either causing the incontinence or interacting with urologic and neurologic disorders to worsen the condition. Patients with nocturia or nocturnal incontinence should be examined for signs of congestive heart failure or venous insufficiency with edema.

Urinalysis should be performed to look for evidence of infection, hematuria, and glucosuria. Clean urine specimens are often difficult to obtain from frail incontinent patients, but can be performed reliably without first resorting to in-and-out catheterization. For men who cannot void spontaneously, a condom-type catheter can be used after cleaning the penis to collect a specimen that accurately reflects bladder urine. While there is a clear relationship between acute symptomatic urinary tract infection and incontinence, the relationship between asymptomatic bacteriuria and incontinence is controversial. In nursing home populations, there is no benefit to treating bacteriuria in patients with chronic, stable incontinence. For patients in other settings, it is difficult to make clear recommendations. For the initial evaluation of incontinence among noninstitutionalized incontinent patients, it is reasonable to initially eradicate the

bacteriuria and observe the effect on the incontinence.

A determination of PVR should be performed in patients at risk for retention to exclude significant urinary retention. Neither the history nor the physical examination is sensitive or specific enough for this purpose in geriatric patients. Such patients include those with diabetes, neurologic disorders, symptoms of voiding difficulty or a history of urinary retention, and those on anticholinergic medications. The PVR determination can be done by portable ultrasonography if equipment is available. To be accurate, the PVR determination should be done within a few minutes of a spontaneous continent or incontinent void. PVR values of less than 100 mL in the absence of straining to void generally reflect adequate bladder emptying in geriatric patients, whereas PVR values greater than 200 mL are abnormal; values in between must be interpreted in the context of other patient symptoms. Among men, a noninvasive measurement of urinary flow rate may be helpful in indentifying obstruction and/or bladder contractility problems. Many urologists and continence clinics that see older men have such devices.

Clinical practice guidelines do not recommend a complex urologic, gynecologic, or urodynamic evaluation for all incontinent older patients. Many patients can be treated with a trial of behavioral and/or drug therapy after the initial evaluation is completed and potentially reversible factors are addressed. **Table 53-7** lists examples of criteria for referring incontinent geriatric patients for further urologic, gynecologic, and/or urodynamic evaluations.

TABLE 53-7 EXAMPLES OF CRITERIA FOR REFERRAL OF INCONTINENT GERIATRIC PATIENTS FOR FURTHER UROLOGIC, GYNECOLOGIC, OR URODYNAMIC EVALUATION

CRITERIA	DEFINITION	RATIONALE
History		
Recent history of lower urinary tract or pelvic surgery or irradiation	Surgery or irradiation involving the pelvic area or lower urinary tract within the past 6 months	A structural abnormality relating to the recent procedure should be sought
Recurrent symptomatic urinary tract infections	Three or more symptomatic episodes in a 12-mo period	A structural abnormality or pathologic condition in the urinary tract predisposing to infection should be excluded
Physical Examination		
Marked pelvic prolapse	A prominent cystocele that descends the entire height of the vaginal vault with coughing during speculum examination	Anatomic abnormality may underlie the pathophysiology of the incontinence, and selected patients may benefit from surgical repair
Marked prostatic enlargement and/or suspicion of cancer	Gross enlargement of the prostate on digital examination; prominent induration or asymmetry of the lobes	An evaluation to exclude prostate cancer may be appropriate
Postvoid Residual		
Difficulty passing a 14-French straight catheter	Impossible catheter passage, or passage requiring considerable force or a large, rigid catheter	Anatomic blockage of the urethra or bladder neck may be present
Postvoid residual volume ≥ 200 mL	Volume of urine remaining in the bladder within a few minutes after the patient voids spontaneously in as normal a fashion as possible	Anatomic or neurogenic obstruction or poor bladder contractility may be present
Urinalysis		
Hematuria	Greater than 5 red blood cells per high-power field on microscopic examination in the absence of infection	A pathologic condition in the upper urinary tract, bladder, or urethra should be excluded
Therapeutic Trial		
Failure to respond to adequate trials of behavioral and/or pharmacologic therapy	Persistent symptoms that are bothersome to the patient after adequate trials of behavioral and/or drug therapy	Urodynamic evaluation may help guide specific therapy

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

MANAGEMENT

Several therapeutic modalities are used in managing incontinent patients (**Table 53-8**). Special attention should be paid to the management of acute incontinence, which is common in older patients in acute care hospitals. A common, often overused, approach to older incontinent patients in acute hospitals is indwelling catheterization. In some instances, this practice is justified by the need for accurate measurement of urine output during the acute phase of an illness, yet often it is unnecessary and poses a substantial and unwarranted risk of catheter-induced infection and interferes with mobility. Although other procedures may be more difficult and time consuming, making toilets and toilet substitutes accessible and combining this accessibility with some form of scheduled toileting is a more appropriate approach. Using launderable or disposable and highly absorbent bed pads and undergarments may be more costly than catheters, but results in less morbidity than catheter use. All the factors that can cause or contribute to a reversible form of incontinence (see **Table 53-3**) should be attended to in order to maximize the potential for regaining continence.

TABLE 53-8 ■ TREATMENT OPTIONS FOR GERIATRIC URINARY INCONTINENCE

Behavioral Interventions (see **Table 53-10**)
Patient dependent
Pelvic muscle exercises
Bladder training
Bladder retraining
Adjunctive techniques
Biofeedback
Electrical stimulation
Weight loss
Caregiver dependent
Scheduled toileting
Habit training
Prompted voiding
Drugs (see **Table 53-12**)
Bladder relaxants
α-Agonists
α-Antagonists
Estrogen
Periurethral injections
Botulinum toxin A cystoscopic injections
Surgery or Procedure Based
Bladder neck suspension (retropubic suspension or sling procedure)
Removal of obstruction or pathologic lesion
Sacral neuromodulation
Percutaneous tibial nerve stimulation
Mechanical Devices
Urethral plugs (female only)
Artificial sphincters
External penile clamps
Nonspecific Supportive Measures
Education

Modifications of medication intake
Avoid caffeine and alcohol
Use of toilet substitutes
Environmental manipulations
Garments and pads
Catheters
External
Intermittent
Indwelling

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

Management should be guided by the type of incontinence, and more importantly by patient and/or family preferences. Patients should be carefully questioned about the degree of bother the incontinence is causing, and how much risk and cost they are willing to undertake to treat it. Supportive measures are critical in managing all forms of incontinence and should be used in conjunction with other, more specific treatment modalities. Education, environmental manipulations, appropriate use of toilet substitutes, avoidance of iatrogenic contributions to incontinence, modifications of diuretic and fluid intake patterns (especially caffeine), treatment of constipation, and good skin care are all important. Additionally, in women there is evidence that modest weight loss (~ 10% of body weight) leads to reduction in urinary incontinence episodes.

Specially designed incontinence undergarments and pads can be very helpful in many patients, but they must be used appropriately. Although they can be effective, several caveats should be raised:

1. Garments and pads are a nonspecific treatment.
2. Many patients are curable if treated with specific therapies, and some have potentially serious factors underlying their incontinence that must be diagnosed and treated.
3. Patients often prefer more specific incontinence therapy designed to restore a normal pattern of voiding and continence.
4. Incontinence garments and pads are expensive and rarely covered by third-party payers.

To a large extent, the optimal treatment of persistent incontinence depends on identifying the type or types. **Table 53-9** outlines the primary treatments for the basic types of persistent incontinence in the geriatric population. Each treatment modality is briefly discussed below.

TABLE 53-9 ■ PRIMARY TREATMENTS FOR DIFFERENT TYPES OF GERIATRIC URINARY INCONTINENCE

TYPE OF INCONTINENCE	PRIMARY TREATMENTS
Stress	Pelvic muscle (Kegel) exercises Other behavioral interventions α-Adrenergic agonists (none are FDA indicated for such use in the United States) Periurethral injections Surgical bladder neck suspension
Urgency	Bladder training Bladder relaxants In men: α-antagonists
Functional	Behavioral interventions (caregiver dependent) Environmental manipulations Incontinence undergarments and pads
High postvoid residual	Surgical removal of obstruction Intermittent catheterization (if practical)

	Indwelling catheterization

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

Behavioral Interventions

Many types of behavioral interventions have been described for the management of urinary incontinence. These may be categorized as **patient dependent** (ie, require adequate function and motivation of the patient), in which the goal is to restore a normal pattern of voiding and continence, or **caregiver dependent**, which can be used for functionally disabled patients, in which the goal is to keep the patient and the environment dry. **Table 53-10** summarizes these interventions. The patient-dependent interventions generally involve the patient's continuous, self-monitoring use of a record such as the one depicted in **Figure 53-3**. In several studies, behavioral therapies have been shown to be equivalent to drug therapy, with approximately three-fourths of patients reporting improvement. Frequently, these behavioral interventions are the preferred treatment modality by patients.

TABLE 53-10 EXAMPLES OF BEHAVIORAL INTERVENTIONS FOR URINARY INCONTINENCE

PROCEDURE	DEFINITION	TYPES OF INCONTINENCE	COMMENTS
Patient Dependent			
Pelvic floor muscle (Kegel) exercises	Repetitive contraction and relaxation of pelvic floor muscles with use in everyday situations that precipitate leakage	Stress and urgency	Requires adequate function and motivation; biofeedback often helpful for teaching
Bladder training	Use of education, bladder records, pelvic muscle, and other behavioral techniques	Stress and urgency	Requires trained therapist, adequate cognitive and physical functioning, and motivation
Bladder retraining	Progressive lengthening or shortening of intervoiding interval, with intermittent catheterization used in patients recovering from overdistension injuries with persistent retention	Acute (eg, postcatheterization with urge or overflow, poststroke)	Goal is to restore normal pattern of voiding and continence; requires adequate cognitive and physical function and motivation
Caregiver Dependent			
Scheduled toileting	Routine toileting at regular intervals (scheduled toileting)	Urgency and functional	Goal is to prevent wetting episodes; can be used in patients with impaired cognitive or physical functioning; requires staff or caregiver availability and motivation
Habit training	Variable toileting schedule based on patient's voiding patterns	Urgency and functional	Goal is to prevent wetting episodes; can be used in patients with impaired cognitive or physical functioning; requires staff or caregiver availability and motivation
Prompted voiding	Offer opportunity to toilet every 2 h during the day; toilet only on request; social reinforcement; routine offering of fluids	Urgency, stress, mixed, functional	Same as above; 25%–40% of nursing home residents respond well during the day, and can be identified during a 3-d trial

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

To be successful, patient-dependent interventions require a functional, motivated patient capable of learning and

practice. These interventions also require a skilled, enthusiastic trainer and frequent patient contact, though positive results can be achieved by motivated patients who are self-directing their behavioral treatment with assistance of a pamphlet or book. Pelvic floor muscle (Kegel) exercises can be effective in men and women for the treatment of urge, stress, mixed stress-urge incontinence, and incontinence following prostatectomy. These exercises consist of repetitive contractions of the pelvic floor muscles. These exercises can be taught by brief verbal or written instructions, or instruction provided by having a patient squeeze the examiner's inserted finger during a vaginal or rectal examination (without doing a Valsalva maneuver, which is opposite of the intended effect). Once learned, the exercises should be practiced many times throughout the day (eg, three sets of 15 contractions building up from 3–10 seconds in duration). Computer-assisted or manual biofeedback can be especially helpful for teaching patients who bear down (increasing intra-abdominal pressure) when attempting to contract pelvic floor muscles. Biofeedback involves the use of bladder, rectal, or vaginal pressure or electrical activity recordings, or the examiner's finger in the vagina or rectum with a hand placed on the abdomen, to train patients to contract pelvic floor muscles while leaving the abdominal muscles relaxed. Electrical stimulation, introduced either vaginally or rectally, and magnetic stimulation have also been used to help identify and train muscles in the management of stress incontinence and inhibit involuntary bladder contractions in patients with urgency incontinence. The applicability of pelvic floor electrical or magnetic stimulation is somewhat limited because of equipment needs and that it may not be acceptable to many older patients in the United States.

Once these muscles are strengthened, and better muscle control is achieved, the patient must be taught to use the exercises in everyday life under circumstances that precipitate the incontinence in order for them to be effective. With practice, a pelvic floor muscle contraction can be done immediately prior to a cough, laugh, or sneeze to assist with stress incontinence and used in rapid serial contractions to abort detrusor contractions associated with urinary urgency. Pelvic floor muscle exercises have also been shown to be effective in certain situations to prevent urinary incontinence and, if done preoperatively, will allow a more rapid return to continence in the postoperative period.

Other forms of patient-dependent interventions include bladder training and bladder retraining. Bladder training involves the educational components taught during biofeedback, without the use of biofeedback equipment. Patients are taught pelvic muscle exercises and urge suppression strategies to manage urgency and are taught to use bladder records regularly. There is some evidence that these techniques are as effective as biofeedback in a selected group of cognitively intact, motivated older patients. Bladder retraining as described here is used primarily after a period of temporary bladder catheterization. **Table 53-11** is an example of a bladder-retraining protocol. This protocol is applicable to patients who have had an indwelling catheter for monitoring of urinary output during a period of acute illness or for treatment of urinary retention with overflow incontinence. Such catheters always should be removed as soon as possible, and this type of bladder-retraining protocol should enable most indwelling catheters to be removed from patients in acute care hospitals as well as some residents in long-term care settings. A patient who continues to have difficulty voiding after 1 to 2 weeks of such a bladder-retraining protocol should be examined for other potentially reversible causes of voiding difficulties. When difficulties persist, a urologic referral should be considered to rule out correctable lower genitourinary pathologic conditions.

TABLE 53-11 EXAMPLE OF A BLADDER-RETRAINING PROTOCOL

Objective: To restore a normal pattern of voiding and continence after the removal of an indwelling catheter

1. Remove the indwelling catheter (clamping the catheter before removal is not necessary)
2. Treat urinary tract infection if present
3. Initiate a toileting schedule. Begin by toileting the patient:
   a. Upon awakening
   b. Every 2 h during the day and evening
   c. Before getting into bed
   d. Every 4 h at night
4. Monitor the patient's voiding and continence pattern with a record that allows for the recording of:
   a. Frequency, timing, and amount of continent voids
   b. Frequency, timing, and amount of incontinence episodes
   c. Fluid intake pattern
   d. Postvoid catheter volume
5. If the patient is having difficulty voiding (complete urinary retention or very low urine outputs, eg, ≤ 240 mL in an 8-h period

while fluid intake is adequate):

a. Perform bladder ultrasonography or in-and-out catheterization, recording volume obtained, every 6 to 8 h until residual values are ≤ 200 mL

b. Instruct the patient on techniques to trigger voiding (eg, running water, stroking inner thigh, suprapubic tapping) and to help completely empty bladder (eg, bending forward, suprapubic pressure, double voiding)

c. If the patient continues to have high residual volumes after 3 to 4 wk, consider urodynamic evaluation

6. If the patient is voiding frequently (ie, more often than every 2 h):

a. Perform postvoid residual determination to ensure the patient is completely emptying the bladder

b. Encourage the patient to delay voiding as long as possible and instruct the patient to use techniques to help completely empty bladder

c. If the patient continues to have frequency and nocturia, with or without urgency and incontinence:

(1) Rule out other reversible causes (eg, urinary tract infection medication effects, hyperglycemia, and congestive heart failure)

(2) Consider trial of bladder relaxant if postvoid residuals are low

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

The goal of caregiver-dependent intervention such as scheduled toileting, habit training, and prompted voiding is to prevent incontinence episodes rather than to restore a normal pattern of voiding and complete continence. Highly motivated caregivers and cooperative patients are essential for these interventions to be successful on an ongoing basis. Scheduled toileting involves putting the patient on the toilet at regular intervals, usually every 2 to 3 hours during the day regardless of the presence or absence of the patient's expressed desire to void. Habit training involves a schedule of toileting that is individually modified according to the patient's pattern of continent voids and incontinence episodes. *Prompted voiding* is a behavioral protocol that involves focusing the patient's attention on his or her bladder by asking if the patient is wet or dry, asking (prompting) the patient to attempt to void (up to three times) every 2 hours during the day, toileting the patient if he or she responds positively, giving personal interaction as a social reward for attempting to toilet and maintaining continence, and offering fluids routinely. Between 25% and 40% of nursing home residents respond very well to daytime prompted voiding, and these responders can be identified by carrying out a 3-day trial of the intervention. Care for incontinence at night should be individualized. Routine incontinence care can be very disruptive to sleep. Because older people tend to awaken frequently at night, one way to individualize toileting is to check on the patient every hour or two, and only prompt to toilet when the patient is found awake.

Drug Treatment

Table 53-12 lists the drugs used to treat incontinence. Better data for efficacy in older patients are now available for some drugs. In general, carefully selected older research participants have been able to achieve roughly equivalent efficacy from drug treatment compared to their younger counterparts. Drug treatment should generally be prescribed in conjunction with one or more behavioral interventions.

TABLE 53-12 DRUGS COMMONLY USED IN THE UNITED STATES TO TREAT URINARY INCONTINENCE

DRUGS	DOSAGES	MECHANISMS OF ACTION	POTENTIAL ADVERSE EFFECTS
Bladder Relaxants for Urgency Incontinence	In general, reduced dosages for renal and hepatic impairment		
Antimuscarinic		Increase bladder capacity; diminish involuntary bladder contractions	
Darifenacin (Enablex)	7.5–15 mg qd		Anticholinergic, lower dose if reduced hepatic function
Fesoterodine (Toviaz)	4–8 mg qd		Anticholinergic
Oxybutynin (Ditropan, immediate release, available as generic)	2.5–5.0 mg tid		Anticholinergic (dry mouth, blurry vision, elevated intraocular pressure,

			delirium, constipation)
Patch (Oxytrol)	3.9 mg qd Patch applied twice weekly		Above, but with less dry mouth, available over-the-counter
Oxybutynin gel (Gelnique)	3% pump or 10% gel packet One application daily		Above, but with less dry mouth
Solifenancin (Vesicare)	5–10 mg qd		Anticholinergic, lower for severe renal impairment or reduced hepatic function
Tolterodine (Detrol)	1–2 mg bid		Anticholinergic, lower dose for severe renal impairment or reduced hepatic function
Tolterodine (Detrol LA)	4 mg qd		Above, but with less dry mouth
Trospium chloride (Sanctura)	20 mg bid 20 mg once daily qhs with CrCl < 30 or in patients > 75 yo Give on an empty stomach > 1 hour before a meal		Anticholinergic
Trospium chloride (Sanctura XR)	60 mg q am Give on an empty stomach > 1 hour before a meal		Avoid in severe renal impairment or reduced hepatic function
Beta-3-agonist		Inhibits bladder contraction	
Mirabegron (Myrbetriq)	25-50 mg qd		Beta-3-agonist, max 25mg/day with CrCl 15-20, reduced hepatic function; (hypertension, tachycardia)
Vaginal Estrogen**		Strengthen periurethral tissues and reduces inflammation from atrophic vaginitis	Contraindicated in women with a personal history of gynecologic cancer, relative contraindication in women with a personal history breast cancer
Topical	0.5–1.0 g per application		
Vaginal ring (Estring) (estradiol acetate)	One ring every 3 months		
Drugs for Stress Incontinence**		Increase urethral smooth-muscle contraction	
Pseudoephedrine*** (Sudafed)	30–60 mg tid		Headache, tachycardia, elevation of blood pressure
Duloxetine (Cymbalta)	30-60 mg daily		Nausea, xerostomia, headache
Drugs for Overactive Bladder Symptoms including Urgency UI in Men**		Relax smooth muscle of urethra and prostatic capsule	
Alpha adrenergic antagonist			
Doxazosin (available as generic, or Cardura)	1–8 mg qhs		Postural hypotension, dizziness, lowers blood

			pressure
Terazosin (available as generic, or Hytrin)	1–10 mg qhs		Same as above
Prazosin (Minipress)	1–2 mg tid		Same as above
Alfuzosin (Uroxatral)	10 mg qhs		Less effects on blood pressure
Silodosin (Rapaflo)	4-8 mg qd		Less effects on blood pressure; CrCl 30-50 use 4mg qd
Tamsulosin (Flomax)	0.4–0.8 mg qd		Less effects on blood pressure (when used at 0.8 mg dose, greater blood pressure effects)
Phosphodiesterase Inhibitors		Inhibits PDE type 5, enhancing effects of nitric oxide-activated increases in cGMP	
Tadalafil	5 mg daily		Orthostatic hypotension, flushing, headache (contraindicated with terazosin/doxazosin/prazosin)
Other phosphodiesterase inhibitors given daily may be effective			
5-alpha reductase Inhibitor		Inhibits type II 5-alpha reductase, interfering with conversion of testosterone to 5-alpha-dihydrotestosterone	
Finasteride	5 mg daily		Sexual dysfunction, gynecomastia, decreased overall risk of prostate cancer with increased risk of high-grade prostate cancer
Dutasteride	0.5 mg daily	Inhibits type I and II 5-alpha reductase, inhibiting conversion of testosterone to dihydrotestosterone	Sexual dysfunction, decreased overall risk of prostate cancer with increased risk of high-grade prostate cancer

*for urgency UI associated with atrophic vaginitis

**the primary initial treatment for stress UI is behavioral, with consideration of surgery for severe stress UI, there are no FDA approved medications for stress UI

***contraindicated in patients with hypertension and cardiovascular disease

**** can be used in combination with bladder relaxants

For urgency incontinence, drugs with bladder smooth-muscle relaxant properties are used and are available in two different classes: antimuscarinic (anticholinergic) and β_3-agonist (noradrenergic). Antimuscarinic drugs are available in immediate-release, controlled-release, and topical preparations, while β_3-agonist therapy is available in a once-daily formulation. Most studies suggest a reduction of 60% to 70% in the frequency of incontinence episodes with drug therapy in selected older adults. While different drugs are likely equivalent on average, a particular patient who does not respond to one drug (either because of lack of efficacy or presence of adverse effects) may benefit from a trial on a different agent within the category. Antimuscarinic drugs may have bothersome systemic anticholinergic side effects, especially dry mouth and constipation. They should be used carefully in patients with glaucoma and severe

gastroesophageal reflux. One β_3-agonist is available. It does not have the anticholinergic side effects of antimuscarinics, but could potentially lead to elevated blood pressure and should not be used in persons with uncontrolled hypertension. Bladder relaxants may rarely precipitate urinary retention in some patients; men with some degree of outflow obstruction, diabetic patients, and patients with impaired bladder contractility are at the highest risk and should be followed carefully. For older men with overactive bladder symptoms (with or without urinary incontinence), α-adrenergic antagonists may likely be a better choice for first-line drug therapy. Bladder relaxants may also be used as single drug therapy in men, and the combination of a bladder relaxant and an α-antagonist may be more effective in many older men. Patients with Alzheimer disease must be followed for the development of drug-induced worsening of cognitive function or delirium when placed on antimuscarinic medications because of their anticholinergic effects, although it is unusual. Studies suggest that cognitive impairment, especially of memory and learning are associated with antimuscarinic drug therapy. The results of these studies should not, however, preclude a treatment trial in this patient population when they make frequent attempts to toilet yet remain incontinent. The use of long-acting antimuscarinic drugs for urgency incontinence has become commonplace, but it is important to recognize that the cheaper, immediate-release preparations are equally efficacious, but require more frequent dosing and have a higher incidence of bothersome side effects (particularly dry mouth).

Drug treatment for stress incontinence is less efficacious than is drug treatment for urgency incontinence, and no drug is approved for this indication in the United States. Stress incontinence drug treatment involves a combination of an α-agonist and topical estrogen therapy (in women). Pseudoephedrine is an occasionally used oral agent for stress incontinence. Duloxetine, a drug approved for depression in the United States, also has α-adrenergic effects on the lower urinary tract through a spinal cord mechanism, and is approved for the treatment of stress incontinence in several countries. Drug treatment is appropriate for motivated patients who (1) have mild-to-moderate degrees of stress incontinence, (2) do not have a major anatomic abnormality such as a large cystocele, and (3) do not have a contraindication to α-agonist drug therapy, such as poorly controlled hypertension. Previous data on the use of oral estrogen for urinary incontinence, using hormonal replacement dosages, had shown equivocal benefits. More recent studies have shown, for either opposed or unopposed oral conjugated estrogen therapy, an increased risk for previously continent women of developing and worsening of incontinence. Other forms of oral estrogen (estradiol) and topical estrogen are still used, either chronically or on an intermittent basis (ie, 1- to 2-month courses), and may be effective for the treatment of irritative voiding symptoms and urgency incontinence in women with atrophic vaginitis and urethritis. Although no specific topical treatment regimen has been shown to be more effective than others, therapy usually involves 0.5 to 1 g of vaginal cream nightly for 1 to 2 weeks and then a maintenance dose two or three times per week or a controlled, slow-release vaginal ring. Several months of therapy are often necessary to observe therapeutic benefit.

Many older women have symptomatically and urodynamically a combination of both urgency and stress incontinence. If urgency incontinence is the predominant symptom, a combination of estrogen and bladder relaxant would be appropriate. Behavioral interventions are also an effective approach for women with mixed incontinence.

Drug treatment in the setting of chronic urinary retention or urinary incontinence with high postvoid residual, with either a cholinergic agonist or an α-adrenergic antagonist, is usually not efficacious. Although α-adrenergic blockers, daily phosphodiesterase inhibitors, and 5α-reductase inhibitors are useful for treatment of symptoms suggestive of benign prostatic hyperplasia, they may not obviate the need for surgical intervention or requirement for catheter drainage in patients with bladder outlet obstruction who have chronic urinary retention or urinary incontinence with high postvoid residuals (ie, residuals consistently greater than 200–300 mL).

Surgical Approaches

Surgery is a well-established treatment for stress urinary incontinence. Surgery should be considered for older women with stress incontinence and for women with a significant degree of pelvic prolapse associated with stress incontinence or incontinence with urinary retention who are unresponsive to nonsurgical treatment. As with many other surgical procedures, patient selection and the experience of the surgeon are critical to success. Any woman being considered for surgical therapy should have a thorough evaluation, before undergoing the procedure. Urodynamics are not necessarily required for stress incontinence or stress-predominant mixed incontinence without voiding difficulties. In general, surgical treatment is designed to correct urethral closure problems and to remedy defects in support of the urethra-vesicular angle. Newly modified techniques of bladder neck suspension, tension-free vaginal tapes, and the use of periurethral collagen injections can be done with minimal risks. Periurethral injections appear to be most appropriate for women with intrinsic urethral weakness. Two or more sessions of injections are usually necessary to

maintain effectiveness. Many older women with severe incontinence associated with intrinsic urethral weakness require a sling procedure rather than a simple bladder neck suspension. Men with stress urinary incontinence (and usually with continuous urinary leakage) can be treated with the implantation of an artificial urinary sphincter (or other similar mechanical device designed to reversibly block urine outflow in the penile urethra). Newer "sling" procedures have been used in men, also.

While procedural approaches have previously been considered only for stress incontinence, there are now approaches for the treatment of urgency incontinence unresponsive to medical and behavioral treatment. Newer approaches include neuromodulation and botulinum toxin A injection. Percutaneous tibial nerve stimulation (PTNS) is a minimally invasive procedure, which provides electrical stimulation using a small needle electrode placed in proximity to the posterior tibial nerve as it travels near the medial malleolus of the tibia. Patients undergo weekly 30-minute stimulation sessions in an outpatient clinical setting for up to 12 weeks. PTNS is generally well tolerated with minimal discomfort and has demonstrated effectiveness in adults without underlying neurogenic bladder. Sacral neuromodulation involves a two-stage operation with general anesthesia and implantation of a pacemaker-like generator near the hip and sacral leads to stimulate the pudendal and sacral nerves. The procedure can be a safe, effective, and durable treatment, though cure rates for older adults and those with multiple medical comorbidities have been lower than in younger, healthier populations. The use of botulinum toxin A for refractory urgency incontinence has proven effective in several randomized, double-blind, controlled studies, and is now approved by the US Food and Drug Administration. Botulinum toxin A is accomplished via cystoscopic injections into multiple bladder sites under direct visualization. Benefit is believed to be because of an effect on both efferent and afferent pathways, and early trial results suggest that the therapy lasts 6 months and is equally effective in older and younger age groups.

Surgery may be indicated in men in whom incontinence is associated with outflow obstruction. Men may have either chronic urinary retention, or acute urinary retention that is *precipitated* (use of an anticholinergic drug, recent instrumentation, or α-agonist drug) or *spontaneous*. Those who have had complete acute urinary retention requiring mechanical drainage, and particularly those with *spontaneous* retention, are likely to have another episode within a short period of time and should be evaluated for a prostatic resection, as should men with incontinence associated with enough residual urine to be causing recurrent symptomatic infections or hydronephrosis. In men who do not meet these criteria, the decision should be based on weighing carefully the degree to which the symptoms bother the patient, the potential benefits of surgery (obstructive symptoms often respond better than irritative symptoms), and the risks of surgery (which may be minimal with newer prostate resection techniques).

MECHANICAL DEVICES, UNDERGARMENTS, CATHETERS, AND OTHER SUPPORTS

Three basic types of catheters and catheterization procedures are used for the management of urinary incontinence: external catheters, intermittent straight ("in-and-out") catheterization, and chronic indwelling catheterization. External catheters generally consist of some type of condom connected to a drainage system. Improvements in design and observance of proper procedure and skin care when applying the catheter decrease the risk of skin irritation, as well as the frequency with which the catheter falls off. Existing data suggest that patients with external catheters are at increased risk of developing symptomatic infection compared to incontinent adults depending on absorbent pads or diapers. External catheters should be used only to manage intractable incontinence in male patients who do not have urinary retention and who are extremely physically dependent. An external catheter for use in female patients is available commercially, but is not widely used.

Intermittent catheterization can help in the management of patients with urinary retention and overflow incontinence. The procedure can be carried out by either the patient or a caregiver and involves straight catheterization two to four or more times daily, depending on residual urine volumes. The goal is to keep residual urine volume generally less than approximately 300 to 400 mL. In the home setting, the catheter should be kept clean (but not necessarily sterile). Studies conducted largely among younger paraplegic patients show that this technique is practical and reduces the risk of symptomatic infection compared with the risk associated with chronic catheterization. Self-intermittent catheterization is also feasible for older female outpatients who are functional and willing and able to catheterize themselves. The technique may be especially useful following removal of an indwelling catheter in a bladder-retraining protocol (see **Table 53-11**). However, older nursing home residents, especially men, may be difficult to catheterize. Anatomic abnormalities commonly found in the lower urinary tracts of older patients may increase the risk of infection because of repeated straight catheterizations. In addition, using this technique in an institutional setting, which may have an abundance of organisms relatively resistant to many commonly used

antimicrobial agents, may yield an unacceptable risk of nosocomial infections. Using sterile catheter trays for these procedures would be very expensive. Thus, it may be extremely difficult to implement such a program in a typical nursing home setting.

Chronic indwelling bladder catheterization has higher risks than other forms of management, and should be used only as indicated. On occasion, experts may recommend suprapubic catheters over urethral catheters for chronic use. For either type of bladder catheterization, when used for periods of months to years, has been shown to increase the incidence of a number of complications, including chronic bacteriuria, bladder stones, periurethral abscesses (urethral catheters), urethral injury including penile erosion (urethral catheters), and even bladder cancer. Elderly nursing home residents managed with chronic indwelling bladder catheters are at relatively high risk of developing symptomatic infections. The limited evidence available to date does not suggest that routine changing of indwelling bladder catheters is warranted, though this is a common practice. Given these risks, it seems appropriate to recommend that the use of chronic indwelling bladder catheters be limited to certain specific situations (**Table 53-13**). When indwelling catheterization is used, certain principles of catheter care should be observed in an attempt to minimize complications (**Table 53-14**). In situations where there is reduced urinary output, increased leakage around the catheter, or increased pain, it is important to perform an abdominal and genital examination to make certain the catheter is in the bladder and not obstructed. In these situations, it is often necessary to replace the catheter.

TABLE 53-13 INDICATIONS FOR CHRONIC INDWELLING CATHETER USE

Urinary retention that
Is causing persistent overflow incontinence, symptomatic infections, or renal dysfunction
Cannot be corrected surgically or medically
Cannot be managed practically with intermittent catheterization
Skin wounds, pressure sores, or irritations where incontinent urine contributes to excessive moisture and results in poor healing
Care of terminally ill or severely impaired for whom bed and clothing changes are uncomfortable or disruptive
Patient preference

Adapted from Kane RL, Ouslander JG, Itamar B, et al. Essentials of Clinical Geriatrics. 5th ed. New York, NY: McGraw-Hill; 2003.

TABLE 53-14 KEY PRINCIPLES OF CHRONIC INDWELLING CATHETER CARE

SUMMARY OF MAJOR RECOMMENDATIONS
Category I. Strongly Recommended for Adoption
Educate personnel in correct techniques of catheter insertion and care
Catheterize only when necessary
Emphasize hand washing
Insert catheter using clean technique is an acceptable and more practical alternative to sterile technique
Secure catheter properly
Maintain closed sterile drainage
Obtain urine samples aseptically
Maintain unobstructed urine flow
Category II. Moderately Recommended for Adoption
Periodically reeducate personnel in catheter care
Use smallest suitable bore catheter
Avoid irrigation unless needed to prevent or relieve obstruction
Refrain from daily meatal care with povidone-iodine solution as this may result in an increased infection rate
Do not change catheters at arbitrary fixed intervals
Category III. Weakly Recommended for Adoption
Consider alternative techniques of urinary drainage before using an indwelling urethral catheter
Replace the collecting system when sterile closed drainage has been violated

Spatially separate infected and uninfected patients with indwelling catheters
Avoid routine bacteriologic monitoring

Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA. Guideline for prevention of catheter-associated urinary tract infections, 2009. http://www.cdc.gov/hicpac/cauti/001_cauti.html. *Accessed November 17, 2014.*

In men with postprostatectomy urinary incontinence who are not candidates for or do not desire surgical therapy, an external penile clamp for compression of the urethra may be a useful adjunctive therapy. Patients must be able to remember, monitor, and physically be able to remove the clamp every 2 hours. Some women with urinary incontinence and pelvic prolapse may respond well to use of a vaginal pessary, which is a device to slow the progression of prolapse by adding support to the vagina and increasing tightness of the tissues and muscles of the pelvis. Pessaries are made of rubber, plastic, or silicone, and come in a variety of types. Conclusive trials about which devices are better than others, or how well the devices compare to other treatments have not yet been reported. The ideal device would be easy to insert, be of low cost, have few adverse effects, and would control leakage. Often patients need to be individually fitted with the device.

There are a variety of available absorbent products and undergarments that can help patients contain leakage, including disposable inserts, reusable and single-use adult diapers, and disposable underwear. Additionally, there are pads that can protect beds and/or chairs. Controlled studies have been performed comparing one type to another, and criteria for success of these devices revolve around fit, odor control, cost, and ability to hold urine. More frequent changing of pads is expensive and inconvenient, but frequently helps control odor. Less frequent changing leaves skin wetter and likely more vulnerable to friction and abrasion. Most consumers select products by trial and error and are unaware of the range of products and services available. These products are available at drug stores, supermarkets, and medical supply stores.

In general, older adults want general information on urinary incontinence and sources of help. There are multiple consumer advocacy groups for those with incontinence that are dedicated to improving the lives of patients with urinary incontinence, for example, the National Association for Continence (www.nafc.org), and the Simon Foundation (www.simonfoundation.org) in the United States, that provide educational materials, reviews of available products, and links to researchers and manufacturers who provide incontinence materials.

FECAL INCONTINENCE

Fecal incontinence is less common than urinary incontinence. Its occurrence is relatively unusual in older patients who are continent of urine. Thirty to fifty percent of older patients in institutional settings with frequent urinary incontinence, however, also have episodes of fecal incontinence. This coexistence suggests common pathophysiologic mechanisms.

Defecation, like urination, is a physiologic process that involves smooth and striated muscles, central and peripheral innervation, coordination of reflex responses, mental awareness, and physical ability to get to a toilet. Disruption of any of these factors can lead to fecal incontinence.

The most common causes of fecal incontinence are problems with constipation and laxative use, neurologic disorders, and colorectal disorders (**Table 53-15**). In patients who are fed by enteral tubes, hyperosmotic feedings can precipitate diarrhea and fecal incontinence. Diluting the feedings or using slow continuous infusion is sometimes helpful. Constipation is extremely common in older persons and, when chronic, can lead to fecal impaction and incontinence. The hard stool (or scybalum) of fecal impaction irritates the rectum and results in the production of mucus and fluid. This fluid leaks around the mass of impacted stool and precipitates incontinence. Constipation is difficult to define; technically, it indicates fewer than three bowel movements per week, although many patients use the term to describe difficult passage of hard stools or a feeling of incomplete evacuation. Poor dietary and toilet habits, immobility, and chronic laxative abuse are the most common causes of constipation in older persons. Appropriate management of constipation prevents fecal impaction and resulting fecal incontinence. The management of constipation is discussed thoroughly in Chapter 95.

TABLE 53-15 CAUSES OF FECAL INCONTINENCE

Fecal impaction

Constipation
Laxative overuse or abuse
Hyperosmotic enteral feedings
Neurologic disorders
Dementia
Stroke
Spinal cord disease
Colorectal disorders
Diarrheal illnesses
Diabetic autonomic neuropathy
Rectal sphincter damage

Fecal incontinence is sometimes amenable to biofeedback therapy, although many older demented patients are unable to cooperate. For those patients with end-stage dementia, a program of alternating constipating agents (if necessary) and laxatives in a routine schedule (such as giving laxatives and enemas three times a week) is effective in controlling defecation in many patients with fecal incontinence. Functionally dependent patients should be toileted regularly after a meal to take advantage of, or possibly regain, the gastrocolic reflex. Experience suggests that these measures should permit management of even severely cognitively impaired patients. As a last resort, specially designed incontinence undergarments are sometimes helpful in managing fecal incontinence and preventing skin irritation and other complications.

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Chapter 54

Elder Mistreatment

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Learning Objectives

- Elder mistreatment, including physical abuse, sexual abuse, neglect, financial exploitation, psychological abuse, and abandonment, is common and may have serious medical and social consequences.
- Elder mistreatment is significantly underrecognized by clinicians and underreported to the authorities.

Key Clinical Points

1. **Though researchers have described potential risk factors and are working to identify forensic markers associated with elder mistreatment, a high index of clinical suspicion in all encounters with geriatric patients and routine screening are currently the best tools physicians have to identify this often subtle geriatric syndrome.**

DEFINITIONS

In the broadest context, *elder mistreatment* subsumes a variety of activities perpetrated upon an older person by others. There is as yet no universally agreed definition or classification of elder mistreatment. Proposed strategies for defining or classifying elder mistreatment have included using the type of abuse (eg, physical vs verbal abuse), motive (eg, intentional vs unintentional neglect), perpetrator relationship (eg, family vs paid caregiver), and setting (eg, community vs nursing home). Nonetheless, the clinician attempting to care for a victimized older person or to understand the spectrum of elder mistreatment will encounter several thematically similar definitions. For example, the Older Americans Act of 1975 defines elder abuse as "the willful infliction of pain, injury, or mental anguish." This definition has been adopted, and/or modified, by many state protective service agencies that investigate cases of abuse. An encompassing definition created by a 2002 expert panel convened by the National Academy of Sciences added the concept that elder mistreatment involves *a trusting relationship between an older person and another individual in which that trust is violated in some way*. The definition that likely best captures current understanding of elder mistreatment is that developed for the 2014 Elder Justice Roadmap, a report prepared by a large, multidisciplinary team of stakeholders inside and outside the US government:

- Physical, sexual, or psychological abuse, as well as neglect, abandonment, and financial exploitation of an older person by another person or entity
- That occurs in any setting (eg, home, community, or facility)
- Either in a relationship where there is an expectation of trust and/or when an older person is targeted based on age or disability

Table 54-1 lists representative examples of types of elder mistreatment. Whatever definition is employed, a consistent and important feature of elder mistreatment, and other forms of family violence, is that multiple types of mistreatment, such as physical and verbal abuse, neglect, and financial exploitation frequently coexist in the same abuser-victim dyad.

TABLE 54-1 ■ REPRESENTATIVE DEFINITIONS OF ELDER MISTREATMENT

MISTREATMENT CATEGORY	DEFINITION	EXAMPLES
Physical abuse	Acts of violence that may result in pain, injury, impairment, or disease	• Pushing, striking, slapping, force-feeding • Incorrect positioning • Improper use of restraints or medications • Sexual coercion or assault
Neglect	The failure to provide the goods or services necessary for optimal functioning or to avoid harm	• Withholding of health maintenance care • Failure to provide physical aids such as eyeglasses, hearing aids, false teeth • Failure to provide safety precautions
Financial or material abuse	The misuse of the older person's income or resources for the financial or personal gain of a caretaker or advisor	• Denying the older person a home • Stealing money or possessions • Coercing the older person into signing contracts
Psychological, emotional, or verbal abuse	Conduct that causes mental anguish	• Verbal berating, harassment, or intimidation • Threats of punishment or deprivation • Treating the older person like an infant • Isolating the older person from others
Abandonment	The desertion of an older person by an individual who has assumed responsibility for providing care for the older adult or by a person with physical custody	
Violation of a trusting relationship	Meant to encompass all forms of abuse in that all forms involve the older person relying on and trusting another party, who through acts of omission or commission, violates that trust, without regard to intent	

Data from Aravanis SC, Adelman RD, Breckman D, et al. Diagnostic and treatment guidelines on elder abuse and neglect. Arch Fam Med. 1993;2:371; National Center on Elder Abuse. Major types of elder abuse. www.ncea.aoa.gov. Accessed December 12, 2014.

Virtually all experts, clinicians, and reasonable laypersons will agree that egregious instances of physical violence such as punching, hitting, slapping, or assaulting an older person with a gun or other weapon are elder abuse. The most contentious definitional (and clinical) area relates to elder neglect, because the term neglect immediately implies that a caregiving obligation—such as providing food, medicines, or care—has not been met. This, in turn, raises difficult questions that must, with clinical judgment and experience, be considered in the context of the older adult's environment. For example, what are reasonable community standards for the frequency of bathing an assaultive spouse with Alzheimer disease? Does that standard change if the designated caregiver also suffers from chronic diseases that preclude perfect hygiene for their impaired family member? What if this inadequate care enables the "victim" to live at home long after other families would have considered nursing home placement? Who exactly is the responsible caretaker, especially when multiple adult children are available to assume that role, but only one has "stepped up" because of birth order or some other arbitrary circumstance? And is it fair to label that adult child an "elder neglector" when caregiving becomes physically or psychologically impossible?

These difficult questions also highlight the fact that clinicians caring for elder abuse victims often find themselves working closely with alleged perpetrators of abuse and neglect, as these individuals are often the primary caregivers.

Another challenge in conceptualizing and defining elder mistreatment is how to include adults who have been victims of family violence chronically during their adult lives. Do these victims become elder mistreatment sufferers after they reach an arbitrary age cutoff or if they become functionally dependent or suffer cognitive decline?

EPIDEMIOLOGY

However it is defined, elder mistreatment is common. Recent prevalence studies, conducted in different countries, suggest that as many as 10% of community-dwelling older adults suffer from abuse, neglect, or exploitation each year.

Multiple smaller studies suggest that nearly 50% of dementia sufferers are victims of mistreatment by caregivers. Psychological/emotional abuse (4.6%–12.9%), financial mistreatment (3.5%–6.6%), and neglect (5.1%–5.4%) are most commonly reported, with physical mistreatment (0.2%–2.1%) and sexual abuse (0.3%–0.6%) reported less frequently.

Unfortunately, despite its frequency, research suggests that as few as 1 in 24 cases of elder mistreatment is identified by the authorities. Victims may be unable to report abuse due to isolation, severe illness, or dementia, or may be reluctant to report due to fear of reprisal, guilt, desire to protect the abuser, cultural beliefs, or fear of institutionalization. Many older adults who suffer from abuse endure it for years before having it discovered. For others, it may not be until after they have died that their morbidity and early death are considered to be due to abuse. Both of these scenarios lead to delays in identification and intervention.

Much research has focused on identifying risk factors for elder mistreatment perpetrators and victims, with inconsistent results (**Table 54-2**). The most consistent findings relate to the relationship of the abuser to victim; most studies report that spouses and adult children are the most common perpetrators. Studies also show that when adult children are the abusers, sons and daughters are often equally implicated. At least one study found daughters to be the more common abuser. These findings must be viewed cautiously in that women are far more likely to be the de facto or designated care providers to frail older adults and are, therefore, more "at risk" for being accused of mistreatment should caregiving fall short of any arbitrary standard.

TABLE 54-2 ■ POSSIBLE RISK FACTORS FOR ELDER MISTREATMENT

FACTOR	MECHANISM
Victim's poor health and functional disability	Disability reduces the older person's ability to seek help and/or defend self.
Cognitive impairment	Aggression toward caregiver and disruptive behaviors resulting from dementia precipitate abuse. Higher rates of abuse have been found among patients with dementia.
Abuser deviance	Abusers are likely to abuse alcohol or drugs and to have serious mental illness, which, in turn, leads to abusive behavior.
Abuser dependency	Abusers are very likely to depend on the victim financially, for housing, and in other areas. Abuse results from relative's (especially adult children's) attempts to obtain resources from the older person.
Living arrangement	Abuse is much less likely among older persons living alone. A shared living situation provides greater opportunities for tension and conflict that generally precede abusive incidents.
External stress	Stressful life events and chronic financial strain decrease the family's resistance and increase likelihood of abuse.
Social isolation	Older adults with fewer social contacts are more likely to be victims. Isolation reduces the likelihood that abuse will be detected and stopped. In addition, social support can buffer against the impact of stress.
History of violence	Particularly among spouses, prior history of violence in the relationship may be predictive of elder abuse in later life.

Reprinted with permission from Lachs MS, Pillemer K. Current concepts: abuse and neglect of elderly persons. N Engl J Med. 1995;332:437.

Studies suggest that women represent two-thirds of elder mistreatment victims. Also, in cultures where women have inferior social status, older women are at high risk of neglect through abandonment when they are widowed and their property is seized. While current research suggests that older adults with lower socioeconomic status are at greater risk for mistreatment, studies evaluating race and ethnicity have been contradictory. A particularly contentious area has been spawned by the "dependency theory" of mistreatment, which holds that mistreatment occurs when the victim becomes inordinately dependent on the caregiver for a variety of medical and nonmedical needs. Again, studies show an inconsistent relationship between functional disability in an older adult and elder mistreatment. In fact, a more consistent finding in the literature is the converse—the perpetrator is often dependent on the older adult victim for financial support and housing. Characteristically, an adult child unable to achieve independence is reliant on the older person for these needs.

Inconsistencies in findings from risk factor research may be related to the heterogeneous nature of elder

mistreatment cases. Older adult protective services workers and clinicians experienced in elder mistreatment know that the term elder mistreatment subsumes many situations—abusive spousal relationships that have "aged," caregivers to dementia patients who lash out in frustration, and physically abusive adult children with poorly managed mental health or substance abuse problems are but a few examples. Epidemiologic studies that attempt to discern risk factors without acknowledging this reality probably are measuring an "average" effect, thus possibly missing important sets of risk factors among subgroups of abused or neglected older populations.

Whatever risk factors are identified in previous and future research should not foster a complacency wherein an absence or paucity of such factors causes the clinician to lower his or her guard. Elder mistreatment crosses all ethnic and socioeconomic boundaries. A high index of clinical suspicion is critical for identification.

PATHOPHYSIOLOGY

Theories of elder mistreatment abound; three deserve detailed discussion here, because they may have clinical relevance with regard to the types of interventions contemplated in confirmed cases of mistreatment. The most commonly cited theory contends that family violence is a learned behavior; abused children grow up to potentially abuse not only their children, but also perhaps spouses and their parents. This is sometimes referred to as the transgenerational violence theory of mistreatment.

The dependency theory of mistreatment holds that abuse is fostered by situations in which victims have a degree of functional and/or cognitive disability that results in activities of daily living impairment and overwhelming care needs. Closely associated with this paradigm is another theory—that of the "stressed caregiver."

The psychopathology of the abuser theory shifts focus away from the victim and argues that elder mistreatment is firmly rooted in mental health problems of the abuser. Examples include personality disorders, poorly or undertreated schizophrenia, alcoholism, and other substance abuse problems.

Discerning the underlying causes of elder mistreatment is essential in fashioning an intervention plan (see "Management" later in this chapter).

PRESENTATION

For a variety of reasons, the identification of elder mistreatment is one of the most difficult clinical challenges in geriatric medicine. First, many highly prevalent chronic diseases in older adults may have clinical manifestations that mimic abuse. If elder abuse is present, the clinician may ascribe those findings to chronic disease rather than family violence. Conversely, the clinician may erroneously attribute findings from another disease to elder mistreatment. Second, the setting in which an elder mistreatment evaluation occurs is often quite challenging. The assessment may be hurried (eg, the emergency department is the often chaotic environment where acute injuries are evaluated). The presence of the suspected abuser only adds pressure to what is already likely to be a stressful encounter. The perpetrator, and also the victim, may have incentives to actively conceal the mistreatment from the clinician. Lastly, the competent identification and management of mistreatment may create significant additional work and propel the clinician into a world that he or she is likely to be unfamiliar with—a world that includes mandatory reporting statutes, adult protective service workers, and a criminal justice system with a vocabulary that is foreign to many medical professionals. Given these educational, emotional, and systemic obstacles, it is not surprising that elder mistreatment often is missed or unreported in the context of "customary care." In fact, recent research suggests that only 1.4% of cases reported to Adult Protective Services (APS) come from physicians, and, in a survey of APS workers, of 17 occupational groups, physicians were among the least helpful in reporting abuse.

Elder abuse forensics is a recent area of intense and growing focus. Of particular interest has been whether there are diagnostic and/or clinical signs and symptoms of abuse presentations, either during life or at autopsy, that are pathognomonic for elder mistreatment, as have been identified in child abuse (eg, shaken baby syndrome and bucket-handle metaphyseal fracture). Researchers have begun to search for physical injury patterns associated with abuse. One recent study compared bruises in 67 elder abuse victims to older adults with accidental trauma, finding that victims of elder abuse had bruises that were more often large (> 5 cm) and found on the face, lateral right arm, or posterior torso. A literature review identified 839 reported cases of physical elder abuse and found that two-thirds of injuries that occur in elder abuse are to the upper extremity and maxillofacial region. Medical and laboratory markers potentially suggestive of elder mistreatment have been suggested by experts, including malnutrition, dehydration, alterations in

status of chronic illness, hypothermia/hyperthermia, rhabdomyolysis, and toxicologic findings, but these have not yet been systematically evaluated.

Until rigorous research identifies reliable forensic markers, clinicians need to consider elder mistreatment in the differential diagnosis of many or most of the clinical presentations they encounter. Fractures may result from osteoporosis or force or both. Depression may be related to neurotransmitter imbalances or a hopeless abusive environment. Malnutrition may be the result of any number of chronic illnesses inexorably worsening, or from the withholding of sustenance.

Dramatic injuries or neglect pose no particular diagnostic challenge. Fractures, burns, contusions, and lacerations, in concert with a credible history, immediately lead to the diagnosis. At the other extreme, subtle presentations that mimic chronic disease are highly challenging. Examples include chronic diseases that frequently decompensate despite a care plan and adequate resources (eg, repeated emergency department visits for congestive heart failure or chronic obstructive pulmonary disease exacerbation). Indeed, because elder mistreatment can be defined so broadly, there are very few presenting signs or symptoms in the geriatric patient for which elder mistreatment is not in the differential diagnosis.

Many instruments have been devised for the screening or evaluation of elder mistreatment, but they are not applicable to all settings. The Elder Abuse Suspicion Index (EASI) is a short screening instrument has been validated for cognitively intact patients in a primary setting with a sensitivity of 0.47 and a specificity of 0.75. The EASI (**Figure 54-1**) is a tool to identify older adults at risk of mistreatment and includes five questions for the patient and one for the physician, with more than or equal to one "yes" response suggesting further assessment is needed.

Questions 1 through 5 are answered by the patient. Question 6 is answered by the physician.

1. Have you relied on people for any of the following: bathing, dressing, shopping, banking, or meals?
2. Has anyone prevented you from getting food, clothes, medication, glasses, hearing aids, or medical care or from being with people you wanted to be with?
3. Have you been upset because someone talked to you in a way that made you feel shamed or threatened?
4. Has anyone tried to force you to sign papers or to use your money against your will?
5. Has anyone made you afraid, touched you in ways that you did not want, or hurt you physically?
6. Doctor: Elder abuse may be associated with findings such as poor eye contact, withdrawn nature, malnourishment, hygiene issues, cuts, bruises, inappropriate clothing, or medication compliance issues. Did you notice any of these today or in the last 12 months?

The patient can answer "yes," "no," or "unsure." A response of "yes" on one or more of questions 2 through 6 should prompt concern for abuse or neglect.

FIGURE 54-1. Elder Abuse Suspicion Index (EASI). (From Yaffe MJ, Wolfson C, Lithwick M, et al. Development and validation of a tool to improve physician identification of elder abuse: the Elder Abuse Suspicion Index (EASI). *J Elder Abuse Negl*. 2008;20:276–300.)

All screening instruments may assist the clinician by serving as "checklists" to ensure a thorough evaluation. **Table 54-3** suggests a system-by-system approach. The importance of heightened awareness cannot be overemphasized in considering the diagnosis. Frequently, clues about potential mistreatment come from ancillary staff members (eg, office reception staff) or home care nurses who observe the abuser-victim dyad away from the health care provider. A general sense that something is amiss in the patient's environment such as caustic interaction between parties, poor hygiene or dress, frequently missed medical appointments, or failure to adhere with a clearly designated treatment strategy can all be important clues.

TABLE 54-3 CLINICAL MANIFESTATIONS OF POTENTIAL MISTREATMENT WITH RECOMMENDED ASSESSMENT

TARGET	ASSESSMENT

History from older adult	Interview patient alone; directly inquire regarding physical violence, restraint use, or neglect; ascertain precise details about nature, frequency, and severity of events. Assess functional status (amount of dependence with activities of daily living [ADLs]). Determine who the designated caregiver is if ADLs disability is present.
History from abuser	Potential abuser should also be interviewed alone; this interview is best done by professionals with experience in this area; avoid confrontation in the information-gathering phase. Interview other sources if possible. Assess recent psychosocial factors (eg, bereavement, financial stresses). Ascertain caregiver understanding of patient's illness (eg, care needs, prognosis, etc). Elicit caregiver's explanations for injuries or physical findings.
Behavioral observation	Withdrawal Infantalizing of patient by caregiver Caregiver who insists on providing the history
General appearance	Hygiene Cleanliness and appropriateness of dress
Skin/mucous membranes	Skin turgor, other signs of dehydration; multiple skin lesions in various stages of evolution Bruises, decubiti; evidence of care for established skin lesions
Head and neck	Traumatic alopecia (distinguishable from male pattern alopecia on the basis of distribution) Scalp hematomas Lacerations, abrasions
Trunk	Bruises, welts; shape may suggest implement (eg, iron/belt).
Genitourinary	Rectal bleeding Vaginal bleeding Decubiti, infestations
Extremities	Wrists or ankle lesions suggest restraint use or immersion burn (stocking/glove distribution).
Musculoskeletal	Examine for occult fracture, pain; observe gait.
Neurologic/psychiatric	Thorough evaluation to assess focality of neurologic deficits. Depressive symptoms, anxiety.
Mental status	Formal mental status testing (eg, Mini Mental State Examination); cognitive impairment suggests delirium or dementia and plays a role in assessing decision-making capacity. Psychiatric symptoms including delusions and hallucinations.
Imaging	As indicated from the clinical evaluation.
Laboratory	As indicated from the clinical evaluation (drug levels). Albumin, blood urea nitrogen, and creatinine toxicology.
Social and financial resources	Determine whether there are other members of social network available to assist the older person financial resources. These resources are crucial in considering interventions that include alternate-living arrangements and home services.

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The patient and the alleged perpetrator should be interviewed separately and alone. Although there is an emerging consensus that patients of all ages should be routinely screened for family violence, an optimal strategy or instrument has not emerged. Patients should be asked candidly and calmly about the etiology of any unexplained injuries or other findings. Often patients are at first unwilling to speak candidly about being an elder abuse victim for reasons of embarrassment, shame, or fear of retribution from the perpetrator who is frequently a caregiver.

Interview of the suspected abuser is a tricky and potentially dangerous undertaking. On the one extreme, elder abusers who are presented with an empathetic, nonjudgmental ear to describe their stresses and actions will sometimes

describe their situations at great length and in great detail. On the other hand, all forms of domestic abuse share a pattern wherein abusers gain and control access to their victims. An elder abuser graphically confronted with allegations of mistreatment may move to sequester a frail victim in such a way that a frail isolated older adult loses access to critically needed medical and social services. Whenever possible, assistance from providers skilled in elder abuse evaluation and management should be enlisted to assist in such undertakings.

MANAGEMENT

Elder abuse and neglect are morbid and mortal. Mistreatment is associated with adverse health outcomes for victims, including significant increases in emergency department usage, hospitalization, dementia, depression, and nursing home placement. Also, research has shown that mistreatment victims have a threefold risk of death compared to nonabused controls. Thus, intervention is critical.

Unfortunately, there are no randomized trials of reasonable quality addressing interventions for elder mistreatment. The clinician confronted with a confirmed case of elder abuse is best served by a resourceful approach that combines experience, clinical judgment, and local resources. One developing trend is large interdisciplinary groups who convene regularly to discuss cases of mistreatment, not only for the purpose of planning intervention, but also to consider case-by-case forensics, cross train disciplines, and provide general support to one another in this difficult field. However, there is no evidence-based evaluation of this strategy.

Whatever the approach to intervention, a dogmatic or algorithmic strategy to address all elder mistreatment cases is likely misguided. A rigid, inflexible approach ignores the enormous heterogeneity of the entity, including the type(s) of mistreatment being concurrently perpetrated, the underlying mechanisms, patient comorbidities, caregiver burden issues, and the available resources (both familial and community) that can be brought to bear on the issue. A more sensible approach may be the multipronged strategy increasingly used to treat other geriatric syndromes that have multifactorial etiologies. The paradigm may be a useful one in that elder mistreatment can be likened to geriatric syndromes. That is, there may be multiple "host" and environmental contributors; decompensation may be accelerated by other medical and social problems; and some of the contributors may be more remediable than others. The elder physical abuse victim with severe chronic obstructive pulmonary disease and an abusive schizophrenic child-caregiver will need an entirely different series of interventions than the spouse with progressive dementia who has suffered lifelong domestic violence that is now worsening.

The first step in confronting any confirmed case of family violence is ensuring the safety of the victim. First, the immediate threat of danger to the victim should be ascertained. Even if there is no immediate threat, a *safety plan* is critical in the management of all forms of family violence (**Table 54-4**). What are the specific steps the victim should take if the perpetrator of mistreatment becomes acutely violent? Options include calling the local police department, accessing shelters, emergency department use/hospital admission, or respite care in some evolved systems of long-term care. Additionally, in most states, cases of elder abuse must be reported to adult protective services agencies. This typically results in a home visit to adjudicate the veracity of such a report. State protective service agencies vary widely with respect to their caseloads and available resources; ideally a coordinated approach that brings to bear their expertise and resources in collaboration with the physician and multidisciplinary team produces the best response.

TABLE 54-4 ■ SAFETY PLAN FOR VICTIMS OF ELDER MISTREATMENT OR OTHER VICTIMS OF FAMILY VIOLENCE WITH CAPACITY WHO INSIST ON REMAINING IN AN ABUSIVE ENVIRONMENT

TIME FRAME	ACTIVITY
Prior to violent or abusive episode	Recognize patterns that lead to abusive behavior (eg, abuser alcohol use). Determine who in the social network is available to assist when such an episode occurs through explicit conversations with neighbors, friends, other relatives. Be aware of elder domestic violence programs, shelters, and other resources in the local community available to assist; know their contact numbers. Have essential resources readily available if the patient needs to leave quickly (eg, money, ATM cards, credit cards, driver's license, keys, identification, Social Security card, other important documents). Practice implementing safety plan (eg, mock 911 call). Consider creating a "code" with a friend or neighbor so that the patient can communicate danger in the presence of the

	abuser.
During violent or abusive episode	Implement safety plan quickly and with discretion. Consider appeasing abuser briefly (if this does not cause a danger) so that safety plan may be implemented. Use of self-protective behaviors such as a weapon should be considered with utmost caution.
After violent or abusive episode	Recognize that family violence is a chronic problem that usually recurs and escalates. Change locks as soon as possible. Strongly consider order of protection. Let neighbors and landlord know that abusive individual no longer lives in the home.

The safety plan paradigm will have limited utility in many cases of elder mistreatment, however, because of victim frailty and/or cognitive impairment that limits the use of self-protective behaviors. Frequently, clinicians find themselves in the predicament of caring for an elder mistreatment victim who lacks capacity. In these cases, the likely intervention will involve the appointment of a guardian in collaboration with adult protective service agencies or other elder social service programs in the community that serve such functions. In such a proceeding, the clinician's role is to provide objective evidence that documents the lack of decision-making capacity. The clinician may also have a role in ensuring the alleged perpetrator of mistreatment does not become the guardian.

One of the most frustrating situations for professionals working with victims of family violence is the individual who retains decision-making capacity and insists on remaining in an abusive environment. Here the clinician's role is to educate the patient about the tendency of family violence to escalate and to review the safety plan created. The clinician should also explain to the patient that even if services are refused, the physician remains an important and available resource, should the situation change.

In general, the physician who suspects elder abuse would do well to employ the same creative strategies he or she uses to manage a variety of clinical problems in older adults. There may be local social services agencies in the community who provide an array of services such as meals on wheels or friendly visit. These services could represent a new resource for the patient, but also additional "eyes and ears" to ascertain what the home situation is like. A local adult day care referral might also enable a more detailed ongoing evaluation of a client while decompressing a stressful caregiving situation. A financial management program for the patient with cognitive impairment can shed light on the possibility of financial exploitation. The physician need not diagnose elder abuse while these useful services are being proffered.

SPECIAL SITUATIONS

Elder mistreatment may also occur in institutional settings. The physician and nurse have roles in detecting these cases as well. Substantial regulatory safeguards have been progressively enacted since the 1970s to protect residents of long-term care facilities. These safeguards include mandatory criminal background checks of all employees, ombudsman programs to adjudicate complaints of mistreatment, and components of the Omnibus Budget Reconciliation Act of 1987, which includes residents' rights provisions (eg, minimization of restraints). In some contexts, the failure to create or follow a reasonable plan of care for the long-term care residents may be viewed as abusive or neglectful.

While the focus of elder abuse in long-term care has been on staff abuse of residents, this is probably far less common than previously when regulatory scrutiny was lacking. Recently, resident on resident abuse has been identified as a far more common and pervasive problem among nursing home residents. This includes verbal, physical, and sexual mistreatment. Although there are no prevalence data on the phenomenon, preliminary and indirect evidence suggests that it is highly prevalent. For example, more than 50% of nursing aides in long-term care report the personal experience of being physically hit by a resident in the previous year, typically in the course of providing direct care. Given that the prevalence of dementia and associated behavioral disturbance in long-term care facilities is high, it stands to reason that behavior of this type occurs frequently between residents.

Another recent area of interest has been abuse and neglect that occurs in long-term care environments other than nursing homes (eg, assisted living and board and care environments), because these facilities generally are under considerably less regulation. Interest in mistreatment in assisted-living facilities has also grown in recent years as much sicker patients begin to inhabit these institutions; many believe the higher acuity and generally lower levels of staff

and supervision are a dangerous admixture in which abuse and neglect are more likely to occur. Data are lacking on the prevalence of abuse, or on the type of abusers, in these settings.

Physicians and other care providers have an important role in the detection of these institutional cases, because they may see potential manifestations of nursing home elder mistreatment in facilities or emergency departments as part of providing customary care. Physicians who suspect institutional abuse have an obligation to immediately report their suspicions to the long-term care ombudsman in their state.

SUMMARY

Elder mistreatment is a prevalent problem with many potential manifestations. The epidemiology of injuries and other clinical findings is not completely understood, but this does not preclude the clinician from taking an active role in its detection and management. Studies show elder mistreatment victims to be at substantial independent risk of death and quality-of-life decline. The syndrome should be afforded the same vigilance that health care providers devote to other "traditional" medical problems in geriatrics.

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Part IV

Principles of Palliative Medicine and Ethics

Chapter 55.	Palliative Care and Special Management Issues
Chapter 56.	Pain Management
Chapter 57.	Common Nonpain Symptoms
Chapter 58.	Effective Communication Strategies for Patients With Advanced Illness
Chapter 59.	Palliative Medicine Across the Continuum of Care Including Hospice
Chapter 60.	Spiritual Care
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Chapter 55

Palliative Care and Special Management Issues

Paul Tatum, Shaida Talebreza, Jeanette S. Ross, Eric Widera

Learning Objectives

- Identify the palliative needs of an aging population and recognize the potential benefits palliative care delivers in collaboration with or as part of geriatric medicine practice.
- Describe the unique palliative care needs of special populations including patients with dementia, frailty, or multimorbidity, as well as the needs of lesbian, gay, bisexual and transgender patients, and ethnic and culturally diverse populations.
- Distinguish the various advance care planning formats and tools and adapt a three-step process to prognostication in older adults as part of advance care planning.

Key Clinical Points

1. **Multiple randomized trials show palliative care improves outcomes including quality of life, satisfaction with care, reduced famdistress, and increased hospice utilization and may be associated with longer life expectancy.**
2. **For older adults with multiple chronic illness, a five-step approach to palliative care includes the following:**
   a. **Determine patient preferences.**
   b. **Interpret the evifor treatment with recognition of the limitations applying it to an older adult population.**
   c. **Let prognosis frame clinical management decisions.**
   d. **Consider treatcomplexity and feasibility as part of management decisions.**
   e. **Optimize therapies and care plans.**

INTRODUCTION

Palliative medicine is an essential skill set for health care professionals practicing geriatric medicine or simply caring for older adults. Supporting the needs and goals of older adults as they age is a complex process that often involves a balance between competing goals of life prolongation, functional status preservation and restoration, risk and harm mitigation, and symptom relief. Palliative care aims to ensure that these goals match the individualized care plans through interprofessional care and careful communication and goal setting.

Palliative care for older adults poses distinct challenges. For older patients with diminished reserve to respond to stressors, the potential for harm of interventions can be substantially riskier than younger populations. Cognitive impairment may limit the participation of patients at times when the most difficult decisions need to be made. The interaction of multiple illnesses in multimorbidity may reduce the potential benefit of interventions, which are otherwise therapeutic in single disease state.

It is appropriate given the aging population and the increasing evidence base for palliative care that this edition of *Hazzard's Geriatric Medicine* has significantly expanded geriatric palliative medicine content. For this chapter we will

focus on the palliative needs of an aging population and examine special management issues facing the geriatrician, including cognitive impairment, multimorbidity, and frailty. We will also address issues related to prognostication and advance care planning. Subsequent chapters within the palliative care section will focus on geriatric palliative care issues related to pain management, effective communication, palliative care delivery systems, spirituality, and ethics.

DEFINING PALLIATIVE CARE

Palliative care aims to improve the quality of life for both the patient and the family. Palliative care focuses on providing patients with relief from the symptoms, pain, and stress of a serious illness. It is appropriate for any type of diagnosis, any stage of a serious illness, and importantly, can be provided together with curative treatment.

Specialty palliative care consists of care by an interprofessional team of doctors, nurses, and social workers, chaplains and other individuals with expertise in palliative medicine, who work with patients' other doctors to provide care that matches patients' goals. In addition to palliative care specialists, the core principles of palliative care can be implemented by all health care providers (often described as *primary palliative care*). The key components primary palliative care include symptom management, coordination of care, communication about goals of care and advance care planning, caregiver support, and when needed, referral to specialist palliative care teams.

Hospice Care

Hospice care is a specialized form of palliative care for patients with limited life expectancy. Hospice care provides medical, psychosocial, and spiritual support to the patient. Hospice also supports family members coping with the complex consequences of illness, disability, and functional decline as death nears and includes bereavement support after death of the patient. Hospice care does not aim to shorten or prolong life, but rather provides comfort and support services to help people live out the time they have remaining to the fullest extent possible.

The Medicare Hospice Benefit employs an interdisciplinary team of professionals including doctors, nurses, aides, social workers, and spiritual care coordinators to address the patient's physical, emotional, social, and spiritual needs. Under the Medicare Hospice Benefit, a patient is eligible for hospice care when the patient's attending physician and the hospice medical director certify that she or he is terminally ill with an expected prognosis of less than 6 months "if the disease runs its usual and expected course." The Centers for Medicare & Medicaid Services (CMS) has guidelines entitled local coverage determinations (LCDs) to help physicians determine a prognosis of 6 months or less. These LCDs are available on the CMS website and are *guidelines* to help determine prognosis, they *are not rules or requirements* for hospice admission. The Medicare requirement for hospice eligibility is simply the physician certification that the patient is terminally ill with an expected prognosis of less than 6 months. Once a patient is admitted, the hospice agency is required to provide services that are reasonable and necessary for the palliation and management of a patient's terminal illness and related conditions, including doctor and nursing visits, hospice aide and counseling services, medications, medical equipment and supplies, and short-term respite and inpatient stays to manage pain and symptoms.

PALLIATIVE CARE NEEDS OF AN AGING POPULATION

Health care in the United States has made tremendous advances which have allowed for an aging population. The typical death has been transformed from the nineteenth century picture of an acute illness over a short time from infectious disease into a process of decline over years with increasing morbidity and functional dependency from chronic disease. There is a clear demographic trend of increasing life expectancy. The average age at the time of death in the United States per 2013 data is now 78.8 (81.2 years for females and 76.4 for males) and survivors to age 65 live on average another 19.3 years (**Figure 55-1**). One of the fastest growing demographic groups has been the growth of the age 85 and over population. However, greater longevity comes at a cost. With increases in life expectancy, the burden of serious illnesses has risen significantly.

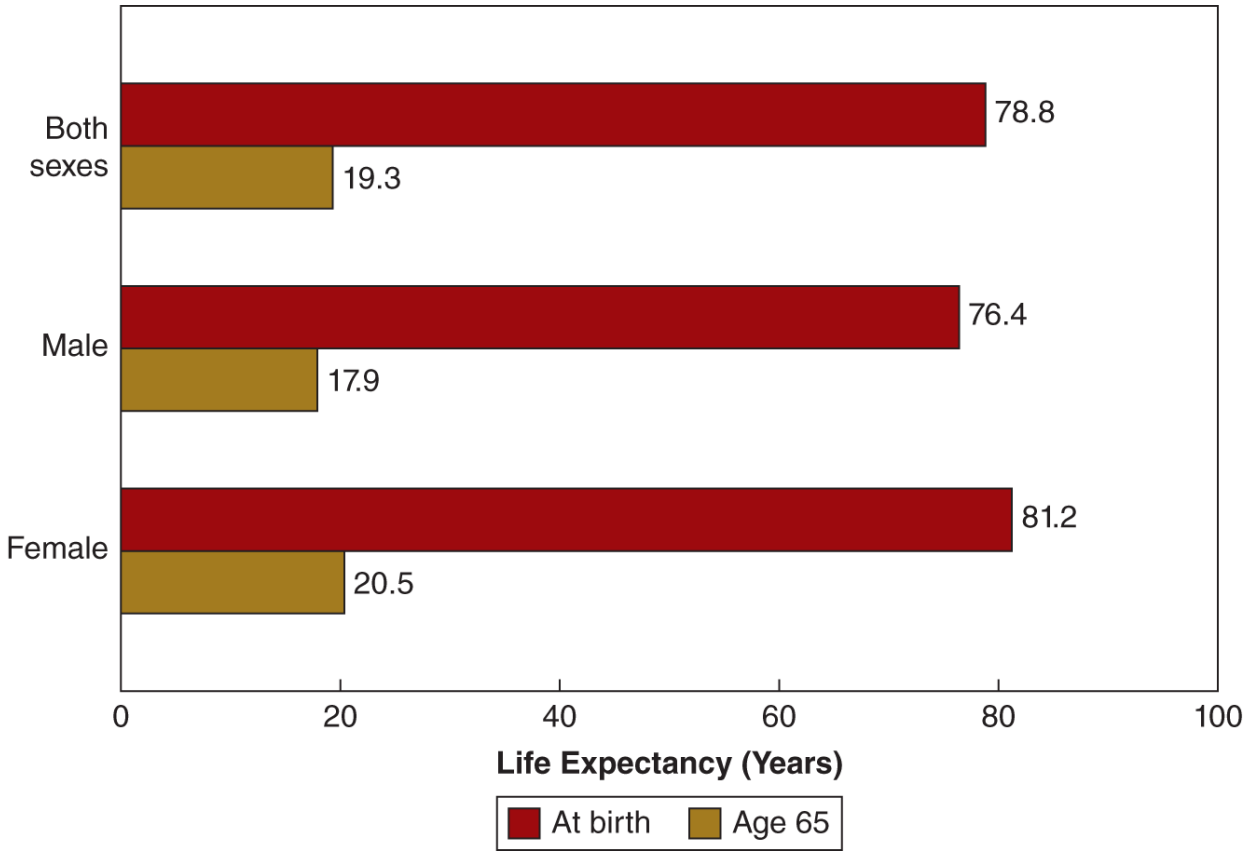


FIGURE 55-1. Life expectancy at selected ages, by sex: United States, 2013. (Kochanek KD MS, Xu JQ, Arias E. Mortality in the United States, 2013. NCHS Data Brief, no. 178. Hyattsville, MD: National Center for Health Statistics; 2014.)

While chronic illness of older adults is increasingly complicated by multiple illnesses, two major diseases, heart disease and cancer, still accounted for nearly half of all 2013 deaths (**Figure 55-2**). Apart from acute respiratory illness, accidents, and suicide, the majority of deaths of older adults will be associated with a period of chronic disease. In 2013, two-thirds of people aged 65 and over had multiple chronic conditions per the Centers for Disease Control and Prevention (CDC).

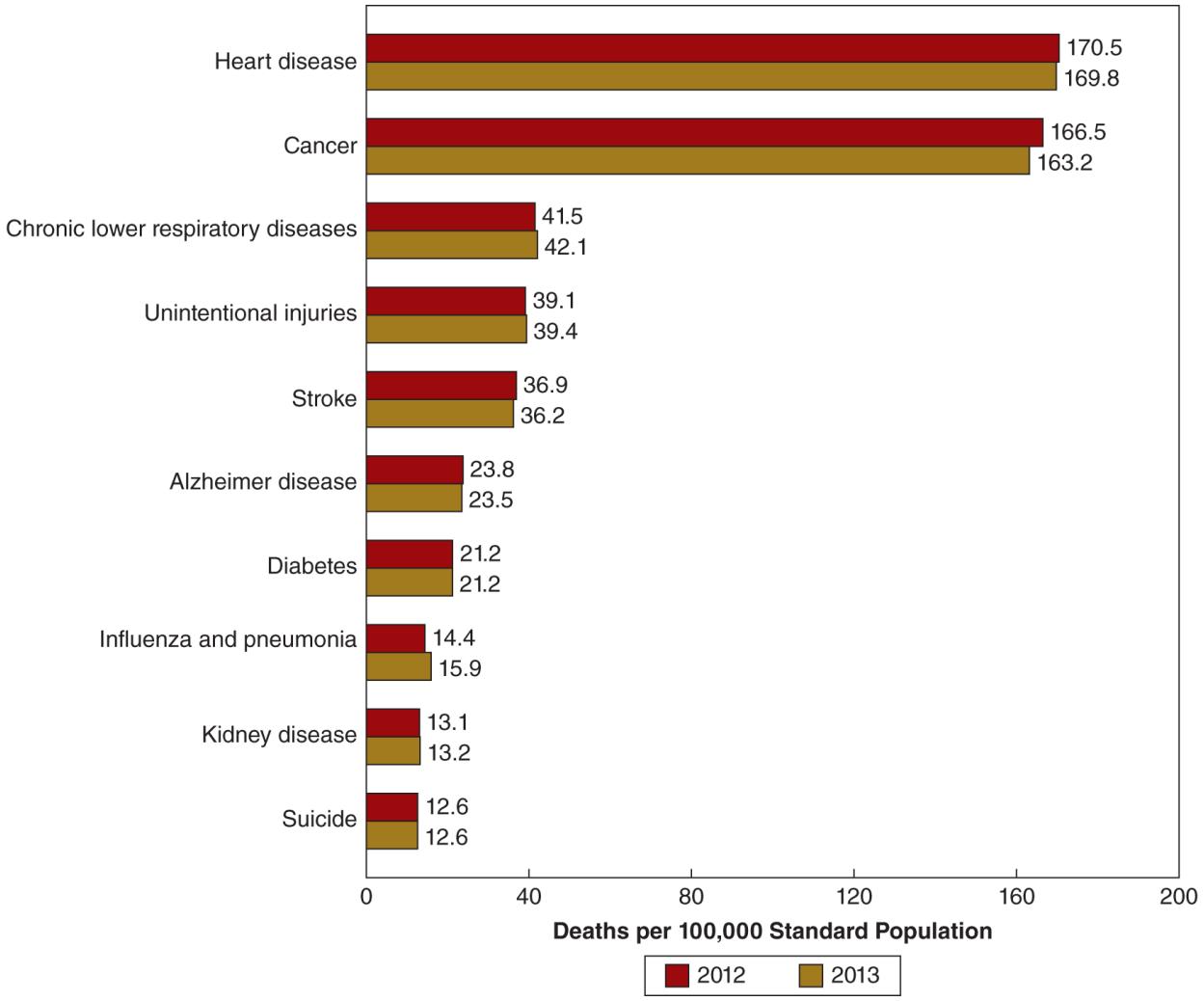


FIGURE 55-2. Age-adjusted death rates for the 10 leading causes of death: United States, 2012 and 2013. Notes: Causes of death are ranked according to number of deaths. (Kochanek KD MS, Xu JQ, Arias E. Mortality in the United States, 2013. NCHS Data Brief, no. 178. Hyattsville, MD: National Center for Health Statistics; 2014.)

As the number of comorbid conditions rise, the complexities of delivering care have had profound consequences. Patients with multimorbidity are at increased risk of disability, institutionalization, poorer quality of life, and higher risk of harm from medical treatments. Overtime, the care that these patients get often becomes more fragmented. A comparison of Medicare beneficiaries from 2000, 2005, and 2009 shows the impact at a health systems level. By 2009, 29% of Medicare beneficiaries spent a portion of their last 30 days of life in an intensive care unit. The average beneficiary had three care transitions in the last 90 days of life, and 14% had a care transition in the last 3 days of life. Although hospice use overall had risen, by 2009 28% of hospice beneficiaries died within 3 days of enrollment on hospice, a benefit designed for those with a prognosis of 6 months or less. Finally, despite extensive national focuses on improving symptom control, the report of proxies about decedents' pain and alarming symptoms in the last year of life actually increased from 1998 to 2010 in a study using data from the Health and Retirement Study.

A final impact of care at end of life of a population with aging and multimorbidity is the significant costs associated with care. While health care inflation slowed during the last recession, future projections show health care spending is projected to be 19.3% of gross domestic product. Care associated with patients with multimorbidity accounts for markedly greater cost. In 2007, two-thirds of Medicare dollars spent were on patients with more than five chronic illnesses. A year of care for a patient with only two to three diseases costs $5698 compared to care for patients with six or more illnesses which costs an estimated $32,658 in 2010 dollars.

Palliative care offers the opportunity for reducing cost while better matching patient care to patient goals.

THE BENEFIT FOR PALLIATIVE MEDICINE

Palliative medicine has been a rapid growing field over the last few years, and as the field matures, there is a growing

body of literature showing its benefit.

The Evidence for Palliative Care Systems

There is now substantial evidence for specialist palliative care interventions including multiple randomized trials which show palliative care improves outcomes including quality of life, satisfaction with care, reduced family distress, and increased hospice utilization. The landmark Temel study demonstrated the value of concurrent care, that is, palliative care delivered early and simultaneously with curative, disease-focused care in advanced lung cancer patients. Early palliative care for newly diagnosed metastatic lung cell cancer patients was associated with higher quality of life, less depression, and a statistically significant longer median survival (11.6 months vs 8.9 months). A recent, larger cluster randomized trial of advance cancer patients with good performance status representing a wide variety of cancer types demonstrated improved quality of life with early palliative care. Notably the statistical significance in many outcomes was not achieved until the fourth month of palliative care, emphasizing the importance of early referral to palliative care to impact quality of life measures beyond pain control. The ENABLE III study is another recent randomized trial which showed that initiating concurrent palliative care at the time of a cancer diagnosis had a significant impact on 1-year survival compared to initiating palliative care 3 months after initial cancer diagnosis (63% early vs 48% delayed) and involved multiple types of cancer not only lung cancer.

Extensive evidence is accumulating for palliative care delivery for noncancer diagnosis as well. A randomized controlled trial of homebound, terminally ill patients with a prognosis of less than 1 year not enrolled in hospice showed in-home palliative care delivery improved patient satisfaction and the chances of dying in home while reducing emergency visits. A randomized trial of hospitalized patients with acute heart failure showed short-term improvement in symptom burden, quality of life, and depressive symptoms. In addition to pain and quality-of-life concerns, management of dyspnea is a key area where palliative care provides benefit to patients. In a randomized controlled trial of patients with advanced illness (cancer, chronic obstructive pulmonary disease, congestive heart failure, interstitial lung disease, and motor neuron disease) integrated palliative care with a breathless support service improved symptom control, and similar to the Temel study, patients with chronic obstructive lung disease and interstitial lung disease lived longer with palliative care.

The Evidence for Hospice

Hospice has been shown in numerous studies to improve symptom control, increase patient satisfaction and quality of life, and help patients and families prepare for death. A major benefit of hospice over usual care is that hospice allows patients to die in their own place of residence when that is the patient's wishes. In 2013 over 66% of hospice patients were able to die in their place of residence. More recent observational studies have suggested that hospice care may be associated with longer survival.

A specific concern of geriatricians is whether hospice adds benefits for patients with dementia in long-term care. In 2001, only 14.4% of Medicare decedents with a dementia diagnosis received 3 or more days of hospice care. By the year 2007, that proportion had grown to 33.6%. However, there is evidence that hospice does provide important value for this population. Nursing home residents with dementia and cancer who received hospice care in the last 30 days of life were less likely to die in a hospital (2%) than those who did not receive hospice (27%). Hospice enrollment increases the likelihood that patients with dementia who have pain receive an opioid.

PALLIATIVE CARE IN SPECIAL POPULATIONS

Palliative care and geriatrics are both designed to serve the needs of the most vulnerable patients with a "common central philosophy of patient-centered commitment to holistic and humane care." Due to the growing geriatric population, there is an unprecedented need to provide excellent palliative care to older adults, especially those with dementia, frailty, and multimorbidity. Partnerships between geriatricians and palliative medicine specialists can be especially useful for management of patients with these conditions, with each specialty working together to ensure the highest level of evidenced-based compassionate care to older adults.

Dementia

Older adults with dementia have significant symptom burden as their disease progresses and as such benefit from combined geriatric and palliative medicine approaches. Patients in the earlier stages of dementia can benefit from

advanced care planning to anticipate future loss in decision-making capacity are lost to alleviate suffering of family and surrogates. As dementia progresses patients are often faced with increasing symptom burden including worsening behavioral and psychological symptoms of dementia. Pain may affect up to 46% of patients with dementia. As patients approach the end of life, the proportion with pain, dyspnea, pressure ulcers, and aspiration increases. Those with advanced disease can benefit from appropriate management of weight loss and swallowing difficulties. Those with end-stage disease can benefit from hospice services.

Health care professionals caring for older adults with earlier stages of dementia should engage patients and their families in advance care planning. Advance care planning discussions with patients in the earlier stages of dementia may result in completion of an advance directive document in which the patient can specify preferences for future care (such as a living will) and/or designate an authorized surrogate decision maker to communicate the patient's preferences in circumstances when they no longer possess medical decision-making capacity (see more details in Chapter 66). For patients with dementia and limited life expectancy, advance care planning discussions may also result in completion of a State Authorized Portable Order for Life-Sustaining Treatments such as the Physician Orders for Life-Sustaining Treatment (POLST) form. In later stages of dementia when a patient lacks decision-making capacity, the patient's surrogate may complete a POLST form according to the patient's wishes. Geriatricians and palliative medicine specialists are both well equipped to conduct these vital discussions. The Gerontological Society of America has resources available to assist clinicians with communication with patients with cognitive and sensory impairments, and palliative care resources are available for communication with patients and families about delivering bad news, discussing prognosis and goals of care. Combining this expertise can lead to exceptional patient-centered care.

In advanced stages of dementia, patients may develop decreased appetite or dysphagia putting them at risk for weight loss and aspiration pneumonia, respectively. An example of the powerful collaborative effort between geriatrics and palliative medicine is evidenced in the American Board of Internal Medicine (ABIM) "Choosing Wisely" initiative. The first recommendation from the American Geriatrics Society (AGS), the American Academy of Hospice and Palliative Medicine (AAHPM), and the Society for Post-Acute and Long-Term Care Medicine (AMDA) is regarding patients with advance dementia and eating difficulties. AGS, AAHPM, and AMDA all recommend *in favor of offering oral assisted feeding* and recommend *against percutaneous feeding tubes* in advanced dementia. Studies have shown that feeding tubes in advanced dementia do not prevent aspiration pneumonia, improve healing of pressure ulcers, or lead to increased survival. In fact, feeding tube usage has been associated with the development of pressure ulcers and the use of pharmacologic and physical restraints. AGS and AAHPM recommend assistance with oral feeding as an evidence-based alternative to feeding tubes for patients with advanced dementia and difficulty eating. AGS and AAHPM agree that assistance with oral feeding places an appropriate focus on comfort and human interaction in the final phase of life instead of focusing solely on nutritional goals.

It is imperative that health care professionals provide appropriate management of behavioral and psychological symptoms of dementia. As discussed in detail in the management of agitation in Chapter 74, management of behavioral and psychological symptoms of dementia should involve (1) identifying the specific problem behavior and its severity, (2) identifying potential triggers for the behavior, (3) removing underlying physiologic and environmental triggers whenever possible, (4) attempting nonpharmacologic interventions to improve behavior, and (5) as a final resort, using recommended targeted pharmacotherapy for behaviors that do not respond to attempts of nonpharmacologic management in situations that risk patient or caregiver safety. As part of the ABIM "Choosing Wisely" initiative, AGS recommends against the use of antipsychotics as first-line treatment for behavioral and psychological symptoms of dementia. Notably, a cluster randomized trial of nursing home patients with behavioral problems using an empiric stepwise protocol to treat pain resulted in a decrease in the number of symptoms. Most patients were treated with the first step of the protocol, acetaminophen. Stronger pain medicines (opioids) may be tried for nonresponders.

Determining a 6-month prognosis in advanced dementia can be challenging. Factors such as irreversible weight loss, low body mass index, functional dependence, and advanced age are associated with limited prognosis in dementia patients. Palliative medicine specialists can often help geriatricians identify patients with dementia who are eligible to receive hospice care. Geriatricians can be a valuable resource for palliative medicine specialists (and others managing these challenging behaviors) with knowledge of appropriate medications for specific behavioral conditions and age-appropriate medication dosing.

Frailty

While the exact definition of frailty remains a subject of debate (see Chapter 46), frail patients are particularly vulnerable to adverse outcomes and have significant palliative care needs. For instance, severely frail older adults have

shown poor response to treatment and may not benefit from intensive rehabilitation efforts. Attempting rehabilitation of the most frail may in fact cause harm. The key to managing the palliative needs of frailty is determining goals and recognizing the patient with poor potential to improve. When in doubt, a therapeutic trial of improving performance status is always appropriate, but if not achieved should prompt a repeat discussion of goals and prognosis.

Determining the severity of frailty and the potential for reversibility can help clinicians recommend appropriate treatment. According to Fried, the frailty syndrome is characterized by a combination of (1) slowed walking speed, (2) weakness, (3) weight loss, (4) decreased activity levels, and (5) exhaustion, Older adults with a Fried score of 1 to 2 are considered "prefrail" and evidence of frailty may not be clinically apparent until the patient is exposed to a stressor such as an infection or hospitalization. Those with a Fried score greater than or equal to 3 are considered frail. Prefrail and frail older adults may respond to efforts to prevent or reverse frailty such as minimizing immobility and polypharmacy, treating pain and depression, maintaining muscle mass and strength through resistance exercise, and ensuring nutritional adequacy. Severe frailty, with a score of 4 to 5 and low cholesterol and albumin levels, has been associated with higher rates of mortality and poor response to treatment. These older adults may instead benefit from hospice services due to the high risk of mortality over 6 to 12 months.

Patients with frailty and multimorbidity may still be eligible for hospice even if they do not have a single terminal illness. While CMS has stated that frailty, debility, or adult failure to thrive are not accepted as the principal hospice diagnosis reported on the Medicare hospice claims form, this does not mean that frail patients are not eligible for the Medicare Hospice Benefit. A patient is considered hospice eligible if the attending physician and hospice medical director have certified the patient to be terminally ill with a prognosis of less than 6 months. This prognosis is determined based on the severity and irreversibility of the patient's frailty as well as their multimorbidity. The hospice Medical Director could utilize the hospice LCDs available on the CMS website to support their determination that the patient has a prognosis of less than 6 months.

Multimorbidity

Providing optimal care for older adults with multiple chronic conditions, or multimorbidity, presents one of the greatest challenges in geriatrics. Patients with multimorbidity have increased use of health care resources, poorer quality of life, higher rates of institutionalization, disability, and death. To address the challenge of providing patient-centered care to older adults with multimorbidity, the AGS convened an expert panel with the goal of developing an optimal clinical approach for this population. The panel created a stepwise approach to patient care that integrates key principles of geriatric and palliative medicine into five domains: (1) patient preferences, (2) interpreting the evidence, (3) prognosis, (4) clinical feasibility, and (5) optimizing therapies and care plans. The following is a summary of the "Patient-Centered Care for Older Adults with Multiple Chronic Conditions: A Stepwise Approach: Expert Panel on the Care of Older Adults with Multimorbidity."

1. ***Patient Preferences:*** The guiding principle of the patient preferences domain is "*eliciting and incorporating patient preferences into medical decision making*." The expert panel emphasizes the importance of eliciting preferences and distinguishes this from simply asking patients to make a treatment decision. Eliciting preferences involves investigating a patient's values and priorities and understanding the rationale that lead to treatment decisions. If a patient were to state that "*Being independent and at home is really important to me. I know my life is short and I do not want to be bedbound or in a state where I couldn't interact with my family. For this reason I do not want to be intubated even temporarily"*; this is an example of a treatment preference, where the rationale of the decision is explained. In contrast, an example of a treatment decision statement is *"I do not want to be intubated."* Patient preferences and treatment decisions should only be elicited after the patient is fully informed about the risks and benefits of the treatment options. This may be done with the use of a decision aid. It is also important for clinicians to accommodate the decision-making style of the patient. Some individuals prefer to make decisions independently, others would like the input of their family or health care provider, and some others may even prefer to completely defer decision making to family or caregivers. Some individuals prefer detailed information while others prefer general knowledge to aid in the decision-making process. Since patients may change their minds over time therefore discussions to elicit preferences are not a one-time event and should occur regularly with significant changes in health. Finally, "the principle of eliciting preferences and involving patients in the decision-making process does not mean that the patient has the right to demand any available treatment without a reasonable expectation of some benefit."
2. ***Interpreting the Evidence:*** The guiding principle of this domain is "*recognizing the limitations of the evidence*

base, interpreting and applying the medical literature specifically to older adults with multimorbidity." The first step to interpreting the evidence involves reviewing the applicability and quality of the evidence, essentially, were older adults with multimorbidity sufficiently included to make the study findings relevant? The next step involves determining if the outcomes of the study are relevant to the patient. Many studies report intermediate outcomes such as lowering cholesterol or blood pressure levels rather than outcomes that affect patients more directly such as myocardial infarction and stroke or quality of life. Studies that report direct outcomes can be more meaningful when managing older adults with multimorbidity, especially those with limited life expectancy. Interpreting the evidence also includes evaluating the reported harms and burdens of the intervention. How does the intervention in the study affect other medical conditions that the older adult with multimorbidity has? The next step involves, determining if the study reports relative risk reduction (RRR) or absolute risk reduction (ARR). Since ARR incorporates the baseline risk in a population, studies that report ARR can be more meaningful for patient outcomes for older adults since they may have higher or lower baseline risk than the general population. For instance, a study may report a 50% RRR, but this could be due to a baseline risk of 2% without treatment minus a 1% risk with treatment. In this situation, although the relative risk reduction is 50%, the absolute risk reduction would only be 1%. The final step of interpreting the evidence involves considering the time horizon to benefit of the treatment. The length of time needed to accrue an observable, clinically meaningful risk reduction for a specific outcome is known as the time horizon to benefit. Similarly, the length of time in which meaningful adverse events occur is known as the time horizon to harm. For example, since the time horizon to benefit for tight glycemic control is many years, it is more likely to harm older adults with multimorbidity with limited prognosis as they will not live long enough to receive benefit and are put at immediate risk of hypoglycemia. Clinicians should engage patients in shared decision making to determine if the immediate risks of the treatment outweigh the potential future benefits.

3. ***Prognosis:*** The guiding principle of this domain is "*framing clinical management decisions within the context of risks, burdens, benefits, and prognosis (eg, remaining life expectancy, functional status, quality of life) for older adults with multimorbidity*." Determining and discussing prognosis with patients and caregivers can help inform treatment decisions. Interventions can be ineffective or harmful when the time horizon to benefit is longer than the patient's life expectancy. Further information about determining and discussing prognosis is available in the prognosis section of this chapter.
4. ***Clinical Feasibility:*** The guiding principle of this domain is "*considering treatment complexity and feasibility when making clinical management decisions for older adults with multimorbidity*." For older adults with multimorbidity treatment regimens may not be feasible due to treatment complexity or cost. These factors should be taken into consideration when recommending interventions.
5. ***Optimizing Therapies and Care Plans:*** The guiding principle of this domain is "*choosing therapies that optimize benefit, minimize harm, and enhance quality of life for older adults with multimorbidity*." Treatments and interventions should be prioritized to minimize risk exposure, maximize benefit, and optimize adherence to the most important pharmacologic and nonpharmacologic therapies. This involves identifying interventions (treatments, procedures, pharmacologic and nonpharmacologic therapies) that may be inappropriate for older adults and engaging patients in a discussion about not starting or stopping them.

Palliative Needs of the Lesbian, Gay, Bisexual, and Transgender Population

Within the United States, and indeed throughout much of the world, societal acceptance of lesbian, gay, bisexual, and transgender/transsexual (LGBT) individuals is rapidly evolving. Same-sex marriage became legal in the United States on June 26, 2015, with the Supreme Court's Obergefell v. Hodges decision. With that decision, federal recognition of benefits for married couples between two people of the same sex was officially sanctioned. However, the LGBT community has long faced health care disparities, and continued legal challenges to Obergefell v. Hodges may persist for the immediate future.

While all persons with serious illness endure difficulties, those patients who are lesbian, gay, bisexual, and transgender/transsexual may face unique issues distinct from the heterosexual population. LGBT older adults have a history of having experienced stigmatization, discrimination, victimization, or violence during their lifespan by their families, school, workplaces, and even health care providers. Health care professionals may discriminate LGBT persons in the form of derogatory comments, refusal of care, and biases. LGBT persons may present at more advanced stages of illness because they are more reluctant to seek health care or they lack health insurance. Compared to the general population that has suicide attempt rates of 1.6%, gays, lesbians, and bisexuals have rates of 10–20%, and

transgender and nongender-conforming persons have the highest suicide attempt rates of 41%. The highest prevalence of lifetime suicide attempts (65%) has been found among those transgender and gender-nonconforming adults with a disability. Health care professionals should be attentive to the possibility of a suicide attempt when caring for an LGBT person who is diagnosed with a serious illness like cancer or a debilitating disabling illness like amyotrophic lateral sclerosis (ALS).

LGBT persons may need to rely on close friends rather than on family for caregiving. Nonfamily caregiving may be due to estrangement from the person's biological family or because LGBT persons are less likely to have children. Informal communities of support are also known as "lavender families" or "families of choice" and should be respected and included as family as identified by patients. The support from the "lavender family" may become essential in caring for an LGBT individual at the end of life. It may be challenging for LGBT persons who need custodial care to find a long-term care facility that is "LGBT friendly". LGBT patients may hide their sexual identities to be able to access a long-term care facility also known as "going back in the closet."

Transgender patients may face several unique stressors. A person who is biologically a man but who prefers to dress and identify as a woman may be faced with having to share a hospital room with a man. Also a person who is genetically a female but who wishes to identify as male, may be faced with not being able to legally make the change because he may have conditions unique or more typical to the female gender such as endometriosis and breast cancer which would not be covered by his health insurance should he legally want to be considered as a man. Having a gender-variant body and requiring assistance for basic needs of daily living like bathing, dressing, or feeding puts the transgender individual in a vulnerable position and at risk of being physically abused.

It is of extreme importance that the LGBT person takes steps to legally document their preferences for health care and other legal matters. Individuals that may be closer to the LGBT person may not be identified as the default surrogate by law should the LGBT person no be able to make his or her own decision; and it is possible that the default decision maker may not be respectful of the individual's chosen gender identity.

LGBT patients should designate a Health Care Power of Attorney (HCPOA) and additionally explicitly give that person the power to direct health care professionals with the preferences of name, pronoun of choice, and appearance consistent with their gender identity. Given that the HCPOA and advance directives are no longer effective as soon as the person dies it is important for LGBT persons to also put in place a Disposition of Bodily Human Remains (DBHR) document so that he or she can name who is the person to have authority over the remains of a person once deceased. For example, a same-sex partner who had HCPOA would not be able to claim the deceased body of his or her loved one unless he or she had been designated to do so in a DBHR document.

LGBT persons also may face challenges during the bereavement process, particularly if in the case of a same sex relationship, the couple had not been openly acknowledged. The surviving individual may experience "silent mourning" and not have access to traditional grief support mechanism.

Ethnic and Culturally Diverse Populations

In addition to the aging demographic changes of the US population, a key change impacting geriatric palliative care is increasing ethnic diversity. Among older adults age 65 and older, approximately 21% are members of a racial or ethnic minority (9% African Americans, 4% Asian or Pacific Islander, 7% Hispanic, 0.5% Native American, 0.1% Native Hawaiian/Pacific Islander, and 0.7% identified themselves as having two or more races) and there will be a trend to increasing diversity in older adults in the future.

Johnson reviewed racial and ethnic disparities in palliative care in 2013 and found growing evidence that racial and ethnic disparities exist in both clinical outcomes as well as in access to palliative care. Disparities in quality of care include lower satisfaction, poor communication, and worse pain management outcomes for minorities. Hospice utilization is lower for minority older adults and there are higher rates of hospice disenrollment among African Americans.

End-of-life care preferences may be significantly influenced by the expected norms of a patient's culture of birth which may differ significantly from US health care's expectations. However, any single patient from any ethnic group may have more or less affiliation with traditional beliefs from their culture of origin. The key is to ask. The phrase, "I am not familiar with your home country, are there any traditions or beliefs that affect your health care choices I should know about?" can begin a discussion.

Patients who are unable to speak the language of the care team are at risk of receiving care that may not match their wishes. Use of family members as interpreters risks information being withheld or incomplete translation. A trained medical interpreter at bedside or a telephone translator service is recommended.

The Institute of Medicine's (IOM) [now known as National Academy of Medicine (NAM)] report on healthcare disparities and unequal treatment determined that patients' attitudes toward health care and treatment preferences were not the major source of disparities. At the level of clinical encounter, factors that lead to disparities include bias or prejudice, stereotypes (beliefs held by the provider about the behavior or health of minorities) and uncertainty about preferences. The key systems factors in disparities per the NAM study were factors such as cultural and linguistic barriers, fragmentation of health care systems, and the types of incentives in place.

For clinicians seeking to learn more about ethnogeriatrics Stanford University offers an excellent online curriculum. In addition, for a point-of-care resource, The AGS publication *Doorway Thoughts* addresses issues and concerns providing relevant details regarding the beliefs, traditions, and customs that would apply to clinical encounters with an older adult from 15 groups of diverse ethnic backgrounds.

PROGNOSTICATION IN OLDER ADULTS

Prognostication is a vital aspect of decision making as it provides patients and families with information to determine realistic and achievable goals of care, is used in determining eligibility for benefits such as hospice, and helps in targeting interventions to those likely to live long enough to benefit from a proposed intervention. For example, it may take many years for the benefits to accrue for preventative interventions such as cancer screening and tight glycemic control. For frail older adults whose life expectancy is less than this time horizon to benefit, they are exposed to potential immediate harms of these preventative interventions without the possibility of receiving the benefits.

Prognostication can be broken into three general steps: (1) estimating the probability of an individual developing a particular outcome over a specific period of time, (2) the act of communicating the prognosis with the patient and/or family, and (3) the interpretation of the prognosis by the patient and/or family.

Step 1: Estimating Prognosis

Estimating prognosis in geriatric populations is more complicated than in younger populations, as older adults are more likely to have more than one chronic progressive illness that impacts life expectancy. Estimation of prognosis in multimorbid older adults requires clinicians to account for interaction of their medical problems, clinical and laboratory findings, and functional and cognitive status. While prognostication based on clinician judgment is correlated with actual survival, it is subject to numerous biases, most importantly that clinicians tend to overestimate patient survival by a factor of 3 to 5. Prognostic indices that incorporate age and clinical characteristics such as multimorbidity and functional status may improve the accuracy of prognostication compared to clinician judgment alone. A helpful repository of published geriatric prognostic indices can be found at www.ePrognosis.org.

Step 2: Communicating Prognosis

Numerous studies have shown that most individuals and their families want prognostic information, yet they are often not given the opportunity to discuss it with health care providers. This is despite evidence that effective communication around end-of-life issues can provide benefits to patients and families, without worsening of anxiety, hopelessness, or depression.

When delivering prognosis, it is first helpful to ask about the patient's understanding of their illness and perception of what the future may have in store for them. It is also helpful to assess the readiness of the patient and/or family member to have a discussion of prognosis by asking them permission to talk about it. Based on this information, the clinician should deliver prognostic information tailored to the patient's current desire and level of understanding. When delivering prognostic estimates, clinicians should acknowledge the inherent uncertainty in most prognostic estimates. One way to do so is by giving ranges in prognostic estimates (ie, days to weeks, weeks to months, months to years to live) or by giving the best case, worst case, and most common scenarios. In addition, delivering information on prognosis is likely to bring emotional reactions in patients and their family members. Use of empathic statements, including naming the emotion, and the use of therapeutic silence, can be helpful in supporting patients and their surrogate decision makers.

Step 3: Interpreting Prognosis

Patients' and surrogates' personal estimates of prognosis are often different, and generally more optimistic than what is communicated to them by health care providers. Furthermore, few surrogates solely rely on prognostication

information delivered by physicians to determine their own prognostic estimates. Rather, their interpretation of prognosis is influenced by many factors, including perceptions of the patient's strength, will to live, unique history, individual observations of physical appearance, and the surrogate's presence, optimism, intuition, and faith. Given this information, it is helpful when delivering prognosis to include the factors that influence the clinician's prognostic estimate, as it may also influence the patient's or surrogate's interpretation of prognosis. It is also valuable to enquire how the clinician's prognostic estimate influenced how the patient or surrogate is currently thinking about the prognosis.

ADVANCE CARE PLANNING AND ADVANCE DIRECTIVES

Advance care planning is a process of ongoing communication that allows patients (or their proxy/surrogate) to discuss with their health care professionals their values, preferences for treatment, and goals of care. Advance care planning is a process because the values or priorities of people may change as they go through life. Ideally, health care professionals should facilitate the advance care planning process for all patients in an ongoing system rather than a one-time decision. Advance care planning focuses on meaningful discussions between health care providers, patients and their surrogate decision makers to ensure there is (1) shared understanding of the patient's prognosis, goals, and treatment options, and (2) shared decision making establishing a care plan that aligns recommended treatments with patient preferences. In a *relatively healthy* person the focus of the discussion may be on choosing a health care proxy and making some goals of care choices based on hypothetically catastrophic situations. In someone with a *predictable progressive condition* such that the person is likely to lose functional or cognitive abilities, such as someone with ALS, dementia, or other chronic conditions, the conversation should include information on prognosis. Additionally considerations should be given for treatment options with significant long-term impact such as initiating hemodialysis. In *a seriously ill* person, the choices are less hypothetical and an actual decision regarding treatment may be needed. In this circumstance, it is important to inform patients (or their proxies) of the risk, benefits and alternative treatments available. Considerations should also be given to deactivating devices such as implantable cardioverter-defibrillators in patients close to dying. Clinicians should also consider initiating goals of care discussions if they answer "no" to the question "Would you be surprised if this patient dies in the next year?" Overall there is evidence that discussions of goals of care with seriously ill persons lead to improved clinical outcomes, do not increase anxiety or lead to loss of hope, and help reduce distress in the surrogate decision makers.

Advance directives are written documents that state a patient's preferences for addressing future medical decisions. Advance directives can be executed at any time by a competent adult person. Advance directives go into effect when the person is no longer capable of making health care decisions. There are many decision aids tools available to assist patients in identifying their goals and preferences.

A surrogate decision maker is a person who is authorized to make decisions about health care on behalf of the patient if they are incapacitated. Overall this is based on a hierarchy of closeness to the patient (eg, spouse, adult children, parents, etc). The hierarchy order may vary between states.

A Durable Power of Attorney for Health Care (DPOA-HC) or Health Care Proxy allows a patient to designate a person to make health care decisions on behalf of the patient should they lose decision-making capacity. This document does not specify wishes for medical care. The ideal DPOA-HC is someone who the patient knows well, is a competent adult, and is willing/able to assist in health care decision making respecting the preferences of the patient should the need arise. It is particularly important to designate a DPOA-HC when the patient is estranged from their family, or the person who may know them best would not be in the hierarchy of surrogate decision makers such as a person who wants to name a friend. The DPOA-HC becomes the first person in the hierarchy of surrogate decision makers.

A Living will allows a patient to specify in writing wishes for future medical care in the hypothetical situation where they lose decision-making capacity.

A Physician Orders for Life-Sustaining Treatment (POLST) form is not an advance directive (which outlines an older adult's preferences for *future* care) but rather a standing medical order specifying decisions regarding *current* medical care for patients with progressive chronic illnesses. These types of orders are available in certain states. The POLST form translates patient preferences for resuscitative efforts, artificial nutrition, and other life-sustaining treatment measures into an effective state-authorized medical order. These forms accompany patients in different settings (home, hospital, nursing home).

Do not resuscitate orders document the patient's preference of not having resuscitation attempted in the event of

cardiorespiratory arrest. In the hospital setting, this is a physician order. In other environments there is the out of hospital do not resuscitate form completed by the patient, physician, and witnesses. When having conversations about cardiopulmonary resuscitation (CPR), it is important to emphasize the overall lack of success of this intervention except for in instances of out of hospital cardiac arrests of those who are relatively healthy. Only 15% of patients who undergo in hospital CPR survive to hospital discharge. When taking into consideration older frail patients undergoing CPR and the presence of serious conditions like metastatic cancer, sepsis, or multiple organ failure, make the possibility of surviving CPR to discharge practically nil.

CONCLUSION

An essential component of geriatric medicine is the routine delivery of effective primary palliative care that includes attention to symptom management, prognostication, communication, advance care planning, and individualized care plans. Appropriate referrals to specialty-level palliative care should also be considered when palliative needs are great, given the increasingly robust evidence base of benefit for both palliative care and hospice.

FURTHER READING

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Chapter 56

Pain Management

Bruce A. Ferrell

Learning Objectives

- Classify different types of pain.
- Describe key pathophysiologic findings in chronic pain.
- Review key aspects of pain evaluation and management.

Key Clinical Points

1. **Older persons are more likely to underreport pain; underlying illnesses and cognitive impairment may make evaluation and treatment more difficult.**
2. **Careful evaluation of pain requires a thorough history and physical supplemented by validated pain scales.**
3. **Aggressive pharmacologic pain management, including the use of opioids, is appropriate in older adults but must require careful monitoring and attention to underlying comorbid conditions.**

OVERVIEW

Pain is one of the most common symptoms for which patients seek medical attention. Approximately 116 million Americans are afflicted by chronic pain. Epidemiologic studies suggest three in five persons over age 65 report pain that lasted a year or more, and more than 15% report daily pain. In general, the most common causes of pain in older persons are probably related to musculoskeletal disorders such as back pain and arthritis. Neuralgia is also common, stemming from diseases such as diabetes, herpes zoster, and trauma such as surgery, amputation, and other nerve injuries. Nighttime leg pain (eg, cramps and restless legs) is also common, as is claudication. Cancer and its treatment, although not as common as arthritis, is often a source of severe pain. For patients near the end of life, the distress of cancer-related pain has resulted in an obligation for clinicians to provide effective comfort and palliative pain management. Management of persistent pain is associated with a number of negative outcomes in older adults. Depression, decreased socialization, sleep disturbance, falls, adverse drug events, and slow rehabilitation have all been associated with either the presence of pain or its treatment in older people. Older patients rely heavily on family and other caregivers near the end of life. For these patients and their caregivers, pain can be especially distressing. Caregiver strain and caregiver attitudes can have substantial impact on pain. In the final analysis increased utilization of health services and societal costs of treatment most likely exceeds $560 billion per year.

The approach to pain management is often different in older versus younger persons. Older persons may underreport pain. They often present with concurrent illnesses and multiple problems, making pain evaluation and treatment more difficult. Dementia, delirium, a higher incidence of side effects to medications and higher potential for complications and adverse events related to many treatment procedures make pain assessment and management more difficult. Despite these challenges, pain can be effectively managed in most older patients. Moreover, clinicians have an ethical and moral obligation to prevent needless suffering and provide effective pain relief, especially for those near the end of life.

HOW AGING AFFECTS PAIN PERCEPTION

The effect of aging on pain perception has been a topic of interest for many years. Older persons often present with altered presentation of common diseases. For example, older persons have been observed to present with apparently painless myocardial infarction and painless intra-abdominal catastrophes. The extent to which these observations are attributable to age-related changes in pain perception remains uncertain. Anatomic studies, as summarized in **Table 56-1**, have observed some age-related changes in the nervous system that might alter pain perception. Some of these findings include decreased numbers of various pain receptors in the skin and other organs, altered nerve conduction, and some central nervous system changes that may affect sensory processing. Most of these studies were based on cross-sectional studies of animal and postmortem specimens.

TABLE 56-1 AGE-RELATED CHANGES IN PAIN PERCEPTION

COMPONENT	AGE-RELATED CHANGE	COMMENTS
Pain receptors	• 50% decrease in Pacini corpuscles • 10%–30% decrease in Meissner/Merkel disks • Free nerve endings—no age change	Few studies largely limited to skin
Peripheral nerves	• Myelinated nerves Decreased density Increase abnormal/degenerating fibers Slower conduction velocity • Unmyelinated nerves Decreased number of large fibers (1.2–1.6 μn) No change in small fibers (0.4 μn) Substance P content decreased	Evidence of change in pain function is lacking; findings are not specific to pain
Central nervous system	• Loss in dorsal horn neurons Altered endogenous inhibition and hyperalgesia • Loss of neurons in cortex, midbrain, and brain stem 18% loss in thalamus Altered cerebral-evoked responses Decreased catecholamines, acetylcholine, GABA, and 5HT Endogenous opioids—mixed changes Neuropeptides—no change	Findings not specific to pain

Data from Gibson SJ, Helme RD. Age differences in pain perception and report: a review of physiological, psychological, laboratory and clinical studies. Pain Rev. 1995;2:111–137.

Likewise, a large number of physiologic studies of pain perception also exist. These studies typically use a heat probe, electrical stimulation, or other methods to induce pain in volunteers in an effort to identify a pain threshold or pain tolerance level. These studies have shown mixed results, with some showing increased, some showing decreased, and some showing no change in pain perception with aging in normal volunteers. Moreover, it has been difficult to conduct a formal meta-analysis using all of these studies because of flaws in many of these studies concerning sampling errors and methodological differences. In the final analysis, most investigators have concluded that actual age-associated changes in pain perception are subtle and probably not clinically significant.

On the other hand, older adults often present with concurrent illness and sensory impairments that may mask pain complaints. Cognitive impairment, sensory neuropathies, and visual and hearing impairment, each may make communication of pain complaints more difficult and thus appear to be a perceptual problem. Older patients may be more stoic; they may expect pain with aging and fear diagnostic tests, other interventions, or the meaning of pain. These issues can make pain assessment and measurement much more difficult in older people.

CLASSIFICATION OF PAIN

Pain is quite variable in description, character, and intensity among individuals. For the purpose of understanding, predicting, and treating pain, a variety of classification schemes have been used. For diagnostic purposes, it may be helpful to categorize pain as acute or persistent. The old term "chronic pain" is now considered obsolete, and the newer term "persistent" is used to reduce the common biases and negative stereotypes associated with the label "chronic pain patients" in the past. For treatment purposes, it may be more helpful to categorize pain as nociceptive versus neuropathic.

Acute Versus Chronic (Persistent) Pain

Acute pain is defined by a distinct onset, obvious cause, and short duration. Trauma, burns, infarction, and inflammation are examples of pathologic processes that result in acute pain. Acute pain is often associated with autonomic nervous system signs, including tachycardia, diaphoresis, or elevation in blood pressure. The presence of acute pain usually indicates an acute injury or acute disease, and the intensity of acute pain often indicates the severity of injury or disease. Thus, acute pain should trigger an urgent search for an underlying cause that might be life threatening or require immediate intervention. The effective management of acute pain is important to facilitate diagnostic tests. Preoperative pain management of acute pain makes anesthesia easier and postoperative pain control better. In some cases, management of acute pain can help prevent development of chronic pain syndromes.

Chronic pain is usually defined by its persistence beyond an expected time frame for healing, usually longer than 3 months. Intensity of chronic pain is often out of proportion to the observed pathology and associated with prolonged functional impairment, both physical and psychological. Autonomic signs are often absent. Underlying causes of chronic pain are often associated with chronic disease and are less remedial.

Chronic pain is often more difficult to manage in older patients because the underlying cause is less curable and many treatment strategies are short lived, difficult to maintain, or associated with long-term side effects. Chronic pain usually requires a multidimensional approach to treatment, including use of both analgesic drug and nondrug strategies with attention to sensory, emotional, and behavioral components of the pain experience.

Nociceptive Versus Neuropathic Pain

For treatment purposes, it may be helpful to identify the underlying mechanism of pain perception. Treatment aimed at specific pathophysiologic pain mechanisms may be more effective. Pain problems that result largely from stimulation of pain receptors are called nociceptive pain. Nociceptive pain may arise from tissue injury, inflammation, or mechanical deformation. Examples include trauma, burns, infection, arthritis, ischemia, and tissue distortion. Pain from nociception usually responds well to common analgesic medications.

Neuropathic pain results from pathophysiologic processes that arise in the peripheral or central nervous system. Examples include diabetic neuralgia, postherpetic neuralgia, and posttraumatic neuralgia (postamputation or "phantom limb" pain). In contrast to nociceptive pain, neuropathic pain syndromes are often persistent and difficult to treat. They may, however, respond to nonconventional analgesic medications such as tricyclic antidepressants and anticonvulsant drugs. For these syndromes, it is important to recognize them early and to begin treatment with adjuvant analgesic strategies before development of long-term complications of persistent pain including physical and psychological disability.

There are other physiologic mechanisms of pain, including mixed nociceptive and neuropathic syndromes and pain syndromes of unknown mechanisms. Treatment for these is more problematic and often unpredictable. Examples include recurrent headaches and some vasculitic syndromes. Finally, psychologically based pain syndromes are those with psychological factors that play a major role in the pain experience. Examples include somatoform disorders and conversion reactions. These patients may benefit from specific psychiatric intervention, as traditional pain strategies are often ineffective.

PATHOPHYSIOLOGY OF PERSISTENT PAIN

Theoretical Mechanisms

Over the last 30 years, a number of physiologic observations may help understand and provide effective approaches to

patients with some types of persistent pain. Multiple mechanisms have been identified that can promote or facilitate persistent or chronic pain. Many of these observations implicate or elucidate mechanisms by which an initial nociceptive stimulus may evolve over time to a true neuropathic mechanism of persistent pain.

Animal studies in the 1980s demonstrated that permanent changes can occur in the spinal cord in response to nerve injury. Nociceptor sensory neurons terminate in the most superficial laminae of the dorsal horn in the spinal cord. In contrast, low threshold sensory fibers activated by touch, pressure, vibration, and normal ranges of movement of joints terminate in the deep laminae of the dorsal horn. Experiments in rodents have shown that physical rearrangement of this circuitry may occur after peripheral nerve injury, with new growth of the low-threshold afferents seen in the zone normally occupied exclusively by nociceptor terminals. Additionally, after peripheral nerve injury, the neuromodulators brain-derived neurotrophic factor and substance P, normally expressed only in C-fibers, may begin to be expressed in large-diameter A-fiber neurons. These permanent changes may result in persistent pain perception following a nerve injury.

Sensitization of neurons may occur peripherally or centrally. Tissue inflammation may result in changes in the chemical environment of the peripheral nociceptors. Damaged cells may release intracellular contents and synthesize substances including cytokines, chemokines, bradykinin, histamine, prostaglandins, and growth factors. Inflammatory cells are recruited to the site of damage, and some of these proinflammatory mediators directly activate the nociceptor and produce pain (nociceptor activators); others sensitize the terminal so that it becomes hypersensitive to subsequent stimuli. Central sensitization amplifies the synaptic transfer from the nociceptor to dorsal horn neurons. Initial sensitization to synaptic transfer is activity dependent, triggered by nociceptor input into the spinal cord. Later transcriptional changes in the molecular machinery of the dorsal cell sustain the sensitization beyond the initiating stimulus. N-methyl-D-aspartate (NMDA) receptors appear to be integral to this central sensitization process. Thus, previously subthreshold synaptic inputs to nociceptive neurons now generate an augmented action potential output. The increase in excitability of the dorsal horn cell means that it can be activated by normally subthreshold inputs, with increased response to suprathreshold inputs.

Increased excitability of injured and neighboring uninjured sensory neurons can generate pacemaker-like ectopic action potential discharges, resulting in sensory inflow independent of a peripheral stimulus. These changes may manifest at the site of the injury, at a neuroma, or in the dorsal root ganglion. These ectopic signals arise due to multiple factors including upregulation of sodium channels, channel subunits, or signal receptors in myelinated neurons; or downregulation of potassium channels.

Loss of neurons and the resulting imbalance of sensory inflow may contribute to the abnormal sensations. This paradoxical increase in pain perception with neuron dropout is not well understood. Conceivably, this may be related to changes in neurotrophic factors, compensatory local changes in the surrounding neurons or dorsal root ganglion/dorsal horn of the spinal cord, changes in related glia, and/or changes in cortical interpretation of afferent input.

Finally, a reduction in inhibition can have an effect similar to increased excitability. Pharmacologically blocking γ-aminobutyric acid (GABA) produces a pattern of pain hypersensitivity similar to that of neuropathic pain, with prominent tactile allodynia. GABA blockade recruits previously absent Aβ fiber inputs to lamina II cells, effectively uncovering a previously silent synaptic pathway. Partial nerve injury reduces inhibition in the superficial dorsal horn, with selective loss of GABAergic inhibitory synaptic currents due to apoptosis in inhibitory interneurons. One week after nerve injury that produces hypersensitivity to pain, neurons begin to undergo apoptosis in the dorsal horn.

For clinicians, when pain symptoms fail to respond to traditional treatment, conventional approaches may be supplemented by a mechanism-based approach in efforts to individually tailor targeted therapy. Unfortunately, data regarding the determination of the precise pain mechanism in a given patient, and the effectiveness of therapy targeted to the mechanism, are preliminary, but current knowledge provides a framework for future investigation and clinical trials.

OPIOID-INDUCED HYPERALGESIA

Opioid-induced hyperalgesia (OIH) is thought to result from nociceptive sensitization related to chronic opioid exposure. The precise mechanism, while not yet understood, is generally thought to result from neuroplastic changes in peripheral and central sensitization of pronociceptive pathways. The findings and clinical prevalence of OIH are not known and may be difficult to distinguish clinically from the concept of tolerance. Clinicians may suspect OIH when opioid treatment's effect seems to wane in the absence of disease progression or pain levels increase despite increasing

opioid dosages. Treatment remains controversial, but may include reducing opioid doses, discontinuing opioids altogether, supplementing therapy with NMDA receptor modulators, or opioid rotation to methadone.

CLINICAL EVALUATION OF PAIN

Pain assessment is the most important part of pain management. Any pain complaint that has an impact on physical function or quality of life should be recognized as a significant problem. Unfortunately, there are no objective biological markers of pain. The most accurate and reliable evidence for the existence and intensity of pain is the patient's description.

Pain History and Physical Examination

Assessment of pain should begin with a thorough history and physical examination to help establish a diagnosis of underlying disease and form a baseline description of pain experiences. The history should include questions to elicit: when the pain started, what events or illnesses coincided with the onset, where does it hurt (location), how does it feel (character), what are the aggravating and relieving influences, and what treatments have been tried. Past medical and surgical history is important to identify coexisting disease and previous experience with pain and analgesic use. The review of systems should probably focus on the musculoskeletal and nervous system because of the frequency of which these pain problems often occur in older persons. Any history of trauma should be thoroughly investigated because falls, occult fractures, and other injuries are common in this age group. Care must be taken to avoid attributing acute pain to preexisting conditions and recognize that chronic pain may fluctuate with time. Injuries from minor trauma and acute disease such as gout or calcium pyrophosphate crystal arthropathy can be easily overlooked. Finally, many older persons do not use the word "pain," but may refer to their problems as "hurting," "aching," or other descriptions. It is important to probe for and identify pain in the patient's own words so that references for subsequent follow-up evaluations are clearly established.

A physical examination should confirm any suspicions suggested by the history. Because of the frequency with which problems are often identified, the physical examination should probably concentrate on the musculoskeletal and nervous systems. Tender points of inflammation, muscle spasm, and trigger points should be palpated. Observation of abnormal posture, gait impairment, and limitations in range of motion may trigger a need for physical therapy and rehabilitation. Evidence of kyphosis, scoliosis, and abnormal joint alignments should be identified. A systematic neurologic examination is also important to identify potential sources of neuropathic pain. Focal muscle weakness, atrophy, abnormal reflexes, or sensory mpairments may indicate peripheral or central nervous system injury. Mottled skin in a denervated extremity, presence of a Charcot joint, orthostatic hypotension, impaired gastric emptying, or incontinence may indicate autonomic nervous system dysfunction that can imply sympathetically maintained pain or a complex regional pain syndrome.

Assessment of functional status is essential to identify self-care deficits and formulate treatment plans that maximize independence and quality of life. Functional status can also represent an important outcome measure of overall pain management. Functional status can be evaluated from information taken from the history and physical examination, as well as the use of one or several functional status scales validated in older people.

A brief psychological and social evaluation is also important. Depression, anxiety, social isolation, and disengagement are all common in patients with persistent pain. There is clearly a significant association between persistent pain and depression, even when controlling for overall health and functional status. Therefore, assessment should, at least, include a screen for depression. Psychological evaluation should also include consideration of anxiety and coping skills. Anxiety is common among patients with acute and persistent pain, which requires extra time and frequent reassurance from health care providers. Persistent pain often requires effective coping skills for anxiety and other emotional feelings that can be learned. For those with significant psychiatric symptoms, referral for formal psychiatric evaluation and management may be required. In these patients, cognitive-behavioral therapy, specific counseling, supportive group therapy, biofeedback, or some psychoactive medications may be necessary for developing and maintaining effective coping strategies as well as management of major psychiatric complications. Social networks should also be explored for availability and involvement of family and other caregivers. Family and informal caregivers are often involved and can have a substantial impact on overall pain management. Evaluation of caregivers is necessary when complicated or high-tech pain management strategies are contemplated, such as continuous analgesic infusions. Some pain management strategies can place substantial demands on caregivers, resulting in substantial caregiver stress. Needs for frequent transportation, administration of pain treatments, and

technical training may result in substantial stress for nonprofessional caregivers, which can result in work absence and emotional and physical illness.

Pain Assessment Scales

A variety of pain scales are available to help categorize and quantify the magnitude of pain complaints. Results of these scales are helpful in documentation initially and periodically to maximize treatment outcomes. Results can be recorded in flowchart or graph, making it easy to identify stability or changes in pain over time. Since there are no "gold standards," the validity of pain scales relies largely on face value, correlation with other known scales (concurrent validity), correlation with pain-related constructs (convergence), and experience in many populations over several years.

Pain scales can be grouped into multi- and unidimensional scales. In general, multidimensional scales with multiple items often provide more stable measurement and evaluation of pain in several domains. **Table 56-2** summarizes some of the multidimensional scales available. For example, the Brief Pain Inventory has been shown to capture pain in terms of intensity, location, and interference with activities. At the same time, multidimensional scales such as the McGill Pain Questionnaire are often long and time consuming and can be difficult to score at the bedside, making them difficult to use in a busy clinical setting. **Table 56-2** provides a description of several available multidimensional scales for pain. For the last 10 years, data have been accumulating on some of these scales in older persons.

TABLE 56-2 MULTIDIMENSIONAL SCALES FOR PAIN MEASUREMENT

	DESCRIPTION	TARGET	VALIDITY	RELIABILITY	ADVANTAGES	DISADVANTAGES
McGill Pain Questionnaire	Subjects asked to identify words descriptive of individual pain from 78 words grouped in 20 categories; plus four other items (including a five-point word descriptive scale of pain intensity) at the moment [PPI] scored separately	All pain	Good	Good	Multidimensional, extensively studied over a long time; may discriminate between types of pain	Long, difficult to score
Short-form McGill Pain Questionnaire	15 words scored on Likert scale, plus a visual analog and PPI scales	All pain	Good	Good	Shorter than original McGill; not studied as deeply as original	May not discriminate between pain types
Wisconcin Brief Pain Inventory	16-item scale; items scored separately	Cancer pain	Good	Good	Multidimensional	Studied largely in cancer pain
Memorial Sloan Kettering Pain Scale	Four-word descriptor scales	Cancer pain	Good	Good	Multidimensional	Studied largely in cancer pain
Geriatric Pain Measure	24-item questionnaire; 22 items scored dichotomously; two items scored 0–10	Ambulatory older adults	Good	Good	Multidimensional; tested in older adults	Limited experience; sensitivity to change unknown
Neuropathic Pain Scale	10 items each scored 1–10	Neuropathic pain			Specific for neuropathic pain	Individual item analysis may be more helpful than changes in total score
Western Ontario and McMaster Universities Arthritis Index (WOMAC)	41 items in five domains: pain, stiffness, physical function, social function, and emotional function	Arthritis	Good	Good	Specific for arthritis	Difficult to use clinically
Roland and Morris Disability Questionnaire	24 items scored yes or no	Back pain	Good	Good	Specific for back pain	May not be generalizable to other pain syndromes
Hurley Discomfort Scale	Designed to score discomfort behaviors in patients with severe Alzheimer disease	Acute pain	Probably fair	Reasonable	Does not rely on self-report	Relies on behavioral observation
Osteoarthritis Pain Behavior Observation System	Designed to score position, movement, and behavior among adults	Osteoarthritis of knee	Compared to 0–10 scale $r = 0.45$	Test-retest for more than 10 weeks $r = 0.53$	Does not rely on verbal ability	Limited to osteoarthritis of knee

Adapted from Ferrell BA. Pain. In: Osterweil D, Brummel-Smith, K, Beck JB, eds. Comprehensive Geriatric Assessment. New York, NY: McGraw-Hill; 2000:389.

One example of a behavioral scale is the Hurley Discomfort Scale. This instrument was developed for the assessment of discomfort in patients with profound dementia. The scale consists of nine items scored by a trained examiner after observing the behavior of a noncommunicative patient. Behavioral observations such as breathing, vocalization, facial expression, body language, and restlessness are scored on Likert scales. Testing of the scale has

demonstrated reasonable reliability and stability over time. The scale requires some skill and experience to administer, which may be problematic for some clinical settings.

Unidimensional scales consist of a single item that usually relates to pain intensity alone. These scales are usually easy to administer and require little time or training to produce reasonably valid and reliable results. They have found widespread use in many clinical settings to monitor treatment effects and for quality assurance indicators. **Table 56-3** describes some unidimensional scales that are commonly used, but a large number of variants that have similar characteristics and produce similar results are also available. Unidimensional pain scales often require framing the pain question appropriately for maximum reliability. Subjects should be asked about pain in the present tense (here and now). For example, the interviewer should frame the question: "How much pain are you having right now?" Alternatively, the interviewer can ask: "How much pain have you had over the last week?" or "On average, how much pain have you had in the last month?" The latter questions require accurate memory and integration of pain experiences over time, which may be more difficult for some older patients. Recent studies in those with cognitive impairment have shown that pain reports requiring recall are influenced by pain at the moment. Thus, it may be more useful to use unidimensional scales in this population to assess pain at the moment, much the way vital signs are used.

TABLE 56-3 UNIDIMENSIONAL SCALES FOR PAIN MEASUREMENT

	DESCRIPTION	VALIDITY	RELIABILITY	ADVANTAGES	DISADVANTAGES
Visual analog	100-mm line; vertical or horizontal	Good	Fair	Continuous scale	Requires pencil and paper
Present pain intensity	Six-point 0–5 scale with word descriptors (subscale of McGill Pain Questionnaire)	Good	Fair	Easy to understand, word anchors decrease clustering toward middle of scale	Usually requires visual cue
Graphic pictures	Happy faces; others	Fair	Fair	Amusing	Requires vision and attention
Sloan Kettering Pain Card	Seven words randomly distributed on a card	Good	Fair	Ease of administration	Requires visual cue
Verbal 0–10 scale	"On a scale of 0–10, if 0 means no pain and 10 means the worst pain you can imagine, how much is your pain now?"	Good	Fair	Probably easiest to use	Requires hearing

Adapted from Ferrell BA. Pain. In: Osterweil D, Brummel-Smith K, Beck JB, eds. Comprehensive Geriatric Assessment. New York, NY: McGraw-Hill; 2000:390.

Pain Assessment in Those With Cognitive Impairment

Cognitive impairment, delirium, dementia, Alzheimer disease, or stroke can present substantial challenges to pain assessment. Fortunately, it has been shown that pain reports from those with mild-to-moderate cognitive impairment are no less valid than other patients with normal cognitive function. Commonly available instruments, such as those in **Table 56-3**, are feasible for use in most patients with cognitive impairment. Patients with severe cognitive impairment may represent substantial challenges, for which no generalizable methods for pain assessment have been identified. Although it has been assumed that those in deep coma do not experience pain, it is not clear that such brain damage necessarily results in complete anesthesia. Patients with "locked-in syndrome" (having intact perception and cognitive function but no purposeful motor function and no means of communication) may suffer severely. Unfortunately, no reliable methods exist to assess pain in these individuals. Health care providers must be aware of these situations and provide analgesia empirically, especially during procedures or for conditions known to be uncomfortable or painful. More often, the majority with severe cognitive impairment can and do make their needs known in simple yes or no answers or behavioral changes such as grimacing, groaning, or increased agitation. For example, those with profound aphasia can often provide accurate and reliable answers to yes and no questions when confronted by a sensitive and skilled interviewer. For these patients, it is important to be creative in establishing communication methods for the

purpose of pain assessment.

Although pain is an individual experience, the use of family and caregivers in the assessment of pain can sometimes be helpful. Among patients with cognitive impairment, the history is often only obtainable from family or close caregivers. Family and caregivers are an excellent source of qualitative information about general behavior, medication usage, and actions that seem to aggravate or reduce pain. Family and caregivers are, however, limited in their interpretation of events and behaviors. In fact, evidence suggests that proxies are not always very accurate or reliable in estimating pain intensity. Studies of older patients having cancer suggest that caregivers may overestimate pain intensity and distress. It is often distressing to family and other caregivers who feel helpless in managing severe pain. Both physicians and nurses may underestimate pain as well as provide inadequate pain medication. In the final analysis, family and close caregivers can be valuable sources of qualitative information, but they probably should not be relied on entirely for quantitative assessment of pain intensity or distress, especially among those patients able to communicate their pain experiences.

MANAGEMENT OF ACUTE AND PERIOPERATIVE PAIN

The treatment of acute pain relies largely on short-term use of analgesic medications and resolution of the underlying cause. A variety of nondrug strategies have also been shown to be helpful. The choice of analgesic medications and other strategies to be used may depend on the severity of pain, availability of technical equipment and expertise, expectations for resolution of underlying injury, and individual patient characteristics.

The most common approach to treating acute pain relies on the World Health Organization recommendations for choosing the potency of analgesic drugs based on the intensity of pain. Pain of mild intensity usually responds to nonopioid drugs, used alone or in combination with other physical and cognitive-behavioral interventions. Pain of moderate intensity often requires more intensive efforts such as weak opioids or low doses of more potent opioid drugs. Many of these drugs are compounded with nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen to achieve enhanced relief with only modest exposure to the risk and side effects of many potent opioids. Severe pain usually requires potent opioid analgesic medications given alone or in combination with other analgesic strategies. For severe trauma or postoperative pain, intermittent intravenous, continuous intravenous, or spinal anesthesia may provide faster and more continuous pain relief. Finally, when patients present with acute pain, even though establishing a diagnosis is a priority, symptomatic pain treatment should not be held while investigations are proceeding. It is rarely justified to defer analgesia until a diagnosis is made. In fact, a comfortable patient is better able to cooperate with diagnostic procedures.

Acute and postoperative pain is dynamic. Without treatment, sensory input from damaged tissue causes alterations in spinal cord neurons, which result in enhanced responses. Pain receptors also become more sensitive after injury. Studies have demonstrated long-lasting changes after brief painful stimuli. These observations may explain why long-standing pain is more difficult to suppress. Thus, patients should be encouraged to take pain medications continuously or to prevent pain before it becomes severe and requires higher doses of medication suppress. In general, it may be helpful to provide continuous analgesics initially, with intermittent or “prescribed-as-needed” doses reserved for breakthrough or intermittent pain as the injury resolves.

Aggressive pain prevention and control before, during, and after surgery can have both short- and long-term benefits. Good preoperative pain control has been shown to make postoperative pain easier to control. Postoperative patients who use analgesia via a continuous infusion pump with self-administered boluses for breakthrough pain report less pain and are more satisfied with their pain control. These patients use less medication, have fewer postoperative complications, and tend to be discharged earlier compared to similar patients who are given similar drugs on an intermittent or “as-needed” basis.

The importance of preoperative patient education cannot be overemphasized. Studies have shown that preoperative patient education and preparation dramatically enhance postoperative outcomes and improved pain management. Patients given complete information about specific procedures including detailed descriptions of expected discomfort postoperatively often have less pain, use less pain medication, and have earlier discharges.

MANAGEMENT OF PERSISTENT PAIN

The management of persistent pain often requires a multimodal approach of drug and nondrug pain management

strategies. Although analgesic medications are the most common strategy employed, the concurrent use of cognitive-behavior therapy and other nondrug strategies may be essential to reduce long-term reliance on medications alone, which have substantial side effects when used on a long-term basis. Persistent pain management is often a labor-intensive effort. Not unlike the effort required during warfarin anticoagulation, pain management requires frequent monitoring and often requires frequent adjustments. Indeed, older patients with chronic pain benefit particularly from physicians, nurses, and restorative personnel who are able to employ an interdisciplinary approach to complex problems.

In general, persistent pain is more difficult to relieve than acute pain. Patients should be given an expectation of pain relief, but it is unrealistic to suggest or sustain an expectation of complete relief for some patients with persistent pain. The goals and trade-offs of possible therapies need to be discussed openly. Sometimes a period of trial and error should be anticipated when new medications are initiated and titration occurs. Review of medications, doses, use patterns, efficacy, and adverse effects should be a regular process of care. Ineffective drugs should be tapered and discontinued.

Economic issues are also important in the management of persistent pain. It is appropriate to consider economic issues and make balanced decisions while basic principles of assessment and treatment are followed. Health care professionals should be aware of the costs and economic barriers patients and families may encounter with the strategies often prescribed. These issues include lack of Medicare reimbursement for some strategies, limited formularies, delays in referrals in some managed care environments, delays from mail-ordered pharmacies, and limited availability of strong opioid medications in some pharmacies.

ANALGESIC MEDICATIONS

Any patient who has pain that impairs functional status or quality of life is a candidate for analgesic drug therapy. Analgesic medications, for the most part, are safe and effective in older adults, but they carry a balance of benefits and burdens. For some classes of pain-relieving medications (eg, opioids), older patients have been shown to have increased analgesic sensitivity. However, older adults are a heterogeneous population; thus, optimum dosage and known side effects are difficult to predict. Recommendations for age-adjusted dosing are not available for most analgesics. In reality, dosing for most patients requires beginning with low doses with careful upward titration, including frequent reassessment for dosage adjustments and optimum pain relief.

The least invasive route of drug administration should be used. Some drugs can be administered from a variety of routes such as subcutaneous, intravenous, transcutaneous, sublingual, and rectal. Most drugs are limited to only a few safe routes of administration, but new delivery systems are being created each year. The oral route is preferable because of its convenience and relatively steady blood levels produced. Significant drug effects are often seen in 30 minutes to 2 hours for most analgesics given orally, which may be a drawback in acute, rapidly fluctuating pain. Intravenous bolus provides the most rapid onset and shortest duration of action, which may require substantial labor, technical skill, and monitoring. Subcutaneous and intramuscular injection, although commonly used, has disadvantages of wider fluctuations in absorption and rapid falloff of action compared to oral routes. Transcutaneous, rectal, and sublingual routes are also more difficult to predict but may be essential for those with difficulty swallowing.

Timing of medications is also important. Fast-onset, short-acting analgesic drugs should be used for episodic pain. Medications for intermittent or episodic pain can usually be prescribed as needed. For continuous pain, medications should be provided around the clock. In these situations, a steady-state analgesic blood level is more effective in maintaining comfort. Most patients with continuous pain also need fast-onset short-acting drugs for breakthrough pain. Breakthrough pain includes (1) end-of-dose failure as the result of decreased blood levels of analgesic with concomitant increase in pain prior to the next scheduled dose; (2) incident pain, usually caused by activity that can be anticipated and pretreated; and (3) spontaneous pain, common with neuropathic pain that is often fleeting and difficult to predict.

The use of placebos is unethical in clinical practice, and there is no place for their use in the management of acute or persistent pain. Placebos, in the form of inert oral medications, sham injections, or other fraudulent procedures, are only justified in certain research designs where patients have given informed consent and understand that they may be receiving a placebo as a part of the research design. In research, placebos help identify and measure random or uncontrollable events that may confound results of some research designs. In clinical settings placebo effects are common, but they are neither diagnostic of pain nor indicative of a therapeutic response. The effects of placebos are short lived, and most patients eventually learn the truth, resulting in loss of patient trust and more needless suffering.

Acetaminophen

Acetaminophen is the drug of choice for older adults with mild-to-moderate pain, especially that of osteoarthritis and other musculoskeletal problems. As an analgesic and antipyretic, acetaminophen acts in the central nervous system to reduce pain perception. Although it may have some minor drug interactions (eg, warfarin), given in a dose of 650 to 1000 mg four times a day, it remains the safest analgesic medication compared to traditional NSAIDs and other analgesic drugs for most patients. Unfortunately, acetaminophen overdose can result in irreversible hepatic necrosis. Therefore, the maximum daily dose should never exceed 4000 mg/day.

According to the Food and Drug Administration (FDA), acetaminophen is the leading cause of acute liver failure in the United States. Half of acetaminophen-related liver failure cases are associated with accidental overdose. A hepatotoxic metabolite, generated by oxidative metabolism in the liver is responsible for hepatic necrosis. Unfortunately, there is little specific information on the general vulnerability of older adults to this hepatotoxicity compared to younger patients. The FDA has considered adopting a lower maximum recommended dose of 3250 mg/24 h and has asked manufacturers of combination prescription products to limit the amount of acetaminophen to 325 mg per tablet. Patients who take over the counter cold and allergy remedies that contain acetaminophen may exceed the maximum daily dose. Patient education and limiting the exposure to acetaminophen may help reduce the risk of serious liver injury which can lead to liver failure, liver transplant, or death.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs have analgesic activity both peripherally and centrally. They are potent inhibitors of prostaglandin synthesis, which have effects on inflammation, pain receptors, and nerve conduction and may have central effects as well. There are two major NSAID-sensitive cyclooxygenase enzymes (COX-1 and COX-2) synthesized in a variety of organs. COX-1 is present in most organ systems and plays a role in normal organ function such as gastric mucosal blood flow and barrier function, renal blood flow, hepatic blood flow, and platelet aggregation. COX-2, normally present in lower concentrations, is an inducible enzyme in response to injury or inflammation. Selective inhibition of COX-2 gives rise to analgesic and anti-inflammatory activity with less organ toxicity compared to the nonselective inhibition of both enzymes. Clinical trials have found COX-2 inhibitors to be similarly effective to traditional NSAIDs in terms of peak pain relief and total pain relief and in reducing joint inflammation in patients with arthritis. Safety profiles of these agents have shown a 50% reduction of gastrointestinal (GI) injury when used alone, but little data are available to support additional GI injury with concomitant use of proton pump inhibitors or misoprostol. Thus, patients at risk of cardiovascular events who are taking a COX-2–specific NSAID should also consider low-dose aspirin to offset this effect. Unfortunately, the COX-2 drugs remain expensive and the cost-benefit ratio remains controversial.

Nonspecific inhibitors of COX enzymes (most older NSAIDs) are still appropriate for short-term use in inflammatory arthritic conditions such as gout, calcium pyrophosphate arthropathy, acute flares of rheumatoid arthritis, and other inflammatory rheumatic conditions. They have also been reported to relieve the pain of headache, menstrual cramps, and other mild-to-moderate pain syndromes. These drugs can be used alone for mild-to-moderate pain or in combination with opioids for more severe pain. They have the advantage of being nonhabit forming. Individual drugs in this class vary widely with respect to anti-inflammatory activity, potency, analgesic properties, metabolism, excretion, and side effect profiles. Moreover, failure of response to one NSAID may not predict the response to another. A disadvantage of NSAIDs (including COX-2–specific inhibitors) is that these all demonstrate a ceiling effect, that is, a level at which increase in dose results in no further increase in analgesia. A large number of NSAIDs are now available; however, there is no evidence to support a particular compound as the NSAID of choice. Several compounds are available over the counter without a prescription. **Table 56-4** lists COX-2 and other selected NSAIDs for pain.

TABLE 56-4 SELECTED NONSTEROIDAL ANTI-INFLAMMATORY DRUGS FOR PAIN[a]

DRUG	MAXIMUM DOSE	DESCRIPTION	COMMENTS
Celecoxib (Celebrex)	200 mg BID	Selective COX-2 inhibition; pain and anti-inflammatory activity similar to other NSAIDs	Less gastric toxicity; less platelet inhibition
Relafen (Nabumetone)	2000 mg/24 h (q24h dosing)	Partially COX-2 selective; gastric toxicity may be less;	Avoid maximum dose for prolonged periods

		occasionally requires q12h dosing	
Aspirin	4000 mg/24 h (q4–6h dosing)	Prototype NSAID	Salicylate levels may be helpful in monitoring
Salsalate (Disalcid)	3000 mg/24 h (q6–8h dosing)	Hydrolyzed in small intestine to aspirin	Older adults may require dose adjustment downward to avoid salicylate toxicity; salicylate levels may be helpful in monitoring
Ibuprofen (Motrin by prescription; Advil, Nuprin, and others OTC[b])	2400 mg/24 h (q6–8h dosing)	Gastric, renal, and abnormal platelet function may be dose dependent; constipation, confusion, and headaches may be more common in older persons	Avoid high doses for prolonged periods of time
Diclofenac (Voltaren and Cataflam)	50 mg TID	Nonspecific COX inhibitor	As for ibuprofen
Diclofenac topical cream (Voltaren 1% Gel)	Apply 2–4 g QID up to 32 g/24 h	Systemic absorption is small. Fever, heating pad may enhance systemic absorption	Presumed safety profile
Naproxen (Naprosyn by prescription; Aleve and others OTC[†])	1000 mg/24 h (q8–12h dosing)	Same as ibuprofen; may require a loading dose	Same as ibuprofen
Choline magnesium trisalicylate (Trilisate)	5500 mg/24 h (q12h dosing)	Lower effect on platelet function	Salicylate levels may be helpful to avoid toxicity
Indomethacin (Indocin)	200 mg/24 h (q8–12h dosing)	Extremely high toxicity in frail older adults; should be reserved for acute inflammatory conditions (eg, gout, etc)	Keep dose to a minimum (25 mg q8h) and for short-term use only; avoid use for osteoarthritis or other noninflammatory problems
Ketorolac (Toradol)	IM[c]—120 mg/24 h (30–60 mg loading dose; followed by half the loading dose, 15–30 mg q6h limited to not more than 5 d) PO[d]—60 mg/24 h (q6h dosing limited to not more than 14 d)	Substantial gastrointestinal toxicity as well as renal and platelet dysfunction; relatively high postoperative complications have been documented	Duration of treatment limited because of high toxicity; reduce dose in half for those < 50 kg or > 65 y

[a]A limited number of examples are provided. For comprehensive lists of other available NSAIDs and a host of brand names, clinicians should consult other sources.
[b]OTC indicates over the counter or available without prescription.
[c]IM, by intramuscular injection.
[d]PO, per oral route or by mouth.

High-dose NSAIDs for long periods of time should be avoided in older patients. Of major concern is the high incidence of adverse reactions in older adults, including GI bleeding, renal impairment, and bleeding diathesis from platelet dysfunction. The concomitant use of misoprostol, histamine-2 receptor antagonists, proton pump inhibitors, and antacids is only partially successful at reducing the risk of significant gastrointestinal bleeding associated with NSAID use. Also, the side effect profiles of gastroprotective drugs in this population must be weighed against their limited benefits. These gastroprotective medications do nothing to prevent the renal impairment and other side effects. For those with multiple medical problems, NSAIDs are associated with increased risk of drug-drug and drug-disease interactions. NSAIDs may interact with antihypertensive therapy. Thus, the relative risks and benefits of NSAIDs must be weighed carefully against other available treatments for older patients with chronic pain problems. For some patients, long-term opioid therapy, low-dose or intermittent corticosteroid therapy, or many other nonopioid analgesic

drug strategies may have fewer life-threatening risks compared to long-term, high-dose NSAID use.

All NSAIDs, have prothrombotic effects that could increase the risk of stroke, transient ischemic attack (TIA), or myocardial infarction. For this reason, patients at risk for these cardiovascular events may be candidates for low-dose aspirin as well. Moreover, NSAIDs can exacerbate hypertension and congestive heart failure. Although the overall incidence of these adverse events is low, older patients often have a higher prevalence of comorbidities that predispose to these toxicities. It is also important to remember that the GI advantages of COX-2–selective NSAIDs are significantly reduced when used in combination of low-dose aspirin. Although the opinion has been that naproxen may be the safest from a cardiovascular perspective, the FDA has not approved labeling that would endorse this view.

Opioid Analgesic Medications

Opioid analgesic medications act by blocking receptors in the central nervous system (brain and spinal cord), resulting in a decreased perception of pain. Many opioids also act similar to local anesthetics and have recently found widespread use in epidural anesthesia. Selected opioid analgesic medications are listed in **Table 56-5**. Opioid drugs have no ceiling to their analgesic effects and have been shown to relive all types of pain. Advanced age is associated with a prolonged half-life and prolonged pharmacokinetics of many opioid drugs. Thus, older adults may achieve pain relief from smaller doses of opiate drugs than younger people.

TABLE 56-5 SELECTED OPIOID ANALGESIC MEDICATIONS FOR PAIN[a]

DRUG	STARTING DOSE (ORAL)	DESCRIPTION	COMMENTS
Morphine (Roxanol, MSIR)	30 mg (q4h dosing)	Short-intermediate half-life; older people are more sensitive than younger people to side effects	Titrate to comfort; continuous use for continuous pain; intermittent use for episodic pain; anticipate and prevent side effects
Oxymorphone (Opana)	10–20 mg (q4h dosing)	Slightly more potent than morphine	Caution in opioid-naïve patients; ?advantage over morphine
Codeine (plain codeine, Tylenol #3, other combinations with acetaminophen or NSAIDs)	30–60 mg (q4–6h dosing)	10% of codeine is metabolized to morphine, which is responsible for most analgesia; subject to genetic enzyme polymorphisms	10%–30% of patients cannot metabolize to morphine
Hydrocodone (Vicodin, Lortab, others)	5–10 mg (q3–4h dosing)	Toxicity similar to morphine; acetaminophen or NSAID combinations limit maximum dose	Constipation, nausea, and drowsiness may limit effectiveness
Oxycodone (Roxicodone, Oxy IR; or in combinations with acetaminophen or NSAIDs such as Percocet, Tylox, Percodan, and others)	20–30 mg (q3–4h dosing)	Toxicity similar to morphine; acetaminophen or NSAID combinations limit maximum dose; oxycodone is available generically as a single agent	Same as above
Hydromorphone (Dilaudid)	4 mg (q3–4h dosing)	Half-life may be shorter than morphine; toxicity similar to morphine	Similar to morphine
Hydromorphone ER (Exalgo)	8 mg q24h	Sustained-release wax matrix tablet	Taken with alcohol may cause immediate release
Sustained-release morphine (MS Contin, Oramorph, and Kadian)	MS Contin—30–60 mg (q12h dosing) Oramorph—30–60 mg (q12h dosing)	Morphine sulfate in a wax matrix tablet or sprinkles; MS Contin and Oramorph should not be broken or crushed; Kadian capsules can be opened	Titrate dose slowly because of drug accumulation; rarely requires more frequent dosing than recommended on package insert; immediate-release opioid

	Kadian—30–60 mg (q24h dosing)	and sprinkled on food but should not be crushed	analgesic often necessary for breakthrough pain. Must not crush or chew. Taken with alcohol may result in immediate release and overdose
Sustained-release oxymorphone (Opana ER)	5 mg q12h in opioid-naïve patients	Titrate 5–10 mg q12 every 3–7 d	Do not crush or chew
Sustained-release oxycodone (Oxycontin)	15–30 mg (q12h dosing)	Similar to sustained-release morphine	Similar to sustained-release morphine
Methadone (Dolophine)	2.5–5 mg (q12h)	Oxidized by CP450 system; may have NMDA receptor activity; no toxic metabolites; highly lipid soluble; analgesic half-life shorter than serum half-life	High risk for drug accumulation in older persons; titrate slowly every 3–5 d
Transdermal fentanyl (Duragesic)	25-μg patch (q72h dosing)	Reservoir for drug is in the skin, not in the patch; equivalent dose compared to other opioids is not very predictable (see package insert); effective activity may exceed 72 h in older patients	Drug reservoir is in skin, not patch. Titrate slowly using immediate-release analgesics for breakthrough pain; peak effect of first dose may take 18–24 h; not recommended for opioid-naïve patients
Fentanyl lozenge on an applicator stick	Rub on bucal mucosa until analgesia occurs, then discard	Short half-life; useful for acute and breakthrough pain when oral route is not possible	Absorbed via bucal mucosa, not effective orally
Tramadol (Ultram)	50 mg TID	Partial opioid and serotonin agonist; may cause drowsiness, nausea, and constipation	Has ceiling effect > 300 mg/24 h; lowers seizure threshold; in combination with other serotonin-manipulating drugs may be associated with serotonin syndrome
Tapentadol (Nucynta)	50 mg q4–6h moderate-to-severe pain	Partial opioid and norepinephrine reuptake receptor activity	Similar to other opioids

[a]A limited number of examples are provided. For comprehensive lists of other available opioids, clinicians should consult other sources.

Opioid drugs have the potential to cause cognitive disturbances, respiratory depression, constipation, and habituation in older people. Drowsiness, cognitive impairment, and respiratory depression associated with opioids should be anticipated when opioids are initiated and doses are escalated rapidly. These effects occur in a dose-dependent fashion and can be used to judge dose escalations. If patients have unrelieved pain with little drowsiness or cognitive impairment, doses may be safely escalated. Tolerance usually develops in a few days to these side effects, at which time, patients usually return to a fully alert status and baseline cognitive function. Until tolerance develops, patients should be instructed not to drive and to take precautions against falls or other accidents. But once tolerance to these effects has developed, patients can return to normal activities including driving and other demanding tasks, despite high doses of opioid drugs. In fact, cancer patients are often observed to improve physical function once pain is adequately relieved on opioid analgesics.

Constipation is a side effect of opioid drugs to which older patients do not develop tolerance. The management of constipation usually includes increasing fluid intake, maintaining mobility, and use of cathartic medications. Some patients find relief with remedies like prune juice or other natural laxatives. Other patients may require more potent osmotic laxatives such as milk of magnesia, lactulose, or sorbitol. But for many patients opioid-induced constipation may require potent stimulant laxatives such as senna or bisacodyl. It should be remembered that stimulants should not be used until impactions have been removed and obstruction has been ruled out. Finally, some patients require regular

enemas to ensure bowel evacuation during high-dose opioid administration for severe pain.

Nausea also occasionally complicates opioid therapy. Nausea from opioid medications may result from several mechanisms and may wane as tolerance develops. Traditionally, antiemetics such as prochlorperazine, chlorpromazine, and antihistamines have been the mainstay of treatment for nausea in younger patients. Low-dose haloperidol has also been used, anecdotally noting lower side effect profile compared to other neuroleptic drugs. All of these agents have high side effect profiles in older patients, including movement disorders, delirium, and anticholinergic effects. Thus, clinicians should choose antiemetic medications with the lowest side effects and continue to monitor patients frequently.

Tolerance is a pharmacologic phenomenon that occurs with many drugs. Tolerance is defined by diminished effect of a drug associated with constant exposure to the drug over time. For opioid drugs, tolerance is difficult to predict. In general, tolerance to drowsiness and respiratory depression occurs much faster than tolerance to analgesic properties of the drug. Previous reports that described tolerance among patients having cancer, resulting in the need for massive doses of morphine to achieve adequate analgesia, were probably misinterpreted because those patients also had rapidly advancing cancer. More recent studies of opioid-managed arthritis pain have noted that tolerance was not often significant. In fact, some patients have been noted to remain on stable doses of opioids for many years without demonstrating significant tolerance to the analgesic effects.

Dependency is also a pharmacologic phenomenon associated with many drugs, including corticosteroids and β-blockers. Dependency is present when patients experience uncomfortable side effects when the drug is withheld abruptly. Drug dependence requires constant exposure to the drug for some period of time, but it is difficult to predict. The minimum dose and time relationship between drug exposure and development of dependent withdrawal symptoms is not precisely known, but it appears to vary with individual opioid compounds. Symptoms associated with opioid withdrawal may include anorexia, nausea, diaphoresis, tachycardia, mild hypertension, and mild fever. Worsening symptoms may include skin mottling, gooseflesh, and frank autonomic crisis. Fortunately, these symptoms can be ameliorated easily by tapering opioids over a few days. In severe cases, clonidine given short term in titrated doses will usually control serious autonomic signs. It is important to remember that physiologic effects of opioid withdrawal are usually not life threatening compared to serious withdrawal common with alcohol, benzodiazepine, or barbiturate withdrawal.

Addictive behavior is defined by compulsive drug use despite negative physical and social consequences and the craving for effects other than pain relief. Patients who are addicted often have erratic behavior that can be observed in a clinical setting in the form of selling, buying, and procuring drugs on the street, and the use of medication by bizarre means such as dissolving tablets for self–intravenous administration. It is now clear that drug use alone is not the major factor in the development of addiction. Other medical, social, and economic factors play immense roles in addictive behavior. It is also important to not construe certain behaviors as necessarily addictive behaviors. Hoarding of medications, persistent or worsening pain complaints, frequent office visits, requests for dose escalations, and other behaviors associated with unrelieved pain has coined the term “pseudoaddiction.” Laws, regulations, and unintentional behavior by prescribing clinicians may require patients to hoard medication and seek other physicians for additional help. In fact, true addiction is rare among patients taking opioid analgesic medications for medical reasons. This is not meant to imply that opioid drugs can be used indiscriminately, only that fear of addiction and side effects do not justify failure to treat pain in older adult patients, especially those near the end of life.

The Role of Opioids in Persistent Pain

Over the last few decades, increasing numbers of patients with persistent noncancer-related pain have been treated with long-term opioid therapy. This practice has been associated with observations of large increases in adverse drug events, including drug misuse, abuse, addiction, diversion, unintentional overdoses, and deaths. The statistics indicate serious concern. In 2010 drug overdose deaths exceeded 38,000 with 57% attributed to prescribed drugs, and 75% of those related to prescribed opioids. Although the prevalence of opioid and other substance abuse is substantially higher in younger patients, older patients are not immune from the risk. Opioid treatment for persistent noncancer pain in older persons is associated with increasing risk of falls and all-cause mortality. Patients on chronic opioid treatments have increased risk of overdose and use of multiple prescribers. Other factors more predictive of developing opioid use disorder include male sex, higher average daily dose, longer duration of treatment, presence of a mental health disorder, and higher rates of utilization of medical and psychiatric services. Because of higher use in the current “baby boomer” cohort, illicit and nonmedical drug use among older adults is expected to rise in the future.

The use of long-term opioid treatment for noncancer pain remains controversial. Evidence of effectiveness in the

wide variety of diseases seen in this population is lacking, with most studies being short term and observational as well as limited to mostly younger patients. Recent reviews have emphasized the absence of controlled randomized trials and lack of evidence for safety and effectiveness of long-term opioid treatment. Some organizations have advocated against the use of long-germ opioids for managing patients with persistent noncancer-related pain.

Several organizations have offered guidelines on the clinical prescribing of opioids for the treatment of persistent noncancer pain. Some are specific to older adults. Common elements of these guidelines are summarized in **Table 56-6**. As with much of the other data on opioid use in older persons, data are limited on the efficacy of various risk mitigation strategies, including patient agreements, urine drug screening, and pill counts. Nonetheless, these efforts along with other support mechanisms might be an option as part of a more comprehensive individualized care management plan.

TABLE 56-6 ■ COMMON ELEMENTS IN OPIOID-PRESCRIBING GUIDELINES

1. Higher doses require caution. Greater than 100–200 mg (oral morphine equivalents per day) may be associated with higher risk of overdose events.
2. Methadone poses risks for:
   a. Prolonged QTC ECG abnormalities and risk for cardiac complications
   b. Respiratory suppression due to unique pharmacokinetics with risk for drug accumulation and overdose complications particularly during opioid rotation from other opioids to methadone
3. Reduce doses by 25%–30% during opioid rotation to avoid inadvertent overdose.
4. Benzodiazepines and opioids are a high-risk combination particularly in older adults.
5. Risk-mitigating strategies for drug misuse and abuse may be helpful.
   a. Validated risk assessment questionnaires
   b. Urine drug testing in patients at high risk for abuse and diversion

Adapted from Nuclols TK, Anderson L, Popescu I, et al. Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain. Ann Intern Med. 2014;160(1):38–48.

Other Nonopioid Medications for Pain

A variety of other medications not formally classified as analgesics have been found to be helpful in certain specific pain problems. The term “adjuvant analgesic drugs,” although frequently used, is a misnomer in that some of these nonopioid drugs may be the primary pain-relieving pharmacologic intervention in certain cases. **Table 56-7** provides some examples of nonopioid drugs that may help certain kinds of pain. The largest body of evidence available relates to the use of these drugs for neuropathic pain, such as diabetic neuropathies, postherpetic neuralgia, and trigeminal neuralgia. Tricyclic antidepressants, anticonvulsants, and local anesthetics are the most frequently used nonopioid analgesics for neuropathic conditions. In general, these drugs have had limited success in pain syndromes that are not associated with neuropathic mechanisms. Most reports have found that these agents are only partially successful. Typically, approximately 50% to 70% of patients have a measurable response, and of those most experience only partial relief. Thus, these drugs are often not panaceas and are rarely totally successful as single agents. One exception may be trigeminal neuralgia, where carbamazepine is probably the drug of choice. Usually these agents work better in combination with other traditional drug and nondrug strategies, in an effort to improve pain and keep other drug doses to a minimum. Failure of response to one particular class of drugs does not necessarily predict failure of another class of agents. In general, nonopioid medications for neuropathic pain should be chosen according to lowest side effects. Treatment should usually start with lower doses than recommended for younger patients, and doses should be escalated slowly based on known pharmacokinetics of individual drugs and appropriate knowledge of disease-specific treatment strategies. Unfortunately, most of the nonopioid medications for pain management have high side effect profiles in older people. Thus, these medications often have to be monitored carefully.

TABLE 56-7 ■ SELECTED NONOPIOID MEDICATIONS FOR PAIN[a]

DRUG	DESCRIPTION	COMMENTS
Antidepressants: amitriptyline, desipramine, nortriptyline, and others	Older adults are more sensitive to side effects, especially anticholinergic	Complete relief unusual; used best as adjunct to other strategies; start low and increase

	effects; desipramine, or nortriptyline is a better choice than amitriptyline	slowly every 3–5 d
Serotonin-norepinephrine reuptake inhibitors (SNRIs): venlafaxine (Effexor) and duloxetine (Cymbalta)	Venlafaxine—25–37.5 BID or TID; titrate q4d Duloxetine—60 mg qd	Venlafaxine—taper gradually Duloxetine—do not crush or chew; taper gradually
Anticonvulsants: clonazepam and carbamazepine	Carbamazepine may cause leukopenia, thrombocytopenia, and rarely aplastic anemia; clonazepine side effects may be similar to other benzodiazepines in older adults	Start low and increase slowly; check blood counts on carbamazepine
Gabapentin (also an anticonvulsant) (Neurontin)	Less serious side effects than other anticonvulsants	Start with 100 mg and titrate up slowly; TID dosing; monitor for idiosyncratic side effects such as ankle swelling, ataxia, etc; effective dose reported 100–800 mg q8h
Pregabalin (Lyrica)	Similar to gabapentin. Start at 50 mg TID and gradually increase. Taper dose to discontinue	Side effects similar to gabapentin
Antiarrhythmics mexiletine (Mexitil)	Common side effects include tremor, dizziness, and paresthesias; may rarely cause blood dyscrasias and hepatic damage	Avoid use in patients with preexisting heart disease; start low and titrate slowly; monitor ECGs; q6–8h dosing
Local anesthetics: lidocaine (intravenous), lidocaine transdermal patch (Lidoderm), and capsaicin	IV lidocaine associated with delirium Transdermal patch has minimal systemic absorption Capsaicin depletes nerve endings of substance P	IV lidocaine may predict response to anticonvulsants and antiarrhythmics May apply up to three patches alternating 12-h intervals to improve pain, reduce denervation hypersensitivity, and decrease systemic absorption May take 2 wk to peak effect
Tramadol (Ultram)	Partial opioid and serotonin agonist; more of a norepinephrine antagonist; may cause drowsiness, nausea, vomiting, and constipation	Has ceiling effect; dose > 300 mg/24 h usually not tolerated because of nausea; q4–6h dosing; reduces seizure threshold
Muscle relaxants (baclofen, chlorzoxazone [Paraflex], and cyclobenzaprine [Flexeril])	Sedation; anticholinergic effects; abrupt withdrawal of baclofen may cause CNS irritability	Mechanism of action not precisely known; monitor for sedation and anticholinergic effects; taper baclofen on discontinuation
Substance P inhibitors (capsaicin) available OTC; for topical use only	Burning pain during depletion of substance P may be intolerable by as many as 30% of patients; may take 14 d for maximum response; avoid eye contamination	Start with small doses; can be partially removed with vegetable oil
NMDA inhibitors: ketamine and dextromethorphan	N-Methyl-D-aspartate antagonists (NMDA) Ketamine: potent anesthetic Dextromethorphan: common cough suppressant	Ketamine only available IV Both may cause delirium
Drugs for osteoporosis: calcitonin and bisphosphonates	Pain relief mechanisms unknown	Not effective on pain other than osteoporosis
Corticosteroids: prednisone and dexamethasone	Decrease inflammation in many tissues	Classic corticosteroid side effects limit overall usefulness in chronic pain

[a]A limited number of examples are provided. For comprehensive lists of other available medications for pain, clinicians should consult other sources.

Antidepressants have been the most widely studied class of nonopioid medications for pain. The mechanism of action for these drugs is not entirely known but probably has to do with interruption of norepinephrine and serotonin-mediated mechanisms in the brain. For neuropathic pain, the major effect of these drugs is not their mood-altering capacity, although this may also be helpful in those with concurrent major depression. More is probably known about tricyclic antidepressants than the other subclasses. A randomized placebo-controlled trial of amitriptyline, desimipramine, and fluoxitine indicated that desimipramine may be as effective as amitriptyline, but fluoxitine is no better than placebo for the treatment of diabetic neuropathy. Thus, desimipramine may be a better choice because it has a lower side effect profile in older adults than amitriptyline. Unfortunately, tricyclic antidepressants have been criticized for high anticholinergic side effects in older patients, which often limit their effectiveness.

The newer serotonin-norepinephrine reuptake inhibitors (SNRIs) including venlafaxine and duloxetine have been shown to have modest effect on diabetic neuralgia, and duloxetine is FDA approved for use in diabetic neuropathy. Studies of these drugs have indicated small but statistically significant effect sizes.

Studies of the selective serotonin reuptake inhibitors (SSRIs), which may have lower side effect profiles for older adults, have not been shown effective for pain management. In fact, none have shown significant effect on pain despite being highly effective for depression.

It has been known for many years that some medications with antiepileptic activity may relieve the pain of trigeminal neuralgia (tic douloureux). Drugs such as Dilantin, Tegretol, and valproic acid may also help diabetic neuralgia and other neuropathic pains in some patients. In general, the usefulness of these drugs has been limited by their high side effect profiles in older adults and the fact that most patients respond only partially, making the overall risk/benefit ratio rather large in this population. Indeed, these drugs are not simple analgesics and should not be used for the relief of trivial aches and pains. Of recent interest has been the effectiveness of gabapentin for treatment of diabetic and postherpetic neuralgias. Clinical observations suggest that this agent has a significant analgesic effect on neuropathic pain with a much lower side effect profile compared to other antiepileptic drugs and most antidepressants as well.

Several local anesthetics have also been shown to relieve neuropathic pain when administrated systemically, in addition to their known local anesthetic effects. Intravenous lidocaine has been found to sometimes predict the response to other anticonvulsant and systemically administered local anesthetics. Mexiletine, similar to lidocaine but active orally, has also shown some activity against neuropathic pain of diabetic neuralgia. Although this drug also has a high risk/benefit ratio, some studies have reported response rates at lower doses than are often recommended for cardiac arrhythmias.

The use of cannabinoids for the management of pain appears to be increasing. Unfortunately, dose, administration and prescribing information remains experientially determined with often unpredictable levels from many nonstandard plant varieties and preparations provided in many dispensaries. Anecdotal evidence indicates some patients may benefit from mild anxiolytic effects of the drug in an individualized dose range with side effects often related to inadvertent and unpredictable overdose. This has been particularly problematic among naïve users of oral preparations. Unfortunately, continued federal classification of cannabinoids has hindered research and standardization in the use of these products.

Finally, chronic pain associated with osteoporosis has often been shown to improve with calcitonin. Most investigators of the effects of calcitonin on osteoporosis have reported anecdotally that pain improves significantly. These studies have not been designed as pain studies, and more sophisticated assessment of pain in these studies would be welcome, but results thus far are encouraging.

ANESTHETIC AND NEUROSURGICAL APPROACHES TO PAIN MANAGEMENT

A wide variety of anesthetic and neurosurgical approaches to pain is available, and some require highly specialized skills. Although it is beyond the scope of this chapter to review details of all of these techniques, a few deserve mention.

Trigger point injections have been used extensively for the treatment of myofascial pain syndromes. Myofascial pain with trigger points was first recognized more than 50 years ago. In a relatively high percentage of cases, trigger points may initiate a reflex mechanism that produces referred pain, tenderness, and muscle spasm. With local injection of the trigger point, followed by stretching and reconditioning of the muscles, the myofascial pain syndrome usually subsides. More recently, similar results have been obtained using ice massage or vapocoolant spray applied topically, followed by specific muscle stretching and physical therapy techniques. Nonetheless, for many myofascial pain

syndromes, trigger point injection with dilute local anesthetics may be highly effective when combined with specific physical therapy.

Continuous drug infusions are highly effective for providing steady-state analgesic drug levels. Continuous infusions can be maintained by implantable pumps or external devices to deliver intravenous, subcutaneous, intrathecal, or epidural medications. Continuous infusions of opioid drugs have found widespread use in severe chronic cancer pain, especially among those near the end of life. Other uses have included continuous infusion of muscle relaxants for patients with severe muscle spasm from spinal injury, multiple sclerosis, or end-stage Parkinson disease. The techniques are very expensive, but they are often reimbursed by third-party payers including Medicare. These issues have raised ethical concerns about the application of high-tech strategies for patients who might be equally well managed using oral medications that are not reimbursable. In general, these methods should be used only when oral medications become ineffective or the oral route of administration is no longer viable. More work needs to be done to justify these risky and expensive techniques that need to be carefully monitored in nursing homes, home care, and other low-tech long-term care settings.

NONDRUG STRATEGIES FOR PAIN MANAGEMENT

Nondrug strategies, used alone or in combination with appropriate analgesic medications, should be an integral part of the care plan for most older patients with significant pain problems. Nondrug strategies for pain management encompass a broad range of treatments and physical modalities, many of which carry low risks for adverse effects. Used in combination with appropriate drug regimens, these interventions often enhance therapeutic effects, while allowing medication doses to be kept low to prevent adverse drug effects.

Among the nondrug interventions, the importance of patient education cannot be overstated. Studies have shown that patient education programs alone significantly improve overall pain management. Such programs often include content about the nature of pain, how to use pain diaries and pain assessment instruments, how to use medications appropriately, and how to use self-help nondrug strategies. Whether conducted in groups or individually, education should be tailored for individual patient needs and level of understanding. Written materials and methods of reinforcement are important to the overall success of the program. Education on the use of heat and cold can be especially helpful for some patients.

Physical exercise is important for most patients with pain. A program of exercise can be tailored to most patients' needs and is extremely important for rehabilitation, and the maintenance of strength and endurance. Clinical trials of older patients with chronic musculoskeletal pain have shown that moderate levels of exercise (aerobic and resistance training) on a regular basis are effective in improving pain and functional status. Initial training for chronic pain patients usually requires 8 to 12 weeks, with supervision by a professional who can focus on the needs of older people with musculoskeletal disorders. There is no evidence that one form of exercise is better than another, so programs can be tailored for the individual's needs, lifestyle, and preference. Water aerobics may be especially helpful for older patients with arthritic pain. The intensity of exercise along with frequency and duration must be adjusted to avoid exacerbation of the underlying condition while gradually increasing and later maintaining overall conditioning. Stretching to relieve muscle spasm and prevent further muscle injury is another critical exercise intervention. It is important to remember that feeling better often gives rise to a false impression that the discipline of regular exercise is not necessary. Continued encouragement and reinforcement is often required. Unless complications arise, the program of exercise should be maintained indefinitely to prevent deconditioning and deterioration.

Psychological strategies have also been shown to be helpful for some with significant pain. Cognitive therapies are strategies aimed at altering belief systems and attitudes about pain and suffering. Cognitive therapies include various forms of distraction, relaxation, biofeedback, and hypnosis. Behavioral therapies are strategies aimed at enhancing healthy behaviors and discouraging abnormal behavior that is unpredictable and self-defeating. Cognitive therapy can be combined with behavioral approaches, and together they are known as cognitive-behavioral therapy. Cognitive-behavioral therapy, in its purest form, includes a structured approach to teaching coping skills, which might be used alone or in combination with analgesic medications and other nondrug strategies for pain control. Effective programs can be conducted by trained professionals with individual patients or in groups, and there is some evidence that the effect is enhanced with caregiver involvement. Although it may not be appropriate for those with significant cognitive impairment, there is evidence from randomized trials to support the use of cognitive-behavioral therapy for many patients with significant chronic pain.

Finally, a variety of alternative therapies are also used by many patients. Many patients seek alternative medicine

approaches with and without the knowledge or recommendation of their physician or other primary care provider. Alternative medicine approaches to chronic pain may include homeopathy, spiritual healing, or the growing market of vitamin, herbal, and natural remedies. Although there is little scientific evidence to support these strategies for pain control, it is important that health care providers not abandon patients or leave them with a sense of hopelessness.

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Chapter 57

Common Nonpain Symptoms

Christine Ritchie, Alexander K. Smith, Christine Miaskowski

Learning Objectives

- To describe the prevalence of common nonpain symptoms in older adults
- To address the evaluation and management of fatigue and dyspnea
- To review how multimorbidity influences symptom management

Key Clinical Points

1. **The presence of multiple co-occurring symptoms in older adults is common.**
2. **Screening for common symptoms should be a routine component of a comprehensive geriatric assessment.**
3. **Because the evidence base for symptom management in older adults is sparse, especially for those with multiple chronic conditions, a thoughtful approach that is informed by patient preferences is necessary to optimize benefit and minimize adverse effects.**

OVERVIEW: COMMON NONPAIN SYMPTOMS IN OLDER ADULTS

Advances in medicine have led to our ability to stave off many acute life-threatening events and have contributed to the development of numerous co-occurring chronic conditions defined as multimorbidity. The experience of multiple conditions is often characterized by an array of symptoms associated with these conditions and/or their treatments. The presence of bothersome symptoms in older adults may contribute to illness burden in ways that may not be predictable on the basis of any one diagnosed disorder. However, these symptoms have a negative influence on older adults' function and quality of life (QoL).

Many symptoms are addressed throughout this textbook: anorexia is covered in Chapter 34, sleep disorders in Chapter 49, dizziness in Chapter 50, pain in Chapter 56, depressed mood and anxiety in Chapters 71 and 73, and constipation in Chapter 95. The focus of this chapter is overall symptom assessment, evaluation and management of fatigue and shortness of breath, especially for those with advanced illness, and special considerations in the context of multimorbidity.

Multiple symptoms occur frequently in chronically ill older adults. Because many individual conditions, such as cancer, heart failure, and chronic obstructive pulmonary disease (COPD), are associated with high symptom burden, their accumulation contributes to a large and complex array of symptoms (**Figure 57-1**). Among older oncology patients, the average number of symptoms reported on the Memorial Symptom Assessment Scale (MSAS) was 10. In a population-based sample of older adults using a 10-item symptom tool, the average number of symptoms was 3.7 and one-third of the population had five or more. In this cohort, the most common nonpain symptoms were fatigue (48%), weakness (39%), constipation (36%), anxiety (36%), anhedonia or depression (37%), shortness of breath (35%), and poor appetite. In a study of 318 adults followed by a housecalls program, 43% reported severe burden from one or more symptoms. The symptoms with the highest severity ratings were depression, pain, loss of appetite, and shortness of breath. Few longitudinal studies of the general older adult population have assessed changes in the symptom experience over time. Among 754 older adults in their last year of life, the monthly occurrence of one or more

"restricting symptoms" was fairly constant in the first half of the year prior to death (20%). At approximately 5 months prior to death, the rate increased rapidly from 27% to 57% in the month prior to death.

	Cancer	CHF	COPD	CKD	Dementia	AIDS
1.	Pain (84%)	Breathlessness (88%)	Breathlessness (97%)	Fatigue (88%)	Breathlessness (46%)	Fatigue (73%)
2.	Fatigue (69%)	Fatigue (88%)	Fatigue (88%)	Sleep Disturbance (82%)	Constipation (40%)	Pain (69%)
3.	Anorexia (66%)	Pain (75%)	Dry Mouth (85%)	Anorexia (55%)	Pain (39%)	Dry Mouth (54%)

FIGURE 57-1. Prevalence of nonpain symptoms in older adults. AIDS, acquired immunodeficiency syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

OVERALL EVALUATION OF SYMPTOMS

Other than questions elicited through the history and physical, a systematic approach to symptom assessment is not as well integrated into geriatric practice as it is into oncology or palliative medicine. For example, comprehensive geriatric assessment (CGA), as currently configured, does not include assessment of pain or nonpain symptoms. This omission is unfortunate, because the goal of the CGA is to develop a care plan to maximize the overall health of aging individuals. Assessment and management of symptoms that are common in the old and frail aligns well with this goal.

Many symptom measures were developed initially for cancer patients and only evaluate symptoms over short time intervals. Other symptom measures focus on a particular disease without capturing the impact of nonindex conditions on symptoms. With few exceptions, nondisease-specific symptom inventories are not available for older adults with multiple conditions. One screening tool developed from a community-dwelling population of 1000 older adults, the Brief Symptom Inventory, assesses 10 common symptoms in older adults: shortness of breath, feeling tired or fatigued, problems with balance or dizziness, weakness, daily pain, stiffness, constipation, poor appetite, anxiety, and anhedonia. The tool shows discriminant and convergent validity. For more comprehensive symptom assessments, most instruments have been borrowed from oncology. The MSAS measures the occurrence, severity, and distress of 32 symptoms and the Edmonton Symptom Assessment Scale measures 9 common symptoms on a 0 to 10 numerical scale. These instruments have been used to assess symptoms and multiple dimensions of the symptom experience in both geriatric and palliative care noncancer patients. The large number of items in the MSAS can be a practical barrier to its use in the clinical setting.

EVALUATION AND MANAGEMENT OF FATIGUE AND DYSPNEA

Evaluation of Fatigue

The prevalence of generalized fatigue in older adults varies from 5% to almost 70% depending on the assessment used, the characteristics of the older adult population, the time of day fatigue is assessed, and the cut-points used to indicate

fatigue. Regardless of the assessment tool, fatigue is associated with decreased function and increased mortality. In a study of 492 older primary care patients, the question "Do you feel tired most of the time?" identified older adults with a one and a half to almost twofold increased risk of mortality over 10 years. Other assessments for fatigue tend to be more involved and many tools exist, again, predominantly derived from oncology. The Brief Fatigue Inventory, a nine-item instrument that assesses severity of fatigue and the impact of fatigue on daily functioning in the past 24 hours, has good psychometric properties but has been predominantly used in cancer populations. More recently, the concept of fatigability developed as a complement to the symptom of fatigue. Fatigability measures how fatigued an individual feels in relation to defined activities (eg, how fatigued a person feels after a 5-minute treadmill test. It offers a more standardized way to measure fatigue but is more difficult to integrate into standard practice.

Questions in the assessment of fatigue should address (1) when the fatigue began, whether the onset was sudden or more gradual; (2) the pattern of fatigue over the course of a day; (3) what exacerbates or improves the fatigue; and (4) the impact that fatigue has on daily function and relationships. Sleep characteristics and medications should be reviewed. Because psychological factors are often associated with fatigue, systematic assessment for depression is warranted.

The biopsychosocial model, commonly used to characterize pain, applies well to other symptoms, including fatigue. The biopsychosocial model posits that psychological, social, spiritual, and physical factors influence an individual's symptoms (**Figure 57-2**). In the case of fatigue, other factors such as depression, social isolation or complexity, and spiritual distress may influence the experience of fatigue. A number of physical conditions are characterized by fatigue including electrolyte disturbances, occult malignancy, polymyalgia rheumatica, occult hepatitis, or HIV. Fatigue may be a silent harbinger of anemia or infection. In older adults, where atypical presentations of acute conditions are common, new-onset fatigue may indicate a recent myocardial infarction (MI) or heart failure. Hypogonadism is a less common cause of fatigue. Findings from the history and physical examination should dictate further diagnostic evaluation.

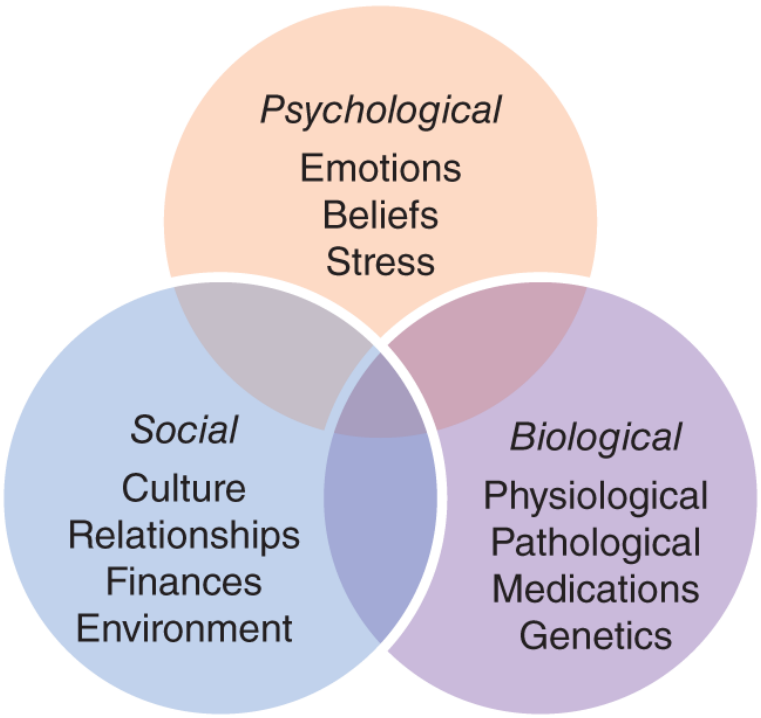


FIGURE 57-2. Biopsychosocial model.

Management of Fatigue

Very few studies have addressed the management of fatigue in older adults. Nonpharmacologic approaches that have promise include increased graded exercise therapy and cognitive behavioral therapy (CBT). However to date, the authors know of no clinical trials that evaluated the use of CBT for fatigue in older adults. Improvement of older adults' sleep hygiene through both nonpharmacalogic and pharmacologic strategies (see Chapter 49) may reduce fatigue. While antidepressants may be beneficial, antidepressants with strong anticholinergic effects should be avoided

(see Chapter 73). In the palliative care setting for older adults with advanced or life-limiting illnesses, psychostimulants such as methylphenidate or modafenil may be considered. In a study of predominantly older prostate cancer patients (ages 52–94), methylphenidate reduced fatigue severity compared to control. However a number of patients had to discontinue treatment due to increased blood pressure and tachycardia. A recent within-person crossover trial cast doubt on methylphenidate treatment of fatigue in advanced cancer. Among 43 participants who alternated between methylphenidate and placebo three times over a 9-day period, no improvement in fatigue during days with methylphenidate was observed. In older adults with known cardiovascular disease or arrhythmias, psychostimulants should not be used. While anecdotal reports touted the benefit of donepezil in treatment of opioid-induced fatigue in cancer patients, a subsequent clinical trial did not support these claims. In summary, fatigue is a common condition in older adults with likely multiple factors contributing to its prevalence.

Evaluation of Dyspnea (Breathlessness)

Due to the high rates of COPD and heart failure in older adults, along with an array of other comorbid conditions, shortness of breath (dyspnea) is very common in older adults. In an Australian primary care practice, over half of those who presented with shortness of breath were over the age of 65. The prevalence of dyspnea in community-dwelling older adults ranges between 17% and 62%, depending on the population studied and cut-point used to define "dyspnea." Dyspnea will likely occur at some point during a number of serious illnesses experienced by older adults (eg, cancer, heart failure, advanced lung disease), and at the end of life. The biopsychosocial model applies to dyspnea as well as it does to fatigue. Anxiety, disappointment, financial stressors, and questions about meaning often contribute significantly to the experience of dyspnea. Dyspnea, in turn, serves as a source of patient and caregiver distress and is associated with decreased quality of life, decreased function, and increased health care utilization.

Physiologic mechanisms of dyspnea often fall under three categories: increased respiratory effort due to obstruction (eg, COPD, asthma, masses) or restriction (eg, obesity, pleural effusion); weakness (eg, multiple sclerosis, amyotrophic lateral sclerosis); or ventilation/perfusion mismatch (eg, anemia, pulmonary embolism, heart failure). More subtle systemic changes can contribute to the occurrence of dyspnea, especially at the end of life. For example, in the National Hospice Survey, 24% of patients with no known cardiopulmonary disease experienced dyspnea. The most appropriate measure of shortness of breath is the older adult's self-report. Dyspnea does not always correlate with hypoxia, hypercarbia, or the presence of tachypnea. Most self-report tools to assess dyspnea come from the obstructive lung disease literature. One of the most common assessment tools is the Medical Research Council (MRC) breathlessness scale. First published in the 1950s, the MRC scale characterizes, through five statements, a range of disability caused by level of breathlessness (**Table 57-1**). It correlates well with other dyspnea scales and with other direct measures of function, such as walking speed.

TABLE 57-1 MEDICAL RESEARCH COUNCIL BREATHLESSNESS SCALE

GRADE	DEGREE OF BREATHLESSNESS
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on level ground or walking up a slight hill
3	Walks slower than most people on level ground, stops after a mile or so, or stops after 15 min walking at own pace.
4	Stops for breath after walking about 100 yd or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

Management of Shortness of Breath

Nonpharmacologic approaches to breathlessness have few side effects, unlike morphine for example, and avoid polypharmacy, a major concern in the older adults. They should be considered alongside pharmacologic approaches as first-line therapy. Nonpharmacologic approaches that can be helpful in the treatment of dyspnea include the use of a fan, breathing techniques, mindfulness and relaxation, anxiety management, and energy conservation. Breathing techniques that can reduce the sensation of dyspnea include pursed lip breathing, prolonged exhalation, and posture modification. In addition to mindfulness and relaxation, guided imagery and distraction strategies (eg, music, TV, reading by self or caregiver) were shown to reduce the sensation of breathlessness.

In patients with COPD and hypoxia, long-term oxygen therapy increases quality of life and prolongs survival. Likewise, in a subset of patients with COPD, noninvasive ventilatory support such as with bilevel positive airway pressure (BiPAP), can improve quality of life and prolong survival. In patients with advanced cancer and other nonpulmonary causes of dyspnea, the value of oxygen in improving outcomes is less clear. These results may be in part due to the fact that less than half of advanced cancer patients with dyspnea are hypoxic. In a study of nasal cannula-delivered air versus nasal cannula-delivered oxygen (median age 65), no difference was found in dyspnea relief between the two modalities when patients were not hypoxic; in two studies of hypoxic cancer patients, more benefit from oxygen was noted. Recent studies of noninvasive ventilation in advanced cancer patients suggest that it may improve symptoms. In a multisite study of 200 predominantly older adults with advanced cancer (mean age 71), noninvasive ventilation was more effective than oxygen in reducing dyspnea and decreasing the amount of morphine needed to control symptoms. However, more patients in the noninvasive ventilation arm discontinued treatment primarily due to mask intolerance and anxiety.

Pharmacologic treatment for dyspnea should first and foremost be directed to the underlying cause of dyspnea, if known. Treatment may include a β-agonist for COPD or a diuretic in the case of heart failure. In a subset of patients, breathlessness persists at rest or on minimal exertion despite optimal treatment of the underlying chronic condition. These patients are described as having refractory dyspnea. In patients with refractory dyspnea, opioids may be beneficial. A number of studies of opioids for the treatment of refractory dyspnea in the setting of advanced illness demonstrate some benefit. However, the findings of reduced dyspnea (compared to control) are not consistent, and many studies remain underpowered to produce conclusive findings. Unfortunately, many of these studies use morphine, which has active metabolites (eg, morphine-6-glucornide, morphine-3-glucoronide). Morphine-3-glucoronide builds up in renal insufficiency, common in older adults, and is responsible for symptoms of neurotoxicity (eg, hyperalgesia, allodynia, myoclonus). In older adults, opioids are associated with decreased mental functioning. For some patients, decreased mental functioning will not be acceptable despite its potentially positive impact on breathing.

IMPACT OF MULTIMORBIDITY ON SYMPTOM MANAGEMENT AND PATIENT DECISION MAKING

For older adults, multimorbidity is the norm not the exception. Almost two-thirds of Americans age 65 and older have 2 or more of the 10 most common chronic conditions (ie, hypertension, coronary heart disease, stroke, diabetes, cancer, arthritis, or hepatitis; weak or failing kidneys during the past 12 months; asthma; or COPD). The percentage of patients with chronic illness is expected to grow by 43% between 2003 and 2023, only amplifying the impact and challenge of multimorbidity among older adults. For older adults, multimorbidity is the norm, not the exception. The implications for these older adults are that they often have to navigate exchanges with disparate clinicians, as well as the use of multiple medications, complex treatment regimens, drug-disease and drug-drug interactions, and high symptom burden.

Symptom Management in Multimorbidity

Multimorbidity can constrain options for management of symptoms. Many pharmacologic treatments for symptoms have adverse effects that are magnified in multimorbidity. For those with heart failure or hypertension, nonsteroidal anti-inflammatory agents often exacerbate those conditions. For those with cognitive impairment, opioids may make confusion more marked. Well known to those caring for older adults, initiation of one medication for one condition or symptom often leads to side effects that require use of a second medication to manage the side effects—the "pharmacologic cascade." Analgesics provide an apt illustration of this phenomenon. The use of a nonsteroidal anti-inflammatory agent (for those in whom it is not contraindicated) often requires additional medications to reduce the risk of potential negative gastrointestinal (GI) (eg, the addition of a proton pump inhibitor to reduce risk of GI bleeding) or cardiovascular (eg, the addition of aspirin to reduce the risk of MI or stroke) outcomes. In the case of opioids, patients must routinely be started on bowel stimulants or other laxatives to avoid the expected side effect of constipation. Even without taking into account these challenges, many medications used to address symptoms have not been evaluated in older adults or in adults with multimorbidity. Among the symptom-focused studies done in older adults with advanced illness or multimorbidity, the most evidence exists for management of pain, and to a much lesser degree, dyspnea in cancer. There is a dearth of evidence for how to manage symptoms in nonnoncancer illnesses, let alone in patients with several diseases. Therefore, the true benefits and the true risks are largely unknown. For this

reason, pharmacologic management of symptoms warrants thoughtful discussions with the patient and/or family caregivers, as well as cautious initiation and careful monitoring of both the positive and negative effects of the treatment. For many older adults, symptom management involves both relief of discomfort and development of new drug-induced challenges. Anticipatory and ongoing discussion of the benefits and burdens of pharmacologic symptom management in the context of the patient's goals and preferences offers an ongoing person-centered approach to improving the older person's quality of life.

The Role of Patient Preference in Symptom Management

Given the lack of evidence for optimal symptom management for older adults in general and in particular for older adults with multimorbidity, treatment strategies for symptom management are preference sensitive—that is there is often more than one reasonable treatment option, or a particular option offers uncertain benefit. For preference-sensitive decisions, the clinician must understand what is most important to the patient to determine what might be the best treatment option. A starting point may involve asking patients to prioritize a set of universal health outcomes that can be applied across individual diseases. Typical outcomes would include living as long as possible, maintaining function, staying cognitively intact, and alleviating pain and other symptoms. Other outcomes might include staying out of the hospital or dying at home. While not always mutually exclusive, understanding how patients prioritize these various outcomes can help guide decisions about symptom management. This broad-based approach provides a more unified starting point, rather than asking patients or caregivers to make specific treatment decisions.

Optimal decisions regarding symptom management requires that the patient is adequately informed about the expected benefits and harms of different treatment options for their symptoms, recognizing that in many instances optimal information is lacking. Actual decision-making preferences vary widely by patients and family caregivers. Some individuals prefer to make the decision themselves, while others prefer that the decision for a specific treatment be made by the clinician. In either instance, most individuals want their opinion used to guide the decision-making process. Then, the clinician can develop a management plan and evaluate at regular intervals whether the management plan remains concordant with patient's wishes. Re-evaluation of treatment plans are critical as studies suggest that older adults with multimorbidity engage in dynamic reassessments of their conditions, as they shift between experiencing disruption from the condition and finding the ability to adapt to the condition's challenges.

The following case illustrates these decision-making issues. Consider an 86-year-old man with advanced COPD who presents to the emergency department acutely dyspneic. He wants to live a few more days to say goodbye to family members and friends, even if it means living in the hospital. He does not want to be intubated or sent to the intensive care unit (ICU). He agrees to try BiPAP while initiating diureses. He expresses immediate profound relief of dyspnea upon securing the mask. However, the next morning, he asks that the mask be removed as it seems suffocating. He has had the opportunity to talk to his family and the distress associated with the BiPAP mask no longer makes it worthwhile. The patient's clarity around what is important to him can guide the clinician in these preference-sensitive treatment decisions.

SUMMARY

Experiencing multiple symptoms is common in older adults and particularly common in older adults with multimorbidity. For most symptoms, pharmacologic and nonpharmacologic approaches have some evidence base. Unfortunately, the evidence base is very limited for older adults, especially for those with multiple chronic conditions. Because the evidence base for symptom management is so sparse, treatments are preference sensitive and should take into account the values and preferences of older patients and their caregivers. Universal outcomes around function, cognition, comfort, and survival may be good starting points regarding which treatment options make the most sense. Ultimately more research will be needed to ascertain which treatments are the most beneficial for older adults and those with multimorbidity.

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Chapter 58

Effective Communication Strategies for Patients With Advanced Illness

Brook Calton, Wendy Anderson

Learning Objectives

- Describe a suggested six-step process for addressing goals of care and treatment preferences with patients who are seriously ill.
- Identify unique challenges in communicating with seriously ill older adults and strategies to address them.
- Summarize several key communication techniques including Ask-Tell-Ask and SPIKES.

Key Clinical Points

1. **Data suggest patients and families generally desire to have open conversations with their medical providers around their goals of care, treatment preferences, and end-of-life wishes.**
2. **Conversations around goals, values, and treatment preferences should be held over time, as a patient's health status and/or perspectives evolve.**
3. **Clarifying patients, and families, understanding as well as effectively addressing emotions around serious illness can help make these conversations easier.**

INTRODUCTION

Older adults are living longer, and with more chronic diseases, than ever before. In 2012, an estimated 43.1 million adults were over the age of 65, comprising 13.7% of the US population. About 67.3% of Medicare beneficiaries have two or more chronic conditions and 14% have six or more. In fact, the majority of hospice diagnoses are now noncancer related, such as congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), or dementia. Taken together, these data suggest effective communication around advanced illness is of ever-increasing importance for our older adults facing longer life trajectories, complex chronic illness, and debility and decline. Having achieved longevity, many older adults living with advanced illness prioritize goals such as function, comfort, and family support. Skillful communication is needed to ensure the treatments we offer align with these goals.

Effective communication with patients and families can have a number of benefits. It has been shown to improve diagnostic accuracy, health outcomes, treatment adherence, and patient satisfaction. In addition, effective end-of-life communication has been associated with decreased intensity of care, increased quality of life, and improved quality of dying for patients.

Studies consistently confirm the majority of patients facing advanced illness desire to have honest conversations about their goals, values, and end-of-life care with their providers. A recent systematic review of advance care planning in older adults found between 61% and 91% of older individuals wanted to discuss their end-of-life care with their providers. Benefits cited by patients included assurance their wishes would be respected, an opportunity to address important medical care and treatment issues before cognitive impairment or being physically unwell occurred, and to assist loved ones with decision making. They felt this responsibility to begin the discussion lies with physicians, they wanted to have the conversation in an open and honest manner, and preferred these conversations began early in their illness course.

However, despite the fact that communication around advanced illness is not only beneficial but also desired by most patients, this communication often remains inadequate. In studies, only an estimated 2% to 29% of frail older adults have discussed some form of end-of-life plans with a health care professional. In general, these discussions are often dominated by the clinician—in one study of 60 recorded patient-internist advance directive discussions, physicians spent 70% of the time talking and initiated more detailed discussions about patient values and goals fewer than 33% of the time. There are a number of challenges to effective communication that may contribute to the gaps described above. Potential barriers and suggested solutions are presented in **Table 58-1**.

TABLE 58-1 PROVIDER BARRIERS AND SUGGESTED SOLUTIONS TO ENHANCE COMMUNICATION

BARRIER	SUGGESTED SOLUTIONS
Provider time	• Reserve specific (and if possible, longer) visits for goals of care, advance care planning conversations • Have conversations over time, in small chunks, rather than in crisis only • Utilize resources (eg, prepareforyourcare.org) that help patients and family to reflect on their wishes before and after visits
Provider training	• Engage in standardized communication training during medical school and residency • Participate in Continuing Medical Education (potential resources include Vital Talk and the American Academy of HealthCare Communication)
Prognostic uncertainty	• Acknowledge uncertainty upfront with patients • Frame discussions within best, worst, and most likely scenarios • Use prognostic calculators (eg, eprognosis.org)
Fear of offending patients	• Routinize goals of care and advance care planning conversations with all patients • Ask patient for permission to have conversation and how much information they want

In this chapter, we will provide an approach as well as key skills to prepare providers for having important conversations about goals of care and advance care planning with patients and families. We will also discuss unique challenges and situations specific to communication with older adults.

SUGGESTED APPROACH TO COMMUNICATING WITH PATIENTS WITH ADVANCED ILLNESS

Communication around advanced illness can take many forms. Potential conversations may include, but are not limited to, providing prognostic information, discussing treatment preferences, engaging in advance care planning, and transitioning to comfort care and/or hospice. It is important to remember, particularly in the outpatient setting, that any of these topics should be thought of as a process, that occurs over time using open and honest communication that accounts for the patient's personal desire for information.

It is likely that patients' goals and preferences will shift over time as their illness progresses and/or what is important to them changes. Below we provide a suggested six-step approach that can be adapted to any of the conversations described above.

Step 1: Prepare

In the outpatient setting, if possible, it is optimal to ensure an adequate amount of protected clinic time to have the conversation. Encourage the patient to bring family or caregivers with them that they would like to hear and/or participate in the conversation. Clarify medical treatment options and prognostic information with other providers engaged in the patient's care prior to the visit. In the inpatient setting, it is important to arrange for a private place to have the conversation and again, invite key family members, caregivers, and health care providers (ie, consulting MDs, bedside nurses, chaplains, etc) based on the patient's preferences. Prior to the conversation, meet briefly with the participating health care providers (premeeting) to agree upon an agenda, prognosis, suggested treatment course, etc.

Step 2: Clarify Patient's Understanding of Illness and Preferences for Information/Decision Making

Any conversation around advanced illness requires that the provider first assess the patient's understanding of their illness. If the patient is unable to participate in the conversation, the same process should be undertaken with the patient's family and/or designated medical decision maker, depending on the circumstances. This step, using open-ended questions, facilitates the provider's ability to successfully provide education around the patient's illness, discuss treatment options based on a shared understanding of the patient's condition, and avoid potential misunderstandings (**Table 58-2**).

Next, the patient's preferences for information and medical decision making should be clarified. This is critical because while most patients desire information about their illness and want to be involved in decision making, a significant minority do not. Asking these questions (and then proceeding accordingly) will build the patient's trust and empower them in these conversations (**Table 58-3**).

Step 3: Education and Exploration

Step 3 involves patient education and exploration of patients' hopes and values to facilitate medical decision making.

Once you have a sense of the amount of information the patient desires, the foundational communication skill Ask-Tell-Ask can be useful for providing patient education. You've already done the first "Ask" in step 2, by eliciting the patient's understanding of their illness. The provider should next "Tell" the patient in straightforward language the information they are hoping to convey (ie, help them better understand their illness, treatment preferences, bad news, etc) in short, digestible chunks. The second "Tell" is an additional check for understanding or perspective. An easy way to ask is, *"To make sure I was explaining things clearly, can you summarize what I just said?"* This Ask-Tell-Ask cycle is often repeated several times during the same conversation, to ensure information is provided in a sensitive manner in digestible pieces.

Understanding a patient's hopes and values can help to the provider provide sound medical advice in line with what is most important to the patient. See **Table 58-4** for a list of suggested questions.

Step 4: Respond to Emotions

Providers often focus on the details of medical care and miss emotional cues. Responding to emotional cues is a key aspect of successful communication, building trust, and supporting patients. Clinicians can express empathy nonverbally and verbally. Eye contact, open body position, leaning in toward the patient, and when appropriate, light touch, can be useful tools for showing nonverbal empathy. An invaluable tool for expressing verbal empathy employs the mnemonic "NURSE". Details of the mnemonic and sample language are provided in **Table 58-5**.

Step 5: Guide Decision-Making

Every conversation is different, and in many cases, exploring hopes, values, and emotions can be extremely beneficial, even when there is no specific medical decision to make. If there are decisions to make, the next step involves providing options to the patient that are consistent with what has found out is important to them. Providers do not need to identify every possible option, particularly those that are inconsistent with the patient's expressed goals. Information should be given in small chunks and jargon should be avoided. In many situations, based on what is understood about the patient's decision-making preferences from step 2, providers can ask for permission to provide a recommendation based on the patient's values and what is known about the medical circumstances. Many patients and families may need time and multiple discussions before they can make big changes in care or decisions, for example, to enroll in hospice or decide whether to go into a nursing home. In practice, this often means not expecting a decision to be made at the end of one discussion. Suggested language is in **Table 58-6**.

Step 6: Summarize and Plan

To close the conversation, the provider should summarize any decisions that were made during the discussion, offer to answer questions, and arrange a plan for follow-up. This is also an opportune time to reaffirm nonabandonment regardless of the outcome of the conversation and the goals of care. In both the outpatient and inpatient setting, this is also an opportune time to thank the patient for having this difficult conversation and remind them you are hoping this process of exploration and decision making will be an ongoing one, as time goes on and their health evolves.

TABLE 58-2 ■ SUGGESTED LANGUAGE FOR ELICITING PATIENTS' UNDERSTANDING OF THEIR ILLNESS

"Tell me how things are going for you."

"Just so we're on the same page, could you tell me what you have heard about your medical condition?"

"What do you understand about your current health situation?"

"What do you think is causing your illness?"

TABLE 58-3 SUGGESTED LANGUAGE FOR ELICITING PATIENT'S PREFERENCES FOR INFORMATION AND MEDICAL DECISION MAKING

Preferences for Information

"How much do you want to know about your illness?"

"I have information about your condition. Some patients want to know the details; other patients want me to talk to someone else. How do you feel?"

"Are you the type of person who wants detailed information about their health?"

Preferences for Medical Decision Making

"How involved would you like to be in medical decisions regarding your illness?"

"How do you like to make medical decisions with your doctors?"

"Some patients prefer to make medical decisions entirely on their own, others prefer to make the decision jointly with their doctor, and others prefer the doctor to decide for them. Where do you fall?"

TABLE 58-4 SUGGESTED LANGUAGE FOR EXPLORING HOPES AND VALUES

Psychosocial Aspects of Illness

"What is the most difficult part of this illness for you and your family?"

What Gives Life Meaning

"As you think about what lies ahead, what is most important to you?"

"What do you enjoy?"

"How do you weigh quantity vs quality of life? What does quality of life mean to you?"

Hopes and Concerns

"When you think about the future, what do you hope for?"

"What do you fear about your illness?"

"When you think about getting very sick, what worries you the most?"

TABLE 58-5 NURSE STATEMENTS AND SUGGESTED LANGUAGE

SKILL	TASK	SUGGESTED LANGUAGE
N: Name	State the patient's emotion	*"It sounds like this experience has been frustrating."*
U: Understand	Empathize with and legitimize the emotion	*"I can understand why you're nervous."*
R: Respect	Praise the patient for things they are proud of/have done well	*"You've taken incredible care of your mother."* *"I'm impressed by how thoughtfully you've approached this decision."*
S: Support	Show support	*"No matter what decision we make, I'll be here for you."*
E: Explore	Ask the patient to elaborate on the emotion	*"Tell me more about how you're feeling."*

TABLE 58-6 PROVIDING A RECOMMENDATION, SUGGESTED LANGUAGE

TASK	SUGGESTED LANGUAGE

Restate primary goal(s) and confirm understanding.	*"Given what you have told me, it sounds like you want to continue treatments that may extend your life if your quality of life is similar to what it is now, even if that means coming back to the hospital."* *"What I understand as most important to you is that you remain comfortable and we get you back home. Is that right?"*
Suggest possible plan(s) of care to meet goals.	*"Have you heard of hospice? In my experience, it can be one of the best programs for achieving the goals you mentioned for symptom management and care in the home."* *"I'm hearing that you don't want a lot of medical interventions. Given that, I think we should consider focusing on symptom control as opposed to putting you on life support or doing CPR if your breathing gets worse. What do you think?"*

CPR, cardiopulmonary resuscitation.

STRATEGIES TO ADDRESS COMMUNICATION CHALLENGES WITH OLDER ADULTS

Communicating with older adults can come with a unique set of challenges. Specific age-related issues (ie, hearing and/or vision loss, decline in memory, slower processing of information) alongside psychosocial factors related to aging (ie, loss of identity, lessening of power/influence of one's life, and separation from family and friends) can impact communication. Studies have found in general, providers spend less time and take more of a paternal approach with older patients. Older patients may withhold information about symptoms or conditions the patient considers "normal for their age," such as pain—potentially hindering successful management of these important issues.

Hearing

Hearing loss is the third most common chronic condition reported by older adults.

Although older adults can compensate to a certain extent by devoting more cognitive effort to comprehension, this practice may limit the patient's ability to encode information into long-term memory, draw interferences, and follow complex conversations. Tips for communicating with patients with hearing loss include the following:

- Increase volume of speech slightly, speak a bit slower, and present information as clearly as possible.
- Avoid shouting. Speaking loudly raises the pitch of the voice, making it difficult for patients with hearing impairment to understand.
- Keep good eye contact and sit directly facing the patient so the patient can supplement what they hear with lip reading. Keep lips at the patient's face level.
- Minimize use of the computer if possible.
- Make sure the meeting space is as quiet as possible. Close the door to noisy hallways. Turn off background music and TVs.
- Make use of pocket-talkers and encourage the patient to use their hearing aides, when available.

Memory Loss and Dementia

Working memory declines with age. Working memory is important for processing complex sentences (specifically, sentences with multiple imbedded clauses), which are common when discussing serious news, goals of care, and advance care planning with patients with advanced illness. To enhance comprehension, providers should attempt to break up individual pieces of information into separate sentences that could stand on their own. Ask-Tell-Ask (described earlier in this chapter) is a useful tool for confirming comprehension.

In cases where a patient suffers from dementia advanced enough to impair their ability to make their own medical decisions (or the patient lacks decision-making capacity for other reasons, such as delirium), effective communication with surrogate decision makers is critical. Important medical decisions by surrogates for patients with advanced dementia are common. In a study of 323 health care proxies for patients with advanced dementia, 40% recalled making at least one medical decision—the most common being around feeding (27.2%) and infections (20.7%). In a study of nursing home residents living with advanced dementia and in their last 3 months of life, surrogate decision makers

who had an understanding of the patient's poor prognosis and the expected clinical complications in advanced dementia were much less likely to elect burdensome interventions than surrogates who lacked this understanding. This finding demonstrates the need for providers to, over time, educate the family for what to expect in the advance stages of dementia and to foreshadow what decisions may arise in the future.

In situations where a medical decision does need to be made by a surrogate decision maker for a patient with advanced dementia (or a patient who otherwise lacks capacity), the following communication approach is recommended. First, background information should be obtained, including reviewing the patient's advance directive with the surrogate decision maker, if available and assessing what conversations the surrogate decision maker has had with the patient previously regarding their values and treatment preferences. This information may be sufficient to make some medical decisions, and in most situations, preferences on an advance directive should be honored.

When further discussion is needed, the next decision-making step relies on substituted judgment—asking what the patient would have wanted if he or she could tell us. Time spent with the surrogate decision maker reflecting on the patient's values (ie, what brought the patient pleasure of life, what did quality of life mean to them) can be invaluable in aiding with complex medical decisions. These include deceptively simple probes like, *"Tell us about your mother."* We recommend, for this step, bringing the patient's "voice" into the decision-making process; for example, "*What would your mother choose if she could tell us?*" or, *"Knowing your mother, what do you think would be most important to her right now?"* An appeal to substituted judgment may remove some of the burden, by framing the decision as the patient's own choice rather than the surrogate's.

When there is no reasonable basis on which to interpret how a patient would have made a medical decision, decisions should be made that are in the best interest of the patient. That is, the best path to promote the well-being of the patient as a unique person, in the context of their relationships, values, religion and spiritual beliefs, and culture. Providers should encourage surrogates to weigh the harms and benefit of various treatment options, including pain and suffering, the degree of and potential for benefit, and any impairment that will result from the treatment in question. Provider treatment recommendations, based on your understanding of the patient's values, can be very helpful here—and are encouraged. When best interest standards apply, the question becomes, *"What do you think is best for your mother?"* Occasionally, conflicts between what providers and surrogates feel is best to do arise, including questioning whether the surrogate is truly making decisions in the patient's best interest. Providers are encouraged to consult with their medical center's administration regarding next steps in these difficult, ethical situations.

Managing Caregivers in the Room

Family members and caregivers often accompany older adults to medical appointments. It is particularly important that caregivers (specifically, surrogate decision makers) be present for key conversations regarding an older adult's goals of care so they too can understand the patient's preferences. However, a common occurrence is that caregivers of older adults may unintentionally (or intentionally) fall into a pattern of "speaking for" the older patient. Sometimes, but not always, this is due to difficulties in communication including hearing or vision problems or memory impairment.

Although it is sometimes necessary for a caregiver to provide supplemental information, it should not serve as a substitute for direct communication between the older adult patient and provider. Maintain direct eye contact with the patient, allow extra time for the patient to answer questions, and avoid speaking in the third person about the patient. To help establish the patient's sense of autonomy and participation in their health care, continually attempt to redirect the conversation back to the patient if you find the caregiver is tending to talk over the patient.

Prognostic Uncertainty

As mentioned in the introduction, older adults are living longer, with more chronic conditions that affect their quality of life and prognosis. When it comes to prognosticating, this population can be more challenging to the provider than, for instance, patients with a more predictable, terminal illness such as metastatic cancer. Prognostic uncertainty may heighten providers' hesitancy to discuss prognosis with these complex patients. However we know these conversations are important, and desired by patients. In one study of frail older patients with a mean age of 73, a life-limiting illness, and a need for assistance in at least one instrumental activity of daily living, over half of the patients whose physician had never discussed prognosis reported wanting to discuss it. While providers often consider prognosis conversations as important to medical decision making (including, but not limited to, chronic disease management, cancer screening, initiation of dialysis, and advance care planning), many older adults find this information helpful in determining life choices (ie, financial decisions, long-term care and housing, and quality-of-life considerations like spending time with family). Using prognostic indexes, many of which can be found on the user-friendly E-Prognosis website

(www.eprognosis.com) can help inform your estimates alongside the clinical picture for your individual patient. Additional techniques for approaching conversations where prognostic uncertainty is present are presented in **Table 58-7**.

TABLE 58-7 ADDRESSING PROGNOSTIC UNCERTAINTY

TASK	SUGGESTED LANGUAGE
Acknowledge it is difficult to make a 100% certain prediction about the patient's prognosis	*"Like the weather, it is difficult for me to be 100% accurate regarding how long you have to live."*
Use NURSE statements to respond to the patient's emotion around uncertainty	*"I can imagine it's frustrating to not know exactly what will happen."*
Provide prognostic estimates using ranges, ie, days to weeks, weeks to months, months to years	*"My best estimate is that you have weeks to months to live."*
Provide estimates that relate to a population of patients, not just the patient in front of you	*"In patients with medical issues similar to yours, the data suggest patients live an additional 1–2 years."*
Ask open-ended questions that enhance understanding of what is important to your patient	*"How do you view your quality of life currently?"* *"How do you think about balancing quality of life with quantity?"* *"When you think about the future, what do you hope for?"* *"Would there be any circumstances under which you would find life not worth living?"*
After addressing emotion, gently encourage patients and families to refocus on the present, as opposed to fixating on an uncertain future	*"What can we do now, given that we are unsure of exactly what the future will bring?"*

SPECIAL SITUATIONS

Discussing Bad News

Bad news is defined as any news that drastically and negatively alters the patient's view of his/her future. Although we often associate discussing bad news with the practice of oncology, all providers, regardless of specialty, are called upon to discuss bad news with patients. Bad news may relate to a diagnosis (ie, terminal, chronic, cancer, etc), prognosis, test results significant for disease progression, a bad outcome, or even medical mistakes. For older adults, bad news may come in the form of a loss of independence, such as being deemed unsafe to continue driving a car or, requiring a higher level of care that will force the patient to move from their home of many years. It is important to remember that (1) most patients want to know bad news (in studies, 75%–90%) and (2) how a patient responds to news is influenced by a patient's perspective, life experiences, occupation, personality and coping skills, religion, and social support.

When bad news is communicated in an effective manner, it can have an important impact on patient satisfaction and decreasing patient anxiety and depression. Discussing bad news poorly can not only negatively impact patient outcomes, but can also have short-term (ie, anxiety) and long-term (ie, feelings of failure, regret, identification, higher rate of "burn-out") effects on the provider. Challenges to discussing bad news include, but are not limited to, providing information consistent with the patient's understanding of their disease, concerns about not taking away patient's hope, and addressing emotion. A useful roadmap for discussing bad news uses the acronym SPIKES (**Table 58-8**).

TABLE 58-8 SPIKES FOR DISCUSSING BAD NEWS

S: Setup	• Ensure a private space where everyone can be seated • Obtain collateral information from other providers • Check in with yourself regarding your emotional status and worries regarding the conversation
P: Perception	• Use Ask-Tell-Ask to assess the patient's current understanding of their condition

	• Clarify misunderstandings
I: Invitation	• Find out how much information the patient wants to know (ie, *"How would you like me to talk with you about your test results?" or "I have some serious news about your health; would you like me to discuss it with you or someone else?")*
K: Knowledge	• Convey the bad news in plain language without jargon (ie, *"The CT scan shows your cancer is not responding to the chemotherapy" or "Unfortunately, your vision has gotten worse to the point I think it is unsafe for you to be driving")* • Pause for 10–15 seconds after you have delivered the bad news to allow time for processing and emotion
E: Empathize	• Use empathetic statements to respond to patient emotions (draw upon the mnemonic NURSE found in **Table 58-5**) • Resist the temptation to make things better • Consider using "I wish" statements *(ie, "I wish I had better news" or "I wish things had turned out differently")*
S: Summarize and Strategize	• Summarize the clinical information and plan next steps • Provide reassurance you will not abandon the patient • Ask patient to summarize information in his/her own words to check for understanding

Tube Feeding in Advanced Dementia

Outcomes including death, aspiration pneumonia, functional status, and patient comfort are similar, if not better in some cases, for careful hand feeding compared to tube feeding in patients with advanced dementia (ie, bed-bound, unable to ambulate, and typically limited, if any, ability to communicate verbally alongside feeding difficulties, such as refusal of food, dysphagia, and/or recurrent aspiration). Additionally the risk of hospitalization, emergency room (ER) visits, agitation, use of physical and chemical restraints, and incidence of pressure ulcers all appear to be higher with tube feeding as compared to careful hand feeding. Given this data, the American Geriatrics Society, in their "Choosing Wisely Campaign," does not recommend percutaneous feeding tubes in patients with advanced dementia and recommends oral assisted feeding instead.

Despite data that feeding tube placement in advanced dementia is unlikely to provide benefit, and may even cause harm, one of the most common communication challenges providers caring for older adults face revolves around these decisions. Insufficient education of patients and surrogates on the potential risks of tube feeding likely contributes to this challenge as does the important social and symbolic role food plays in many cultures and religions.

One of the best strategies for effectively addressing this issue is to start the conversation early. In most cases, outpatient providers will have an opportunity over months to years to observe their patient with advanced dementia's swallowing ability and progressively decreasing oral intake. After ruling out reversible causes, providers should continually educate patients (if able to engage), family members, caregivers, and surrogates that feeding difficulties are a sign of progressive, advanced dementia and you anticipate they will worsen over time. Ask-Tell-Ask, summarized earlier, can be a particularly useful skill here to assess what a patient or family understands and provided targeted education around the natural history of dementia and feeding difficulties.

Discussions regarding preferences for feeding support should begin early in the course of dementia, ideally when the patient's cognition is intact enough to express their own preferences. These discussions should not be delayed until a crisis develops. Any decisions made with the patient should be documented in the medical record and an advance directive. This decision-making process includes aligning what patients and families are hoping for, with the realistic expectations and potential outcomes of tube feeding. Questions that can be particularly helpful, both early in the patient's illness and in crisis situations (ie, recurrent hospitalizations for aspiration pneumonia in a patient with advanced dementia) include, *"What do you hope a feeding tube would do for you (or your loved one)?," "What worries do you have about feeding tubes?,"* and *"Have you seen any other patients with severe dementia with a feeding tube?—What do you think that experience was like for them?"*

End-of-Life Preferences

As older adults with advanced illness reach the end of their life it is important to be sure that the patients' wishes regarding resuscitation and ICU care are confirmed and documented. However, perhaps even more important is that

the patients' wishes, including desire for hospitalization, hopes for what the end of their life would look like, and preferred place of death are discussed. These subtler preferences are often left unexplored but when done, can have a significant positive impact for both patients and their families. For instance, data suggest most patients desire to die at home; however only 34% of patients with Medicare successfully do so. There are a number of explanations for this disparity—one of which is that many providers do not ask about the patient's desired place of death. When the provider understands the patient's preference for dying at home, they can arrange the appropriate community resources, such as home-based palliative care, home health, and/or hospice care and provide targeted patient education and anticipatory guidance to families and caregivers to help the patient achieve this goal. Suggested language for exploring a patient's end-of-life preferences, beyond resuscitation, is below:

- *"If you were close to the end of your life, what would be most important to you?"*
- *"Do you have a sense of where you would prefer to be at the end of your life?"*
- *"Some patients feel strongly they'd like to die at home, while others don't have a preference. Do you?"*

CONCLUSION

Effective communication with older adults with advanced illness requires a diverse and flexible set of skills. Techniques including Ask-Tell-Ask, use of NURSE statements to address emotion, and the SPIKES model for delivering bad news can be invaluable in overcoming some of the challenges to caring for older adults, including sensory deficits, memory problems, and prognostic uncertainty for patients facing multimorbidity and/or frailty. Despite the challenges, having these important conversations can be extremely rewarding. Most patients want to discuss these important issues with their providers. Furthermore, conversations around a patient's quality of life, goals of care, and advance care planning allow clinicians to match our treatment recommendations to patient's ultimate goals and values to provide them with the best care possible.

FURTHER READING

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WEB RESOURCES

American Academy of Healthcare Communication
Eprognosis.org
www.prepareforyourcare.org
http://www.vitaltalk.org

Chapter 59

Palliative Medicine Across the Continuum of Care Including Hospice

Nelia Jain, Alexander K. Smith

Learning Objectives

- The percentage of older adults in the United States is increasing, and this population tends to have multiple chronic conditions with acute exacerbations and progressive debility.
- Highlighting the ideal delivery of palliative care across the care continuum, and contrasting this model with the deficiencies present in the current system, we illustrate areas for improvement for the delivery of palliative care for older adults.

Key Clinical Point

1. **The palliative care needs of older adults differ from those of children and younger adults and are best served by delivering palliative care services in a variety of care settings.**

INTRODUCTION

Consider Mrs. M, an 88-year-old woman with moderate congestive heart failure, mild cognitive impairment, and painful osteoarthritis, who ambulates with the assistance of a walker. Mrs. M is widowed and lives in assisted living. Her daughter, who lives in the same city, provides assistance with medications, and accompanies her to appointments with her primary care doctor and cardiologist. Mrs. M enjoys her weekly routine, which includes caring for her small dog, meals with friends at the assisted living, and trips to church with her daughter on Sundays. This routine is stable until one day when she falls and breaks her hip. She undergoes a surgical "pinning" procedure at the local hospital. Her posthospital course is complicated by delirium and pain. She is transferred to a skilled nursing facility for rehabilitation. After 2 months in the skilled nursing facility, Mrs. M is unable to return to the assisted living facility because she consistently requires daily assistance with bathing and dressing. She moves in with her daughter and enrolls in a home-based primary care program. A new routine is established, and she enjoys regular visits from her great grandchildren. However, 2 years later, her cognitive impairment has progressed to mild dementia. Overwhelmed with Mrs. M's daily care needs, her daughter admits her to a nursing home. Mrs. M is hospitalized three times over the next year. She enrolls in hospice after the third hospitalization and survives another year.

The case of Mrs. M illustrates the need for a truly integrated system of palliative care that meets the medical and social needs of older adults across the care continuum. Palliative care is fundamentally about improving quality of life for persons with serious and advanced illness. The types of care that would help support Mrs. M's quality of life vary as her health circumstances and care settings change. These include, but are by no means limited to (1) a home safety evaluation, including pragmatic steps such as the installation of grab bars and a shower chair; (2) an advance care planning conversation that helps her daughter understand her mother's goals, values, and preferences; (3) a provider who can care for her across settings; (4) treatment of pain due to osteoarthritis; (5) assessment and treatment of postoperative pain and delirium; and (6) training and support for her daughter, the family caregiver.

Unfortunately, the reality of our health care system is that it is disjointed, dysfunctional, and often does a poor job of matching treatments to patient goals. In this chapter, we will describe the ideal of a palliative care system for older adults that delivers integrated care across the care continuum, including hospice. We will contrast this ideal with the

barriers to and lack of an integrated system for delivery of palliative care across the continuum. We will identify opportunities for improvement. We begin by discussing the tremendous overlap between the fields of geriatrics and palliative care.

GERIATRICS AND PALLIATIVE CARE AS PARTNERS

The case of Mrs. M illustrates the blurred boundaries between geriatrics and palliative care (**Figure 59-1**). Geriatrics and palliative care both emphasize improving quality of life in late life. Both fields require excellence in management of persons with multimorbidity, dementia, and disability. Both fields emphasize attention not just to the patient, but also the patient's caregiver, and the situation of the patient within the context of family and community. Both fields are directed primarily toward the sickest older adults, those that account for about half of health care spending in the United States.

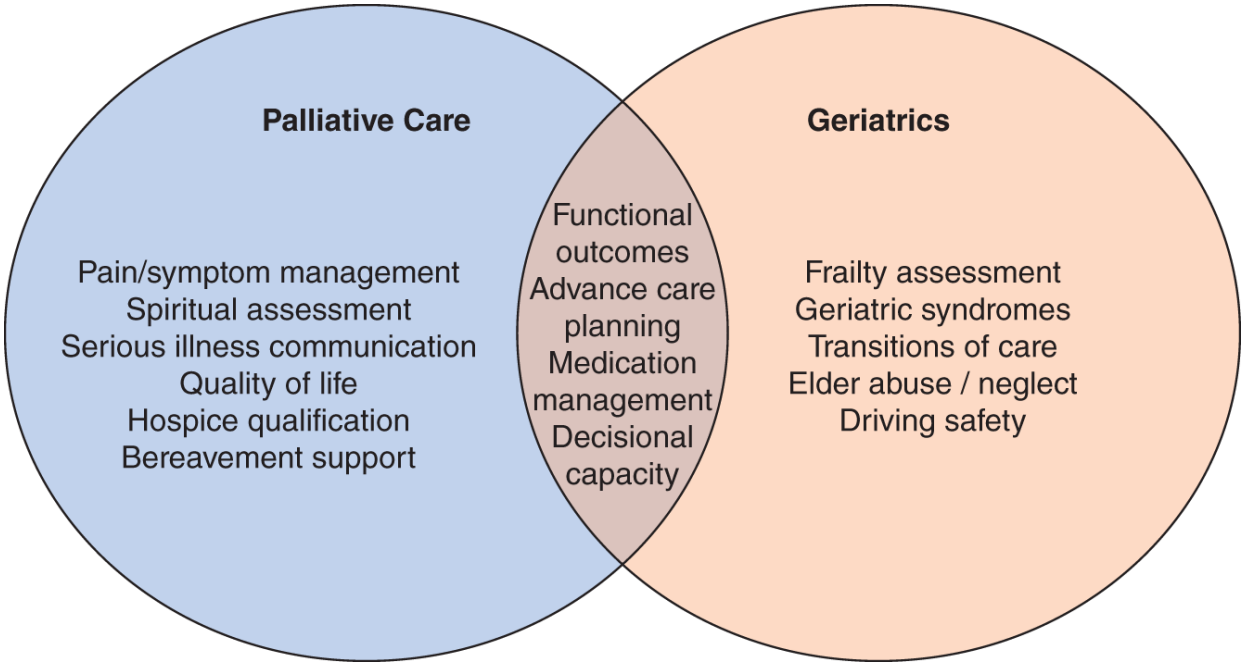


FIGURE 59-1. Intersection of palliative care and geriatrics.

By 2030, the number of Americans aged 65 or older is predicted to approach 71 million. Eighty percent of all older adults have at last one chronic condition, and 50% have at least two or more chronic conditions. In the setting of multiple chronic illnesses, older adults are often living with progressive disability for longer periods of time. They face repeated institutionalization and difficult transitions. Older adults' family and physicians often have a poor understanding of their goals of care and have rarely engaged in discussion regarding treatment preferences.

There is increasing recognition that palliative care does not equate to "comfort care only" for the terminally ill, and this shift has largely been spurred by the needs of the aging population. The recognition that palliative care can have a major impact on symptom management, communication, and caregiver support for all patients with advanced illness from the time of diagnosis is an invaluable step toward improving the quality of life for older adults dealing with multiple chronic illnesses.

While the fields of geriatrics and palliative care share common core principles, they best serve patients when applied in parallel (at the same time) rather than in series (geriatrics, then palliative care). By simultaneously advocating for the holistic care of older adults, recognizing the specialized knowledge base and skills possessed by each discipline, and ensuring competency of future trainees in both geriatrics and palliative care, providers from both fields will be able to work together to target the sickest 5% of our population at highest risk, and match these patients with delivery models best suited to address their needs.

THE IDEAL OF A CARE CONTINUUM

The ideal of a continuum of care has been defined as, "A client-oriented system composed of both services and integrating mechanisms that guides and tracks clients over time through a comprehensive array of health, mental health, and social services spanning all levels of intensity of care." The introductory chapter in this section on Palliative Care introduced the concept that palliative care is appropriately initiated from the time of diagnosis with serious or advanced illness (see Chapter 55). For many, though not all, serious and advanced illnesses are diagnosed in the outpatient setting. The ideal care continuum, therefore, would integrate palliative care into the settings where patients spend the most time after diagnosis, that is, in their homes. This would involve robust outpatient palliative care clinics and home-based palliative care services. In addition, specialty palliative care cannot possibly meet the needs of all patients with serious and advanced illnesses; therefore, we must train others in palliative care, particularly providers caring for the majority of older adults.

As patients develop more serious conditions, such as advancing disability and dementia in the case of Mrs. M, they may require care in more acute institutional settings like skilled nursing facilities, hospitals, and nursing homes. The ideal continuum of care would track patients as they move between settings, coordinate care across providers, and offer comprehensive services as people move between the outpatient and inpatient setting. As a patient's goals shift toward a focus on quality of life, high-quality palliative care services should take on a greater role in care, and be available in all settings.

THE REALITY OF PALLIATIVE CARE FOR OLDER ADULTS

Palliative care has been noted to improve quality of life and symptom management for patients, increase satisfaction of patients and their family members, and reduce health care costs. However, in the current health care system, palliative care is most readily made available to patients during times of crisis (acute inpatient hospitalization) or at the end of life (hospice). The majority of older adults' last months and years are still spent in the community, with institutionalization occurring only in the very late stages of life. There has been less progress noted in the area of nonhospice palliative care in nursing homes or the outpatient setting, including assisted living and home-based programs, suggesting that the current level of palliative care services do not adequately address the needs of older adults.

As discussed in Chapter 55, palliative care needs for geriatric patients differ from the needs of younger adults. Older adults tend to have prolonged illness duration with numerous chronic and complex medical conditions. Older patients experience greater functional and cognitive decline, and they also have increased caregiving needs for longer periods of time. While older adults typically die of chronic, slowly progressive illnesses with multiple acute exacerbations, current Medicare coverage is targeted to the acute episodes of illness. This has resulted in palliative care that has been implemented in a reactionary fashion to these acute episodes. This approach insufficiently addresses patients' longer-term needs and creates missed opportunities for palliation along the disease trajectory (**Figure 59-2**).

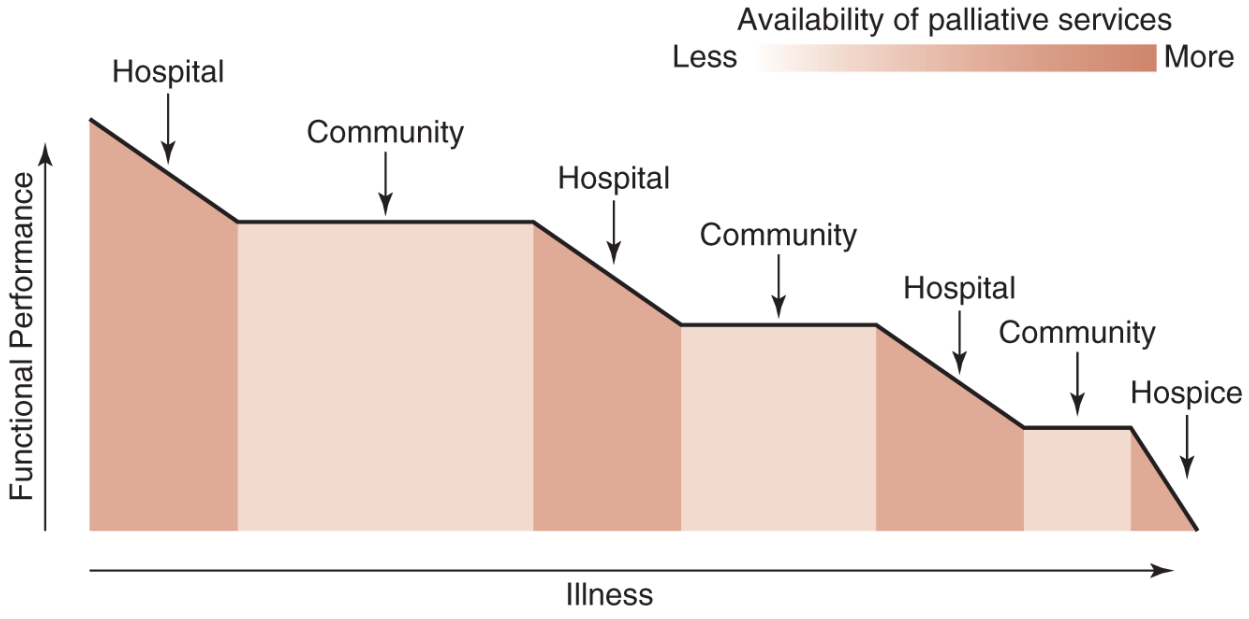


FIGURE 59-2. Gaps in palliative care services for older adults.

In order to adequately address the needs of older adults, palliative care must be instituted in a timely manner, earlier in the course of a patient's illness. Upstream involvement of palliative care in the care of older adults, particularly while they are still residing in the community, allows for increased opportunities for shared decision making, constant evaluation of a patient's prognosis and symptom burden, and longitudinal care throughout different care settings. In addition to routine palliative care, providers have the opportunity to work with patients' primary care physicians and specialists to emphasize function, financial planning, and maintenance of social roles within a community. The comprehensive approach will allow palliative care providers to build relationships with patients. In the future, this foundation will aid in easing transitions to higher levels of care and discussing shifting the focus of care from curative to fully palliative in the setting of progressive debility and decline.

Primary, Secondary, and Tertiary Palliative Care

A useful framework for considering the range of palliative care services across the continuum is the concept of primary, secondary, and tertiary palliative care developed by von Gunten. At the level of primary palliative care, all physicians and other relevant health care professionals will possess the basic skills and competencies to provide palliative care. For cases requiring additional expertise, the model suggests a secondary palliative care level in which specialists in palliative care will be available on a consultative basis to assist in the care of the patient. Finally, at the tertiary level, palliative care providers will assume responsibility for patients at institutions, such as hospice, where specialist knowledge is taught and practiced.

Within this framework, an organized approach to the identification, assessment, and management of the older adult's complex medical conditions is key. The focus should lie in identifying the needs of the patient and recognizing which level of palliative care will best meet these needs. A systematic approach will allow providers to adequately address the physical, social, and spiritual needs of older adults and target discussions to the current state of their disease, estimated prognosis, and available treatment options. For this model to be successful, increased emphasis needs to be placed on research and education in palliative care. Furthermore, the majority of reimbursement for palliative care needs to extend beyond that devoted to the last 6 months of life, in order to ensure adequate access to palliative care services across the care continuum.

PALLIATIVE CARE IN THE HOME

There are an increasing proportion of older adults living at home with chronic illness with intensive symptom management and advance care planning needs who do not qualify for hospice. The ideal home-based palliative care model is comprised of an interdisciplinary team of physicians, nurses, social workers, chaplains, home health aides, and pharmacists (similar to the home hospice model) who are able to provide services in coordination with the primary care provider and specialists. Services would include pain and nonpain management, medication management, discussions about health care decision making and goals of care, caregiver support, attention to spiritual concerns, arranging respite care, and assistance with the transition to hospice if needed. Specifically tailored to the chronically ill older adult, home-based palliative care should include home safety evaluations, offer health benefits and education to caregivers, consider costly aggressive disease-directed treatment if there is opportunity to enhance quality of life, and ensure timely access to medications and 24/7 access to a health care provider in order to ensure continuity of care and manage acute crises. The home-based palliative care organization would benefit from a relationship with other institutions such as hospitals, primary care clinics, specialty clinics, nursing homes, and hospice agencies in order to increase the referral base as well as promote longitudinal care across the care continuum.

Studies on existing models of home-based palliative care have demonstrated beneficial outcomes. The patient populations receiving home-based palliative care include patients with both cancer and noncancer diagnoses (dementia, cardiac disease, pulmonary disease). Benefits noted include improved symptom scores in areas such as depression, dyspnea, and anxiety, decreased overall cost of care, increased completion of advance directives, and increased rates of dying at home. Fewer visits to the emergency department and lower rates of hospitalization have been observed, without a difference in overall survival. Rates of referral to hospice are higher than among control patients without home-based palliative care. Of the patients who do enroll in hospice, those who have received home-based palliative care prior to this transition are noted to have longer days of enrollment in hospice as compared to those with usual care.

Despite the positive impact home-based palliative care programs have been shown to have on communitydwelling

patients with serious and advanced illnesses, the advancement of palliative care in the arena of home-based care has been limited, largely due to economic barriers such as insufficient reimbursement for services, and lack of incentive to reduce costs. Organizational barriers exist as well, primarily driven by the lack of adequate staff in the outpatient setting and the lack of adequate training for health care staff. At present, there is no standardization of home-based palliative care practices or institutional support, leading to difficulty in translating the beneficial outcomes that have been noted in existing home-based palliative care models to the broader population. In order to adequately improve the quality of life and decrease psychological distress of older adults, there needs to be increased movement towards palliative care in the community setting, with an emphasis on the financial benefit of cutting overall health care costs. These shifts in care will support the goal of most older adults to remain in their community for as long as possible and increase the number of people who are able to die at home as opposed to the hospital.

PALLIATIVE CARE IN THE CLINIC

Another example of community-based palliative care is palliative care that occurs in an outpatient clinic. Similar to home-based primary care, palliative care in the clinic setting provides the foundation for development of an early relationship between providers and older adults, improves communication between primary care providers and other subspecialty providers, and increases satisfaction with care from the perspective of patients and their families. These clinics also serve as an appropriate setting for posthospital discharge follow-up for patients seen by inpatient palliative care teams.

There are a variety of existing models of palliative care clinics in our current health care system (Improving Outpatient Palliative Care [IPAL]). Some clinics are affiliated with particular specialties by which they generate all of their referrals, but they are otherwise stand-alone clinics that function independently. Other clinics share space and staffing with a primary care clinic or specialty clinic, or are completely embedded within this clinic framework. Additionally, clinics vary in the focus of their care, ranging from providing task-specific to symptom-specific palliative care. Palliative care clinicians will often choose between providing care in a consultative (secondary palliative care) or comanagement fashion for the majority of patients, while some patients will be taken care of entirely by the palliative care specialist (tertiary palliative care). Finally, some clinics have the capability to extend their services beyond the clinic and into the community, providing visits to clinic patients who become homebound or transfer to a facility (**Figure 59-3**).

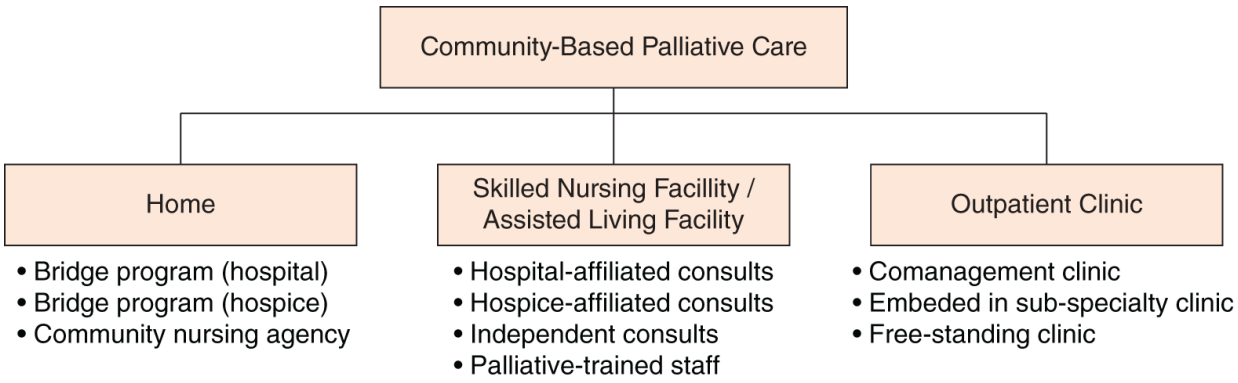


FIGURE 59-3. Palliative care delivery models in the community.

Outpatient palliative care services have been associated with improved patient outcomes, such as significant symptom improvement and high satisfaction with services. Care provided in palliative care clinics has also been associated with better maintenance of performance status, increased discussions about advance care planning and end–of-life care, and better long-term outcomes for caregivers. Patients receiving care in palliative care clinics in addition to usual care experience fewer hospital days and skilled nursing facility days, as well as increased hospice use. Providers also benefit, with increased rates of satisfaction observed in referring providers as well as palliative care clinicians.

There are several limitations that impede the delivery of ideal palliative care in the clinic setting. Patients with severe and advanced illness, particularly those with chronic illnesses, are always at risk of declining to the point that they are unable to make their outpatient clinic appointments. Unless clinics are associated with bridge programs

designed to extend palliative care services to homes and facilities until patients qualify for hospice, provided the latter is an acceptable option to them, chronically ill patients with progressive debility often experience a gap in the continuation of their palliative care services. In addition, clinics are often limited by their hours of operation and limited staffing, particularly lacking coverage by a health care provider 24 hours a day to manage any acute crises that may arise. Finally, given the heavy reliance on referrals from the inpatient setting, primary care clinics, and subspecialty clinics, palliative care clinics require a certain amount of "buy-in" from other disciplines in order to continue to function. As the population with chronic conditions continues to grow and age, increased attention to increasing the number and availability of palliative care clinics, increasing reimbursement of palliative care services, and developing relationships between hospitals, long-term care institutions, and community-based home care organizations is needed to ensure that this population of patients will be able to receive palliative care outside of the hospital setting.

PALLIATIVE CARE IN LONG-TERM CARE FACILITIES

There are an estimated 1.5 million assisted-living beds in the United States, with a significant growth in demand expected in the next 20 years in proportion to the rate of aging of the population. In adults over the age of 65, approximately 25% of people will die in a nursing home, with projections of an increase to up to 40% of older Americans by 2030. The majority of residents in long-term care facilities are older adults, experience progressive frailty and functional impairment, and require increased assistance in activities of daily living. For older adults in long-term care facilities, life expectancies are typically shorter in the order of years. With projections suggesting that the number of frail older adults may triple or quadruple in the next 30 years, closer examination is called for on the state of palliative care services in long-term care facilities. For many long-term care residents, hospice is the only form of secondary or tertiary palliative care available.

What is known about palliative care services in long-term care facilities at present is limited. There are several studies that demonstrate residents in assisted-living facilities and nursing homes suffer from uncontrolled symptoms, depression, existential suffering, and difficulty adjusting to the long-term care facility as their permanent place of residence. Despite this information, surveys suggest that providers in nursing home believe they are providing quality primary palliative care to their residents. This is in contrast to qualitative interviews performed with family members of nursing home and assisted living facility residents who identified several issues with the current level of palliative and hospice care: (1) insufficient recognition of symptoms, needs, and illness trajectories of dying persons, (2) low expectations of nursing homes requiring significant advocacy on the part of family members for their dying loved ones, (3) physicians "missing in action," (4) regulations that reinforce task-focused rather than patient-centered care, and (5) late or a low rate of hospice referrals noted. In addition, family members of loved ones who died in a nursing home have reported higher rates of unmet needs and dissatisfaction with care compared to family members of patients who die at home.

A number of significant barriers to providing adequate palliative care in long-term care facilities exist. Demographics of patients in long-term care facilities, particularly nursing homes, are changing, with increased numbers of patients with chronic illness and multiple medical problems. A large percentage of these patients have noncancer diagnoses, leading to increased difficulty with prognostication and late referrals to hospice. Nursing home residents often undergo frequent, potentially burdensome transitions between the long-term care facility and the hospital. These issues are further complicated by the fact that there is often high staff turnover at long-term care facilities, making it difficult to sustain palliative care educational efforts and ensure palliative care competency amongst staff.

Increasing support for palliative care services in long-term care facilities requires a paradigm shift from current approaches to care and reimbursement strategies in assisted living facilities and nursing homes. Up until now, nursing home staffs have viewed their role as providing restoration of function and health. Staffs are sometimes hesitant to relinquish or comanage residents with whom they have had long-standing relationships when patients elect to exercise the Medicare hospice benefit. Yet, staffs also express frustration over the lack of physician presence or the unwillingness of physicians to address goals of care or communicate changes in prognosis to patients and their families. Polls of nursing home staff consistently demonstrate that they believe it is important to have an understanding of the principles of palliative care, be able to assess and manage pain and nonpain symptoms, and take care of patients at the end of life.

With current reimbursement policies focusing on rehabilitation needs and sustenance, a seemingly high proportion

of patients undergo aggressive restorative treatment such as intravenous hydration or insertion of feeding tube placement instead of shifting to aggressive palliative care or hospice care. In addition, short-stay residents in nursing homes who are paid for under the Medicare skilled nursing facility benefit following a hospitalization are only able to access the Medicare Hospice benefit if they revoke the skilled nursing facility benefit and pay for room and board out of pocket. These out-of-pocket costs are a major financial disincentive to short-stay residents to exercise the Medicare hospice benefit.

Guidelines for quality palliative care in nursing homes emphasize that palliative care does not require patients to forgo curative treatments nor relinquish subacute rehabilitation or hospitalization (National Consensus Project Guidelines for Quality Palliative Care). Three different models of delivering palliative care services in nursing homes have been proposed: (1) hospice partnerships, (2) external palliative care consultation services, and (3) facility-based palliative care teams. Sustainability is the key. Measures that are critical to sustainability of palliative care interventions in the long-term care facility setting include ongoing education efforts, "buy-in" of palliative care by nursing home staff and physicians, increased availability of nurses and patient aides, and working relationships with hospitals and community organizations including hospice to ensure continuity of palliative care across all settings.

PALLIATIVE CARE IN THE HOSPITAL

Of all settings, palliative care services in the acute inpatient setting have enjoyed the most successful implementation and advancement in the last 20 years. In the inpatient setting, palliative care teams are interdisciplinary, comprised of a mix of physicians, social workers, nurses, and chaplains. These teams offer expertise in symptom management, support to medical teams as well as patients, knowledge about community-based palliative care services and hospice organizations, and assistance in prognostication over a variety of illnesses.

At present, approximately two-thirds of all US hospitals have some form of palliative care services. Up to 85% of hospitals with more than 300 beds provide comprehensive interdisciplinary palliative care. Given that the majority of patients with advanced or serious illness will spend some time in the hospital throughout the course of their illness, and that up to 50% of adult deaths occur in the hospital setting, ensuring adequate palliative care services in the inpatient setting is another area of particular importance. There is increasing evidence that inpatient palliative care interventions improve the quality of clinical care, increase patient and family satisfaction, improve transitions of patients out of the hospital, and reduce health care costs (see Chapter 55). Patients who receive inpatient palliative care consultations incur less laboratory and radiology costs, are less likely to be admitted to the intensive care unit (ICU), and spend less days in the ICU once admitted compared to patients receiving usual care, particularly among patients who die during hospitalization.

Despite the advancements that have been made in inpatient palliative care, as well as the positive patient and family outcomes that have been observed, challenges remain in the delivery of palliative care in the inpatient setting. Inpatient palliative care teams continue to struggle with timing of consultation, with the median time of consultation observed to be 2.5 days prior to discharge. In addition, providers face constant turnover of treatment teams, hesitation to move away from a curative focus, and varying levels of knowledge about and alignment with palliative care from primary medical providers. Due to the acuity and complexity of medical issues present in the hospitalized patient population, it is often difficult for palliative care providers to address all of the needs of these patients during the acute hospitalization, particularly ensuring longitudinal care upon discharge across all settings.

In order to address deficiencies that remain in the delivery of palliative care in the inpatient setting, experts have called for a systematic approach to palliative care consultations. As it is not sustainable that palliative care specialists will be able to meet the needs of all patients with serious or advanced illness, they call for an improvement in basic primary palliative care skills among all clinicians responsible for the care of this patient population, and involving palliative care consultants when additional expertise is needed. Success in this approach requires evaluation of patient's palliative care needs from day of admission, with constant monitoring of progress on these fronts as well as reevaluation to identify new palliative care needs as they arise throughout the hospitalization (**Figure 59-4A** and **4B**).

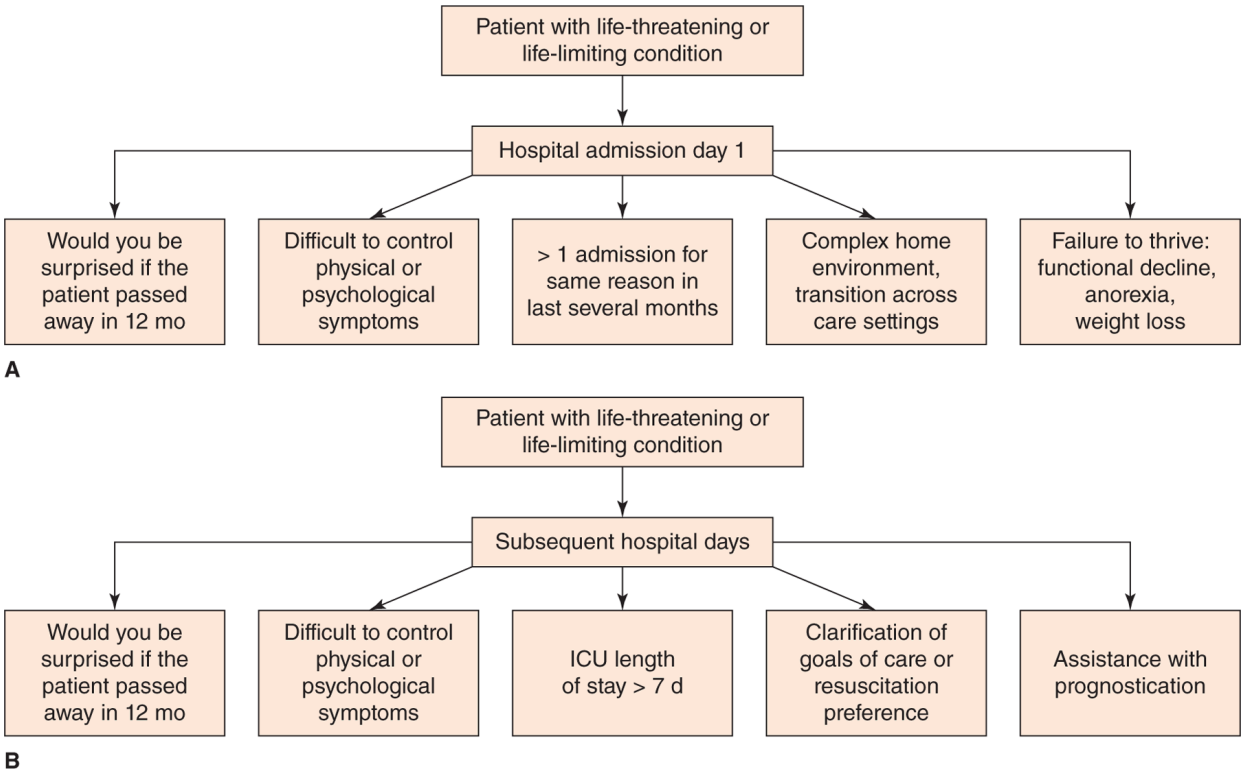


FIGURE 59-4 **A.** Inpatient criteria: guide for primary teams to prompt palliative care consultation on day of admission. **B.** Inpatient criteria: guide for primary teams to prompt palliative care consultation on subsequent days of hospital admission.

The ICU is one of the locations in the inpatient settings with the most barriers to successful delivery of palliative care. In a culture of immortality and inflated sense of the likely success of life-prolonging interventions, it is often challenging to deliver quality palliative care. Studies have demonstrated that patients, families, and medical providers all possess unrealistic expectations about prognosis and efficacy of ICU interventions. Surveys show that patients and caregivers would benefit from more honest and open discussions regarding prognosis and appropriate therapies based on patients' values and goals. ICU clinicians should all receive training in core skills of primary palliative care, including serious-illness communication skills and symptom management. Palliative care "bundles" have been suggested to improve communication and promote the comfort of critically ill patients (IPAL-ICU). Key quality measures in these bundles include early identification and documentation of surrogate decision makers and advance directives, regular symptom assessment, involvement of social work and spiritual care, and regular family meetings to update patients and family on the status of patient's illness. By emphasizing compassionate communication, symptom management, and shared decision making, palliative care can be successfully integrated for critically ill patients at all stages of illness.

Hospice

Hospice care is the most well-known provider of palliative care services in the community. Hospice care is a philosophy of care in which patients facing a life-limiting illness are approached in a holistic manner, with a focus on medical care and symptom management, as well as an interest in the emotional, spiritual, and future planning needs of the patient and family. There are now more than 3600 hospice organizations nationally, and these organizations serve over 1 million people. Research on hospice care has demonstrated increased survival compared to usual care, increased patient and family satisfaction with end-of-life care, increased rates of patients dying in their location of choice, and decreased inappropriate health care resource utilization.

However, there is variability in the utilization of hospice care across care settings. First and foremost, despite tremendous growth in the use of hospice services over the last 30 years, hospice care is still underutilized. A substantial number of patients who would prefer to die at home still die in the hospital. At present, the majority of patients receive hospice care at home (**Figure 59-5**). The proportion of deaths in a nursing home is expected to increase dramatically over the next 10 to 15 years. Nationally, hospice is not available in all long-term care facilities, and only 6% of residents in nursing homes elect the hospice benefit annually, far lower than one would expect given the short lengths of stay prior to death for many long-term care facility residents.

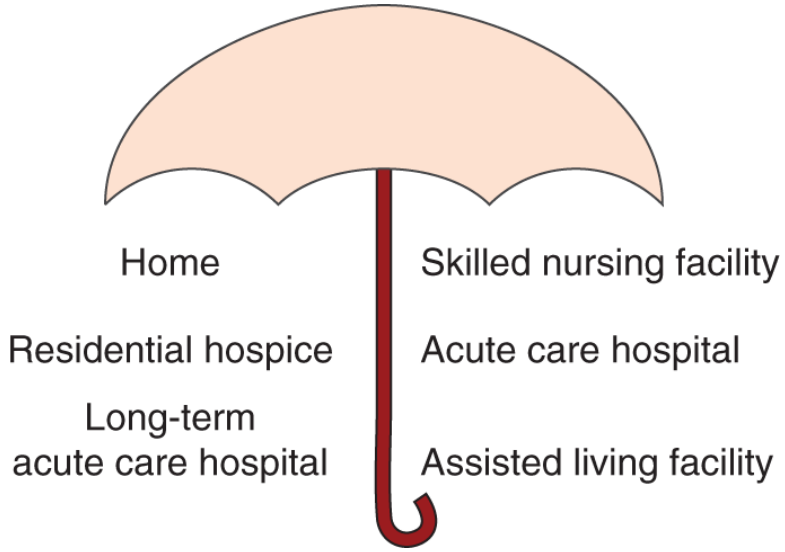


FIGURE 59-5. Care settings that fall under the umbrella of hospice care delivery.

The Medicare hospice benefit requires that patients have a life expectancy of 6 months or less. An unfortunate but common misconception is that palliative care and hospice care are equivalent. This leads to missed opportunities for palliative care involvement in patients with a prognosis of more than 6 months, as well as late referrals to hospice care until providers are confident the patient is dying. This has translated to a median length of stay in a hospice organization of 22 days, of which 35% of patients die in the first 7 days. The extent of comprehensive palliative care delivered by hospice organizations also varies, with larger hospice organizations having the ability to provide more intensive services such as 24-hour physician staffing, ethics committees, and regularly using standardized assessment tools for pain and symptom management.

As discussed previously, the diseases affecting older adults are largely chronic in nature, with fluctuating trajectories marked by acute exacerbations and difficulties in prognostication. To avoid the continued pattern of late referrals of older adults to hospice until they are in an advanced terminal state efforts will need to be shifted upstream, with increased emphasis on improved palliative care delivery across care settings, and increased communication between palliative care teams with community hospice organizations. Access and utilization of hospice care by older adults will improve by expanding coverage of hospice services to patients with longer life expectancies and eliminating the need for patients to choose between hospice services and other home-care or institutional-level services. By reconceptualizing the framework by which hospice care is delivered, patients may be able to benefit from the supportive and holistic care provided by hospice agencies for longer periods of time.

CONCLUSION

The field of palliative care has enjoyed significant advancements over the years. Its rapid growth is evidenced by an increased number of physicians choosing to train in the field and the increased availability of palliative care teams in a variety of care settings. The more widespread implementation of palliative care has led to improved quality of life and symptom management for patients; improved satisfaction among patients, families, and health care providers; and, decreased health care costs. However, the presence of adequate palliative care for older adults has lagged behind. Older adults have unique palliative care needs that are best met by providing longitudinal palliative care across the care continuum. Upstream implementation of palliative care at the time of diagnosis of advanced or serious illness will help older adults reside longer in their communities, maintain their level of function, cope with care transitions, and participate in shared decision making regarding their treatment preferences. The health care system will also need to change in order to train providers in primary palliative care skills, expand access to secondary and tertiary palliative care particularly in the community, and increase coordination of care among institutions and community organizations. Addressing these gaps in the current palliative care models will improve the quality of palliative care delivered to older adults across the care continuum.

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Chapter 60

Spiritual Care

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Learning Objectives

- Describe characteristics of spirituality in old age.
- Review approaches to spiritual screening, assessment, and treatment/care planning.
- Identify tested spiritual care interventions.
- Address ethical considerations in spiritual care.

Key Clinical Points

1. **Spirituality is an important coping strategy for the older adult population who experience age-related losses, disabilities, physical illnesses, and mortality confronted in old age and is associated with a number of positive outcomes.**
2. **Spiritual screening or history should be a routine part of a comprehensive clinical assessment and can identify spiritual distress and spiritual resources of strength and integrate these into the whole person assessment and treatment or care plan.**
3. **Generalist spiritual care is the responsibility of all members of the clinical team; the team should also include referral to and collaboration with specialist spiritual care professionals.**
4. **Studies suggest benefits of spiritual interventions such as spiritual reminiscence and dignity therapy.**

OVERVIEW

Aging and dying are integral and normal parts of living. In today's society, however, dying and aging are still treated as an illness or something to be avoided at all costs. While there have been remarkable improvements in the care of chronically ill and dying patients, there is still much that needs to be done to ensure that all people can have the opportunity to be treated with dignity and respect. As people age there are challenges of chronic conditions and illnesses. For health systems that value fast-paced, shorter visits, the older adult may not get the full attention needed to address all their concerns. Further complicating this is the increased complexity of health care systems. Lengths of hospital stays are shorter than in the past and communities are ill equipped to deal with people with chronic illness and multiple health concerns. With this focus on disease and cure there is little emphasis on dignity and the value of lived life at all stages of life. The full stories of patients are being lost in an increasingly physically focused health system.

Thus, as people age and deal with severe illness and face dying, they often feel less of a person than when they were younger and healthier. All too often people die in hospitals or nursing homes, alone and burdened with unnecessary treatment; treatment they would have refused if they had the chance to talk about their choices with their clinicians long before their end of life. Older adults and those with serious, life-threatening illnesses are often not listened to. Their wishes, their dreams, their fears may go unheeded. This can lead to intense suffering—psychosocial and spiritual as well as physical. Yet in a complicated health system, the patient who suffers often has no one that can listen to his or her despair, grief, and isolation. There may be no one to give voice to their inner pain and sense of

purposeless and disconnection from life and others.

Spirituality and health focuses on the inner life of people and how they find meaning, purpose, and connectedness to the significant or sacred. Spirituality is a fundamental element of human experience. It encompasses the individual's search for meaning and purpose in life and the experience of the transcendent. Spirituality also encompasses the connections one makes with others, his or herself, nature, and to the sacred realms, inside as well as outside of traditional religion. Viewed in this way, spirituality can be a key factor in how people cope with illness, experience healing, and achieve a sense of coherence.

There is a significant body of literature that highlights the role of spirituality in aging. As we age, spirituality—broadly defined as a search for ultimate meaning and purpose and the experience of connection to the transcendent, to others, to nature, and to the significant or sacred—plays a more dominant role in our lives than when we were younger. As the finitude of life on earth becomes more obvious as we age, the questions about meaning, purpose, and connection become more critical for us. The diagnosis of chronic or life-threatening illness can lead to spiritual struggles for patients. The turmoil may be short for some patients and protracted for others as individuals attempt to integrate the reality of their diagnosis with their spiritual beliefs. The journey may result in growth and transformation for some people and in distress and despair for others, and in both for many people. In a recent study of 203 older patients, 65.0% reported some spiritual distress and 22.2% reported at least one severe unmet spiritual need. Spiritual distress is associated with depression, poor health outcomes, poorer recovery of independence of activities of daily living (ADLs), and increased mortality in older patients.

Over the last 25 years guidelines have been developed in multidisciplinary spiritual care with spiritual care being defined as "That care which recognizes and responds to the needs of the human spirit when faced with trauma, ill health, or sadness, and can include the need for meaning, for self-worth, to express oneself, for faith support, perhaps for rites or prayer or sacrament, or simply for the sensitive listener. Spiritual care begins with encouraging human contact in compassionate relationship, and moves in whatever direction need requires." Preeminent consensus panels, including the National Quality Forum (2006) and the National Consensus Project for Quality Palliative Care (2009) include spiritual care as one of eight clinical practice guidelines in palliative care settings.

The multidisciplinary spiritual care model described in a consensus conference in the United States entitled "Improving the Spiritual Domain of Quality Palliative Care" is framed in the biopsychosocial and spiritual context as whole person care. Spiritual care is an essential domain of palliative care and has two parts: assessment and treatment of spiritual distress. The provision of spiritual care is dignity based and focuses on addressing the full story of all patients—body, mind, and spirit. It is about providing compassionate care to people in their suffering as well as in their joy.

SPIRITUALITY IN GERIATRICS

As people age, spiritual perspectives become more important in their lives than to younger adults. In a longitudinal study, Wink et al. tracked two cohorts of people who were born in the late 1920s and 1930s and tracked them through childhood and adolescence and then conducted four in-depth semistructured interviews through adulthood. Final interviews with 154 older people showed a significant increase in spirituality from late-middle to older adulthood.

Spirituality is an important coping strategy for the older adult population who experience age-related losses, disabilities, physical illnesses, and mortality confronted in old age. Spirituality may bring a sense of connectedness to self, others, and the significant or sacred; promote positive relationships with other people; and improve psychological well-being. In a cross-sectional study of medically ill hospitalized older adults, religiousness and spirituality significantly predicted greater social support, better cognitive function, fewer depressive symptoms, and greater cooperativeness.

Spirituality is also important in family caregivers. Studies have shown that caregivers of patient with Alzheimer dementia who have a strong spirituality tend to have improved coping skills, greater ability to deal with stress, and an increased sense of coherence.

In another study of 277 geriatric outpatients, Daaleman et al. found that, spirituality, but not religiosity, was an important predictor of self-appraised good health, after adjusting for age, race, quality of life, physical functioning, and depression. Soo You et al. examined the relationship between spirituality and depression among 152 older adults living alone in communities in Korea. The results of their study showed that spiritual activities and spiritual well-being scores were significantly associated with a higher level of general health and lower level of depression, but there were no relationships between the variables of attendance and importance of religion with general health and depression.

Singh et al. also reported that higher spiritual well-being among medically ill older patients in India was associated with lower rates of depression.

A qualitative study of women aged 80 and older, showed that spirituality was an important source of hope and comfort that helped them promote and maintain resilience in later life. On the other hand, higher levels of religious struggle (eg, questioning God's love) in older adults were associated with higher mortality. Possible explanations for the religious struggle–mortality connection include poor physical health (eg, number of medical diagnoses, impairments in activities of daily life, self-rated health), social alienation, and emotional distress.

In another study, Fry examined the relative influence of specific dimensions of religiosity, spirituality, and personal meaning in life as predictors of well-being in samples of community residing and institutionalized older adults. He found that existential measures of personal meaning, and spirituality were significant predictors of well-being after adjustment for demographic variables or other traditional measures such as social resources, physical health, or negative life events. In a sample of 65 Korean older people, Moon et al. found that religiosity and spirituality had significant effects on depression and quality of life especially among Protestants and Catholics. An 18-month follow-up study of 231 older adults following spousal loss showed that spiritual health efficacy was a strong predictor of quality of life and life satisfaction for men and associated with self-esteem in both men and women who had lost their spouse. In another study, Kirby et al. interviewed 233 British older people and found that spirituality acted as a significant predictor of total physical well-being and moderated the negative effect of frailty on physical well-being.

The Spiritual Stage of Older Age

Many believe that spiritual growth is a part of aging because there is a "motivational and emotional quest for meaning." On the other hand, psychological mechanisms, such as cognitive changes, socioemotional selectivity theory, and increase in introspection in older adulthood, are proposed to describe spiritual developmental changes in later life. Gerotranscendence is a relatively new term, used to describe the developmental spiritual stage associated with older age. Tornstam developed the gerotranscendence theory as a positive development toward a transcendent outlook on life "a shift in metaperspective, from a materialistic and rational vision to a more cosmic and transcendent one, normally followed by an increase in life satisfaction."

In this stage, people begin to detach from those parts of their life such as titles, money, the acquisition of things and even illness or debility, in favor of a more focused attention on those things that matter most, on legacy building and mentorship, on relationships, as well as a new understanding of fundamental existential issues Three dimensions of gerotranscendence have been described through empirical testing: cosmic transcendence (universe), solitude transcendence (self), and coherence transcendence (social and personal relationships) (**Table 60-1**).

TABLE 60-1 THE DIMENSIONS AND SIGNS OF GEROTRANSCENDENCE

DIMENSIONS OF GEROTRANSCENDENCE	SIGNS
The cosmic transcendence (universe)	• Time and childhood. Changes in the definition of time and the return of childhood. • Connection to earlier generations. Increasing attachment. • Life and death. A disappearing fear of death and a new comprehension of life and death. • Mystery in life. Acceptance of the mystery dimension of life. • Rejoicing. From grand events to subtle experiences; the joy of experiencing the macrocosmos through the microcosmos materializes.
The solitude transcendence (self)	• Self-confrontation. The discovery of hidden aspects of the self—both good and bad occurs. • Decrease of self-centeredness. • Development of body transcendence. Care of the body continues, but the individual is not obsessed with it. • Self-transcendence. A shift occurs from egoism to altruism. • Ego-integrity. The individual realizes that the disparate pieces of life's jigsaw puzzle form wholeness.
The coherence transcendence (social and	• Changed meaning and importance of relations. One becomes more selective and less interested in superficial relations, exhibiting an increasing need for solitude.

personal relationships)	• Role-play. An understanding of the difference between self and role takes place, sometimes with an urge to abandon roles. A new comforting understanding of the necessity of roles in life often results. • Emancipated innocence. The addition of innocence to maturity. • Modern asceticism. An understanding of the petrifying gravity of wealth and the freedom of "asceticism" develops. • Everyday wisdom. Reluctance to make simple duality categories of right from wrong is discerned and a preference for withholding judgments and advice is developed. Transcendence of the right-wrong duality ensues.

From Tornstam L. Gerotranscendence: The contemplative dimension of aging. J Aging Stud. 1997;11(2):143–154.

Spirituality is critical for nurturing several qualities of gerotranscendence and is more fundamental for development toward gerotranscendence than the natural process of aging. Data show that spiritual practices and spiritual beliefs are positively correlated to a higher comprehensiveness toward life, a higher gerotranscendence, and life satisfaction. Patients with a strong involvement with spirituality have a better quality of life and greater meaning and purpose, even in the face of terminal illness. In healthy aging, attention to the spiritual dimension can help the older person reframe what may seem like a limited phase of life to one that is expansive and full of opportunity for inner growth and for contributing to the next generations.

Nursing home and assisted living residencies for the older adults do not always support the final spiritual stage of life. Quiet, not forced activities may be what are needed. Compassionate presence and deep listening to suffering is essential for people as they deal with their suffering and existential distress. These approaches may be more meaningful than religious rituals.

Spiritual Distress of the Aging and Dying

As people face their dying some spiritual issues may become prominent in the older person or the dying patient. These are considered sources of spiritual distress and are cited in the National Comprehensive Cancer Network guidelines for the diagnosis of spiritual or existential distress. These are listed in **Table 60-2**. This spiritual distress is often manifested as an intense suffering for the patient. It is critical that clinicians are able to diagnose spiritual distress and attempt to alleviate it. Unlike treating physical pain with medications, there are no quick or standardized solutions to the care of people's spiritual or existential suffering. But having a clinician listen to the patient as they talk about their suffering and express compassion and care is an important step in helping patients cope with their suffering. The role of the clinician is to help the patient give voice to that suffering. In externalizing the distress and talking about it, the patient often comes to a resolution on her own. In aging or in chronic illness, people can face these issues many times. There is no linear stage whereby one experiences hope and never again feels hopeless. Spiritual journeys are dynamic and fluid. Issues are revisited many times. However, over time for many, some resolution takes place. Some of the spiritual issues faced by chronically ill and dying patients are summarized in **Table 60-2**.

TABLE 60-2 SPIRITUAL CONCERNS OF AGING

SPIRITUAL ISSUES OF AGING	KEY FEATURE FROM HISTORY
Lack of meaning and purpose	Lack of meaning Concerns about afterlife Questions about the existence and meaning of suffering
Despair/hopelessness	Despair as absolute hopelessness No hope or value of life
Not being remembered	Separated from community No sense of relatedness
Guilt/shame	Feeling that one has done something wrong or evil Feeling the one is bad or evil
Anger at God/others	Displace anger toward religious representatives or others Inability to forgive

Abandonment by God/others	Lack of love, loneliness
Feeling out of control	Deep sense of lack of control over physical and mental function
Spiritual or existential suffering	Loss of faith or meaning
Reconciliation	Need for forgiveness or reconciliation from self or others
Grief/loss	The feeling and process associated with the loss of person, health, relationship

SPIRITUALITY IN GERIATRICS CARE

A convincing body of evidence has emerged demonstrating that spirituality is an integral element of geriatrics care that is associated with patient's quality of life, satisfaction of care, more hospice use, less aggressive care at end of life, and decreased medical costs. Spiritual care involves serving the whole person, addresses questions of identity, meaning, and purpose, affirms the inherent dignity and value of all persons, and respects different spiritual perspectives and practices—that may or may not be expressed in religious terms.

While referrals to chaplains are the most prevalent form of spiritual care in the literature, it is particularly important to involve all health care providers (eg, physicians, nurses, social workers) in generalist spiritual care—that is, the practice of compassionate care and the integration of spirituality in their routine medical care practice. In clinical care chaplains are the spiritual care specialists and other clinicians are the spiritual care generalists. Generalist spiritual care involves empathy, compassion, respect, sensitivity, and comfort. Spiritual care also fosters trusting, intimate, and meaningful relationships. Out of these relationships with their clinicians, patients may be able to find meaning, hope, and resilience in the middle of suffering.

Young suggested three general guidelines for generalist spiritual care in hospitalized older patients. These include (1) listening actively to what a hospitalized patient is saying (both verbally and nonverbally), (2) identifying his or her religious or spiritual concerns, and (3) responding to those concerns either directly or by referral. The first step in communicating about spiritual issues is to listen to spiritual themes such as meaning, hope, relationships, religious beliefs, and values. As health care provider actively listens to an older patient, it will be possible to know the patient's full story and to recognize the spiritual concerns of the patient. Inherent to this aspect of spiritual care is the practice of compassionate presence, which can be characterized as being fully present with another as a witness to the patient's suffering. The experience of compassionate presence by the clinician to the patient may result in a sense of healing by the patient within the context of the relationship with the clinician. Once the health care provider hears the spiritual themes of the patients, they can start asking open-ended questions to invite the patient to share their inner story. The clinician can listen for how important the patient's spirituality is in their lives and whether the patient's spirituality impacts his/her health.

Important components in the implementation of spiritual care in geriatrics care include a spiritual screening and history for the nonchaplain clinicians and a full spiritual assessment by a board certified chaplain.

Spiritual Screening

Spiritual screening usually is performed at the time of an initial intake by any clinician, whether it is at an inpatient, nursing facility, or even during admission into home hospice. The primary objectives of the spiritual screen are as follows:

- Assess for spiritual emergencies
- Identify patients who may benefit from an in-depth spiritual assessment

Spiritual screening need not be an overly complicated task and may necessitate only a few simple questions incorporated into initial screening. For example, "How important is religion and spirituality in your coping?"

If patient responds that they are important, then a follow-up question could be, "How well are those resources working for you at this time?"

If the patient describes difficulty with coping and/or that spiritual or religious resources are not working well for him or her, a referral to a trained chaplain is advised.

Spiritual History

As with other components of the medical history, a spiritual history is important for clinicians to take, especially during the initial consultation. The goal is to better understand how a patient's spiritual needs and resources may complement or complicate the patient's overall care. A spiritual history typically is asked in the context of a comprehensive social history. Targeted questions are employed to invite the patient to share his or her spiritual and/or religious beliefs, and help guide the patient to explore questions of meaning. The questions are not meant as checklists, but as guides to help the clinician invite the patient to share his or her beliefs, hopes, fears, and concerns. Ultimately, for clinicians, the spiritual history can serve the following goals:

- To better understand the patient's beliefs and values
- To identify spiritual themes and assess for spiritual distress (meaninglessness, hopelessness) and spiritual resources of strength (hope, meaning and purpose, resiliency, spiritual community)
- To connect with the patient in a deeper and more profound way
- To empower the patient to find inner resources of healing and acceptance
- To identify spiritual and religious beliefs that might affect health care decision making

Finally, the spiritual history serves as a primary opportunity to identify patients who may benefit from referral to chaplains or other resources. An example of a spiritual history is the FICA spiritual history tool, which was initially developed by a focus group of primary care physicians. It is validated, widely used, and integrated into some medical health records. The format of the tool is presented in **Table 60-3**.

TABLE 60-3 THE FICA SPIRITUAL HISTORY TOOL

F—Faith and belief	• Do you consider yourself spiritual or religious? • Do you have spiritual beliefs that help you cope with stress? • If the patient responds "No," the clinician might ask, "What gives your life meaning?" *Sometimes patients respond with answers such as family, career, or nature.*
I—Importance	• What importance does your faith or belief have in your life? • Have your beliefs influenced how you take care of yourself in this illness? • What role do your beliefs play in regaining your health?
C—Community	• Are you part of a spiritual or religious community? • Is this of support to you and how? • Is there a group of people you really love or who are important to you? *Communities such as churches, temples, and mosques, or a group of like-minded friends, can serve as strong support systems for some patients.*
A—Address in care/assessment	• How would you like me, your health care provider, to address these issues in your health care? • Use this category to assess for spiritual distress

Spiritual Assessment

For patients who the clinician feels would benefit from a more in-depth conversation with a chaplain, referral for a more formal spiritual assessment is advised. The spiritual assessment is an in-depth, extensive, ongoing conversation and can be performed with patients from any religious or spiritual tradition and belief system. The primary objectives are the following:

- Develop a relationship with the patient in a clinical setting
- Identify spiritual issues and confirm, elaborate, or make a spiritual diagnosis
- Develop a spiritual care plan that can be shared with the treatment team

The aim is to understand the patient's needs and resources by first listening to the patient's story. There is no specified set of questions. That is, the assessment strategy is a process without a defined script, which is necessary because the content area itself is not amenable to a formulaic structure. As a result, it requires extensive training,

which is part of the certification process for professional chaplains.

Multidisciplinary Collaboration

As with other aspects of geriatrics care, multidisciplinary collaboration is important when it comes to addressing spirituality. All members of the multidisciplinary team interact with patients, including responding to and addressing all dimensions of patient care: spiritual, religious, and existential as well as the physical, psychological, and social. Each of these components of care provides insight into the patient's suffering and his or her ability to manage that suffering. Teams occur in inpatient as well as outpatient clinical setting and in communities such as neighborhood community support settings, nursing home, continuum of care facilities, and senior communities.

Chaplains can advise other members of the clinical team on how to work with patients' spiritual issues, provide spiritual counseling, and contribute to a comprehensive treatment or care plan. Chaplains also can coordinate the involvement of community spiritual care professionals (eg, other clergy, pastoral counselors, or spiritual directors). The role of chaplains is supported by many organizations including Joint Commission for Accreditation of Hospitals, Center to Improve Palliative Care, and others.

Treatment

Once spiritual distress or issues are identified, they need to be addressed as part of the assessment and treatment plan. Clinicians can also document the patient's spiritual and psychosocial resources of strength and note those in the assessment and plan. This plan should be based on the biopsychosocial and spiritual model of care, or what many have called "whole person care." An example of such a plan is presented next. Ms. Brenda Lee is 86 years old, has four children, eight grandchildren, and she is a widow. Ms. Lee has been admitted to a skilled rehabilitation facility following a below-the-knee amputation (BKA) secondary to long-standing diabetes. She also has a history of breast cancer, which is in remission. She has done well with surgery but has been resistant at times to physical therapy in the hospital. Prior to admission she was not regularly adherent to her medication. She denies depression but says she now fears that she will be a burden to her family. She wonders if God is punishing her for something she did and that is why all of this is happening to her (**Table 60-4**).

TABLE 60-4 WHOLE PERSON ASSESSMENT AND TREATMENT PLAN

	Ms. Brenda Lee is an 86 y old s/p BKA, recovering well from surgery, insulin-dependent diabetes well controlled in hospital, last HbA_{1c} 7.0, h/o breast cancer, in remission for 8 y. Has been resistant to physical therapy at times, has h/o of noncompliance with medication, also describes fear of being a burden to her family and expresses some distress about being punished by God.
Physical	Rehabilitation, encourage adherence to physical therapy. Continue with Lantus, regular glucose monitoring in the rehab, adherence to diet.
Emotional	Referral to counselor for support therapy regarding feeling like she is a burden.
Social	Referral to social work for discharge planning, family meeting. Patient has strong family support.
Spiritual	Explore perception of illness as punishment; chaplain referral, explore punishment concept and adherence. Patient has strong spiritual practice that has helped her in the past during difficult times.

Her spiritual history using the FICA tool is summarized as below:

- F: Nondenominational Christian; her children and God give her meaning
- I: Very important in her life, prays daily, attends bible study and Sunday services; believes illness is punishment from God
- C: Active in church
- A: Referral to pastoral chaplain in rehab and connect her with her pastor and outpatient pastoral counseling

Referral to chaplain and spiritual director for a life review and further explorations of reconciliation, regret, and loss of previous state of functioning, which may be resulting in some meaning issues for her. She has spiritual

strengths that help her be at peace. This plan shows how important it is to address all dimensions of the patient's care. Spiritual suffering can significantly impact patient's and family's quality of life and is therefore a critical aspect of good medical care delivery.

Examples of Spiritual Care Interventions for Older Adults

The first part of the treatment plan for any patient is what all clinicians can do. This includes compassionate presence and deep listening to the patient's concern and witnessing to the suffering of the patient. There are several tested interventions that are based on meaning making and life review. Some activities to support these types of spiritual interventions are explored below.

Spiritual reminiscence Spiritual reminiscence developed by MacKinlay and Trevitt is a "particular way of communication that acknowledges the importance of spirituality and seeks to engage the person in a more meaningful and personal way." Talking about previous life events with emphasis on meaning, gives older people a chance to reframe some of these events and come to a new understanding of the meaning and purpose of their lives. In a recent randomized controlled trial, Wu et al. assessed the efficacy of a 6-week spiritual reminiscence on older patients with mild or moderate dementia. Results showed that the intervention group showed significant improvement in hope, life satisfaction, and spiritual well-being. In another study of 113 older adults with dementia, small groups met weekly over 6 weeks or 6 months for spiritual reminiscence. Qualitative and quantitative analysis showed that life story with an emphasis on meaning and spirituality helped participants to find meaning in life in the present, develop stronger relationships between staff and residents, and develop strategies to accept changes of later life, including losses of significant relationships and increasing disability.

Dignity therapy As people age, their sense of dignity can be threatened by illness and care need. Loss of dignity in older people is associated with high levels of psychological and spiritual distress and loss of the will to live. Chochinov proposed dignity therapy (DT), as a brief individualized psychotherapy, designed to address psychosocial and existential distress among patients. The intervention uses 10 core questions that guide an interview, including "What are your most important accomplishments, and what do you feel most proud of? What are your hopes and dreams for your loved ones? What have you learned about life that you would want to pass along to others?" Dignity therapy was designed primarily for the terminally ill patients. Recent studies by Chochinov and other investigators confirmed the feasibility and effectiveness of this intervention for older people in care homes as well. A recent systematic review study found robust evidence for DT's acceptability, especially in psychosocial-spiritual care.

Worship/prayer Prayer is the most universally recognized spiritual/religious practice. According to Gallup surveys in 2010, more than half (55%) of Americans pray every day. Wachholtz and Sambamthoori found that the use of prayer to address health concerns significantly increased from 43% in 2002 to 49% in 2007 in the United States. Prayer has been classified as a spiritual treatment modality by the National Center for Complementary and Integrative Health (NCCIH). In a 6-year follow-up study with almost 4000 older individuals, Helm et al. looked at how the frequency of private religious activities affected overall survival. After dividing the groups into those with impaired versus unimpaired ADLs, they found a protective effect of religious activities on the survival of those with good ADLs. Other prayer-based intervention such as prayer wheel may promote psychological well-being in older adults as well.

Examples of spiritual health intervention are summarized in **Table 60-5**.

TABLE 60-5 SPIRITUAL HEALTH INTERVENTION

INTERVENTION	EXAMPLES OF EVIDENCE
Meditation, prayer	Benson H. *The Relaxation Response*. New York, NY: William Morrow & Co; 1975; Koenig HG, McCullough ME, Larson DB. *Handbook of Religion and Health*. New York, NY: Oxford University Press; 2001.
Mindfulness-based interventions (MBIs)	Kabat-Zinn J. Mindfulness-based interventions in context: past, present, and future. *Clin Psychol*. 2003;10(2):144–156.
Gratitude	Wood AM, Froh JJ, Geraghty AW. Gratitude and well-being: a review and theoretical integration. *Clin Psychol Rev*. 2010;30:890–905.
Forgiveness/reconciliation	Worthington EL Jr. *Dimensions of Forgiveness: Psychological Research and Theological Perspectives*. Philadelphia, PA: Templeton Foundation Press; 1998.

	McCullough ME, Pargament KI, Thoresen CE (eds). *Forgiveness: Theory, Research, and Practice*. New York, NY: Guilford; 2000.
Meaning-oriented therapy	Breitbart W, Heller KS. Reframing hope: meaning-centered care for patients near the end of life. *J Palliative Med*. 2003;6:979–988.
Dignity therapy	Chochinov HM, Hack T, Hassard T, Kristjanson LJ, McClement S, Harlos M. Dignity therapy: a novel psychotherapeutic intervention for patients near the end of life. *J Clin Oncol*. 2005;23:5520–5525.
Organized religious activities	Hewson P, Rowold J, Sichler C, Walter W. Are healing ceremonies useful for enhancing quality of life? *J Altern Complement Med*. 2014;20(9):713–717. Hewson PD, Rowold J. Do spiritual ceremonies affect participants' quality of life? *Complement Ther Clin Pract*. 2012;18(3):177–181.

ETHICAL CONSIDERATIONS

The ethical principles that guide health care providers—such as beneficence, respect for individual dignity, the relief of suffering, respect for patient autonomy—obligate the clinician to understand the individual values and goals of patients as much as possible.

The process of formulating advance care planning with patients and their families and designated surrogates similarly requires a deep appreciation of that person's value system. Assisting patients to fashion their own individualized advance directive when confronting a terrible diagnosis or in anticipation of severe illness or gradual decline is a conversation, which cannot occur without an exploration of the patient's spiritual value system.

Virtue Ethics, Personal Beliefs of Clinicians, and Respect for Boundaries

In the United States more than half of patients over 65 years attend church regularly, and the rate of belief in God is much higher among patients than among their health care providers. Still, a considerable majority of United States' physicians say in surveys that they do believe in God.

Many religious persons believe that their illness is somehow connected to their spirituality, while almost all physicians have a more scientific or materialistic view of decline, disease, and dying. However, whether the clinician considers herself "religious" or not religious, she needs to separate her own beliefs from those of patients and their families. The secular or atheistic clinician cannot ignore the important influence that spiritual or religious beliefs may have on many of her patients. Religious traditions differ in their weighing of life-extending treatments, and the religious clinician cannot impose his beliefs on the treatment choices of his patients.

An essential attribute of the virtuous clinician is the doctor's ability to separate out personal preferences or biases from scientific or evidence-based knowledge. Self-awareness mitigates the awful "healer's power" of physicians and other health care providers to impose their will on patients who might opt for less invasive or less stringent treatments. At times the belief systems of clinicians may result in the application of treatments, or the withholding of treatments, that do not cohere with the spiritual beliefs of their patients. For example, some clinicians may undertreat pain in fear of hastening death, or may apply life-extending technologies such as ventilators despite prognostic futility. The clinician who is aware of his or her own biases should respect that patient choices should follow patient values and should not impose personal religious beliefs when treatments are optional or controversial. If the patient's belief system is strong, the clinician may need to defer to the competent choice of the patient. An extreme example of this is in the case of persons who profess the Jehovah's Witness faith; it is well recognized that surgeons should respect their objection to the transfusion of blood and physicians who cannot accept this therapeutic limitation should not agree, in elective situations, to take on the responsibility of a Jehovah's Witness as a patient.

Prayer Ethicists agree that a clinician should not impose his or her spiritual beliefs on his patients. A clinician should not routinely offer to pray with his patients; such an invitation or offer could be viewed as coercive. If a patient invites the clinician to pray with her, how should the clinician respond? In that case, the clinician could suggest that someone else, preferably a chaplain, should lead the prayer, which allows the clinician, whether secular or religious, to participate by remaining with the patient in respectful silence and prevents any appearance that the clinician is imposing his beliefs on the patient and their family. If the clinician is comfortable with being part of the patient's prayer, the clinician could suggest that the patient pray and the clinician can then witness that prayer and participate to

the degree the clinician is comfortable without imposing the clinician's own beliefs in that encounter. Again, the emphasis should always be on the spiritual values and the healing of the individual patient.

CONCLUSION

Our health care system needs to treat spirituality as essential to the care of all people. Thus, the spiritual experience is just as important as the physical experience of illness, aging, and dying. Fundamental to spiritual care is the relationship-centered care that all health care professionals engage in. At the root of this care is the deep and profound respect we show to each other and to our patients. That respect transcends the admiration of people's stature or accomplishments. Mohamad Reaz Abdullah writes that genuine respect for another is when the "divinity in the individual that is common to all beings is respected, then the meaning of respect is taken on golden wings to a new height."

People, regardless of age, want to be treated with respect, want to be really listened to, and want to be involved in their care. This is even more important in the geriatric population. As people age, they are challenged with more health issues, greater personal losses, and for many, an increased need to be dependent on others. Hearing or vision impairment or other medical conditions, such as cognitive impairment, can lead to difficulty in understanding. Respecting older patients means taking the time to be fully present and assuring them that we are listening to their whole story—not just the biomedical one. It includes a careful spiritual history and attention to spiritual interventions, when appropriate.

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Chapter 61

Ethics

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Learning Objectives

- Discuss the steps in the CASES approach and how it is used to address ethical dilemmas.
- Define moral distress and identify risk factors for developing it.
- Explain the steps in the SPIKES approach to breaking bad news.
- Review the pros and cons of advance care planning (ACP), advance care directives, POLST forms, and goals-of-care discussions.
- Understand the need for surrogate decision making to ensure appropriate care of many older adults.
- Explore the concepts of substituted judgment versus best interest.
- Recognize how an incapacitated patient's legal decision maker is identified.
- Gain insight into the experience of surrogate decision makers and potential for surrogate distress after making difficult medical decisions.
- Describe the indications for palliative sedation.
- Recognize the barriers to cessation of driving.
- Discuss examples of ethical dilemmas that arise in nursing homes when the desire to maintain quality-of-care indicators is in conflict with promoting patient preferences and quality end-of-life care.

Key Clinical Points

1. **Health care professionals who work with older patients may encounter ethical dilemmas which arise out of conflicts in values about the right thing to do.**
2. **Patients with decisional capacity have the right to make decisions that their medical teams and families don't agree with.**
3. **Moral distress is a condition in which clinicians feel forced to provide care they believe is wrong, which can lead to burnout and to them leaving their jobs and professions.**
4. **The majority of people want to be told if they have dementia.**
5. **By participating in ACP and completing advance directives, people can identify preferred surrogate decision makers, and provide guidance to those decision makers about their goals and care preferences for future care if they lose decisional capacity.**
6. **Making medical decisions for loved ones can be very stressful for surrogate decision makers and even lead to posttraumatic stress disorder.**
7. **Most states and the Veterans Administration (VA) have laws designating a legal hierarchy of surrogates.**
8. **Through a process of shared decision making, patients or their surrogates share information about their goals and care preferences with clinicians, and their clinicians share pertinent medical information and make care recommendations based on the patient's values and goals.**

9. **Palliative sedation is a legal intervention of last resort to promote relief of intractable suffering for terminally ill patients who have comfort as their primary goal of care.**
10. **Physician aid in dying (PAD), also called physician-assisted suicide, is legal in some US states and countries. Euthanasia is not legal in the United States, but is legal in Belgium and the Netherlands.**
11. **Patients may raise the topic of PAD as a way to begin a conversation about the end of life. Clinicians should view this as an opportunity to talk about sources of intractable suffering and fears about dying regardless of whether or not they live in a state where the practice is legal.**
12. **Questions about whether or not to report concerns about an older individual's driving are answered by weighing the clinician's duty to protect the patient's safety, with the duty to maintain confidentiality, and the duty to protect the public. Some US states have mandatory reporting requirements.**
13. **Ethical issues prevalent in nursing homes include not only those in which the patient's and family's care goals are in conflict, but also those in which regulations are in conflict with quality end-of-life care.**

INTRODUCTION

Health care professionals who work with older patients in diverse settings such as patients' homes, assisted living facilities, skilled nursing facilities, outpatient clinics, and hospitals may encounter ethical dilemmas in their work. Ethical dilemmas pertinent to older patients may include questions about the balance of patient privacy versus patient safety, patients' abilities to make their own medical decisions, decisions about preferred treatments at the end of life, and decisions made by surrogate decision makers.

In this chapter, we will discuss a framework for thinking about ethical dilemmas, and provide an overview of the ethics topics especially relevant to the care of older adults. Sections include an approach to thinking about ethical dilemmas, moral distress in professional caregivers, breaking bad news, advance care planning (ACP), surrogate decision making, end-of-life decisions, ethical issues in driving, and ethical challenges in the nursing home setting.

AN APPROACH TO THINKING ABOUT ETHICAL DILEMMAS

Case

Mrs. C is an 88-year-old woman with congestive heart failure, hypertension, atrial fibrillation, and chronic kidney disease. She lives alone in her own home. She was hospitalized last month for delirium secondary to a urinary tract infection. She is admitted again this month after a fall. While in the hospital, she is evaluated by physical therapy and occupational therapy who both recommend a short stay in a nursing home for rehabilitation. Mrs. C refuses to go to a nursing home and demands to return to her home. Her medical team insists that going directly home is not a safe discharge plan, and wants to require her to go to rehabilitation.

Question: What is the ethically appropriate discharge for Mrs. C?

Health care professionals working with older patients may encounter ethical dilemmas, regardless of their discipline or work setting. Ethical dilemmas usually stem from a conflict in values between stakeholders. For example, an older patient with multiple comorbidities, who values being alive regardless of his condition, may disagree with his physician about the best way to manage his advanced kidney disease. To add complexity, older adults are a heterogeneous group with diverse values, preferences, and goals that may or may not be influenced by their race, ethnicity, or religious backgrounds. In terms of their beliefs about end-of-life care, for example, older patients have more heterogeneous views than their clinicians. Because of this heterogeneity, clinicians should not assume that they know a patient's values and goals without engaging in a conversation with the patient.

Ethical dilemmas may be distressing to health care professionals. Although health care professionals learned about ethics in their training, many are not familiar with a standard approach to thinking about and responding to ethical

dilemmas. Without knowledge of such an approach, ethical dilemmas encountered may lead to moral distress and burnout. Familiarity with a framework and using a standard approach to thinking about ethical dilemmas may help health care professionals to find ways to resolve them, while honoring patient preferences, and reducing their own stress.

Different frameworks for approaching ethical dilemmas exist. One approach is the four-box method from Jonsen et al., in which important information about the patient's medical condition, preferences, quality of life, and other contextual features of the case, is collected. Another is the CASES approach to ethical dilemmas which has been developed and is used by ethics consultants throughout the VA health care system (**Table 61-1**). Although this approach was developed for use by ethics consultants, the approach also can be applied by others who are trying to better understand ethical dilemmas. Since the second step of the CASES approach is similar to the four-box method, let us apply the CASES approach to the case of Mrs. C above.

TABLE 61-1 THE CASES APPROACH

1. **C**—Clarify
   a. Does this case involve an ethics concern about the right thing to do?
   b. What is the conflict in values that is leading to the concern?
      i. Values are defined as strongly held beliefs, ideals, principles, or standards that inform ethical decisions or actions.
2. **A**—Assemble the relevant information
   a. What type of information is needed?
      i. Medical facts
      ii. Patient's preferences and interests
      iii. Other parties' preferences and interests
      iv. Ethics knowledge
         1. Codes of ethics, ethics guidelines, and consensus statements
         2. Published literature
         3. Precedent cases
         4. Institutional policy and documents, and law
         5. Outside ethics experts
   b. Which stakeholders need to be interviewed?
3. **S**—Synthesize the information
   a. Analyze the information
      i. Review the range of ethically justifiable options
      ii. Weigh the different potential outcomes and the impact of these outcomes on the stakeholders
4. **E**—Explain the synthesis
   a. Communicate the ethically justifiable options to the key stakeholders
5. **S**—Support the consultation process
   a. Follow up with stakeholders

Adapted from Berkowitz KA, Chanko BL, Foglia MB, et al. Ethics consultation: Responding to ethics questions in health care. 2nd ed. http://www.ethics.va.gov/docs/integratedethics/ec_primer_2nd_ed_080515.pdf. Accessed April 28, 2016.

The first step of the CASES approach is to Clarify whether the dilemma is really about ethics or something else, such as a legal issue. This is done by identifying whether there is a conflict in values between two of the involved stakeholders. To do this, the health care professional tries to understand the perspectives and values of the involved stakeholders, and identifies which values are in conflict. In the case of Mrs. C, the conflict in values is between Mrs. C, who doesn't want to go to a nursing home for rehabilitation, but wants to go home, and her medical team who believes that sending her home would be harmful to her. This dilemma also can be viewed as a conflict between ethical principles. In the case of Mrs. C, the conflict in principles is between honoring Mrs. C's autonomy/self-determination and promoting her clinicians' beneficence/nonmaleficence.

In the second step of the CASES approach, information relevant to the case is Assembled. This information includes medical information, patient preferences, other parties' preferences, and ethics knowledge. In the case of Mrs. C, we already know that she has multiple medical problems, lives alone, is in her second hospitalization, and is

staunch in her refusal to go to a nursing home for rehabilitation. Knowing her reason for refusing this would be helpful. For example, she might tell us that her husband died in a nursing home after a prolonged decline from dementia, and that she gets flashbacks and panic attacks whenever she enters a nursing home. Or, she might tell us that she needs to get home to care for her frail neighbor. We would want to hear more from Mrs. C's medical team about their concerns, and what they believe they can and cannot allow their patients to do. In thinking about this case, it also might be helpful to look at the hospital's policies around informed consent and refusal of care, and to look in the literature to see if anyone has written about this issue.

Once we have gathered the relevant information about Mrs. C's case, including the perspectives of the involved stakeholders, we would need to begin to consider the different possible options and the impacts on stakeholders of each option. In the case of Mrs. C, an important aspect of the case is whether she has decisional capacity to make the "poor" decision to return to her home or not. (Decisional capacity is discussed in Chapter 12.) In assessing her capacity, it would be important to find out if she understands the risks and benefits of going to a nursing home for rehabilitation versus going home directly.

If Mrs. C has decisional capacity to make the decision to go home, her medical team cannot force her to go to a nursing home against her will. In light of this, her team should not simply send her home, but should think about ways to promote her continued recovery and safety at home. This might include arranging for more resources in her home, such as a visiting nurse/PT/OT, Meals on Wheels, and a product she could use to quickly call for help in the future. Or it might involve brainstorming about how to get help for her frail neighbor, so she would feel more comfortable going to the nursing home for rehabilitation.

If Mrs. C does not have decisional capacity to make the decision to go home, then the medical team will need to involve her legal surrogate decision maker to help make this decision. Since some states have laws forbidding placement of individuals in nursing homes against their will, finding a solution could prove to be difficult, and might involve substantial negotiating and developing creative solutions.

When the CASES approach is used by health care professionals to understand the nuances of ethical dilemmas in their work, the last two steps of the approach are less critical than they are for ethics consultants. These last two steps are included for ethics consultants to help ensure that their recommendations are shared with those involved with the case and that appropriate follow-up occurs. However, as a health care professional uses this approach and gains a deeper understanding of a case, he/she may want to share that information with others who are involved.

ETHICAL DILEMMAS CAN LEAD TO MORAL DISTRESS IN PROFESSIONAL CAREGIVERS

Case

Mr. G is a 78-year-old skilled nursing facility resident with multiple medical problems, including mild dementia, who is admitted to the intensive care unit with pneumonia and possibly sepsis. He is intubated. Over the next 2 weeks, he develops acute respiratory distress syndrome (ARDS), *Clostridium difficile* colitis, and a pressure ulcer. His renal function is deteriorating. He remains delirious and unable to participate in medical decision making.

Mr. G's advance directive states that he wouldn't want life-prolonging measures for a terminal condition, and would want care focused on comfort. His wife, whom he designated as his health care agent through a Durable Power of Attorney for Health Care, insists that treatments with the goal of life prolongation be continued. His nurses are concerned that his prognosis is poor and his preferences aren't being honored. His physicians say he isn't "terminal" yet.

His nurses are concerned that he has pain. They note that he grimaces when they care for him. His wife refuses for him to have pain medications because of a fear that they will prevent him from waking up.

When the doctors, nurses, social workers, and the chaplain have tried to talk to Mrs. G about his goals of care or his pain management, she becomes agitated and threatens lawsuits. Team members are frustrated. There are rumors that Mrs. G is demented, in denial, revengeful, and wanting to keep him alive for his pension. Some have commented that scarce resources are being wasted in keeping him alive.

Question: In reading this case, can you sense the distress experienced by those caring for Mr. G?

Moral distress is a term that was coined by Jameton in 1984. Moral distress occurs when you are prevented from doing what you believe is right because of institutional barriers, and are forced to act contrary to your core values. In other

words, you believe you are being forced to provide care that is wrong. Although moral distress has been studied most in nursing, it has been documented in numerous health care professions, and even in health care management. Health care professionals who interact with older patients may personally experience moral distress, and also may interact with colleagues who are experiencing it.

There are numerous root causes of moral distress (**Table 61-2**). These causes may be due to clinical factors of a case, but also may be due to individual characteristics of members of the care team, or to institutional factors. Multiple members of the care team may experience moral distress about a given case, but may experience this distress from different aspects of the case.

TABLE 61-2 ROOT CAUSES OF MORAL DISTRESS

Clinical situations	
• Providing unnecessary/futile treatment	• Using resources inappropriately
• Prolonging the dying process through aggressive treatment	• Providing care that is not in the best interest of the patient
• Inadequate informed consent	• Providing inadequate pain relief
• Working with caregivers who are not as competent as care requires	• Providing false hope to patients and families
	• Hastening the dying process
• Lack of consensus regarding treatment plan	• Lack of truth-telling
• Lack of continuity of care	• Disregard for patient wishes
• Conflicting duties	
Internal constraints	
• Perceived powerlessness	• Lack of knowledge of alternative treatment plans
• Inability to identify the ethical issues	• Increased moral sensitivity
• Lack of understanding of full situation	• Lack of assertiveness
• Self-doubt	• Socialization to follow others
External constraints	
• Inadequate communication among team members	• Tolerance of disruptive and abusive behavior
• Differing inter- (eg, RN to MD) or intraprofessional (eg, RN to RN) perspectives	• Compromising care due to pressures to reduce costs
	• Hierarchies within health care system
• Inadequate staffing and increased turnover	• Lack of collegial relationships
• Lack of administrative support	• Nurses not involved in decision making
• Policies and priorities that conflict with care needs	• Compromised care due to insurance pressure or fear of litigation
• Following family wishes of patient care for fear of litigation	

From Hamric AB, Borchers CT, Epstein EG. Development and testing of an instrument to measure moral distress in healthcare professionals. Am J Bioeth Prim Res. 2012;3(2):1–9.

One theory of moral distress holds that one's level of distress does not return to baseline after experiencing an episode of moral distress, but that, with each case, one's "moral residue" increases to a new baseline. Thus over time, there is a crescendo in a clinician's moral residue. This crescendo of moral residue and "untreated" moral distress can lead to burnout, to individuals leaving their positions, and even to individuals leaving their professions. This can be psychologically costly for individuals and financially costly for institutions (**Figure 61-1**).

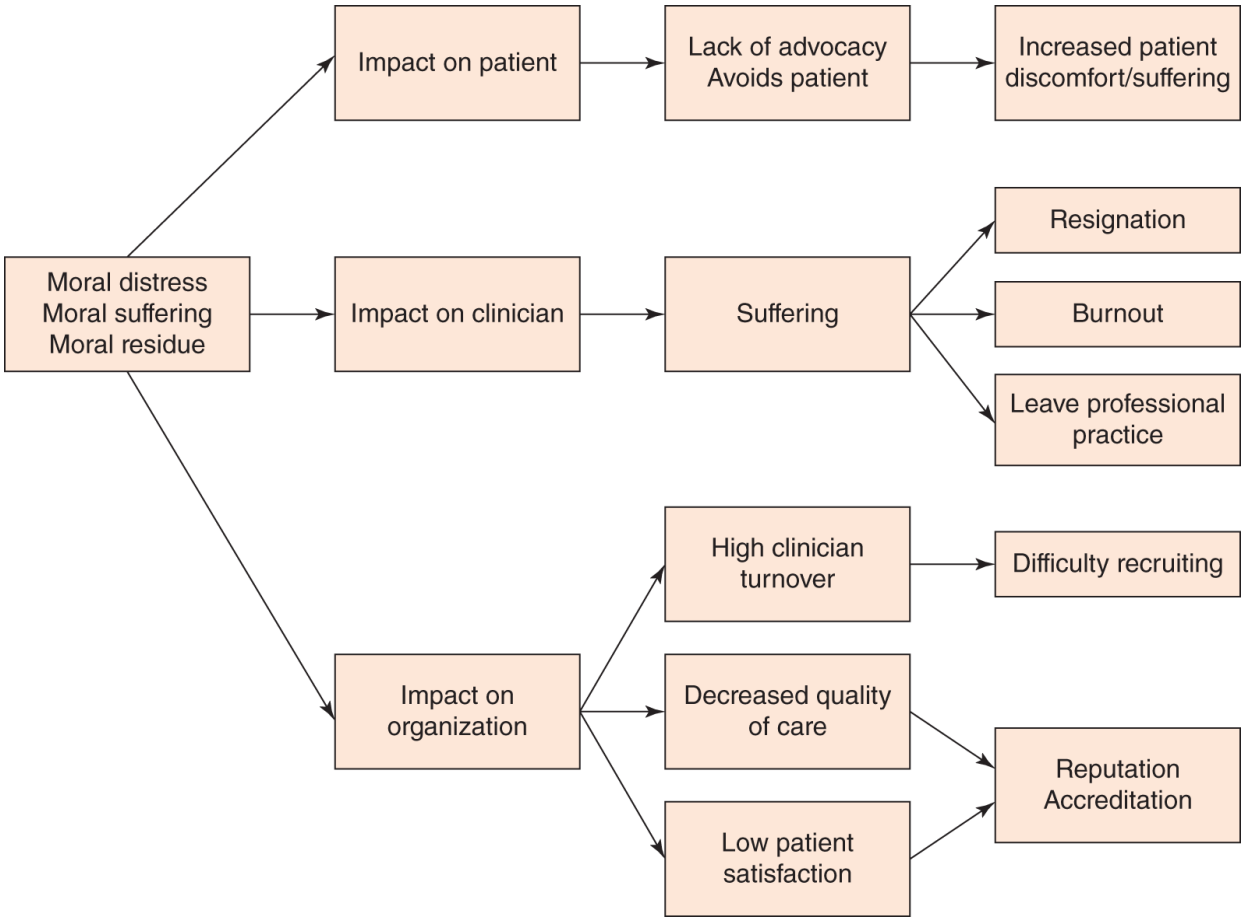


FIGURE 61-1. Impacts of moral distress on the patient, clinician, and organization. (Adapted from Corley MC. *Nurs Ethics*. 2002;9(6):636–650.)

After recognizing that a case is causing moral distress, what can health care professionals do about it? One helpful intervention is for the team to talk about the case and the aspects of the case that are giving each of them moral distress. Self-care interventions for individuals also may be helpful. Finally, if organizational factors are leading to moral distress in staff, these need to be brought to the attention of the organization's management. Helpful information about moral distress and interventions to combat it are available through the American Association of Critical Care Nurses.

TRUTHFUL DISCLOSURE

Case

Mr. W is an 83-year-old man who is brought to see his primary care provider (PCP) by his wife. She confronts the physician outside the examination room and expresses concern that her husband has become more forgetful and no longer is able to pay their bills. She remarks, "If he has Alzheimer disease, please don't tell him."

Question: What is the ethically justifiable option for the clinician after he examines Mr. W?

Not long ago, when Medicine was more paternalistic, physicians did not routinely inform patients when they had life-threatening diagnoses. The rationale for not sharing diagnoses, such as cancer, with patients was that this information would be harmful to them. Most people want to know their diagnoses, however. A recent systemic review of 23 articles with over 9000 participants found that 91% of cognitively intact people and 85% of cognitively impaired people wanted to know if they had dementia. A second study found that there were no increases in rates of depression or anxiety after people learned of a dementia diagnosis.

As Medicine has moved from being paternalistic to being patient centered, the practice of withholding information from patients to protect them has abated. In this era of patient-centered care, patients should be offered the opportunity to learn about their medical conditions. However, patients also have the right to decline to hear about their conditions.

In certain cultures, it is still standard to not share information about serious illness with patients, but with their family members. In some cultures, there is a belief that talking about bad things will make them happen. Thus if a patient doesn't want information, for any reason, giving this information without permission could be harmful.

One method advocated for use when breaking bad news is the six-step SPIKES approach. The steps of this approach are explained in **Table 61-3**.

TABLE 61-3 THE SPIKES APPROACH TO BREAKING BAD NEWS

1. **S—Setting** up the interview
   a. Find a private, quiet room with room for all participants to sit down
   b. Encourage family and involved others to participate
   c. Minimize distractions—turn off sound from pagers and phones
   d. Establish rapport with the patient with eye contact and touch
2. **P**—Assessing the patient's **Perception**
   a. What do the patient and family understand about the patient's medical condition?
   b. Correct any misperceptions
3. **I**—Obtaining the patient's **Invitation**
   a. Ask the patient and family how much information and what kind of information they want or don't want
4. **K**—Giving **Knowledge** and information to the patient
   a. Start with a statement that you're about to share bad news
   b. Share the information succinctly in lay language
   c. Allow time for the patient and family to absorb this information
5. **E**—Addressing the patient's **Emotions** with empathic responses
   a. Acknowledge and validate the patient and family's emotional response
6. **S—Strategy and Summary**
   a. Summarize the conversation and answer questions
   c. Develop a clear plan for what comes next

Adapted from Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES—-A six-step protocol for delivering bad news: application to the patient with cancer. Oncologist. 2000;5(4):302–311.

In response to the case of Mr. W, it would be appropriate to understand Mrs. W's reasons for not wanting her husband to know his diagnosis. Perhaps he has asked her on multiple occasions not to ever tell him if he develops dementia, because of a previous experience with a family member who suffered from dementia. In this case, it might be appropriate not to share this information with Mr. W. Ultimately, however, he has a right to this information, if he wants it. After hearing her reasons, we could use the SPIKES approach to talk to Mr. W. He would be asked about his understanding of his current situation and whether he would want information or not. In the case of dementia, it is appropriate to share information about the diagnosis with a patient with mild dementia who has decisional capacity to make the decision about whether or not to hear the cause of his memory loss. It might not be appropriate to repeat this information over and over to a patient with more advanced dementia, who might experience the emotional reaction to receiving this diagnosis multiple times or might not be able to fully understand what this means.

ADVANCE CARE PLANNING AND GOALS OF CARE

Case

Mrs. Y is a 69-year-old woman who was recently hospitalized after a fall, which was attributed to amyotrophic lateral sclerosis (ALS), a new diagnosis for her. She comes to her PCP, Dr. G, for follow-up. She expressed concern about her future.

Question: What is appropriate for her PCP to discuss at this visit?

Having recently received a diagnosis of ALS, Mrs. Y is understandably concerned about her future. Her physician may

want to explore her knowledge of and concerns about ALS, and engage in ACP to understand her preferred care preferences and goals of care (**Table 61-4**). Use of empathic statements by Dr. G may be helpful. A recent systemic review noted decrease in patient distress and increase in patient satisfaction when clinicians used empathic statements.

TABLE 61-4 DEFINITIONS, APPROPRIATE PATIENTS, AND RESOURCES FOR ADVANCE CARE PLANNING, ADVANCE DIRECTIVES, POLST FORMS, AND GOALS OF CARE DISCUSSIONS

	DEFINITION	APPROPRIATE PATIENT POPULATION	RESOURCES
Advance care planning (ACP)	A process in which patients think about their preferences for care in future situations, communicate their preferences to loved ones, and may document these preferences. ACP may include discussions of both general care preferences, goals of care, and preferences for care in common complications of chronic illnesses.	• Younger and/or healthy patients may want to identify a surrogate decision maker. • Older, healthy patients may want to designate a surrogate and think about their general preferences for care. • Patients with chronic illness may want to do all of the above, and also consider their care preferences for common illness scenarios related to their chronic illness. Depending on their state of residence, they also may want to complete a POLST form. • Seriously ill patients may want to consider all of the above including a POLST form and discuss their goals of care.	• www.nia.nih.gov/health/publication/advance-care-planning • www.prepareforyourcare.org • www.acpdecisions.org • www.elderguru.com/download-the-your-life-your-choices-planning-for-future-medical-decisions-workbook/ • www.theconversationproject.org
Advance directives	Documentation of care preferences which may include living wills and durable power of attorney for health care (DPOAHC). Living wills are intended to guide future care if the individual loses decisional capacity. The majority of DPOAHC documents designate a decision maker should the individual lose decisional capacity. Some documents take effect even if the individual is	• See above. • DPOHC documents are different than financial power of attorney documents.	• www.va.gov/vaforms/medical/pdf/vha-10-0137-fill.pdf • www.agingwithdignity.org/forms/5wishes.pdf

	decisional.		
POLST form, also called MOLST, MOST, POST	Physician Orders for Life-Sustaining Treatment Physician orders for care, usually including sections about resuscitation, preferred levels of care, use of antibiotics, and use of artificial feeding. Varies by state with many states not yet having programs.	• Most appropriate for older patients, seriously ill patients, and residents of facilities.	• www.POLST.org
Goals of care	Information about the patient's preferred general focus of care. It may be part of advance care planning regarding future care, or may be discussed in relation to current illness. Common goals include: • Cure • Life prolongation • Participation in a future event • Remain independent • Maintain clear thinking • Maximize comfort	• Healthy older patients may want to discuss this in the context of advance care planning. • Seriously or acutely ill patients may want to discuss this in the context of their current condition.	• Bernacki RE, Block SD; American College of Physicians High Value Care Task Force. Communication about serious illness care goals: a review and synthesis of best practices. *JAMA Intern Med*. 2014;174:1994–2003.

Dr. G may believe it is important for an ALS specialist to engage in ACP conversations with Mrs. Y. This may be true, but if she has a relationship with Dr. G and trusts him, it is appropriate for him to begin these conversations, and to readdress these issues as her condition progresses. To promote good quality of care, he should share this information with the ALS specialist.

As part of ACP, Mrs. Y first can be encouraged to identify who she would want to make medical decisions for her in the future, if she was unable to make her own decisions. She should appoint that person as her legal future decision maker through a durable power of attorney for health care (DPOAHC). She should inform her surrogate of his/her future role, give him/her a copy of the document, and explain that this only takes effect if she loses the ability to make her own decisions. (Of note, people with some cognitive impairment may be able to designate a decision maker through a DPOAHC, even if they are not able to think abstractly about their future care preferences.)

Next, Dr. G and Mrs. Y can discuss her general preferences for care, such as whether she would want life-sustaining treatments in general scenarios, such as permanent coma or terminal illness. They also may want to address her care preferences in more specific illness scenarios that occur commonly in ALS, such as dysphagia and respiratory failure. Mrs. Y, her loved ones, and her care providers also may want to use available resources to facilitate ACP (see **Table 61-4**).

ACP is a process, and will rarely be completed in one visit. Dr. G may want to continue to discuss these issues periodically, and attempt to include her designated surrogate decision maker(s), and involve others. If she does not complete an advance directive, Dr. G should document these conversations in the medical record, and share them with Mrs. Y's ALS specialist. To ensure that this documentation helps guide her future care, it should be easy to locate in the medical record.

As part of the ACP process, Mrs. Y may eventually complete an advance directive. Although the majority of living wills contain preferences for limitation of care at the end of life, some request life-prolonging care. In recent work

using Health and Retirement Study data, 72% of the older participants had completed an advance directive, with slightly more completing DPOA documents than living wills. Only 2% in this study had preferences for "all possible care" in their living wills. Similarly to other studies, more white individuals completed advance directives than nonwhite individuals.

Living wills are not perfect. First, in order for living wills to be helpful, they must be readily available when needed. Many living wills contain vague statements about forgoing life-sustaining treatments in the event of "terminal" illness. These vague statements may be difficult to interpret. Families and clinicians may not be sure when the preferences outlined in a living are applicable to a given medical situation. Although living wills may not be directly helpful to guide medical decision making, studies have shown that decision making is less stressful for surrogates when they have a sense of their loved one's preferences or have access to that loves one's directive.

Another type of document that can serve to provide information about care preferences is a Physician Orders for Life-Sustaining Treatment (POLST) form. POLST forms were originally developed in Oregon to ensure that patient's preferences were honored during transitions in care. They differ from advance directives because they are physician orders, and are honored by providers such as emergency medical personnel. Many states have adopted or are in the process of adopting POLST forms, which have different names in different states (see **Table 61-4**).

POLST forms usually contain four categories of information. People designate their resuscitation preferences in one section. In the second section, people choose between three different levels of care (comfort care, limited additional interventions, including use of IVs and hospital-level care, and full treatment, such as ICU-level care). A third section designates preferences for receiving antibiotics. The final section covers a person's preferences about artificial nutrition.

Research on POLST has provided information on the use and effectiveness of these forms. Investigators have found that these forms are more apt to be completed by older, white patients. Approximately one-third of forms request the least aggressive treatments in each section; nonwhite subjects are more apt to prefer more aggressive care. High rates of consistency between preferences on the forms and care provided at the end of life has been found.

Another important way to engage patients to think about their care preferences is to discuss their goals of care, or their preferred focus of care (see **Table 61-4**). Mrs. Y may identify that her current goal is to maintain her independence for as long as possible. She also may identify that when she reaches the end stage of ALS, she would then want her goal to shift to maximizing her comfort. Since people can change their minds and goals, it will be important to revisit her preferred goals as her disease progresses.

SURROGATE DECISION MAKING

Case

Mr. H. is an 84-year-old man with Parkinson disease diagnosed approximately 8 years ago. He has relied increasingly on his fiancée, Rose, for help, as he has become more dependent with his activities of daily living (ADLs) and instrumental ADLs (IADLs) over the last year. She has noticed that he appears slightly disoriented, often in the evenings. She notes that he has been more unsteady, and has sustained approximately three falls in the last few months (with no apparent injuries). Last evening, Rose heard a thud and found Robert on the bathroom floor, disoriented and in pain. She called 911, and he was taken to the emergency room (ER) for evaluation.

In the ER, Mr. H appeared obtunded and minimally responsive. He was found to have a moderate-sized subdural hematoma. Neurosurgery was consulted. Although Mr. H had not formally appointed a health care agent through a DPOAHC decisions, given the severity of the his condition and the urgency with which a decision needed to be made, the neurosurgery team discussed his treatment options with Rose, who was at the bedside. They explained to Rose that that they could try to surgically evacuate the hematoma, but that it would be a high-risk procedure, with a fairly low chance of benefit. They explained that options included either going ahead with the subdural evacuation attempt, or focusing on his comfort with the understanding that his prognosis was likely hours to days if this option was pursued. The neurosurgery team felt that the decision was up to Rose, as she knew him best, and asked her to let them know what she decided.

Questions:

1. **If you were part of the neurosurgery team, what else would you want to ask Rose?**
2. **What concerns do you have about this decision-making process as described?**

The physicians involved in Mr. H's case perceive that a decision regarding surgical intervention needs to be made quickly, based on Mr. H's clinical presentation and neuroimaging. It is unclear whether the physicians from the neurosurgical team or the ER team have elicited any information about Mr. H's preferences, which might be evident in an advance directives or prior conversations with Rose. It also is not clear whether Mr. H had actually appointed a legal DPOAHC or health care proxy for health care decisions. These points would need to be clarified for effective clinical decision making to take place (**Figure 61-2**).

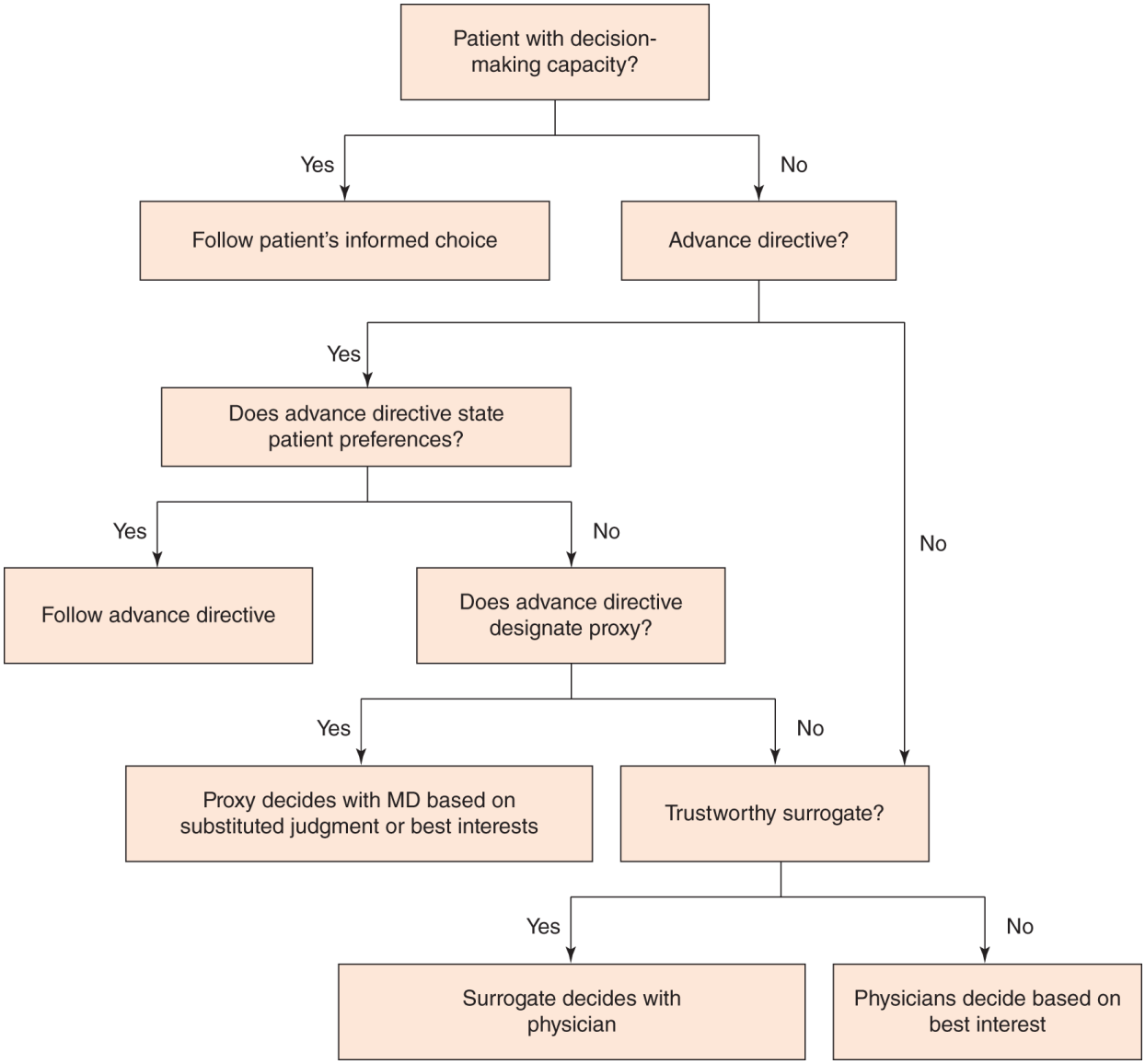


FIGURE 61-2. Approach to decision making when clinical interventions are proposed. (Adapted from Lo B. *Resolving Ethical Dilemmas: A Guide for Clinicians*. 4th ed. Baltimore, MD: Lippincott, Williams & Wilkins; 2009.)

Principles of informed consent include the notion that patients have the right to choose among medically feasible options, as well as the right to refuse unwanted interventions and treatments. The process of informed consent requires that information including the nature of the proposed intervention, along with potential benefits, risks, and longer-term consequences be discussed with the patient. Alternative interventions or treatments, including the option of not going forth with a treatment also needs to be included in the discussion. Given Mr. H's subdural hematoma and obtunded mental status, he does not possess the decisional capacity to participate in an informed consent process, rendering him unable to participate in a discussion regarding his treatment choices. Therefore, a surrogate decision maker needs to step in to make decisions under the principles of *substituted judgment* or *best interests* if one is available (further discussion below). Typically a surrogate is a person designated by the patient (eg, DPOAHC decisions), a court-appointed guardian, or a close family member if the former two designees do not exist.

We operate under the notion that the patient possesses a fundamental legal and moral right to have his or her care

preferences respected. If you were a member of the neurosurgery team, a primary concern on your part would hopefully be to further understand what Mr. H's care preferences or wishes would be, if he were able to decide for himself. Once the neurosurgery team has understood that Mr. H has not assigned a formal DPOAHC decisions, they would want to ask whether he has had conversations with Rose or other family or friends about his preferences for care if he was to become gravely ill. Oral statements to family, friends, or to physicians can serve as advance directives. Written documents such as living wills also can serve as an advance directive and reflect the patient's care preferences (see **Figure 61-2** and **Table 61-5**).

TABLE 61-5 STANDARDS FOR MAKING DECISIONS WHEN PATIENTS LACK DECISION-MAKING CAPACITY

Advance directives
Oral statements to family members or friends
Oral statements to physicians
Written documents
Substituted judgments
Best interests of the patient

From Lo B. Resolving Ethical Dilemmas: A Guide for Clinicians. 4th ed. Baltimore, MD: Lippincott, Williams & Wilkins; 2009.

Understanding any prior conversations or specific directives and knowing his overall values, hopefully Rose would be able to speak on behalf of Mr. H, as though she was relaying his explicit wishes, or "standing in his shoes." This concept illustrates the ethical principle of *substituted judgment*. When such patient preferences are known, it is expected that the patient's surrogate decision maker would operate under this principle, communicating the patient's wishes, and choosing the option that would best fit his stated care preferences.

Sometimes, the patient's preferences seem to be different or possibly in conflict with what the surrogate decision maker wants for that patient. Many surrogate decision makers are called upon to make medical decisions for loved ones under extremely stressful circumstances. Often the surrogate may find it emotionally difficult to advocate for the patient's stated wishes if the wishes are in conflict with what the surrogate would choose for the patient or him/herself. This is especially prevalent when decisions encompass such emotionally charged areas such as life-sustaining treatments and end-of-life care.

Often, the patient's explicit wishes regarding a specific clinical scenario are not known. It can be difficult to anticipate all of the different clinical scenarios and medical decisions that may need to be considered in one's future ahead of time. In Mr. H's case, he would not likely have had a specific prior conversation with Rose about a future hypothetical situation involving the development of a subdural hematoma. In this type of situation, surrogate decision makers often need to rely on the principle of *best interests*. In deciding what satisfies a person's best interests, the surrogate decision maker—ideally with guidance from the primary team of health care providers caring for the patient—is able to objectively weigh risks, potential benefits, and treatment burdens to make an individualized decision for the patient. However, when evidence of the patient's wishes does exist, making decisions by substituted judgment should take precedence so that the patient's care preferences are honored.

It is important to note that the level of stress experienced by surrogate decision makers when asked to make such a decision can be substantial, especially when left completely up to the surrogate. In Mr. H's case, it appears that the neurosurgical team is leaving the decision about whether or not to intervene surgically up to Rose. There are several problems with this approach, including the notion of having a surrogate make a medical decision unilaterally or in isolation without the medical background and knowledge to truly assess surgical risk and anticipate consequences. Rather, a shared decision-making approach would be preferable, in which the surrogate shares information about the patient's wishes, conversations, and values, and the medical team shares medical expertise. The medical team then makes recommendations based on information about the patient's values and goals. This serves to facilitate a more informed decision-making process while mitigating the potential effect of postdecision surrogate guilt, and the very real chance of complicated bereavement, often characterized by the development of depressive symptoms and even posttraumatic stress disorder after the patient's death.

The social worker in the ER finds out that Rose has known Mr. H for the last 20 years, and states that they have been "together" for the last 15 years. Rose explains that he always enjoys gardening and walking his dog, Lucy. In the past, the patient had mentioned to Rose that he would not want any "heroics" and that "if it's my time, let me go!"

When asked about other family members, Rose states that Mr. H has a son in his 40s and a daughter in her 30s. Both live out of state. Mr. H has had monthly contact with his daughter, but his older son has been estranged for the last 10 years.

Mr. H does not have a living will, and has not appointed a DPOAHC decisions. He did have conversations about his general end-of-life wishes with Rose. The attending neurosurgeon explains to Rose that the patient has a very slim chance of meaningful recovery. Given Mr. H's previously expressed wishes regarding end-of-life care and his prior statement that he would want to avoid "heroics," the decision is made to forego surgical intervention. Comfort-focused care is begun.

Later that night, the neurosurgery resident is paged by the hospital operator who connects him to Mr. H's daughter, Angela. She lives out of state and is very concerned about her father. After hearing the explanation of her father's situation, Angela requests that "everything be done" including reconsideration of a subdural hematoma evacuation.

Questions:

1. **Should Angela's request be considered?**
2. **How would you determine who would be the legal surrogate decision maker given this new information?**

HIERARCHY OF SURROGATE DECISION MAKING

It is helpful to know that older adult patients such as Mr. H commonly need a surrogate to make medical decisions on their behalf. Literature supports the notion that approximately half of hospitalized older adults will lack decisional capacity, and need to rely on a surrogate either partially or completely to make medical decisions within the first 48 hours of a hospital admission. Informal surrogate decision making happens frequently, for various types of medical decisions ranging from low-risk interventions to life-sustaining treatments near the end of life. For many older adults, either involving family members or delegating decisions to family members can be customary and preferable for the patient. Many times, informal surrogate decision making does happen without the patient having formally appointed a legal decision maker (ie, DPOAHC decisions). Most surrogate decision makers are daughters, sons, or spouses (in descending order of frequency).

When there is agreement among the primary surrogate and other family members regarding the medical decision at hand, a plan of care is often able to be implemented without issue. However, when conflict or discordant opinions arise among a surrogate and other family members, it can create difficult and challenging situations. Often these differences can be bridged with time taken to communicate with family members through a family meeting. Additionally, input from other specialty teams such as a Geriatric Medicine consult team, a Palliative Medicine consult team, and/or an Ethics consultation can be useful in facilitating communication and in outlining ethical issues at hand.

Many states and the Veterans Administration utilize a legal hierarchical framework to delineate who can make medical decisions for an incapacitated patient (**Table 61-6**). To identify the legal surrogate from the list, one starts at the top, and goes down until there is someone in that category. Patients without any potential surrogates may require appointment of a guardian. Some states do not recognize the concept of a "common law" spouse, in which case a fiancée or partner such as Rose could be potentially relegated lower down on such a list, being akin to a "close friend," depending on the state. States with legal hierarchies also differ in how disputes between surrogates at the same level, such as adult children, should be resolved. Some states require consensus, while others require a majority opinion. A patient's oldest child doesn't automatically hold more decision-making authority than the other adult children. In states that do not delineate such a hierarchy, it is advisable to work to obtain consensus among family or surrogate decision makers.

TABLE 61-6 AN EXAMPLE OF ONE STATE'S LEGAL HIERARCHY OF SURROGATES

New York Family Health Care Decisions Act, 2010
Decisions for adult patients by surrogates should the patient be incapable, in order of priority:
– Durable power of attorney for health care decisions (or health care agent)
– Court-appointed guardian
– The spouse or domestic partner
– An adult child

– A parent
– A brother or sister
– A close friend

In light of these different laws, it is generally advisable that older adults engage in advance care planning and, as part of the process, appoint a health care agent through a DPOAHC decisions to ensure the appointed individual is able to make care decisions when needed. Regarding Mr. H's case, conducting a family meeting with Rose and Angela would most likely be the next step, even if this happens through a conference call with both parties involved. If reasonable consensus could not be reached, determining a legal decision maker may involve adhering to state law regarding surrogate hierarchies if the state he resides in has such a law, or federal law in the case of veterans receiving care within a VA facility. Ethics committee involvement would be important if initial efforts at communication with family members and surrogates are not fruitful in garnering support and consensus in a manner that best reflects Mr. H's previously stated wishes.

DECISION MAKING IN CHRONIC AND ADVANCED ILLNESS

Case

Mrs. S is an 82-year-old woman with mild dementia, coronary artery disease, hypertension, and peripheral vascular disease. She misses a meal in the dining room of her assisted living facility and is found in her apartment lethargic and confused. She is sent to the hospital, admitted to the ICU, and diagnosed with urosepsis. She has a POLST form, which accompanies her to the hospital, with preferences for do not resuscitate (DNR) status, limited additional interventions, antibiotics to prolong life, and a trial of use of a feeding tube.

Despite aggressive care in the ICU, she remains delirious. Over the next 2 weeks in the ICU, she suffers a non-ST segment elevation myocardial infarction (MI), develops a pneumonia thought secondary to aspiration, and her kidney function worsens. Her adult children, who are her legal decision makers, are given regular updates, but are overwhelmed by the numerous medical decisions they are asked to make including whether to insert a temporary feeding tube in her nose, followed later by whether to insert a more permanent tube in her stomach, and whether to start dialysis. Although they had initially told the ICU to do "everything" to make their mother better, short of resuscitating or intubating her, they begin to wonder if they are doing the right thing. They wonder how long their mother would want this level of care continued. During a routine meeting with the family, the ICU team uses the term "futile" and recommends that they change the goal of care to focus on maximizing their mother's comfort.

Question: What should the family and ICU team consider in deciding how to proceed?

In older patients with chronic medical conditions, a multitude of medical decisions may arise during acute illness episodes/exacerbations and in the course of worsening of the chronic conditions. When patients are unable to make their own decisions, surrogates are called on to make these decisions. As noted in the section on surrogate decision making, decision making for others can be stressful for surrogates. As noted in the section on advance care planning, knowledge of a loved one's preferences can reduce the burden of decision making for surrogates. In the case of Mrs. S, her children have attempted to implement her wishes, but her condition has worsened, and they are no longer sure of the right thing to do. In what follows, several decisions related to this case will be discussed.

At the beginning of her hospitalization, Mrs. S's children believed that they were doing what she would want in inserting a temporary nasogastric tube. When she didn't improve despite aggressive interventions and remained unable to swallow safely, her children were less sure if she would want a more permanent tube inserted. Although the literature, position statements from organizations such as the American Geriatrics Society, and the Choosing Wisely campaign have argued against the insertion of feeding tubes in patients with advanced dementia (see Chapters 55 and 66), the appropriate use of feeding tubes in other situations is less clear. In Mrs. S's situation, the decision of whether or not to place a permanent feeding tube depends on her overall goals of care. It is not clearly right or wrong to place it.

Another decision that families often will make for their loved ones is whether to treat infections with antibiotics. Antibiotic therapy is thought to be beneficial and the usual standard of care in conditions such as pneumonia and urinary tract infections, which often arise among older adults. In some patients with advanced serious illness, however, antimicrobials can carry substantial risk and treatment burdens that need to be carefully weighed, especially among

patients receiving end-of-life care. For example, patients receiving antimicrobials are at increased risk of acquiring infections with resistant organisms as well as *Clostridium difficile* infections. Some of the unintended consequences of antimicrobial therapy not only include burdens to the individual patient, but also extend to other patients, and to society through the possible selection of antimicrobial resistance. Studies are conflicting as to whether antimicrobial treatment of pneumonia may provide symptomatic benefit among patients with advanced dementia. A recent prospective study of patients with advanced dementia and pneumonia demonstrated an association between antimicrobials and increased discomfort. For patients receiving comfort-focused care near the end of life, the treatment of pain, fever, and dyspnea with opioids and antipyretics remain effective modalities to provide symptomatic benefit. Whether a course of antibiotics is warranted will depend on the risks and benefits of the treatment and whether providing that course of treatment is consistent with the patient's goals of care.

In living with chronic conditions, older patients may have acute or chronic worsening of their kidney function. The number of older individuals who are beginning chronic dialysis is increasing. Many of these individuals start dialysis while in the hospital for an acute illness. Studies have shown that older people with poor functional status, multiple chronic conditions, and age over 85 when starting dialysis may not necessarily live longer with dialysis. Conservative management programs for older patients with advanced kidney disease who are forgoing dialysis are prevalent in the United Kingdom, but not elsewhere. In deciding about whether or not to begin dialysis, Mrs. S's children need to be fully informed about the risks and benefits of short- and long-term dialysis. As with other decisions, the decision to start dialysis depends on Mrs. S's goals of care.

After a trial of aggressive therapies aimed at life prolongation, Mrs. S's clinicians begin to talk about her situation being "futile." This term is used by health care professionals, but not by lay people, and therefore should not be used in routine conversations with patients or their loved ones. The term is also commonly used when clinicians don't believe that continuing on the current trajectory is "worth it." Different definitions of futility exist, including quantitative futility (very low probability of survival) and qualitative futility (patient's quality of life is below an acceptable standard). These definitions can be problematic because clinicians cannot accurately predict a patient's chances of survival, and may not be able to separate their own views about acceptable quality of life from the patient's view of his/her quality of life. In the case of Mrs. S, decision making might be easier if both the medical team and her family were clear about her goals of care; what makes life worth living for her, and would she consider life to acceptable if she lived in a nursing home, leaving three times a week for dialysis, and being fed through a tube?

When patients are very sick and care is focused on life prolongation, it can be hard for clinicians and family members to step back and examine the big picture. When the goal is to do "everything," medical teams may want to better understand what this means to a patient and family. They should not feel compelled to offer every intervention that is technically feasible. Instead, they should consider whether the intervention is clinically meaningful, and whether it will help to meet the patient's goals of care.

Mrs. S's medical team has recommended a change in the focus of her care from life prolongation to comfort care. Although this may be a clinically acceptable option, as noted in the discussion of shared decision making earlier in this chapter, it is important that care recommendations be based on an understanding of the patient's values and preferences. Although withholding and withdrawing care are ethically equivalent, withdrawing life-prolonging measures may be more psychologically difficult for decision makers.

In deciding how to proceed with Mrs. S's care, consulting a palliative care team may be helpful. The palliative care team could not only help the medical team develop a richer understanding of Mrs. S's values, care preferences, and goals of care by engaging in in-depth conversations with her children about her life, but also support her family during a stressful time.

MANAGING REFRACTORY SYMPTOMS CAUSING INTRACTABLE SUFFERING AT THE VERY END OF LIFE

Case

Mr. P is a 90-year-old man with widely metastatic prostate cancer receiving hospice services in a nursing home. He continues to have severe bone pain from his metastatic disease despite the use of opioids, steroids, pamidronate injections, and a course of palliative radiation. As his opioid doses are increased, he develops myoclonus and confusion. Rotation to two different opioids over the next 2 weeks is minimally effective. His confusion worsens, becoming a hyperactive delirium with bouts of yelling and attempting to climb out of bed. Addition of antipsychotic

medications is only slightly effective. His family and the nursing staff are distressed about his situation and their inability to ensure his comfort and safety.

Question: What are the ethically and legally appropriate options to reduce Mr. P's suffering?

In terminally ill patients such as Mr. P, questions may arise about ways to reduce his intractable suffering and promote his comfort at the very end of life, to ensure a peaceful death. His family may ask if there is something that could be done to end his suffering, such as euthanasia. Those taking care of him may wonder about the use of palliative sedation or physician aid in dying (PAD) (also known as physician-assisted suicide), and whether alternative options exist. The differences between these entities can be confusing to families and clinicians and are defined in **Table 61-7**.

TABLE 61-7 KEY TERMS, DEFINITIONS, AND LEGAL STATUS OF INTERVENTIONS TO MANAGE INTRACTABLE SUFFERING AT THE END OF LIFE

TERM	DEFINITION	STATUS	SOURCE
Palliative sedation Also called terminal sedation, end-of-life sedation, total sedation, and proportional palliative sedation.	Lowering of patient consciousness using medications for the express purpose of limiting patient awareness of suffering that is intractable and intolerable. Terminal sedation is an older term for palliative sedation, fallen out of favor because "terminal" was misinterpreted to imply that the sedation itself caused or hastened death. Proportional palliative sedation is the process of reducing consciousness only as much as needed to reduce patient suffering. Patients may only be mildly sedated, not necessarily sedated to unconsciousness. Deep continuous sedation is used to describe the last step of a gradual process of palliative sedation in which the patient is sedated to deep unconsciousness.	Legal in the United States	Kirk et al. NHPCO Consensus JPSM 2010 AMA Council on Judicial and Ethical Affairs 2008 AAHPM position statement 2014
Respite sedation	Sedation induced for a predetermined period of time to give the patient respite from intractable refractory suffering. At the end of that period of time, sedation is reduced to allow the patient to awaken and assess whether the symptom burden has lifted, and to determine if sedation is still required to effectively address suffering.	Legal in the United States	NHPCO Consensus statement JPSM 2010
Continuous sedation until death (CSD)	Act of reducing or removing consciousness of a terminally ill patient until death, "suggests that the physician chooses a priori to sedate a patient until death without prospectively monitoring the result or modifying the approach as needed on the basis of clinical conditions."	"Standard practice in end-of-life care" Intent to reduce suffering, not to shorten life	(Maltoni) Rys J Bioeth Inq 2012
Voluntary cessation of eating and drinking	"An action of a competent, capacitated person who voluntarily and deliberately chooses to stop eating and drinking with the primary intention to hasten death because unacceptable suffering persists."	Legal in the United States	Ivanovic BMC Pall Care 2014; Quill Ann Intern Med 2000
Physician aid in dying (PAD) Also called physician-assisted suicide (PAS) or physician-assisted death	A practice that "occurs when a physician facilitates a patient's death by providing the necessary means and/or information to enable the patient to perform the life-ending act." Medications are self-administered by the patient, thereby distinguishing it from euthanasia. Physician-assisted suicide is a term being used less often because of the impression that the patient commits suicide.	Legal in some US states, and in Belgium, The Netherlands, and Luxembourg	American Medical Association. E-2.211 Physician-assisted suicide. AMA Code of Medical Ethics. Chicago, IL: American Medical Association; 2006. http://www.ama-assn.org/ama/pub/category/8459.html.

Euthanasia	The administration of a lethal agent by another person, such as a clinician, to a patient for the purpose of relieving the patient's intolerable and incurable suffering by ending the patient's life. Intentionally ending the life of another person, usually with the goal of alleviating or avoiding suffering.	Not legal in the United States Legal in Belgium, The Netherlands, and Luxembourg under specific circumstances with procedures to guide use	American Medical Association. E-2.21 Euthanasia. AMA Code of Medical Ethics. Chicago, IL: American Medical Association; 2006. http://www.ama-assn.org/ama/pub/category/8458.html.

Palliative sedation is legal in the United States. It is an intervention provided to relieve intractable and intolerable symptoms at the end of life, and is accomplished by intentional lowering the patient's level of consciousness using sedating medications. Palliative sedation should be used as an intervention of last resort in the setting of a palliative care interdisciplinary team strategy to achieve symptom control within the spectrum of palliative care interventions. The American Medical Association (AMA), the American Academy of Hospice and Palliative Medicine, and guidelines from Europe, Canada, and Japan consider palliative sedation to unconsciousness to be appropriate as a last resort in terminally ill patients with goals for comfort and severe refractory distressing symptoms including agitated delirium, dyspnea, pain, nausea and vomiting, shortness of breath, urinary retention due to clot formation, gastrointestinal pain, uncontrolled bleeding, and myoclonus. Palliative sedation for existential suffering remains controversial.

The recommendations on palliative sedation from the American Academy of Hospice and Palliative Care in 2014 are summarized as follows: (1) It is ethically defensible if used after careful interdisciplinary evaluation and treatment of the patient; (2) It should be used when palliative treatments that are not intended to affect consciousness have failed or, in the judgment of the clinician, are very likely to fail; (3) It should be used where its use is not expected to shorten the patient's time to death; and (4) It should be used only for the actual or expected duration of symptoms. Ideally, the patient, family, and participating interdisciplinary health care professionals should be in agreement that this intervention is consistent with patient goals and is the right thing to do. Health care professionals who believe that participating in palliative sedation is morally wrong should not be forced to participate in the care of patients undergoing this intervention. Treatment of existential suffering should include the full interdisciplinary team including mental health and spiritual care experts. Respite sedation, or sedation for a limited time with subsequent removal of sedation to reassess patient, may be an alternative approach.

An alternative to palliative sedation is the voluntary cessation of eating and drinking. This practice is legal if chosen because of intractable suffering by a competent person with decisional capacity who is approaching the end of life. Many individuals who are approaching the end of life do not have an appetite, and thus do not experience discomfort from doing this. For others, symptoms resulting from voluntary cessation of eating and drinking may require palliation by a palliative care team. Individuals are encouraged to let their medical teams and families know if they decide to pursue this. However, there are cases in which older individuals who had decided to pursue this were evicted from facilities due to legal concerns.

PAD, also called physician-assisted suicide, is legal in some US states. The patient pursuing PAD intentionally self-administers lethal doses of medications with the intention of ending their suffering. The Death with Dignity laws in Oregon and Washington stipulate that only terminally ill patients who are decisionally intact and voluntarily making this request are eligible to use the law. Interested individuals are required to make two verbal and one written request, and must be adult state residents. Two attending physicians must verify that the patient is terminally ill with intact decisional capacity. The majority of people requesting this is already receiving hospice services, and makes the request because of concerns about loss of autonomy and control. Approximately one-third of individuals who obtain medications do not use them. Finally, patients may raise the subject of PAD with their clinicians as a way to talk about dying. Even if clinicians cannot or will not participate, they should still view this as an opportunity to talk about the patient's sources of unbearable suffering and fears about dying.

Euthanasia is a process by which an individual, such as a clinician, intentionally administers a lethal dose of medication to a terminally ill patient, which directly ends his/her life. In contrast to PAD, euthanasia is not legal in the United States. Internationally, it is legal in Belgium and The Netherlands, which have widespread palliative care policies and availability of palliative care professionals. In these countries the practice of euthanasia is considered one option to manage intractable suffering at the end of life, and is provided in conjunction with palliative care.

The ethical distinction between palliative sedation and euthanasia has been debated, hinging on three areas:

intention, monitoring, and methods. Palliative sedation does not have the intention to hasten death, the patient is monitored to provide the minimum level of sedation required to provide symptom relief, and the medication is carefully titrated to achieve this minimum level of sedation required to provide symptom relief. The AMA asserts that the distinction between palliative sedation and euthanasia may be evident on examination of the medical record, as repeated doses and continuous infusions suggest palliative sedation, while one large dose or rapidly accelerating doses out of proportion to the level of immediate patient suffering may reflect an intention to hasten death. Other indications of inappropriate palliative sedation include inadequate communication and support between patients, relatives, and staff; inadequate evaluation of psychological distress and existential suffering; and inadequate monitoring. There are multiple published guidelines on appropriate indications, monitoring and methods for palliative sedation, and most guidelines include the recommendation that cases in which this procedure is being considered should include a physician with expertise in palliative care.

DRIVING

Case

Mr. J is an 89-year-old man living temporarily in a skilled nursing facility where he is receiving physical and occupational therapy after he fell and sustained a patellar fracture. He is doing well, and the interdisciplinary team informs you that he is close to ready for discharge home. He lives in a one-story home with his wife. He drives to the neighborhood shopping center to meet his friends for lunch, buy groceries, and do other chores. During your assessment, you note that his memory is mildly impaired, with only one out of three items recalled after 5 minutes, and he has difficulty with attention. His clock-drawing test is markedly abnormal, with impaired spacing and numbering.

Questions for the interdisciplinary team: Should he still be driving? What do we do about it?

Decisions regarding older adults' driving ability can lead to ethical dilemmas for health care professionals, especially when the patient is upset at the loss of independence and autonomy that driving provides. Common reasons for recommending driving cessation are epilepsy, stroke, dementia, visual impairment, and medication adverse effects. Strategies to employ when addressing driving decisions with patients are summarized in **Table 61-8**. Some key ethical considerations with regard to driving include protecting the patient's safety, the public, and the patient confidentiality. Protecting Mr. J would include counseling him about conditions or medications that may impair his ability to drive safely. Some states have mandatory reporting requirements for physicians regarding driving ability, and some states have found physicians liable for harm to others because their patients were not warned about conditions or medication side effects that could impair driving performance. Physicians must weigh the responsibility for ensuring patient confidentiality against the responsibility for the patient's safety and public safety. Involving patients and family, and carefully counseling patients, including providing a written letter of recommendations regarding driving cessation, can be helpful to navigate these challenging situations. Careful documentation of patient's risks regarding driving, counseling provided, and additional referrals made to social workers, driving rehabilitation or other professionals, may reduce clinician liability. In addition, physicians must make sure they are in compliance with their own state reporting laws for physicians, available from each state's Department of Motor Vehicles (DMV).

TABLE 61-8 STRATEGIES TO EMPLOY WHEN WORKING WITH OLDER ADULTS REGARDING DRIVING CESSATION

SITUATION	PROPOSED STRATEGIES
Patient threatens to sue physician if reported to Department of Motor Vehicles	• Clearly document how the patient was determined to be an unsafe driver (driving fitness evaluation, assessing driving-related skills [ADReS] battery, driving rehabilitation referral, medications, etc). • Advise patient that the state has the ultimate responsibility to determine licensing. • If physician is mandated to report in that state, physician must report. The physician should also advise the patient of this. • Consult malpractice insurance or legal counsel to determine degree of risk (physicians generally run little risk of liability for following mandatory reporting).

Physician identifies patient as an unsafe driver, state does not have mandatory reporting laws	• Consider referring the patient to a driver's rehabilitation specialist. • Attempt to counsel patient to stop driving voluntarily without revocation of license. • If patient refuses to stop driving, physician must weigh breach of confidentiality vs potential injury to patient and others from a crash.
Patient had license suspended, but continues to drive	• Talk to the patient about why he or she continues to drive. • Involve social work to provide transportation resources and the patient's family to find alternative transportation. • Counsel patient that he or she is breaking the law, cite concerns about patient's safety, and discuss consequences of a crash (being injured, injuring others, financial and legal implications). • Assess patient for cognitive impairment and insight; counsel surrogate decision makers regarding responsibility to prevent patient from driving. • Report patient as an unsafe driver again.
Patient threatens to find a new doctor if physician reports to Department of Motor Vehicles	• Diffuse situation by reiterating how unsafe driving determination was made. • Convey concern for patient's safety, and safety of others who would be affected if patient crashed. • Remind patient that driving safety is part of good health care as much as other physician responsibilities. • Encourage patient to be evaluated by a driving rehabilitation specialist. • Emphasize that the state Department of Motor Vehicles makes the final determination of driving safety. • Maintain professional behavior by not expressing hostility even if he or she seeks a new physician.

Material summarized from Carr DB, Schwartzberg JG, Manning L, Sempek J. Physician's Guide to Assessing and Counseling Older Drivers. 2nd ed. Washington, DC: NHTSA; 2010.

ETHICAL ISSUES IN NURSING HOMES

Case

Mrs. N, a 97-year-old nursing home resident with advanced dementia, who is bedridden and nonverbal, has begun to refuse to open her mouth with meals. Nursing staff approach you regarding their concerns about her weight loss, which is more than 5% in the last month. The charge nurse explains that they need to have a plan regarding this weight loss or it could be cited on their next Department of Health Survey. You explain that weight loss at this stage of the disease is a normal part of the illness trajectory.

Question: How do you balance the concerns of the facility regarding quality measures against your knowledge of the trajectory of illness in dementia?

Common ethical issues encountered in nursing homes are summarized in **Table 61-9**. Balancing the autonomy and safety of nursing home residents with nursing home rules and regulations frequently arises as an important ethics and quality issue. Ongoing education in facilities is needed to reduce rates of antipsychotic and restraint use through patient-centered care and innovative approaches such as the Hand in Hand program (CMS). Quality of care encompasses multiple ethical issues in nursing homes, because it is related to nursing home staffing and expenditures, reimbursement, surveys and regulations, Nursing Home Compare reporting, incentives, and racial disparities. Another common ethical issue reported by nursing home staff occurs when nursing home residents' families request or demand care that is not consistent with the resident's advance directives or is not felt to be beneficial based on current evidence. The use of regional ethics committees may be helpful for smaller community-based nursing homes, and

statewide partnerships between academic programs (such as schools of nursing or medicine) and state agencies to improve quality measures in nursing homes are important areas for ongoing study.

TABLE 61-9 ■ COMMON ETHICAL ISSUES ENCOUNTERED IN THE NURSING HOME SETTING AND STRATEGIES FOR MANAGEMENT

ISSUE	EXAMPLE(S)
Balancing resident preferences against safety requirements within the institutional setting	• Resident with dementia refuses to stay in facility, but has no safe place to go to. • Resident wandering or resisting basic care, such as bathing. Suggested strategy for management: Look at the root cause of these behaviors and try to address the underlying needs, wants or fears underlying the behaviors rather than using medications, ie, enlist family to visit frequently, bring photo albums and other items that will make resident feel more at home.
Balancing resident's wishes against practical issues of available resources	Resident prefers daily showers, but staffing levels do not permit this frequent bathing schedule. Suggested strategy for management: Work closely with staff and residents to approach residents' wishes as closely as possible within the constraints of the facility's resources and staffing levels. Restructure staff tasks to enable person-centered care as much as possible. Explain staffing constraints to resident.
Balancing resident's care preferences against those of his/her surrogate decision maker	Resident's advance directive requests comfort care if diagnosed with terminal illness and resident has end-stage dementia, however, family wishes to transfer resident to hospital for pneumonia. Suggested strategy for management: Educate families on complications that are expected to arise during trajectory of dementia as part of a discussion of patient and family goals, establish trust and rapport with families, and keep families well informed during the course of nursing home stay.
Promoting quality end-of-life care vs helping residents to have financial coverage for their care	Resident with metastatic cancer may not be able to have radiation therapy for painful bony metastases if he/she is on hospice care. Suggested strategy for management: Work closely with hospice provider and facility to identify best way to ensure resident receives the care required to maximize comfort and quality of life.
Promoting quality of care vs facility financial incentives/constraints	Facility may receive greater financial reimbursement for residents who are tube-fed. There may be less incentive to provide careful hand feeding. Suggested strategy for management: Advocate for care that is consistent with residents' needs and wishes, work with facility to identify ways to meet residents' needs within financial constraints of facility without compromising quality of care.
Promoting CMS-defined quality of care vs quality of care at the end of life	CMS identifies weight loss as a quality indicator, yet weight loss is an expected complication in end-stage dementia and at the end of life in most illness trajectories. Suggested strategy for management: Clearly document terminal illness or end-stage disease and expected prognosis in

	medical documentation to support why the weight loss is an expected part of the illness trajectory despite excellent care provided.
Relationship between quality of care indicators and nursing home characteristics	• Higher staffing associated with fewer pressure ulcers. • High certified nursing assistant turnover was associated with higher odds of pressure ulcers, pain, and urinary tract infections, even after controlling for staffing, skills mix, bed size, and ownership. • Higher prevalence of pressure ulcers was seen among African-American residents and in facilities with higher percentages of African-American residents. • Pressure from regulations may result in nursing homes accepting individuals with higher potential for high-quality measures and declining other potential residents (such as individuals with pain, memory limitations, or other issues). Suggested strategy for management: Advocate for culture change and reallocation of facility resources to improve quality of care and enhance team care. Implement team building and quality improvement programs such as TeamSTEPPS and Interact, especially in facilities with poor quality indicators.

In the case, the physician caring for Mrs. N must serve as an advocate for the patient, and educate the nursing facility about the trajectory of dementia and the prevalence of weight loss in end-stage dementia. The physician also must clearly document the patient's stage of illness, expected trajectory of decline, and the patient's and family's goals of care. The physician also can advise the nursing staff regarding the documentation of the care plan so that the nursing home has a patient-centered and appropriate care plan for the weight loss. If necessary, the physician may need to discuss the trajectory of illness with the state surveyors during the Department of Health Survey to help educate them regarding standards of care in end-stage dementia.

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Part V

Organ Systems and Diseases

Chapter 62. Cellular and Neurochemical Aspects of the Aging Brain
Chapter 63. Cognitive Changes Associated With Normal and Pathologic Aging
Chapter 64. Psychoactive Drug Therapy
Chapter 65. Cerebrovascular Disease
Chapter 66. Dementia Including Alzheimer Disease
Chapter 67. Parkinson Disease and Related Disorders
Chapter 68. Other Neurodegenerative Disorders
Chapter 69. Traumatic Brain Injury
Chapter 70. Epilepsy
Chapter 71. Evidence-Based Treatment and Prevention of Major Depressive Episodes in Later Life
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Chapter 74. Management of Agitation in Dementia
Chapter 75. Effects of Aging on Cardiovascular Structure and Function
Chapter 76. Vascular Aging and Atherosclerosis
Chapter 77. Coronary Heart Disease
Chapter 78. Valvular Heart Disease
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Chapter 80. Cardiac Arrhythmias
Chapter 81. Peripheral Vascular Disease
Chapter 82. Hypertension
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Chapter 84. Chronic Obstructive Pulmonary Disease
Chapter 85. Diffuse Parenchymal Lung Disease
Chapter 86. Aging of the Kidney
Chapter 87. Renal Disease
Chapter 88. End-Stage Renal Disease
Chapter 89. Disorders of Fluid and Electrolyte Balance
Chapter 90. Aging of the Gastrointestinal System
Chapter 91. Hepatic Disease
Chapter 92. Biliary and Pancreatic Disease

Chapter 93. Upper Gastrointestinal Disorders
Chapter 94. Common Large Intestinal Disorders
Chapter 95. Constipation
Chapter 96. Oncology and Aging: General Principles
Chapter 97. Breast Disease
Chapter 98. Prostate Cancer
Chapter 99. Lung Cancer
Chapter 100. Gastrointestinal Malignancies
Chapter 101. Intracranial Neoplasms
Chapter 102. Skin Cancer
Chapter 103. Aging of the Hematopoietic System
Chapter 104. White Cell Disorders
Chapter 105. Non-Hodgkin and Hodgkin Lymphomas
Chapter 106. Coagulation Disorders
Chapter 107. Plasma Cell Disorders
Chapter 108. Aging of the Endocrine System and Selected Endocrine Disorders
Chapter 109. Thyroid Diseases
Chapter 110. Diabetes Mellitus
Chapter 111. Dyslipoproteinemia
Chapter 112. Hyperparathyroidism and Paget Disease of Bone
Chapter 113. Aging of the Muscles and Joints
Chapter 114. Biomechanics of Mobility
Chapter 115. Exercise: Physiologic and Functional Effects
Chapter 116. Mobility
Chapter 117. Osteoarthritis
Chapter 118. Osteoporosis
Chapter 119. Hip Fractures
Chapter 120. Myopathies, Polymyalgia Rheumatica, and Giant Cell Arteritis
Chapter 121. Rheumatoid Arthritis and Other Autoimmune Diseases
Chapter 122. Back Pain and Spinal Stenosis
Chapter 123. Foot Problems
Chapter 124. Fibromyalgia and Myofascial Pain Syndromes
Chapter 125. Infection: General Principles
Chapter 126. Pneumonia
Chapter 127. Urinary Tract Infections
Chapter 128. Human Immunodeficiency Virus Infection
Chapter 129. Herpes Zoster
Chapter 130. Influenza and Respiratory Syncytial Virus

Chapter 62

Cellular and Neurochemical Aspects of the Aging Brain

Luigi Puglielli, Mark P. Mattson

Learning Objectives

- Understand how aging affects the brain at the histologic, cellular, and molecular levels and how these changes are linked to cognitive decline and common neurodegenerative diseases.
- Gain a clear understanding of the most prominent biochemical and molecular aspects of the aging brain.
- Learn about the effects of aging on cognition and neurodegenerative diseases.
- Recognize novel active areas of research in the field of cognitive neuroscience.
- Learn how environmental factors influence normal brain aging.

Key Clinical Points

1. **Given the steady increase in average human lifespan, the number of individuals who will experience some degree of cognitive decline is rising.**
2. **Healthy aging is associated with atrophy of the gray matter; however, it is not indicative of presence of a disease.**
3. **Comprehensive clinical evaluation is necessary to differentiate mild cognitive impairment and dementia from normal aging-associated cognitive decline.**
4. **Specific aging-associated histologic, cellular, and molecular changes can predispose to neurodegenerative diseases.**
5. **Environmental factors can be modified to mitigate potential effects of aging on brain functions.**

Many cellular and molecular aspects of brain aging are shared with other organ systems, including increased oxidative damage to proteins, nucleic acids and membrane lipids, impaired energy metabolism, and the accumulation of intracellular and extracellular protein aggregates. However, given the molecular and structural complexity of neural cells that express approximately 50 to 100 times more genes than cells in other tissues, there are age-related changes that are unique to the nervous system. For example, complex cellular signal transduction pathways involving neurotransmitters, trophic factors, and cytokines that are involved in regulating neuronal excitability and plasticity are subject to modification by aging. This chapter describes cellular and molecular changes that occur in the brain during aging and how such changes may predispose to neurodegenerative diseases.

AGING AND COGNITION

A large segment of the world population will experience some degree of cognitive decline during aging (**Figure 62-1**). This decline most typically affects working memory as well as short-term and delayed memory recall; however, a smaller group of individuals will also experience reduced information processing speed and spatial memory. Most of the decline appears to occur after the age of 60 with minimal or nonexistent changes occurring between the age of 20 and 60. Functional magnetic resonance imaging and positron emission tomography studies suggest that the cognitive decline might be linked to the progressive reduction in the volume of specialized memory-forming and -processing brain areas (**Figure 62-2**). Similar age-associated changes have also been observed in nonhuman primates, dogs, rats, and mice, suggesting intrinsic age-associated events. Nonmedical interventions, such as physical exercise, cognitive stimulation, and diet together with treatment of common medical comorbidities, such as obesity, hypertension, hypercholesterolemia, diabetes, and metabolic/hormonal imbalances might help mitigate age-associated declines.

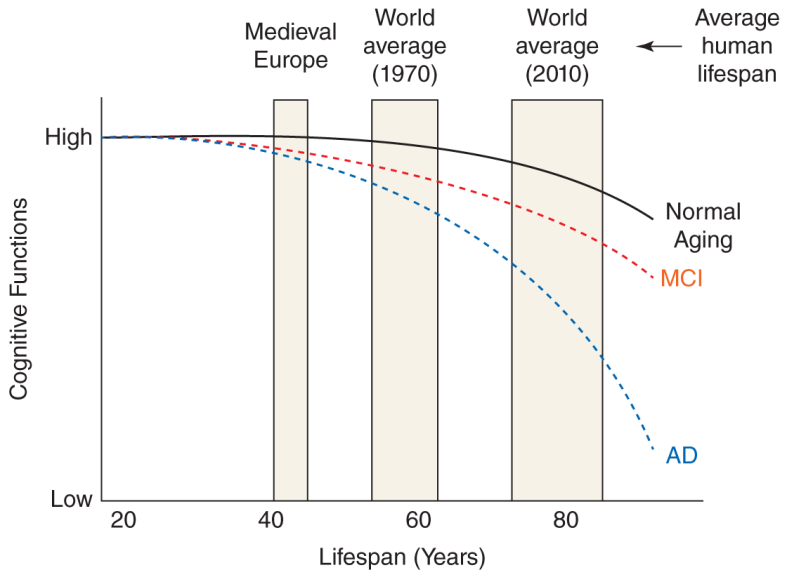


FIGURE 62-1. Cognitive changes as a result of aging. Trends of normal aging, mild cognitive impairment (MCI), and dementia due to Alzheimer disease (AD) are shown. Due to the progressive increase in lifespan, a higher number of individuals can now reach the age where specific cognitive changes (as a result of normal aging, MCI, or AD) are observed.

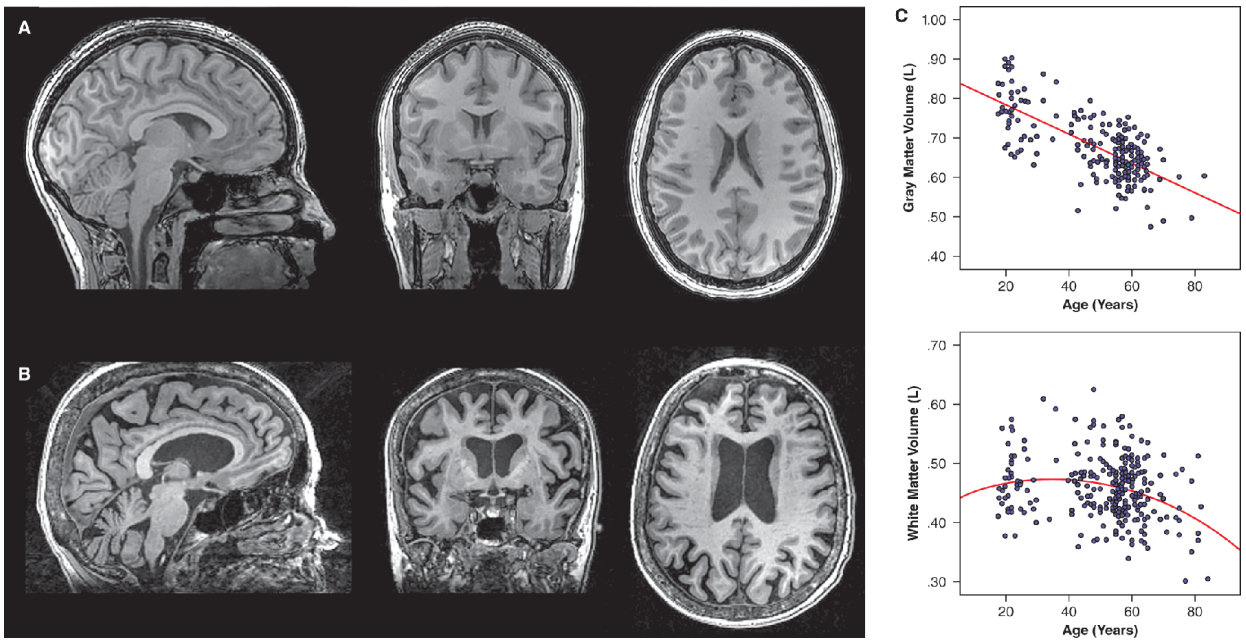


FIGURE 62-2. Volumetric changes in the human brain as a function of age. **A.** Magnetic resonance imaging (MRI) sections from a 24-year-

old healthy woman; **B**. MRI sections from an 80-year-old healthy woman (nondemented, Mini Mental State Examination = 30, *APOE* ε3/ε3). The older brain has more atrophy, larger sulci, larger ventricles, and different shape of ventricles due to loss of tissue. Atrophied cerebellum is also noticeable. **C.** Scatter plots of total gray matter volume (*upper panel*) and white matter volume (*lower panel*) derived from healthy volunteers who underwent T_1-weighted MRI. Gray matter shows a linear decline with age, whereas white matter (largely myelin) shows a nonlinear decline. *(Courtesy of Dr. Barbara Bendlin, Department of Medicine, University of Wisconsin-Madison.)*

It is widely projected that an exponentially increasing number of individuals will suffer from dementia and other cognitive disorders that will affect their daily function and increase mortality (see **Figure 62-1**). In 2000, the number of patients with dementia worldwide was estimated to be over 20 million. This number is projected to exceed 100 million by 2040, with an average of 5 million new cases every year. Rates of increase are not uniform. Developed countries initially shared most of the "dementia burden"; however, as a result of significant improvement in economic and social conditions, developing countries are now experiencing a larger disease burden as well. Consequently, the rate of increase in the number of patients with dementia is projected to be almost 100% in developed countries and over 300% in developing countries. Major attention is now being given to the diagnosis of mild cognitive impairment (MCI), a transitional stage between normal aging and dementia. Patients with MCI display more severe cognitive deficits and more evident brain structural changes. In general, when diagnosed they still retain independence and are able to function normally within the society. However, they are at high risk to develop dementia, most typically Alzheimer disease (AD), with an annual rate of conversion between 10% and 15% (see **Figure 62-1**). Careful memory evaluation, lifestyle changes, and medical correction of existing risk factors might help delay conversion into clinical dementia.

The ability of the brain to reorganize, develop, and prune neural pathways is called synaptic plasticity. There are two components of synaptic plasticity that are thought to be important for learning and memory formation: long-term potentiation (LTP) and long-term depression (LTD). LTP involves a rapid influx of calcium into the neuronal cell, leading to the enhancement of cell excitability by the activation of intracellular signaling cascades that increase protein transcription, translation, and the insertion of new receptors into the cell membrane. LTD has the opposite effect, modulating transcription, translation, and the induction of receptors back into the cell that leads to decreased cell excitability. It is commonly believed that LTP and LTD are the cellular correlates of learning and memory and, therefore, great attention has been devoted into understanding how they are influenced by aging. In general, aged rodents show consistent deficits in induction and maintenance of LTP in the cornu ammonis area 1 (CA1) and in the dentate gyrus, two essential memory-forming areas of the brain. These deficits correlate with performance in hippocampal-dependent memory tasks. Furthermore, LTP is reduced in the hippocampus of aged rats that demonstrate cognitive impairments relative to aged unimpaired (*resilient*) rats. Studies have also demonstrated that aged impaired rats are more susceptible to LTD. Specifically, the stimulus threshold for the induction of LTD is lower in aged rats, perhaps making it easier to erase memories. Finally, mouse models of accelerated aging display early and evident deficits in both LTP and LTD that correlate with memory impairment on behavioral tests.

In conclusion, the normal aging process is accompanied by specific changes in neuronal activities that are related to the formation and consolidation of memory, thus leading to a decline in cognitive functions. Given the significant increase in average lifespan that we are experiencing, the cognitive decline is becoming more evident forcing us to devote significant efforts in understanding the genetic, molecular, and biochemical changes that characterize the aging brain.

STRUCTURAL CHANGES IN THE AGING BRAIN

Aging is characterized by significant molecular, structural, cytoskeletal, neurochemical and vascular changes (see **Figure 62-2**) in the brain. Structural changes (see **Figure 62-3**) are diffuse and affect the cerebellum as well. Gray matter volumes show a linear decline while white matter volumes show a nonlinear decline. At the cellular level, all major cell types in the brain undergo structural changes as a function of age. These changes include nerve cell death, dendritic retraction and expansion, synaptic loss and remodeling, and glial cell (specifically, astrocytes and microglia) reactivity. Such structural changes may result from alterations in cytoskeletal proteins and the deposition of insoluble proteins such as tau and α-synuclein inside neuronal cells and amyloid in the extracellular space. Finally, alterations in cellular signaling pathways that control cell growth and motility may contribute to both adaptive and pathologic structural changes in the aging brain. **Table 62-1** provides a brief summary of the most prominent changes.

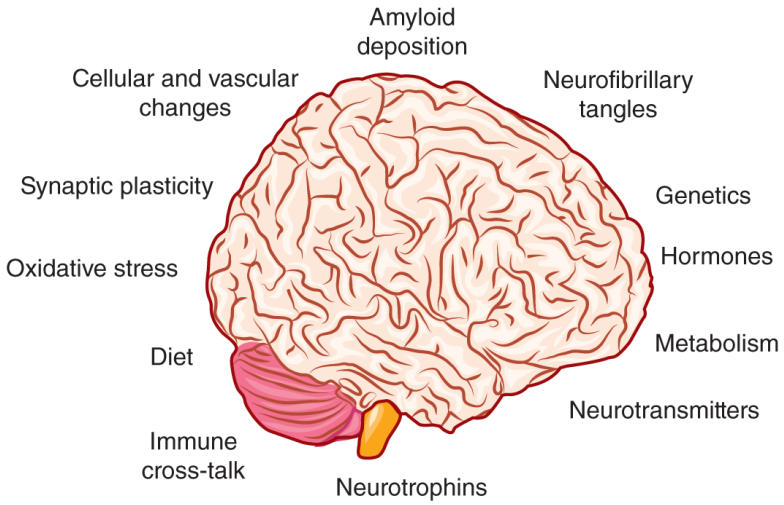


FIGURE 62-3. Simplified view of changes affecting the brain as a function of age.

TABLE 62-1 ■ MOST PROMINENT STRUCTURAL CHANGES OF THE AGING BRAIN

- **Amyloid plaques**—accumulate in the parenchyma; main component: β amyloid
- **Astrocytes**—increased number of activated astrocytes
- **Microglia**—increased number of activated microglia
- **Mitochondria**—changes in morphology
- **Neurofibrillary tangles**—accumulate within neurons; main component: phospho-tau
- **Neuronal loss**
- **Neuronal morphology**—reduced dendritic branches and spines; cell body overall unchanged
- **Synapses**—reduction in number and changes in morphology
- **Vascular**—increase in atherosclerosis and arteriosclerosis
- **Volume**—reduction in gray matter volumes

Cytoskeletal Changes

The cell cytoskeleton consists of polymers of different sizes and protein compositions. The three major types of polymers are actin microfilaments (6 nm in diameter), microtubules (25 nm in diameter) which are comprised of tubulin, and intermediate filaments (10–15 nm in diameter) which are made of specific intermediate filament proteins that differ in different cell types (eg, neurofilament proteins in neurons and glial fibrillary acidic protein in astrocytes). To regulate the processes of filament assembly and depolymerization, and to link the cytoskeleton to membranes and other cell structures, neurons and glial cells employ an array of cytoskeleton-associated proteins. For example, neurons express several microtubule-associated proteins (MAPs) that are differentially distributed within the complex architecture of the cells; MAP-2 is present in dendrites but not in the axon, whereas tau is present in axons but not in dendrites. While there are no major changes in the levels of the most abundant cytoskeletal proteins with aging, there are changes in the cytoskeletal organization and in posttranslational modifications of cytoskeletal proteins. For example, increased amounts of phosphorylated tau occur in some brain regions, particularly those involved in learning and memory (eg, hippocampus and basal forebrain). In addition, there is evidence that calcium-mediated proteolysis of MAP-2 and spectrin (a protein that links actin filaments to membranes) is increased in some neurons during aging. Oxidation of certain cytoskeletal proteins is suggested by studies demonstrating their modification by glycation and covalent binding of the lipid peroxidation product 4-hydroxynonenal (see “Free Radicals and the Aging Brain” later in this chapter). A consistent feature of brain aging in humans and laboratory animals is an increase in levels of glial fibrillary acidic protein, a marker of astrocyte activation, which may represent a reaction to subtle neurodegenerative changes.

Tau proteins are perhaps the most studied microtubule-associated proteins in neurobiology. They consist of a group of alternatively spliced proteins that ensure microtubule-dependent neuronal functions by binding and stabilizing the microtubules. In general, the degree of phosphorylation inversely correlates with binding. As a result,

hyperphosphorylated tau proteins dissociate from microtubules and aggregate to form cytosolic filaments, which ultimately result in neurofibrillary tangles (NFT), pathogenic aggregates that characterize different forms of age-associated frontotemporal dementia (globally referred to as tauopathies) as well as Alzheimer disease. The number and distribution of NFT also increase as a function of age. In addition to the phosphorylation status, the proaggregating properties of tau depend on the differential splicing of the *MAPT* gene, which results in the different tau isoforms. The pattern of phosphorylation and splicing of tau differs in the fetal and adult brain and in the central and peripheral nervous system. It also differs among mammals, probably explaining why only humans and nonhuman primates develop classical NFT. Work in multiple mouse models has shown that abnormal tau metabolism can cause memory deficits. Additionally, mutations in the gene encoding tau proteins (*MAPT*) have been associated with hereditary forms of frontotemporal dementias, whereas polymorphisms in the same gene appear to act as genetic risk factors for sporadic progressive supranuclear palsy and corticobasal degeneration.

Intraneuronal pathogenic aggregates are also observed in other neurodegenerative diseases, underscoring common features. In Parkinson disease, degenerating neurons of the central nervous system accumulate Lewy bodies, which are comprised of α-synuclein, ubiquitin, and neurofilament protein, with associated MAPs (particularly MAP-1b) and actin-related proteins such as gelsolin. In amyotrophic lateral sclerosis, lower motor neurons are filled with aggregates made of superoxide dismutase 1 (SOD1), TDP-43, and neurofilaments, which concentrate in proximal regions of the axon. The specific molecular events involved in the formation of cytoskeletal alterations in different neurodegenerative disorders have not been clearly and definitively established. More information on specific pathogenic aggregates that characterize different neurodegenerative diseases can be found in Chapters 66, 67, and 68.

Synaptic Changes

Synapses are dynamic structural specializations where neurotransmission and other intercellular signaling events occur. There is considerable evidence for synaptic “remodeling” in the brain as we age. Most studies using nonbiased methods indicate that aging does not induce a substantial loss of total neurons in memory-forming and -processing areas of the brain. However, several studies in rodents and nonhuman primates indicate that neurogenesis decreases in the aging brain, with the greatest decline occurring in middle-age groups. In addition to decreased neurogenesis, evidence suggests that aging is accompanied by loss of synapses. As an example, the extent of synaptic loss in the hippocampus has been correlated to the severity of learning impairment observed in aged rodents, supporting the notion that the loss of hippocampal synapses directly contributes to the cognitive impairment. The synaptic loss observed in the hippocampus of aged rats may be due to the loss of both presynaptic and postsynaptic terminals. Ultrastructural studies using electron microscopy have also revealed age-related changes in the type of terminals formed. For example, aged female monkeys with memory impairment have fewer multiple-synapse boutons and twice as many nonsynaptic boutons in the dentate gyrus. Furthermore, aged rodents and monkeys display significant loss of postsynaptic spines in the hippocampus and cortex associated with reduced cognitive performance.

Synapse loss occurs in neurodegenerative disorders and is strongly correlated with clinical symptoms. Accumulating data suggest that synaptic degeneration, resulting from excitotoxic events localized to synapses, may initiate the neuronal death process in Alzheimer disease, Parkinson disease, Huntington disease, and stroke. Glutamate receptors are highly concentrated in postsynaptic dendritic spines, which represent sites of massive calcium influx during normal physiologic synaptic transmission. Age-related decreases in energy availability and increases in oxidative stress, and disease-specific alterations, such as amyloid β-peptide (Aβ) accumulation in AD and trinucleotide expansions of the huntingtin protein, may render synapses vulnerable to excitotoxic injury.

Vascular Changes

As in other organ systems, vessels that supply blood to the brain are vulnerable to age-related atherosclerosis and arteriosclerosis, which render the vessels susceptible to occlusion or rupture (stroke), a major cause of disability and death in the older population. Reduced brain perfusion in the absence of overt stroke may play a role in age-related cognitive dysfunction. Decreased cerebral blood flow occurs with advancing age and is accompanied by declines in cerebral metabolic rate for oxygen and glucose use. Age-related changes in cerebral vasculature are generally similar to those that occur in vessels elsewhere in the body and are therefore likely to result from common cellular and molecular changes, including accumulation of atherosclerotic plaques, oxidative damage to vascular endothelial cells, and an inflammatory response in which macrophages may penetrate the blood-brain barrier.

Age-dependent cerebral vascular changes are strongly linked to heart disease and hypertension. Interestingly, apolipoprotein E polymorphisms are linked to increased risk of both atherosclerosis and Alzheimer disease, with the

apolipoprotein E4 increasing the risk. This association suggests that age-related vascular changes may make an important contribution to the neurodegenerative process in Alzheimer disease. Finally, important transport functions of cells (endothelial cells and astrocytes) that comprise the blood-brain barrier may also be impaired in the aging brain and more so in Alzheimer disease. Many of the same medical, behavioral, and dietary approaches now recognized to forestall cardiovascular disease may also forestall cerebrovascular disease; these approaches include correcting existing risk factors such as hypertension and hypercholesterolemia, engaging in physical and mental activities, preventing and/or correcting obesity, and taking a low-calorie and a high antioxidant diet.

Amyloid Accumulation

Aβ is a 38- to 49-amino acid peptide that arises from a much larger membrane-spanning precursor, the amyloid precursor protein (APP). During normal aging, and to a much greater extent in Alzheimer disease, Aβ forms insoluble aggregates in the brain parenchyma and vasculature. Of the above different Aβ species, the 40- and 42-aa long peptides are by far the most abundant; Aβ40 preferentially accumulates in the vasculature while Aβ42 preferentially accumulates in the parenchyma. Small Aβ aggregates (oligomers) can be neurotoxic, and can increase neuronal vulnerability to metabolic, excitotoxic, and oxidative insults. Aβ aggregates are organized as fibrils of approximately 7 to 10 nm in the amyloid plaques (also referred to as senile plaques), which accumulate in the brain parenchyma and are intermixed with nonfibrillary forms of the peptide and often surrounded by dystrophic neurites.

In addition to Alzheimer disease brains, amyloid/senile plaques are also present in the hippocampus and neocortex of cognitively normal aged individuals and tend to increase in an age-dependent fashion. Although still under debate, it is now becoming apparent that the number and/or distribution of amyloid plaques does not immediately correlate with cognitive decline. The synaptic loss and the number/distribution of neurofibrillary tangles appear to be better predictors of memory deficits. Indeed, the neuronal/synaptic loss of the hippocampal formation, entorhinal cortex, and entorhinal-hippocampal association system appears to be the only feature able to distinguish normal aging from MCI and the early stages of Alzheimer disease. Although amyloid plaques do not closely correlate with memory deficits, a high plaque load is rarely observed in the absence of cognitive impairment.

Detailed information on the mechanisms that lead to the generation and accumulation of Aβ in the brain as well as Alzheimer disease–relevant pathogenic features can be found elsewhere in this book (see Chapter 66).

FREE RADICALS AND THE AGING BRAIN

A free radical is any molecule with an unpaired electron in its outer orbital; in biological systems, oxygen-based molecules are the predominant free radical species. A major oxyradical in cells is superoxide ($O_2^{-\bullet}$) which is generated during the mitochondrial electron transport process; superoxide dismutases (MnSOD and Cu/ZnSOD) eliminate $O_2^{-\bullet}$ by converting it to hydrogen peroxide (H_2O_2). H_2O_2 can be converted to hydroxyl radical (OH•) via the Fenton reaction which is catalyzed by Fe^{2+} and Cu^{+}. Peroxynitrite ($ONOO^{-}$) arises from the interaction of nitric oxide (NO) with O_2^{-}; calcium influx is a major stimulus for NO production. While OH• and $ONOO^{-}$ can cause direct damage to proteins and deoxyribonucleic acid (DNA), their major means of damaging cells is by attacking fatty acids in membranes and initiating a process called lipid peroxidation. Studies of aging have provided compelling evidence that there is an increase in production and accumulation of oxidatively damaged molecules in essentially all tissues of the body during the aging process, including the brain.

Lipid Peroxidation

Levels of lipid peroxidation products such as lipid peroxides and 4-hydroxynonenal are significantly elevated in the brain parenchyma and cerebrospinal fluid in Alzheimer disease. Immunohistochemical analyses of brain tissue from Alzheimer disease and Parkinson disease patients and spinal cord tissue from amyotrophic lateral sclerosis patients, using antibodies directed against 4-hydroxynonenal adducts revealed increased levels of 4-hydroxynonenal in association with degenerating neurons and neuritic plaques suggesting a role for this aldehyde in the neurodegenerative process. Studies of cell culture and animal models of Alzheimer disease and amyotrophic lateral sclerosis show that lipid peroxidation can impair the function of the plasma membrane glucose and glutamate transporters and render neurons vulnerable to excitotoxicity and apoptosis. Administration of antioxidants such as vitamin E to cultured cells and transgenic mice expressing mutations that cause Alzheimer disease or amyotrophic lateral sclerosis can retard the neurodegenerative process, suggesting a causal role for lipid peroxidation in these diseases.

Protein Oxidation

Levels of protein oxidation, measured as protein carbonyls, are significantly elevated in the brains of aged rodents, and such age-associated protein oxidation can be prevented by administration of antioxidants. Studies of membrane structure have provided evidence for oxidation-related alterations in membrane protein conformation in old rodents. Studies of brain tissues of patients with Alzheimer disease and Parkinson disease have revealed increased levels of protein oxidation in vulnerable brain regions and, in particular, in degenerating neurons. Oxidation of proteins impairs their function and is therefore a likely contributor to age-related cellular dysfunction and neuronal degeneration. Progressive addition of sugar residues to many different proteins occurs during the aging process. This process, called glycation, may promote oxidative stress in cells. Two proteins that have been shown to be heavily glycated in Alzheimer disease are Aβ and tau, the major components of plaques and neurofibrillary tangles, respectively.

DNA Damage

Very little nuclear DNA damage occurs in the nervous system during aging, but DNA damage may contribute to the pathogenesis of neurodegenerative disorders. Damage to nuclear DNA in striatum of Huntington disease patients, and in hippocampus and vulnerable cortical regions of Alzheimer disease patients, has been documented. Specifically, levels of 8-hydroxyguanosine are increased. This DNA damage may be caused by oxyradicals, with hydroxyl radical and peroxynitrite being the major culprits. Progressive oxidative damage to mitochondrial DNA occurs during aging, and may be exacerbated in neurodegenerative disorders. Mitochondrial DNA is particularly prone to damage because this organelle is the site where the vast majority of free radicals are generated and because cells do not possess effective systems for repair of damaged mitochondrial DNA. Damage to mitochondrial DNA can lead to failure of electron transport and reduced adenosine triphosphate (ATP) production. Moreover, the important calcium sequestering function of mitochondria may be compromised as the result of age-related DNA damage which may increase neuronal vulnerability to excitotoxicity and apoptosis.

Mechanisms That Promote Oxidative Stress in Aging

Mitochondria-derived oxyradicals are likely to play a central role in the cumulative oxidative damage to various cellular constituents that accrue with aging. Age-related impairments in energy availability and metabolism may contribute to an acceleration of oxyradical production with aging. Levels of cellular oxidative stress (as indicated by oxidation of proteins, lipids, and DNA) are decreased in many different nonneural tissues of rats and mice maintained on a calorie-restricted diet (30%–40% reduction in calories). Recent studies suggest that levels of oxidative stress are also reduced in the brains of calorie-restricted rodents. The current dogma for the underlying mechanism is that reduced mitochondrial metabolism because of reduced energy availability results in a net decrease in mitochondrial reactive oxygen species (ROS) production over time, and hence less radical-mediated cellular damage.

In addition to the oxyradical damage that accrues with usual aging, there are specific initiators of oxidative stress that appear to play key roles in different age-related neurodegenerative disorders. For example, in Alzheimer disease the increased generation and accumulation of Aβ may be a pivotal event that enhances oxidative stress in neurons. There is evidence that increased levels of Fe^{2+} in the substantia nigra plays a role in the degeneration of dopaminergic neurons in Parkinson disease. The damage to neurons in the brain of stroke victims is the result of a combination of factors including excessive calcium influx and the presence of blood components such as Fe^{2+} and thrombin. In Huntington disease, the presence of trinucleotide repeats in the huntingtin protein may induce oxidative stress in striatal neurons by a yet-to-be-determined mechanism.

ALTERATIONS IN ENERGY METABOLISM AND MITOCHONDRIAL FUNCTION IN THE AGING BRAIN

During the aging process, changes that occur in cerebral blood vessels, as well as in the neural cells themselves, appear to result in reduced energy availability to neurons. These age-related changes may be accelerated in several different neurodegenerative disorders including Alzheimer disease and Parkinson disease.

Cerebral Metabolism

Reduced glucose use, and changes in enzymes involved in energy metabolism, may occur during normal aging, but are

not dramatic. Studies of aging rodents document decreases in glucose and ketone body oxidation, oxygen consumption, local cerebral glucose use, and glycolytic compounds (eg, fructose-1,6-diphosphate). Additional studies show that brain cells in older animals exhibit increased vulnerability to metabolic stresses. Incorporation of glucose into amino acids declines in the brain of aging mice, and older people are much more vulnerable to metabolic encephalopathy than young people. In contrast to normal aging, activities of several enzymes involved in energy metabolism are severely reduced in Alzheimer disease brain tissue. Three such enzymes, which are involved in mitochondrial oxidative metabolism, are the pyruvate dehydrogenase complex, the α-ketoglutarate dehydrogenase complex, and cytochrome c oxidase. These defects may result from age-associated oxidative damage to the DNA encoding these enzyme systems and/or reduced activity of the proteins in these systems.

Another factor that may contribute to reduced neuronal energy metabolism is impairment of the function of glucose transporter proteins in neuronal membranes. Studies of postmortem brain tissue of Alzheimer disease patients document reduced levels of glucose transporters, and experimental studies of cultured hippocampal neurons and synaptosomes show that insults relevant to the pathogenesis of Alzheimer disease (exposure to Aβ and oxyradical-generating agents) can impair glucose transport. Impairment of glucose transport and mitochondrial dysfunction would be expected to lead to ATP depletion and render neurons vulnerable to excitotoxicity.

Mitochondrial Function

Age-related structural changes in synaptic mitochondria have been reported and include a decrease in numbers and increase in size. During normal aging levels of mitochondrial protein synthesis are unchanged. However, decreases in synthesis of specific mitochondrial proteins that are components of the electron transport chain occur in aging rodents. Damage to mitochondrial DNA progressively increases in somatic cells during the aging process, with the most pronounced damage occurring in postmitotic cells such as neurons. Mitochondrial dysfunction has been linked to several neurodegenerative disorders. In Parkinson disease there are marked decreases in complex I and α-ketoglutarate dehydrogenase activities. Exposure of cultured dopaminergic neurons to insults relevant to the pathogenesis of Parkinson disease (eg, MPTP and Fe^{2+}) cause mitochondrial dysfunction. In Alzheimer disease, cytochrome c oxidase and α-ketoglutarate dehydrogenase activity levels are markedly reduced in vulnerable brain regions. Interestingly, mitochondrial deficits are also observed in nonneuronal cells, including platelets and fibroblasts, of Alzheimer disease patients. When mitochondria from platelets of Alzheimer disease patients are introduced into cultured neuroblastoma cells, levels of oxidative stress are increased suggesting an important contribution of mitochondrial alterations to the increased oxidative stress present in neurons of Alzheimer disease brain. Mitochondrial alterations in neurons have been documented in studies of mouse models of Alzheimer disease (APP and presenilin mutant mice), Parkinson disease (α-synuclein mutant mice), Huntington disease (huntingtin mutant mice), and stroke (middle cerebral artery occlusion).

NEURONAL ION HOMEOSTASIS IN THE AGING BRAIN

Among the properties of neurons that set them apart from many other cell types is their excitability, which is regulated by a complex array of neurotransmitters and ion channels. Neurons express voltage-dependent sodium channels, as well as multiple types of calcium and potassium channels that are differentially expressed among neuronal populations, and are segregated in different cellular compartments (eg, L-type calcium channels in the cell body, N-type calcium channels in the dendrites, and T-type calcium channels in presynaptic terminals). In addition, neurons possess ion-motive ATPases that play critical roles in reestablishing ion gradients following neuronal stimulation. A variety of age-related alterations in electrophysiologic parameters of neurons have been described in rodents (described earlier in this chapter) and, in some cases, in humans, including increased thresholds for induction of action potentials in cranial nerves, increased after hyperpolarizations in hippocampal neurons, and impaired LTP/LTD of synaptic transmission in the hippocampus. Moreover, a generalized decrease in neuronal inhibition appears to occur during the aging process.

The calcium ion plays fundamental roles in regulating neuronal survival and plasticity in both the developing and adult nervous system. Calcium mediates some of the effects induced by neurotransmitters and neurotrophic factors on neurite outgrowth, synaptogenesis, and cell survival in many different regions of the developing nervous system. Furthermore, in the adult nervous system, calcium regulates neurotransmitter release from presynaptic terminals and influences postsynaptic changes associated with learning and memory processes. Aging may result in decreases in the activity of the plasma membrane calcium ATPase and in levels of calcium-binding proteins, while increasing calcium influx through voltage-dependent channels and increasing the activation of calcium-dependent proteases.

Several studies have measured and determined changes in calcium transmission across the neuronal membrane in aged rodents. The final step in synaptic transmission that triggers LTP or LTD is dependent on the amount of calcium entering the cell. Therefore, changes in calcium conductance across the cell membrane could have significant effects on synaptic plasticity in aged animals. Studies have revealed that aged rats display an increased density of L-type Ca^{++} channels in CA1 pyramidal cells, leading to increased L-type Ca^{++} currents. In addition, CA1 pyramidal cells from aged rodents also show an increased duration of calcium-mediated action potentials. The inward flux of calcium in response to an action potential activates a calcium-mediated inward potassium current. These potassium channels are slower to open and close than calcium channels, which leads to a temporary afterhyperpolarization of the cell following an action potential. Studies have revealed that this phenomenon is increased in aged rodents and rabbits, leading to less frequent firing of action potentials in response to a prolonged depolarizing current. Taken together, these data demonstrate that age-related changes in calcium transmission underly detrimental changes in synaptic plasticity and may partially explain the deficits in plasticity seen over the course of aging.

NEUROTRANSMITTER SIGNALING IN THE AGING BRAIN

A number of alterations in different neurotransmitter systems have been documented in studies of aging rodents, and in analyses of brain tissues from humans with age-related neurodegenerative disorders. While some of these alterations likely result from neuronal degeneration, others appear to occur in the absence of cell injury.

Cholinergic Systems

Acetylcholine is employed as a neurotransmitter in select populations of neurons in the brain, prominent among which are basal forebrain neurons that innervate widespread regions of the neocortex and hippocampus; these cholinergic neurons are known to play key roles in learning and memory processes in humans and rodents. Deficits in one or more aspects of cholinergic signal transduction may occur with aging including choline transport, acetylcholine synthesis, acetylcholine release, and coupling of muscarinic receptors to their GTP-binding effector proteins. Cholinergic deficits are much more severe in Alzheimer disease patients and also differ qualitatively from the changes observed during normal aging. Particularly striking is a reduced ability of muscarinic agonists to activate GTP-binding proteins in cortical neurons. Increased levels of membrane lipid peroxidation in neurons may contribute to impaired cholinergic signaling; for example, Aβ, Fe^{2+}, and the lipid peroxidation product 4-hydroxynonenal can impair coupling of muscarinic receptors to the GTP-binding protein G_{q11}.

Dopaminergic Systems

Prominent reductions in both pre- and postsynaptic aspects of dopaminergic neurotransmission occur during brain aging. Decreases in dopamine levels and dopamine transporter levels in the striatum occur with advancing age, and there is an age-related decrease in levels of D_2 receptor-binding sites in striatum. As with cholinergic signal transduction, there also appears to be an age-related impairment of coupling of dopamine receptors to their GTP-binding effector proteins. The contribution of oxidative stress to changes in dopaminergic signaling has not been established, although the prominent role of oxyradicals in the pathogenesis of Parkinson disease argues that similar oxidative processes contribute to dopaminergic dysfunction during normal aging. These changes in dopaminergic signaling likely play a role in age-related deficits in motor control and may explain the fact that the older adults are susceptible to extrapyramidal effects of dopamine receptor antagonist drugs.

Monoaminergic Systems

Norepinephrine and serotonin are the major monoamine neurotransmitters in the brain. Noradrenergic neurons are located primarily in the locus caeruleus and serotonergic neurons in the raphe nucleus; both types of neurons project to widespread regions of cerebral cortex. There are several subtypes of receptors for norepinephrine, some of which couple to GTP-binding proteins. There are also several subtypes of serotonin receptors; some couple to GTP-binding proteins while others are ligand-gated ion channels. There appears to be increased levels of norepinephrine with aging in some brain regions, while levels of α_2-adrenergic receptors may decrease in cerebral cortex with advancing age. Levels of serotonin may decrease in the striatum, hippocampus, and cerebral cortex. Age-related decreases in levels of evoked serotonin release and of serotonin-binding sites have been reported, and may contribute to affective disorders such as depression.

Amino Acid Transmitter Systems

The amino acid glutamate is the major excitatory neurotransmitter in the human brain. Glutamate stimulates ionotropic receptors that flux calcium and sodium; excessive activation of ionotropic glutamate receptors may play a role in the degeneration of neurons in several age-related disorders including stroke, Alzheimer disease, Parkinson disease, and Huntington disease. Levels of ionotropic glutamate receptors were reported to decrease with aging, but these decreases may be the result of degeneration of the neurons expressing the receptors. The contribution of dysfunction of glutamatergic transmission, in the absence of neuronal death, to age- and disease-related deficits in brain function is unknown. The major inhibitory neurotransmitter in the human brain is γ-aminobutyric acid (GABA). Relatively little information is available concerning the impact of aging on GABAergic systems, although levels of glutamate decarboxylase and GABA-A binding sites may be decreased. Interestingly, GABAergic interneurons are typically spared in various neurodegenerative disorders including Alzheimer disease.

NEUROENDOCRINE CHANGES IN THE AGING BRAIN

A variety of age-related alterations in neuroendocrine systems have been documented. Of particular importance for human brain aging and neurodegenerative disorders are changes in levels of steroid hormones, particularly glucocorticoids and estrogens. There is considerable evidence for age-related alterations in the diurnal regulation of circulating glucocorticoid levels, and an increase in the mean level. Moreover, regulation of the hypothalamic-pituitary-adrenal axis is altered in Alzheimer disease patients, such that plasma levels of glucocorticoids are increased. Increased levels of glucocorticoids, including those induced by physiologic or psychological stress, can increase the vulnerability of hippocampal neurons to injury and death caused by ischemic and excitotoxic insults, suggesting that glucocorticoids may have a negative impact on the outcome of both acute (eg, stroke) and chronic (eg, Alzheimer disease) age-related neurologic disorders. Estrogen (17β-estradiol) may have a beneficial effect on brain aging. Epidemiologic studies suggest a reduced risk of Alzheimer disease in postmenopausal women who take estrogen replacement therapy, and older women who take estrogens perform better on cognitive tasks. Surgical ovariectomy in rodents causes changes in neurotrophin receptor signaling, promotes the generation and accumulation of Aβ, and is associated with memory deficits. These effects are abrogated by exogenous estrogens. Finally, animal and cell culture studies have shown that 17β-estradiol can protect neurons from being damaged and killed by insults relevant to ischemia and Alzheimer disease, including glucose deprivation, exposure to Aβ, and expression of Alzheimer disease–linked presenilin mutations. Results of clinical findings, however, have not provided any convincing evidence that estrogen treatment either reduces risk for Alzheimer disease or related illnesses or enhances cognition. In contrast, findings from the Women's Health Initiative indicated that extended therapy with both opposed and unopposed conjugated equine estrogen (CEE) increased risk for dementia, heart disease, stroke, and cognitive decline in older postmenopausal women.

IMMUNOLOGIC FACTORS IN BRAIN AGING

While the blood-brain barrier limits access of circulating lymphocytes to neurons in the brain, it is becoming increasingly evident that the brain is by no means devoid of immune responses. The brain possesses resident immune effector cells called microglia that may respond to age- and disease-related neurodegenerative processes. Some data suggest that a decline in peripheral immune function during aging may lead to an autoimmune-like phenomenon in the brain wherein microglia is activated. Inflammatory processes are associated with, and contribute to, the neurodegenerative process in Alzheimer disease and other age-related neurodegenerative disorders; these include activation of microglia in the affected brain regions, increased local cytokine production in association with the neuropathologic changes, and activation of components of the complement cascade system. Collectively, the emerging data suggest a role for chronic inflammatory reactions in the pathogenesis of at least some neurodegenerative disorders. Recent studies have revealed that the choroid plexus, an epithelial monolayer that produces cerebrospinal fluid and maintains a dynamic interface between the cerebrospinal fluid and the blood, undergoes age-associated changes that are consistent with a type I interferon effect. Importantly, blocking type I interferon activity in aged mice is sufficient to reestablish a "young" choroid plexus activity and improve memory functions. Also intriguing is the fact that these changes appear to be driven by inflammatory changes that originate from both the brain parenchyma and the systemic

circulation. Together, these results suggest that changes in inflammatory markers in the brain or in the periphery can influence (positively or negatively) memory functions; they also suggest that the choroid plexus plays an important role in the age-associated cognitive decline.

NEUROTROPHIC FACTORS IN THE AGING BRAIN

Cells in the nervous system produce a variety of proteins which serve the function of promoting neuronal survival and growth, and protecting the neurons against injury and death. Examples of such "neurotrophic factors" (also referred to as neurotrophins) include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3, neurotrophin-4, basic fibroblast growth factor (bFGF), and insulin-like growth factor (IGF). Neurotrophic factors are remarkable in that they can protect neurons against a variety of insults relevant to the pathogenesis of age-related neurodegenerative conditions. For example, bFGF can protect hippocampal and cortical neurons against metabolic, oxidative, and excitotoxic insults, and can greatly reduce brain damage in rodent models of stroke. One or more neurotrophic factors have also been shown to protect particular neuronal populations against neurodegenerative disorder-specific insults. Examples are the ability of BDNF to protect dopaminergic neurons against MPTP toxicity (Parkinson disease model) and hippocampal neurons against Aβ-mediated toxicity (Alzheimer disease model). The precise mechanism(s) whereby neurotrophic factors can rescue or prevent neuronal degeneration are unclear, and might be different in different neuronal populations. However, some of the protective effects may be linked to increased cellular resistance to oxidative stress and stabilization of cellular calcium homeostasis. In addition to preserving existing neurons, neurotrophic factors may stimulate the production of new neurons from neuronal stem cells. Such neural stem cells may be able to replace lost or damaged neurons, and are therefore receiving considerable attention for their potential use in the treatment of neurodegenerative disorders. An intriguing feature of neurotrophic factors is that their expression is increased by activity in neuronal circuits. Experimental studies in cell culture and in vivo show that such activity-dependent production of neurotrophic factors plays a major role in promoting neuronal survival and neurite outgrowth. Rearing of rodents in an "intellectually enriched" environment results in expansion of dendritic arbors and increased numbers of synapses in hippocampus and certain regions of cerebral cortex.

The activity and the specificity of neurotrophic factors depend on specific cell-surface receptors. Examples are the tyrosine-kinase family of receptors, TrkA, TrkB, and TrkC, and the p75 neurotrophin receptor ($p75^{NTR}$). These receptors can assemble as homo- and heterodimers, which display different affinity to specific neurotrophic factors and provide signaling specificity. For example, TrkA:$p75^{NTR}$ heterodimers have higher affinity to NGF than TrkA:TrkA and $p75^{NTR}$:$p75^{NTR}$ homodimers. Therefore, depending on how these receptors assemble on the neuronal surface, they can transduce slightly different or completely different signals. During aging the levels of TrkA decrease while those of $p75^{NTR}$ increase, thus an expression pattern that favors the formation of TrkA:TrkA homodimers will switch toward an expression pattern that favors the formation of TrkA:$p75^{NTR}$ heterodimers and $p75^{NTR}$:$p75^{NTR}$ homodimers. While this switch occurs, the levels of NGF remain overall unchanged. However, since the affinity of the above receptor complexes for NGF is different, the signaling cascade will change as a result of aging. As an example, the above TrkA-to-$p75^{NTR}$ switch has been linked to cognitive decline and increased risk of Alzheimer disease in rodents. A TrkA-to-$p75^{NTR}$ switch has also been observed following surgical menopause in rodents, suggesting a possible impact in postmenopausal women.

The above competing activity of neurotrophin receptors is further complicated by the competing activity of neurotrophins. An example is BDNF competing with NGF for binding on TrkA:TrkA homodimers and pro-NGF competing with NGF for binding on $p75^{NTR}$:$p75^{NTR}$ homodimers and TrkA:$p75^{NTR}$ heterodimers. Importantly, levels of pro-NGF increase as a function of age while those of NGF remain unchanged. Mice with increased levels of pro-NGF develop a brain phenotype that resembles Alzheimer disease, and postmortem Alzheimer disease brain tissues express more pro-NGF than age-matched controls. In conclusion, complex scenarios can result as a function of aging leading to different neurotrophin-receptor interactions and, ultimately, to different biological effects. Since some of these changes are brain areas specific, we can expect different physiologic/pathologic outcomes.

GENETIC FACTORS IN BRAIN AGING AND NEURODEGENERATIVE DISORDERS

Several microarray studies have now been performed in mice, rats, nonhuman primates, and humans to analyze the genetic profile of the aging brain. They all indicate that normal aging is not accompanied by a genome-wide

dysregulation of transcription but rather by specific changes that affect only a small subset of genes, which accounts for about 3% to 5% of all the genes expressed in the brain. These changes (**Table 62-2**) will not be discussed here as their overall biological significance is still uncertain. Of note, a similar expression profile was also found in patients with Alzheimer disease supporting the view that a *continuum* might exist between normal aging and Alzheimer disease.

TABLE 62-2 GENETIC PATHWAYS OF THE BRAIN THAT ARE AFFECTED BY AGING

Glucose metabolism	Some up, some down
Fatty acid metabolism and transport	Overall down
Mitochondria β-oxidation	Overall down
Protein synthesis and modification	Some up, some down
Protein turnover	Overall down
Vesicular/protein transport	Overall down
Stress response (antioxidant, DNA repair, metal ion homeostasis, etc)	Overall up
Inflammatory molecules	Overall up
Microglia activation	Overall up
Neurogenesis	Overall down
Growth factors	Overall down
Myelination	Overall up
Synaptic turnover and activity	Overall down
Synaptic plasticity	Overall down
Ca^{++} homeostasis	Overall down
Intraneuronal signaling (kinases, G proteins, etc)	Overall down
Hormonal regulation	Some up, some down

Longevity Genes

It is now evident that specific genetic, biochemical, and molecular pathways are intrinsically related to aging. Some of these pathways were initially identified in lower organisms and then later confirmed in higher organisms while others were immediately identified in higher organisms. These include the insulin-like growth factor 1 receptor (IGF-1R), Delta40p53, and Klotho.

Among them, IGF-1R has probably received more attention. The first evidence that IGF-1R signaling can regulate the progression of aging came from *Caenorhabditis elegans* where mutations that reduce IGF-1R activity were able to increase the lifespan of the animal. Similar results were then obtained in *Drosophila melanogaster* and, later on, in mammals. Importantly, mutations that act on IGF-1R downstream targets were also able to modify the lifespan of the animals providing robust and definitive connection between IGF-1R and aging. Overall, reduced IGF-1R activity extends lifespan and delays age-associated events while increased IGF-1R activity achieves the opposite effects. A partial block of IGF-1R signaling is also achieved by caloric restriction, which extends the maximum lifespan and delays many biological changes that are associated with aging. In humans, genetic variations that cause reduced IGF-1R signaling appear to be beneficial for old age survival and preservation of cognitive functions, suggesting that the mechanisms regulating lifespan and aging via this pathway are evolutionary conserved. Finally, reduced IGF-1R signaling can rescue Alzheimer disease in mouse models.

Delta40p53 is a short N-terminal truncated isoform of the tumor suppressor gene *TP53*. The common *TP53* gene generates at least 12 different proteins through a combination of alternative promoter usage, alternative splicing, and alternative initiation of translation. Of them, p53 is the most “famous” and most studied due to its pathogenic role in many forms of cancer. Delta40p53 (also referred to as p44 or p47) lacks the first N-terminal 39 amino acids of full-length p53 but retains the DNA-binding domain as well as one of the two transactivation domains. Delta40p53 retains some of p53 functions but lacks others; it retains some of the regulatory elements but lacks others. Mice overexpressing

full-length p53 (“Super p53” mice) are resistant to cancer development but have normal maximum lifespan. In contrast, mice overexpressing Delta40p53 ($p44^{+/+}$ mice) display a progeroid phenotype that mimics an accelerated form of aging. The phenotype includes early onset of diabetes, osteoporosis, memory impairment, and reduced lifespan. To date at least five additional mouse models with altered p53 activity have been shown to develop an accelerated aging phenotype providing robust and definitive connection between *TP53* and aging. Recent studies have also shown that Delta40p53 regulates the generation of Aβ as well as the phosphorylation status of tau, suggesting a possible connection with the accumulation of amyloid plaques and neurofibrillary tangles that characterizes the aging as well the Alzheimer disease brain (discussed earlier in this chapter). Interestingly, mice engineered to overexpress p44 develop an accelerated form of Alzheimer disease neuropathology.

Klotho is a cell-surface membrane protein that can also be released in the circulation. Klotho has glycosidase-like activity. Its levels and enzymatic activity decline during aging. Genetic variants of *KLOTHO* are associated with human aging and klotho-deficient mice display a progeroid phenotype that resembles aging. The phenotype includes atherosclerosis, skin atrophy, osteoporosis, reduced fertility, emphysema, memory defects, and reduced lifespan. In contrast, mice overexpressing klotho display increased lifespan and increased resistance to several age-associated features. A possible connection between klotho and IGF-1R has also been delineated. Human variations that lead to increased circulating levels of klotho are associated with greater cortical volumes in the brain. Finally, overexpression of klotho in the mouse enhances cognition and rescues some of deficits that characterize Alzheimer disease.

In addition to the above, polymorphisms that are associated with longevity and preserved physiologic functions have also been identified in two cholesterol-related genes, apolipoprotein E (*APOE*) and cholesteryl ester transfer protein (*CETP*). *APOE* carries cholesterol in the circulation while *CETP* facilitates the transfer of cholesteryl esters and triglycerides between circulating lipoproteins. Individuals normally inherit two APOE alleles, of which there are three isoforms (E2, E3, and E4). The E2 allele has been linked to longevity and reduced incidence of Alzheimer disease. In contrast, the E4 allele has been linked to increased risk for Alzheimer disease. Certain *CETP* variants have been linked to increased levels of high-density lipoproteins (HDL), reduced progression of atherosclerosis, and longevity. The “longevity effect” of *APOE* and *CETP* might be explained, at least in part, by their ability to reduce the progression of atherosclerosis in the vasculature.

Another possible longevity gene is that encoding an isoform of angiotensin-converting enzyme, although its mechanistic links to aging are unclear. Finally, the multigene major histocompatibility system appears to influence lifespan, and may act by sustaining functions of the immune system. Additional information on longevity genes and their impact in age-associated events can be found in Chapter 1.

Disorder-Specific Genes

Considerable progress has been made in characterizing human genetic disorders that cause progeroid syndromes, which are characterized by a disease phenotype mimicking an “accelerated” form of aging. Although progeroid syndromes can be classified as *unimodal* (affecting one tissue/organ) and *segmental* (affecting multiple tissues/organs), the term progeroid syndrome is usually limited to the segmental forms of the disease (**Table 62-3**). Examples include Werner syndrome, Bloom syndrome, Rothmund-Thomson syndrome, Hutchinson-Gilford progeria syndrome, and Cokayne syndrome. Patients affected by these disorders have limited lifespan and develop a complex array of disease manifestations, including type 2 diabetes, osteoporosis, hair loss, skin atrophy, atherosclerosis, cardiomyopathy, heart failure, chronic obstructive pulmonary disease, renal insufficiency, and neurologic abnormalities. The neurologic defects are often subtle and difficult to diagnose; when evident, they include bulbar, extrapyramidal and cerebellar symptoms, deafness, retinopathy, cognitive deficits, corticospinal symptoms, and peripheral neuropathy. Brain imaging shows diffused white matter pathology as well as different degrees of gray matter pathology in memory-forming and -processing areas. The genetic defect has been mapped in most classical forms of progeroid syndromes. Specifically, Werner syndrome has been associated with mutations in *WRN*; Bloom syndrome has been associated with mutations in *BLM*; Rothmund-Thomson syndrome has been associated with mutations in *RECQL4*; Hutchinson-Gilford progeria syndrome has been associated with mutations on *LMNA*; and Cokayne syndrome has been associated with mutations in *ERCC8* and *ERCC6*. All the above genes encode proteins that are involved in different aspects of DNA transcription, repair, or recombination underscoring common pathogenic elements.

TABLE 62-3 SEGMENTAL PROGEROID SYNDROMES WITH COGNITIVE CHANGES

SYNDROME	INHERITANCE	MEAN LIFESPAN (Y)

Ataxia-telangiectasia	Autosomal recessive	~ 45–50
Berardinelli-Seip syndrome	Autosomal recessive	~ 40
Bloom syndrome	Autosomal recessive	Unclear
Cokayne syndrome	Autosomal recessive	~ 20
Down syndrome	Trisomy 21	~ 60
Hutchinson-Gilford progeria	Autosomal dominant	~ 10–15
Rothmund-Thompson syndrome	Autosomal recessive	Unclear
Trichothiodystrophy	Autosomal recessive	~ 10
Werner syndrome	Autosomal recessive	~ 45–50

Although progeroid syndromes manifest with symptoms and physical features that are—at least in part—reminiscent of an accelerated form of aging, they must be viewed as diseases rather than true forms of accelerated aging. It is plausible to assume that the dissection of the molecular phenotype of these diseases will inform us about aging. However, it is also plausible to expect that the underlying defects of human progerias are substantially different from those of normal aging. Additional discussion of human progerias can be found in Chapter 1.

Considerable progress has also been made in identifying genetic factors that play pathogenic roles in Alzheimer disease, the most common form of dementia associated with aging. Specifically, disease-causing mutations in *APP*, *PSEN1*, and *PSEN2* have been identified in familial (early-onset) forms of Alzheimer disease. In addition, several "predisposition" genes have been identified in which polymorphisms increase the risk for developing sporadic (late-onset) Alzheimer disease. Description of the most important polymorphisms identified to date as well as pathogenic roles of *APP*, *PSEN1*, and *PSEN2* can be found in Chapter 66.

The Brain as a Regulator of Lifespan

Among the very first mouse models of extended lifespan were the Ames and the Snell dwarf mice. Both models had a selective defect in the secretion of key hormones from the pituitary gland, specifically, growth hormone (GH), prolactin, and thyroid-stimulating hormone. The 40% to 60% extension of lifespan was also accompanied by evidence of delayed aging. The increased lifespan of the Ames and Snell mice was primarily linked to the deficiency of the GH-IGF1 axis. GH is released in the circulation by the pituitary gland; upon binding to its own receptor in the liver, it causes secretion of IGF1, which then binds to IGF-1R and stimulates IGF-1R signaling. Mice with isolated deficiency in growth hormone secretion (Little mice) or lacking the growth hormone receptor (GHR-KO mice) also displayed longevity. The lifespan extension in the Little and GHR-KO mice was in the 25% to 55% range. Finally, mice with reduced secretion of IGF1 or reduced levels of IGF-1R also displayed different levels of increased lifespan. In essence, the Ames and Snell mice represent the very first evidence that the brain itself (or specialized sets of neurons in the brain) could influence the lifespan of the animals. Following studies in lower organisms (*C elegans* and *D melanogaster*) clearly confirmed this conclusion. More recently, genetic disruption of IRS2, an adaptor protein that acts downstream of IGF-1R and the insulin receptor, in the mouse brain ($bIrs^{-/+}$ and $bIrs^{-/-}$) also caused a significant increase in the lifespan of the animals. Regardless of the specific mechanism(s) involved in the phenotype of the above genetic models, it is now well accepted that in addition to being affected by aging, the brain (or the nervous system) itself can affect aging.

DIETARY FACTORS IN BRAIN AGING AND NEURODEGENERATIVE DISORDERS

It is now evident that the diet can affect one's risk of age-related neurodegenerative disorders. In particular, emerging findings indicate that several dietary risk factors for prominent age-related diseases including cardiovascular disease, cancer, and diabetes are also risk factors for Alzheimer disease, Parkinson disease, and stroke. A summary of possible preventive measures to improve brain health can be found in **Table 62-4**.

TABLE 62-4 PREVENTIVE MEASURES TO PROTECT THE AGING BRAIN

- **Physical exercise**. Improves cardiovascular functions; reduces volume loss; stimulates neurogenesis.
- **Intellectual and outdoor activities**. Stimulate neurogenesis; stimulate synaptic plasticity; increase brain capacity.

- **Diet**. Improved brain health has been associated with diets that include a modest decrease in total calories and high consumption of fruits and vegetables. Antiaging effects have been associated with intake of poly- and monounsaturated fatty acids, vitamins, phytochemicals, polyphenols, and antioxidants.
- **Correction of existing medical conditions**. Examples include hypercholesterolemia, dyslipidemias, diabetes, and hypertension.
- **Minimize environmental stressors**. Disposition to stress is associated with poor brain health.

Calorie Intake

Apart from genetic manipulation, the only known means of increasing the lifespan of rodents and nonhuman primates is by decreasing their calorie intake; both maximum and mean lifespan can be increased by up to 40%. The average lifespan of humans is certainly decreased by overeating, although it remains to be determined whether maximum lifespan can be increased through calorie restriction. Epidemiologic data suggest that individuals with a low-calorie intake are at a reduced risk for Alzheimer disease and Parkinson disease. Biochemical markers of aging, and deficits in learning and memory and motor function, are retarded in rodents maintained on dietary restriction. Neurons in the brains of rats and mice maintained on dietary restriction are more resistant to dysfunction and death in experimental models of Alzheimer disease, Parkinson disease, Huntington disease, and stroke. A 20-year longitudinal study in Rhesus macaques showed that a 30% reduction in daily calorie intake reduced the rate of age-related deaths as well as the incidence of typical age-associated diseases, such as diabetes, cancer, cardiovascular disease, and brain atrophy. The ability of calorie restriction to prevent brain atrophy was observed across several gray matter areas involved in both motor and executive functions. Magnetic resonance imaging also showed preserved volumes and insulin sensitivity in memory-forming and -processing areas while postmortem histology showed reduced astrogliosis. Therefore, a large body of evidence from lower organisms to nonhuman primates delineates a relationship between calorie intake and progression of aging and/or incidence of age-associated events. The mechanism whereby caloric restriction increases the resistance of neurons to the adverse effects of aging is not entirely known. Studies in yeast, worms, flies, rodents, and monkeys suggest that the reduced calorie intake causes a comprehensive metabolic reprogramming that involves key nutrient-responsive signaling pathways.

Folic Acid (Homocysteine)

It was recognized long ago that folic acid deficiency can cause abnormalities in the developing nervous system. Subsequently, it was shown that people with low levels of folic acid tend to have elevated levels of homocysteine and that this condition is associated with increased risk of cardiovascular disease and stroke. Homocysteine is produced during metabolism of methionine, and folic acid plays an important role in removing homocysteine via remethylation. Epidemiologic findings suggest that people with elevated homocysteine levels may be at increased risk of Alzheimer disease and Parkinson disease. Animal studies support a cause-effect relationship between elevated homocysteine levels and neuronal vulnerability to neurodegenerative disorders. For example, hippocampal neurons of APP mutant mice (Alzheimer disease model) and substantia nigra dopaminergic neurons in MPTP-treated mice (Parkinson disease model), exhibit increased vulnerability to degeneration when maintained on a folic acid–deficient diet. By increasing homocysteine levels, folic acid deficiency may promote accumulation of DNA damage by inhibiting DNA repair. In neurons, the increased DNA damage can trigger apoptosis, particularly under conditions of increased oxidative or metabolic stress. Of note, results of clinical studies to date have failed to provide any convincing evidence that folic acid supplementation either reduces risk for dementia or vascular diseases.

Antioxidants

Neurons are subjected to increased levels of oxidative stress during normal aging, and more so in neurodegenerative disorders. It is therefore reasonable to consider the possibility that dietary antioxidants might promote successful brain aging. Epidemiologic findings support a protective effect of antioxidants in fruits and vegetables against stroke, and possibly Alzheimer disease. Studies in animal models of Alzheimer disease, Parkinson disease, Huntington disease, stroke, and amyotrophic lateral sclerosis have documented beneficial effects of some antioxidants. Positive effects have been reported for several commonly used dietary supplements, including vitamin E, creatine, and ginkgo biloba. However, the effects of such antioxidants are relatively subtle compared to the quite striking neuroprotective effects of dietary restriction. Notably, results of a large randomized clinical trial using 2000 units of vitamin E in patients with mild-to-moderately severe Alzheimer disease showed a 6-month delay in progression of cognitive symptoms and a significant reduction in caregiver stress. In contrast, a large randomized clinical trial showed no beneficial effects of

ginko biloba in patients with Alzheimer disease.

Stimulatory Phytochemicals

Epidemiologic findings suggest that individuals who regularly consume vegetables and fruits have a lower risk of developing age-related neurodegenerative disorders compared to those who eat few such plant products. Several phytochemicals have been reported to enhance neuronal plasticity and survival in studies of animal models of neurodegenerative disorders. Examples include sulforaphane, curcumin, allicin, resveratrol, and other grape-derived polyphenols. Instead of functioning as direct antioxidants, many of these beneficial phytochemicals may stimulate mild adaptive stress responses that result in increased production of antioxidant enzymes, neurotrophic factors, and other protective proteins in neurons. The possible therapeutic benefits of several such stimulatory phytochemicals are currently being tested in human subjects with age-related neurologic disorders.

CONCLUSION

Structural changes occur in the brain during aging and appear to be compensatory responses to adverse changes in cellular metabolism that accompany the aging process. There are several biochemical processes that may predispose neurons to dysfunction and death in aging and neurodegenerative disorders. The discovery that the lifespan of an organism can be regulated by specific genetic, molecular, and biochemical pathways has changed our view of aging itself and has spurred active interest in studying the basic biology of aging to understand diseases. At the same time disease-driven research has helped to discover pathways that are relevant for aging. Convergence between age- and disease-related research has yielded an unprecedented body of information that will help us understand how the brain evolves and adapts to aging and how we can modulate these changes to improve the quality of life of a growing segment of our population.

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Chapter 63

Cognitive Changes Associated With Normal and Pathologic Aging

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Learning Objectives

- To describe the expected effects of aging on a variety of cognitive functions
- To identify age-related medical conditions that can negatively impact cognition
- To describe the key clinical features of Alzheimer disease (AD) dementia, as well as current primary tools used for diagnosis
- To describe the differences and similarities between AD dementia and other neurodegenerative diseases

Key Clinical Points

1. **Normal aging is associated with mild changes in circumscribed aspects of cognition; these changes are much less significant than cognitive effects associated with age-related medical conditions and neurodegenerative disease.**
2. **Physical disease is often linked with adverse cognitive consequences and increased risk for neurodegenerative disease; effective management of common age-related conditions may thus reduce the negative impact on cognition that is often considered an unavoidable outcome of aging.**
3. **Late-onset depression in older adults may be a symptom of prodromal neurodegenerative disease.**
4. **Certain medications can lead to adverse cognitive effects and even increased risk for dementia in older adults.**
5. **Alzheimer disease dementia is the eventual clinical manifestation of underlying pathology that is often present for years or decades before symptoms are noticed; thus, careful history-taking and new clinical and research tools may aid in early diagnosis.**
6. **Non-Alzheimer neurodegenerative diseases typically manifest with distinct cognitive and behavioral symptoms early in the disease process, although differentiation becomes more difficult with advancing dementia.**

"Age does not depend upon years, but upon temperament and health. Some men are born old, and some never grow so."

Tyron Edwards

"A man is as old as his arteries."

Thomas Sydenham

The dogma that aging brings inevitable cognitive decline is being challenged by studies of the rapidly expanding oldest segment of our society, adults older than 60 years. Although some aspects of cognition are affected by aging, many changes in cognition previously considered the unavoidable consequence of brain senescence may instead result from

incremental insults on brain function associated with aging-related medical conditions. The detection of such changes, which may stabilize or even reverse with appropriate intervention, and their differentiation from the cognitive changes associated with neurodegenerative disease or other neurologic disorders is a critical task. The primary goal of this chapter is to describe changes in various cognitive abilities that occur with normal aging and with common age-related medical and neurologic conditions.

THE EFFECTS OF NORMAL AGING ON COGNITIVE FUNCTION

General Intellectual Functioning

Age-related changes in intelligence are extremely variable, with notable interindividual differences. Overall, studies of aging have consistently shown that crystallized abilities (information and skills gained from experience) remain relatively intact with aging, while fluid intelligence, which involves flexible reasoning and problem-solving approaches, declines. This general pattern has been documented in both cross-sectional and longitudinal research designs. More specifically, it has been theorized that reductions in speed of information processing may account for many of the age-related changes noted in fluid intelligence. Below, we review the literature on the effects of normal aging on specific cognitive functions, summarized in **Table 63-1**.

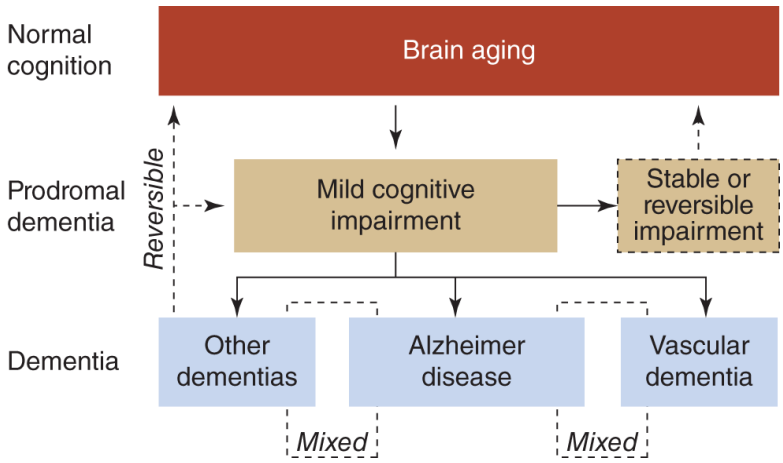


FIGURE 63-1. A conceptual model of mild cognitive impairment (MCI) as prodromal dementia. A minority of persons diagnosed with MCI may remain stable or even improve over time. Although individuals with MCI may decline to vascular or other forms of dementia, the majority of declining MCI patients evaluated in research clinics receive a diagnosis of AD (either in pure form or mixed with other dementia subtypes). (Golomb J, Kluger A, Garrard P, Ferris S. *Clinician's Manual on Mild Cognitive Impairment*. London, UK: Science Press; 2001.)

TABLE 63-1 COGNITIVE EFFECTS OF NORMAL AGING

	PRESERVED COGNITION FUNCTIONS	COGNITIVE FUNCTIONS SHOWING DECLINE
General intellectual functioning	Crystallized, verbal intelligence	Fluid, nonverbal intelligence, speed of information processing
Attention	Sustained attention, primary attention span	Divided attention (possibly)
Executive function	"Real-world" executive functions	Novel executive tasks
Memory	Remote memory, procedural memory, semantic recall	Learning and recall of new information
Language	Comprehension, vocabulary, syntactic abilities	Spontaneous word finding, verbal fluency
Visuospatial	Construction, simple copy	Mental rotation, complex copy, mental assembly
Psychomotor functions		Reaction time

Attention

Attention involves the ability to focus on one or more pieces of information long enough to register and make meaningful use of the data. Attention requires both simple and complex immediate processing and provides a foundation for working memory and other cognitive functions. Sustained attention, or vigilance, entails attending to one type of information over a period of time. After controlling for reaction time and sensory changes, sustained attention and strategies for maintaining vigilance do not appear to change significantly with age. Divided attention, or the ability to concentrate on more than one piece of information at a time, may decline with age although research in this area has produced mixed results. Increased distractibility (difficulty blocking out irrelevant or salient stimuli), decreased use of effective strategies, and reduced processing speed may be responsible for some of the noted declines in divided attention. Pronounced impairment of attention is not typical of normal aging, however, and a complete evaluation of medical and psychosocial issues is warranted for individuals who demonstrate such changes. Attention can be negatively impacted by perceptual or sensory changes, illness, chronic pain, certain medications, and psychological disturbance (in particular, depression and anxiety), all of which are common in an older population. As the ability to effectively attend is a requisite for nearly all other cognitive functions, it is important to identify the cause/s of attentional impairment whenever possible and to implement any changes in medications or treatment that may help to resolve these problems.

Executive Functions

Executive functions include the ability to control and direct behavior, make meaningful inferences and appropriate judgments, plan and carry out tasks, manipulate multiple pieces of information at one time (working memory), complete complex motor sequences, and solve abstract and complex problems. Neuropsychological test performance on executive tasks declines slightly with age, and several current theories posit that deficits in working memory and executive function underlie many age-related changes in cognition. Neurocognitive tasks that require response inhibition, such as the Wisconsin Card Sort Test, Stroop Color Word Test, and Brown-Peterson Distractor Test may be affected.

Alternatively, many have suggested that a reduction in cognitive processing speed rather than executive function per se may be at least in part responsible for decreased performance on executive tasks. It should be noted that changes in the executive system that occur with normal aging are much less severe than the deficits associated with dysexecutive syndromes, including those caused by stroke, heavy and prolonged alcohol use, head injury, and some neurodegenerative diseases. In fact, successful aging appears to produce little impact on “real-world” executive functions requiring planning and executing multiple tasks. Thus, it is important to assess an individual’s actual functional abilities in addition to performance on neuropsychological tests of executive function.

Memory

Memory changes are perhaps the most common cognitive complaints reported by older adults. Patients often wonder if their subjective concerns reflect normal age-related changes or some pathologic condition. For patients with a family history of Alzheimer disease or other dementia, even minor memory failings can cause significant anxiety. One of the difficulties in answering such questions lies in the complex nature of the memory process. Different processes are invoked when learning new information (declarative memory), recalling prior life events (remote memory), recalling general knowledge not tied to a specific event (semantic memory), and remembering procedures for performing tasks such as riding a bicycle (procedural memory). In addition, some conditions result in modality-specific deficits, differentially affecting verbal or visual memory.

A number of models describe the different stages or processes involved in forming and recalling memories. One example, the modal model, describes memory processes in terms of sensory memory, short-term (working) memory, and long-term memory. First, when a patient senses and attends to a given stimulus a large amount of information is briefly held in sensory memory. Information is then rehearsed or manipulated in short-term or working memory. Although many factors are involved in determining what information is transferred to long-term storage, sufficient rehearsal is a common requirement for successful transfer. Thus, it is clear that when a patient complains of memory changes, additional information is required to make sense of the problem.

Although it is true that some older adults continue to demonstrate memory performances comparable to young adults, on average even healthy older adults do show changes in some aspects of memory. For example, when a large group of healthy, nondemented older subjects were followed over a 7-year period, a general memory factor showed

significant decline with time. Other studies have attempted to describe which aspects of memory change with healthy aging. In general, older adults without significant illness demonstrate increased difficulty learning new information compared to younger cohorts. When older adults are given repeated chances to practice learning new information, they demonstrate a slower learning curve and a lower total amount learned.

Although healthy older adults may retain slightly less information after a delay than do younger adults, this effect is less pronounced than the slowed learning rate. For delayed memory tests, patients are generally asked to recall information 15 to 60 minutes after the initial exposure. Although patients recall less information at the delay with age, they generally retain a stable proportion of the information that they initially learned. In general, longitudinal studies of aging show only small declines in delayed memory with age, particularly on tests of visual memory. Some older adults also appear less likely to use cognitive strategies to aid memory than younger subjects. This may be due to generational differences in learning style. However, it may be significant because the use of memory strategies (ie, grouping vegetables and clothing items for easier recall) reduces the age effect observed on free recall tests.

A number of memory processes do not appear to change with successful aging. Remote memory, that is recall of events that occurred in the distant past, remains relatively intact, as does sensory memory. In addition, while older patients often have medical problems that limit physical movement, procedural memory appears to be unaffected by healthy aging. Lastly, semantic memory, such as vocabulary and general information about the world, remains largely unchanged by aging until very late in life.

Longitudinal studies have consistently shown that as groups age, the variability in cognitive performance increases. Overall, studies of healthy aging suggest that there are some statistically significant declines in memory in late life. However, the memory functions of patients who age successfully are typically adequate for the demands of independent living.

Language

Language abilities incorporate multiple levels of processing, and general language functions tend to remain relatively stable with increasing age. Some linguistic abilities, however, particularly those involving language output, show reliable declines in older adults. As with other cognitive functions, there are multiple potential intervening factors, including trauma, illness, and sensory disruption, that may lead to more severe changes in the language functions.

Language comprehension involves discerning the simple and complex rules of language and incorporating both visual and auditory information into a meaningful concept, and is generally associated with few age-related impairments. The ability to recognize basic word structure and word representation is typically measured using “lexical-decision” tasks (in which letters are rapidly presented and the person is asked to identify whether or not it is a word) and simple word reading tasks. While some studies have suggested an inverse relationship between performance on these tasks and age, it is generally believed that such changes are the result of decreased reaction time and processing speed rather than the ability to comprehend word structure and meaning. In addition, there is some indication that the level of lexical processing changes slightly with age, in that older adults tend to rely more on word recognition than do younger adults, while ignoring other factors such as word length. Phonological understanding of language does not appear to change significantly with age, although hearing loss may appear to reduce auditory comprehension. Overall, it is generally accepted that language comprehension remains relatively intact throughout the lifespan.

Basic syntactic abilities also do not appear to change significantly with advancing age, although minor repetitions, longer pauses, and an increased use of pronouns and other vague words while speaking have been noted. Additionally, a recent longitudinal study suggests a decline in spoken grammatical complexity during the eighth decade of life. The authors note, however, that there is high interindividual variability throughout the lifespan in terms of syntactic aptitude.

Semantic abilities require aptitude with naming and retrieving long-stored information. There is a steady increase in vocabulary knowledge throughout middle adulthood, and such knowledge typically remains stable in the later years. A frequent complaint from older adults, however, involves the “tip-of-the-tongue” phenomenon, in which there is a notable struggle with spontaneous word finding. In contrast to the dysnomia that often accompanies dementia, however, such changes appear to result primarily from difficulties retrieving rather than storing information, and thus there is usually a marked improvement when cues are given. Verbal fluency, the rate at which a person can spontaneously produce words belonging to a single phonemic or semantic category, also appears to change somewhat with age. Multiple research findings support a decrease in semantic fluency (“name all the animals you can”) while phonemic fluency (“tell me as many words as you can that begin with the letter F”) generally remains stable. Younger

adults tend to produce more words and change categories more frequently than do older adults on semantic fluency tasks, while older adults may generate the same amount of words but more "clusters" on tasks of phonemic fluency. Thus, older adults likely rely more on structural word knowledge than on word meaning.

Visuospatial Skills

Visuospatial skills are commonly tested by constructional tasks in which patients are asked to draw figures or assemble objects. In general, as patients age, they become slower at completing visuospatial tasks. However, as noted previously, one of the more consistent findings in the field is that normal aging is associated with general slowing of psychomotor and cognitive speed. Therefore, performance on tests of visuospatial functioning is often confounded by slowing. Some studies have attempted to separate the effects of the two domains. For instance, after controlling for processing speed and executive functioning, the effects of age on the commonly used Wechsler Block Design test were dramatically reduced. Similarly, an 11-year follow-up of older adults subjects analyzed both speed and quality of performance (errors) on a parallelogram test. As expected, speed declined with age, but the quality of the performance actually improved significantly. This body of literature suggests that declining speed contributes to some of the findings that report visuospatial processing deficits in normal aging.

Speed does not appear to account for all of the visuospatial changes observed in healthy aging, however. Mental rotations of objects or spatial coordinates, accurate copy of complex geometric designs, and mental assembly of objects typically worsen with age even when unlimited time is allowed to perform such tasks. Furthermore, when speed is included in scoring, some studies have reported disproportionate slowing on visuospatial tasks compared to verbal tasks. Overall, some studies may exaggerate the visuospatial decline observed in normal aging because of the role speed plays in many tasks used to assess visuospatial function. However, abstract spatial abilities may decline with age, even when speed is controlled.

Psychomotor Functions

An age-associated increase in reaction time, related to both a general reduction in the speed of cognitive processing and to changes in peripheral motor skills, has been consistently reported. Age-related declines in brain dopamine activity and periventricular white matter changes may be associated with reduced cognitive speed and basic motor functions. As a result, performance on tests requiring speed and quick reaction to stimuli are likely to decline. As previously noted, increased psychomotor speed and reaction time are believed to underlie many of the age-related changes noted on neurocognitive testing, particularly tasks involving perceptual speed, attention, and working memory. In addition, changes in psychomotor functions can be associated with changes in real-world tasks, such as driving. As a result, it is important to monitor the manner in which physical changes are impacting an individual's level of safety in performing daily activities.

COGNITIVE EFFECTS OF COMMON AGE-RELATED MEDICAL CONDITIONS

In the following section, cognitive symptoms associated with common diseases affecting older adults are reviewed. A summary of these symptoms is presented in **Table 63-2**.

TABLE 63-2 ■ POSSIBLE COGNITIVE EFFECTS OF COMMON AGE-RELATED MEDICAL CONDITIONS

	SYMPTOM COURSE	INCREASED RISK FOR DEVELOPING DEMENTIA?	MEMORY	ATTENTION	EXECUTIVE FUNCTIONS	LANGUAGE	VISUOSPATIAL FUNCTION	PSYCHOMOTOR FUNCTION	BEHAVIOR
Cardiac surgery	Symptom onset immediate after surgery, improvement noted in first year, then further decline possible in some patients	AD, VaD	Verbal and visual memory deficits possible several years after surgery	Reduced attention	Variable	No significant changes noted	May lead to impaired visual organization and construction	Reduced reaction time, general slowing	Depression common after surgery
Hypertension	May improve with antihypertensive treatment	AD, VaD	Verbal and visual recall and recognition deficits in some patients	Reduced attention and vigilance	Impairment in working memory and other executive function	Reduced verbal fluency	May lead to impaired visual organization and construction; more likely with comorbid diabetes	Reduced reaction time, general slowing	Variable
Diabetes	May improve with oral antidiabetic agents	AD, VaD, PD	Verbal memory impairment related to deficits in encoding new information	Reduced complex attention, simple attention variable	Impairments in abstract reasoning and concept formation	No significant changes noted	Variable, more likely with comorbid hypertension	Reduced reaction time, general slowing	Depression common
COPD	May improve with oxygen therapy	AD, VaD	Verbal and visual memory deficits	Reduced attention	Impairment in abstract thinking	No significant changes noted	No significant changes noted	Reduced reaction time, general slowing	Depression common
Sleep apnea	May improve with CPAP treatment	Unknown	Verbal and visual memory deficits	Reduced attention	Impairment in general executive function, especially working memory	No significant changes noted	No significant changes noted	Reduced reaction time, general slowing	Depression and irritability related to sleep disruption
Nutritional deficiency	May improve with supplementation, although effects of low vitamin B_{12} may persists	Wernicke-Korsakoff syndrome	Recall deficits	Reduced attention	Impairment in abstract thinking	No significant changes noted	Nonverbal pattern abstraction, construction impaired in high homocysteine	Reduced processing speed in patients with high homocysteine	Variable
Hypothyroidism	May improve with thyroid treatment, although some patients do not return to baseline	AD	Recall deficits, intact recognition	Variable	Variable	No significant changes noted	Reduced visuospatial function	Reduced reaction time, general slowing	Depression

AD, Alzheimer disease; CPAP, continuous positive airway pressure; PD, Parkinson disease; VaD, vascular dementia.

Cardiovascular Disease

In addition to increasing the risk for developing stroke and/or vascular dementia (VaD), cardiovascular disease potentially jeopardizes cognitive function via multiple mechanisms.

Coronary artery bypass graft (CABG) surgery Cognitive impairment subsequent to CABG surgery has been reported in 30% to 80% of patients at the time of hospital discharge. Factors that increase the risk of postoperative cognitive dysfunction (POCD) include older age, cerebrovascular disease, cardiopulmonary bypass (CPB) time, manipulation of the ascending aorta, and cerebral hyperthermia. A wide range of cognitive deficits, including problems with attention and concentration, processing speed, memory, and visuospatial function, have been noted in patients immediately following surgery. Several reports suggest that postoperative cognitive function stabilizes or even improves after a period of approximately 12 months in those patients who demonstrate initial decline. However, some longitudinal data suggest that such patients are at high risk for continued cognitive deterioration 5 years postsurgery. There is debate in the field regarding whether POCD is due to the surgery itself or whether the surgery unmasks underlying factors such as vascular disease. Post-CABG neurocognitive status is related to overall quality of life, and current recommendations underscore the importance of closely monitoring cognitive status in the years following cardiac surgery.

Hypertension Essential hypertension has been associated with cognitive impairment independent of secondary disease or organ damage, particularly in older patients. Potential cognitive effects of primary hypertension include reductions in mental status, slowed reaction time, reduced attention and vigilance, weakened executive function, poor verbal fluency, and impaired visual organization and construction. Memory functions, including spatial recall, verbal recall, and word recognition, may also be affected in some hypertensive patients. In addition, secondary effects of hypertension may lead to an increased risk for cognitive decline in older age. For example, uncontrolled hypertension

potentiates the development of subcortical white matter lesions, and adversely impacts cerebral blood flow and energy substrate delivery. Recent findings suggest that hypertension is a significant risk factor for dementia and that treating hypertension reduces this risk. In particular, mid-life hypertension increases the risk of later-life cognitive impairment. Hypertension has been identified as one of the major modifiable risk factors for dementia. Interestingly, blood pressure often declines in the period immediately preceding the onset of Alzheimer disease, and it has been suggested that low blood pressure in persons of advanced age may compromise brain function as a result of hypoperfusion. In particular, aggressive sudden lowering of blood pressure in older adults with long-term hypertension may potentially interact with their chronically upregulated cerebral vascular resistance and induce cerebral hypoperfusion. Thus careful monitoring of blood pressure and gradual titration of medication regimens is of particular importance. Additional interest has been focused on the question of whether different methods of treating hypertension may confer particular protective effects on cognition. Additional controlled randomized trials are needed to definitively answer this question.

Nutritional Deficiency

Older adults are at considerable risk for nutritional deficiencies as a consequence of poor diet and malabsorption syndromes. Much research in this area has focused on deficiencies of B vitamins. Lower B_{12} levels have been associated with increased risk of AD. Reduced folate levels may be associated with lowered cognitive function but evidence suggesting increased risk of Alzheimer disease is mixed. Some studies have suggested that supplementation may improve cognitive performance in deficient individuals. Among older adults with cognitive deficits, routine laboratories and repletion is recommended when applicable.

B vitamins play an important role in homocysteine metabolism. Homocysteine is an independent risk factor for cerebrovascular and cardiovascular disease. In patients with both AD and VaD, elevated plasma homocysteine levels have been reported, and recent studies suggest that homocysteine levels are related to cognitive function in normal aging. Reduced performance on tests of mental status, nonverbal pattern abstraction, construction, and processing speed are reported in patients with high plasma homocysteine. Given that plasma homocysteine and folate levels are inversely related, it is conceivable that such cognitive deficits are related to reduced folate rather than to increased homocysteine per se. Recent data suggest, however, that homocysteine increases the risk for cognitive decline independent of both folate levels and other vascular risk factors.

There has been much debate about the potential protective effects of antioxidants in dementia. For example, both deleterious and protective effects of vitamin E have been reported. A recent large-scale clinical trial, however, showed reduced functional decline with high-dose vitamin E supplementation (2000 IU per day) for mild-to-moderate AD. Although these results appear promising, additional work is needed to clarify the risk-to-benefit ratio for vitamin E supplementation.

Type 2 Diabetes Mellitus

Much attention has been given to the rampant epidemic of type 2 diabetes mellitus (T2DM) in older adults, a trend thought to be largely attributable to obesity and physical inactivity. Current prevalence estimates suggest that 20% of adults over 65 years are afflicted with T2DM. The negative impact of T2DM on multiple medical systems is well known. The clear impact of T2DM on cognitive function in older adults is less-widely known, but accruing evidence demonstrates that these patients show pronounced impairment in attention and verbal memory when compared to healthy age-matched adults, and show accelerated cognitive decline over time. Complex attentional impairment is most common, involving the inability to handle multiple streams of information or attend to information in the face of competing stimuli. Verbal memory deficits typically affect the ability to encode new verbal information. The magnitude of such impairment may vary from subtle subjective complaints to pronounced impairment that interferes with daily activities and may interfere with the patient's ability to adhere to complex treatment regimens. The mechanisms causing attentional and memory impairments are likely multifactorial and include vascular factors, as described earlier, in addition to the potential negative effects of hyperglycemia and glucose toxicity thought to cause oxidative injury. Recent work also suggests that insulin resistance, independent of hyperglycemia, may have negative consequences on brain systems mediating memory and attention. This intriguing possibility has implications for therapeutic approaches to treating T2DM, suggesting that strategies focused on improving insulin sensitivity may be preferable to those focused on augmenting insulin levels. Successful treatment of T2DM has been shown to improve cognitive function. The importance of treating and preferably preventing T2DM has been underscored by recent findings that it is a risk factor for various forms of neurodegenerative disease, including AD, VaD, and Parkinson disease.

Chronic Obstructive Pulmonary Disease

Emphysema and chronic bronchitis obstruct airflow, resulting in hypoxemia and hypercapnia. Cognitive dysfunction is commonly observed in chronic obstructive pulmonary disease (COPD), although the specific skills affected appear to be broad and diffuse. Deficits in verbal and visual memory, attention, abstraction, psychomotor speed, information processing speed, and IQ have all been reported. These changes in cognition appear to be due to hypoxemia. The decrease in arterial oxygen partial pressure correlates with neuropsychological impairments, and most studies indicate that oxygen therapy results in modest improvements in cognition. Depression is also common in COPD and must be considered as another cognitive risk factor.

Obstructive Sleep Apnea

The prevalence of obstructive sleep apnea (OSA) increases in geriatric populations. Many patients remain unaware of the disorder and report associated symptoms only when specifically queried. Cognitive changes in OSA can be diverse, but generally include attention, concentration, executive functioning, verbal and visual learning, and working memory. Tests of global functioning have also revealed differences compared to healthy older adults without OSA. There is debate regarding whether the cognitive deficits are due to hypoxia, hypersomnolence, or comorbid conditions. However, severity of hypoxemia appears to relate to cognitive functioning, and continuous positive airway pressure (CPAP) treatment improves cognitive functioning in many patients.

Thyroid Dysfunction

There are a number of thyroid disorders that result in hypo- or hyperthyroidism. Hypothyroidism appears to be associated with cognitive changes. Deficits may be observed in visuospatial skills, psychomotor speed, and memory. There is some evidence that the memory deficits are related to retrieval rather than immediate recall or learning; thus, disproportionately better performance may be observed on tests of cued or recognition memory than on free recall tests. Thyroid replacement therapy frequently improves cognitive functioning, although skills may not return to baseline levels in some patients. Hyperthyroid episodes may result in cognitive changes that last for many years. Symptoms may include attention and executive functioning deficits, and memory impairment. Hyperthyroid dementia is less common than in hypothyroidism, and is also generally less severe. The evidence supporting cognitive deficits in adults with subclinical thyroid disease is equivocal. Thyroid hormone abnormalities occur in a large proportion of patients with dementia. Therefore, levels should be routinely monitored as a treatable contributor to cognitive decline.

Depression

Depression is an increasingly common problem in older adults, with prevalence estimates ranging from 11% to 30%. Multiple situational risk factors for depression in older age include the loss of social support, death of family members and close friends, changing social roles, and physical limitations. Depressive symptoms, including lack of initiation, impaired executive function, cognitive slowing, poor attention and concentration, and mild memory impairment can mimic early signs of dementia and may potentially lead to misdiagnosis and/or lack of appropriate medical intervention. As depression is a potentially reversible cause of cognitive impairment, the differential diagnosis between depression and dementia is vital when evaluating older patients. Factors that are useful in discriminating between depression and dementia include the clinical course of symptoms, relationship to a specific crisis or stressful event, history of previous psychiatric problems, quality of effort, and level of impaired processing on cognitive evaluation.

Recent findings suggest that late-onset depression is an independent risk factor for the development of neurodegenerative diseases, such as AD and VaD, and some hypothesize that depression may actually represent a preclinical phase of progressive dementia. In patients with early cognitive loss, depressive symptoms may represent realistic self-evaluation of such decline and/or may coincide with actual changes in neuroendocrinologic status. In the absence of predisposing situational factors, late-onset affective disorders are quite rare. Subcortical vascular ischemic changes are frequently noted in patients with new-onset depression in late life, and such patients frequently have vascular risk factors such as hypertension, cardiovascular disease, and diabetes. For such cases, cognitive ability and independent functional status must be carefully evaluated, and an in-depth qualitative analysis of depressive symptoms may be useful. Major depressive disorder is associated with a range of affective, cognitive, and vegetative symptoms, while depressive symptoms in early dementia are more likely to include cognitive and motivational symptoms (eg, poor concentration, lack of initiation) in the relative absence of central affective disturbance. Continued monitoring of

the cognitive status of depressed older patients is essential in order to rule out progressive cognitive decline.

Medications

A number of medications have the potential to cause both subtle cognitive changes and alterations in overall mental status, particularly in the older adults. Medications known to adversely affect cognitive status include opiates and opioid-like analgesics, benzodiazepines, anticonvulsants, antipsychotic and antidepressant medications, antiparkinsonian agents, central nervous system stimulants, antihistamines and decongestants, and certain cardiovascular medications. Anticholinergic medications, used to treat a variety of conditions including insomnia, bladder spasms, gastrointestinal disorders, dizziness, and others, have been linked to an increased risk for dementia in older adults in a large-scale prospective community-based study. Despite this finding, these drugs are widely prescribed in older adult populations. A variety of other medications, particularly those that readily cross the blood-brain barrier, may impact cognitive function in certain individuals. In addition, drug interactions in older adults can lead to more serious physiologic and cognitive consequences than those observed in younger adults, and adverse medication interactions are more likely to occur in an older population. As a result, changes in cognitive status must be carefully evaluated in light of a patient's current medication profile.

Delirium

Older adults are at a significantly increased risk for developing delirium, particularly following surgery or in response to medication changes or interactions. Delirium is a reversible condition that can be distinguished from most neurodegenerative diseases by a rapid onset of symptoms that include significant disorientation and disturbance in consciousness, reduced awareness of the environment, and attention deficits. While recent memory is generally impaired, altered consciousness is the primary indicator of delirium. Hallucinations, delusional thinking, and other disturbed thought processes may also be present. Delirium usually resolves quickly, but may persist for several weeks. It should also be noted that postoperative delirium may signify the presence of a beginning dementia. A primary concern is to identify and treat the underlying cause while providing a supportive and nonthreatening environment for the patient.

NEURODEGENERATIVE DISEASE

The following section reviews the cognitive and behavioral profiles associated with common neurodegenerative disorders (**Table 63-3**). Early identification of such disorders, many of which are diagnosed solely on these parameters, has become increasingly important due to potential therapies that may delay disease progression.

TABLE 63-3 EARLY COGNITIVE SYMPTOMS ASSOCIATED WITH DIFFERENT DEMENTIA TYPES

	SYMPTOM ONSET	PROGRESSION RATE	MEMORY				ATTENTION	EXECUTIVE FUNCTIONS	LANGUAGE	VISUOSPATIAL FUNCTION	PSYCHOMOTOR FUNCTION	BEHAVIOR
			RECENT	RECOGNITION INTACT?	REMOTE INTACT?	PROCEDURAL INTACT?						
Alzheimer disease (AD)	Insidious	Steady, gradual	Significantly impaired declarative recall	N	Y	Y	Intact primary span; impaired selective/ divided attention	Mildly impaired working memory, response inhibition, general problem solving	Semantic organizational abilities significantly impaired, mild anomia	Simple construction intact, complex visual reasoning impaired	If present, symptoms are mild	Depression common
Lewy body disorders												
PD/PDD	Insidious	Varied	Possible deficits	Variable	Y	N—possible impairments	Intact primary attention span, impaired selective/ divided attention; fluctuations	Difficulty planning/ shifting set	Verbal fluency, mechanical aspects of speech impaired	May be impaired	Resting tremor, bradykinesia, rigidity, postural instability, shuffling gait	Depression common, may exhibit hallucinations/ delusions, less common than DLB
DLB	Insidious	Steady, gradual	Usually less than AD	Variable	Y	Y	Significant fluctuations in attention	Variable	Variable; fluency may be impaired	Impaired construction, copy, visuospatial planning and problem solving	May exhibit a range of parkinsonian symptoms	Hallucinations, delusions, depression
Vascular dementia (VaD)	May be insidious or acute	Stepwise or gradual	Possible deficits	Varies	Y	Y	Intact primary span; impaired selective/ divided attention	Significantly more impaired than AD and relative to performance on verbal memory tasks	Verbal fluency impaired	Relatively preserved, although may be affected by executive impairments	Slowing, possible discrete motor problems depending on distribution of vascular changes	Depression common

Frontotemporal lobar degeneration (FTLD)												
Behavioral variant FTLD (FTLDbv)	Insidious	Steady, rapid	Relatively preserved	Y	Y	Y	Intact primary span; impaired selective/ divided attention	Impaired across a range of executive functions	Verbal fluency impaired	Relatively preserved, although may be affected by executive impairments	May exhibit ideational apraxia	Significant behavioral changes, may include behavioral disinhibition, apathy, loss of empathy/ sympathy, hyper-orality
Primary progressive aphasia (PPA)	Insidious	Steady, varied	Preserved recall, may score poorly on verbal memory tests	Y	Y	Y	Preserved	Preserved	*Nonfluent*: poor articulation, dysarthria, relatively preserved comprehension; *Logopenic*: anomia, impaired repetition; *Semantic:* impaired comprehension, anomia, intact speech rate & prosody	In semantic dementia, may have visual agnosia	*Nonfluent PPA*: buccofacial apraxia	Changes unlikely
Progressive supranuclear palsy (PSP)	Insidious	Steady, gradual	Mild impairment, less than AD	Variable	Y	Y	Impaired selective/ divided attention	Impaired across a range of executive functions	Verbal fluency impaired	May be impaired	Vertical supranuclear gaze palsy, postural instability	Apathy, disinhibition
Corticobasal degeneration syndrome (CBS)	Insidious	Steady, gradual	Variable, may be severe	Variable	Y	Possible impairment	Impaired selective/ divided attention	Impaired across a range of executive functions	May have a variety of language disturbances	Possible	Asymmetric motor symptoms, alien limb syndrome	A variety of neuropsychiatric disturbances possible
Alcohol-related dementias												
Persistent alcohol dementia	Deficits persist after d/c alcohol use	May worsen over time	Impairment on recall, not more than other functions	Variable	Y	Y	Impaired sustained attention	Abstraction, mental flexibility, perseveration, confabulation, impaired judgment, reduced ability to care for self	Preserved	Visual scanning, visuospatial organization impaired	May exhibit cerebellar tremor, impaired gait	Apathy, depression
Wernicke-Korsakoff syndrome	Acute (initial phase)	Steady, gradual (chronic phase)	Significant impairment on declarative recall relative to other deficits (semantic memory spared)	N	N	Variable	Impaired across all attentional functions	Similar profile to persistent alcohol dementia	Preserved	Visual scanning, visuospatial organization impaired	Impaired gait, abnormal reflexes, other movement abnormalities	Personality change prominent feature, inappropriate behavior

Prion disease	Insidious	Steady, rapid	Nonspecific impairments reported	Y	Y	Y	Non-specific impairments reported	Reduced problem-solving ability	Generally preserved	Generally intact	May exhibit impaired reflexes and coordination	Apathy, emotional lability, impaired sleep, appetite loss
Normal pressure hydrocephalus (NPH)	Insidious	Varied, potentially reversible	Not prominently impaired	Y	Y	Y	Primary deficits in attention	Non-specific impairments in executive function reported	Generally preserved	Generally intact	Wide-based gait or other balance disturbance, urinary incontinence	May present with a confusional state
HIV-associated neurocognitive disorder (HAND)	Usually later in the disease course	Varied	Variable	Variable	Y	Y	Non-specific impairments reported	Non-specific impairments in executive function reported	Generally preserved	Generally intact	Slow, loss of coordination	Depression common
Neurosyphilis	Many years after initial infection	Varied, potentially reversible	Variable	Variable	Y	Y	Variable	Variable	Generally preserved	Generally intact	May be ataxic	Hallucinations, delusions, personality change, mood disturbance

DLB, dementia with Lewy bodies; PD, Parkinson disease; PDD, Parkinson disease with dementia.

Alzheimer Disease Dementia

AD dementia, the most prevalent of the primary neurodegenerative disorders, is the clinical manifestation of underlying AD neuropathology, primarily the accumulation of β-amyloid protein and neurofibrillary tangles leading to neuronal loss and synaptic degeneration. Recently updated diagnostic criteria by the National Institutes on Aging and the Alzheimer's Association (NIA/AA) recognize AD as a continuum, with underlying neuropathologic processes often beginning 20 years or more before the onset of clinical dementia symptoms. Thus, the revised criteria permit use of biomarkers that reflect these processes, alongside supporting clinical information, for use in early differential diagnosis. Currently, cerebrospinal fluid (CSF) and imaging studies may be used to determine the presence of β-amyloid deposition and/or neuronal injury to provide additional diagnostic evidence for or against AD as the underlying pathology. In the absence of such tools, however, conventional diagnostic criteria are considered to be reasonably accurate, particularly when the evaluation is comprehensive and includes a complete medical and psychosocial history, medical evaluation, and neurocognitive testing.

The NIA/AA criteria for AD dementia require (1) that the patient meets criteria for dementia (cognitive symptoms that interfere with daily activities that occur within at least two cognitive domains, represent a decline from previous function, and are not better explained by delirium or psychiatric disturbance), (2) evidence for or a reported insidious onset, and (3) worsening cognition by report or observation. The initial cognitive symptoms may be amnestic or nonamnestic to account for variants that present with deficits in cognitive domains other than memory, such as posterior cortical atrophy (which presents with initial visuospatial deficits) or language-predominant forms. The diagnosis is not considered "probable" if another medical/neurologic disease could account for the symptoms. "Possible" AD dementia may be diagnosed if the symptom history is atypical or unclear or if there is a mixed dementia picture.

Patient history A complete medical and psychosocial history is a vital component of any dementia assessment. Such a history should be obtained both from the patient and a reliable informant, preferably someone who has regular contact with the patient and who has an adequate opportunity to observe their daily functional abilities. Typically, a patient in the earliest stages of AD will not exhibit deficits in basic self-care. However, more complex daily tasks, including driving, finances, shopping, and other chores and activities, are likely to be affected. A gradually progressive course and insidious onset of cognitive symptoms is a hallmark of the AD, and thus a careful history regarding the

nature and timing of symptom onset and progression must be obtained. An inventory of all current medical concerns, family history, past major medical problems, and medications must be evaluated in order to rule out conditions that may be either causing cognitive problems or influencing their expression.

Medical examination An important goal of the medical evaluation is to exclude the presence of medical conditions that may be responsible for the observed cognitive deficits. It is critical to investigate potentially reversible causes of dementia such as uncontrolled liver or kidney disease, adverse reactions to medications, and delirium. Laboratory blood tests can aid in ruling out systemic illnesses or organ malfunction. Structural brain scans are used to evaluate major cerebrovascular events, tumors, normal pressure hydrocephalus, and other neurologic conditions, while functional brain scans identify patterns of activity that may be useful in classifying dementia type.

Neuropsychological assessment Neuropsychological assessment of cognitive function not only provides confirmatory evidence for cognitive impairment, but may also aid in clarification of dementia type. Given the extensive variation in rate of AD progression between patients, successive neuropsychological examinations early in the disease can also provide information regarding an individual's rate of progression and remaining cognitive strengths. Perhaps one of the most valuable assets of neuropsychological evaluation is the sensitivity of the tests to early cognitive decline. While there has been debate regarding the usefulness of providing an early AD diagnosis, it is generally accepted that such a diagnosis will allow the patient to avail themselves of current and emerging therapies, as well as to make decisions regarding health care, finances, and legal issues while still competent. In a typical neuropsychological evaluation, patients are given tests that sample a variety of domains of cognitive function. Results are compared to normative data based on age, and also to an individual's estimated premorbid abilities (based on educational and occupational background and performance on tests that tend to remain stable over time). Pattern analysis of test results, in combination with data from the patient history and medical evaluation, is then used to generate diagnostic possibilities. The following sections discuss cognitive impairment patterns typical in patients with AD.

Memory The hallmark of AD, and most often the first cognitive symptom of the disorder, is anterograde amnesia, evidenced by difficulty with learning new information. Deficits are noted in declarative memory as a result of prominent impairment in information encoding, retrieval, and in particular, storage of new material. Patients are likely to exhibit deficits in recent episodic recall, and they or their caregivers often report that misplacing items, forgetting recent events or conversations, and frequently repeating questions or statements. In contrast to impaired episodic recall and difficulty learning new information, procedural memory is rarely impaired, and remote memory remains relatively intact until later stages of the disease.

In order to adequately evaluate short-term memory loss and establish a pattern of impaired retrieval, neuropsychological evaluations include tests of both immediate and delayed verbal and visual recall. Tests such as the Folstein Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and other diagnostic screening instruments assess general mental status and orientation, but are not adequate for a comprehensive understanding of memory impairment. To satisfactorily assess a person's true memory ability, Zec (1993) recommends using tasks that are high in cognitive demand, that exceed the primary memory span (such as story recall and list learning tasks that include at least 10 items), and that have a recognition component. On neuropsychological examination, verbal and visual free immediate and delayed recall and recognition are significantly impaired in AD patients relative to same-age peers, and patients typically exhibit a high number of intrusion errors and repetitions. Semantic recall is generally the most predominantly impaired, and thus verbal recall tasks are often the most sensitive to early memory loss.

Attention and Executive Function Certain aspects of attention and concentration are often impaired early in the disease process, and recent research has supported that it may in fact be one of the earliest abilities affected in AD. While patients with AD are likely to have relatively intact simple attention (eg, primary memory span), tests requiring selective and divided attention are likely to be impaired, particularly as task demands increase. This pattern of performance strongly supports the presence of a deficit in working memory (the ability to simultaneously attend, process, and respond to multiple pieces of information) early in the disease process, and a converging body of evidence supports a primary executive component in AD.

In addition to problems on tasks of complex attention and working memory, patients are likely to exhibit mild deficits in response inhibition, evidenced by intrusion errors and perseverative responses, on neuropsychological testing. Deficits in abstract reasoning, general problem-solving ability, and making appropriate judgments are also commonly noted. In assessing for judgment and abstraction, patients may be asked the meaning of proverbs (eg, "you

can lead a horse to water but you can't make it drink"), and are often given hypothetical situations in which they must decide an appropriate course of action (eg, "What would you do if you were in a crowded shopping mall and saw smoke and fire?"). On these tasks, even early AD patients may provide incorrect or inappropriate responses.

Language Semantic processing is considered the primary language deficit in AD, and is present in more than half of all AD patients at the time of diagnosis. Word finding problems are commonly reported in both AD and normal aging, but patients with AD have more severe deficits and are more likely to produce a significantly higher number of semantic paraphasias and circumlocutions. Patients are generally impaired on tasks of confrontational naming, and, unlike changes that occur with normal aging, are not likely to be assisted by cues. Syntactic processing, in contrast to semantic processing, is typically unaffected in mild AD. For example, patients with early AD can typically process even complex sentences at the same level as their healthy counterparts, and generally remain unimpaired on repetition and fluent speech. Verbal fluency tasks are particularly useful in evaluating both semantic and syntactic processing. Semantic, or category, fluency (eg, "Tell me as many animals as you can") is generally impaired disproportionately to syntactic, or phonemic, fluency (eg, "Tell me as many words that begin with the letter ___") in AD. While decreased information processing and working memory may impair an AD patient's responses on certain syntactic processing tasks, and comprehension and intelligible speech are likely to decline slowly as the disease advances, patients who present first with nonfluent aphasia or impaired comprehension should be carefully evaluated for other conditions.

Visuospatial Function Deficits in visuospatial abilities are frequently seen in AD patients, although they generally appear later than memory and language deficits. Patients may become lost in familiar places (eg, grocery store) or while driving. Eventually, disorientation may lead to confusion in one's own home and subsequent wandering behavior. Early deficits however, are more likely to involve visuospatial problem solving. Neuropsychological tests commonly used involve comparing simple construction or copying, typically not impaired early in the disease, to complex visual reasoning. The presence of constructional apraxia early in the disease may indicate greater pathology in visual processing areas of the brain and has been associated with more rapid symptom progression. In general, more complex drawing tasks, such as three-dimensional figure copy, may be more precise measures of the most common early visual spatial deficits in AD than simple copying tasks.

Motor Function While motor dysfunction has not been typically considered to be a defining symptom of AD, recent research suggests that AD patients may display impairments in gait, motor speed, and general level of activity, such changes may even be evident during the prodromal phase of the disease. In addition, converging evidence provides support for greater overlap between AD and Lewy body dementia, making motor changes such as tremor or gait disturbance more likely in these patients. Importantly, there have been reports of gait disturbance in patients taking cholinesterase inhibitors, a factor that should be carefully monitored when prescribing these medications.

AD patients may also exhibit mild ideomotor and ideational apraxia (deficits in skilled movements) due to concrete responses, lack of sufficient external cues, or a disruption in conceptualization ability. However, moderate-to-severe apraxia is not generally present until later stages of the disease. Incorporating an apraxia assessment into a dementia evaluation is useful, however, particularly for excluding other disorders that may initially present with more severe skilled movement disorders.

Behavioral changes As mentioned previously, depression is common in patients with AD, and may manifest as apathy, indifference, poor initiation, or emotional lability. Irritability, agitation, and paranoid ideation are also common in AD, and may worsen with disease progression, prompting wandering behavior and aggressive outbursts. Repetitive and aimless behavior may also increase as the disease progresses. More severe psychotic symptoms, such as hallucinations and severe delusions, have been reported in some patients with early AD, but are typically rare in the absence of coexisting disorders. Given the wide range of behaviors that may be exhibited in an AD patient, it is imperative that the patient's family be provided with ample dementia education, that they have access to social support, and that they possess the coping skills necessary to provide adequate care.

Awareness of deficits Patients in the early stages of AD typically vary in their level of deficit awareness. Whatever the starting point, deficit awareness declines with disease progression. Even when patients do acknowledge their cognitive decline, however, such awareness may not be "complete" as a result of deficits in executive function. For example, patients may be unable to translate cognitive problems into functional problems, and as a result may not understand how their deficits affect certain activities, such as driving, cooking, and finances. Again, providing the patient's caregivers with access to education can increase the likelihood that patients will comply with physician recommendations to limit certain unsafe behaviors.

Variant AD presentations While most often the primary early deficit in AD involves recent memory, there are several reported cases of variant forms of AD that involve primary deficits in language, visuospatial function, or central executive function. In such cases, differential diagnoses, including frontotemporal dementia, primary progressive aphasia, Lewy body dementia, and others must be carefully considered prior to assigning a diagnosis of AD.

Mild Cognitive Impairment Due to AD

"Mild cognitive impairment" (MCI) describes cognitive impairment in aging that does not meet the criteria for dementia and that is not the result of a known medical condition. In its most common usage, the term is assigned to cognitive impairments thought to be related to underlying AD pathology, although criteria for prodromes of other neurodegenerative dementias (eg, Parkinson disease dementia, frontotemporal dementia) are currently proposed. Current NIA/AA criteria for MCI due to AD include the following: (1) concerns regarding a change in cognition by either the patient, informant, or a skilled clinician, (2) objective impairment in memory in one or more cognitive domains, (3) preserved independence in functional abilities, although patients may require some assistance or have mild impairments on more complex tasks such as financial management, navigation to unfamiliar places, etc, and (4) absence of dementia. Neuropsychological assessment can be particularly useful in distinguishing between normal age-related changes in cognition and MCI. Longitudinal research suggests that 80% of those diagnosed with MCI will go on to develop AD within 5 to 8 years, and will convert at a rate of approximately 10% to 15% per year compared to general population conversion rates of 1% to 2%. Amnestic forms of MCI are more likely to progress to AD than nonamnestic. However, the current criteria acknowledge that even initial nonamnestic presentations may progress to AD. Progression to AD is more likely when multiple cognitive domains are affected. In addition, MCI may progress to other forms of dementia or revert to normal cognition (**Figure 63-1**). Recently proposed research criteria grade the likelihood of progression to AD on the basis of biomarker outcomes: MCI due to AD-high likelihood is assigned when there are positive biomarkers for both βamyloid accumulation and neuronal injury on the basis of imaging and/or lumbar puncture, while the absence of positive biomarkers indicates a process that is unlikely to be related to AD.

Lewy Body Disorders

Dementia with Lewy bodies (DLB) is the second most common identified etiology for neurodegenerative dementia, behind AD. Cognitive dysfunction is also exceedingly common in Parkinson disease; thus it is increasingly recognized that Lewy body disorders account for a sizeable proportion of cognitive disability identified in aging populations. Considered a primary cause of dementia in both diseases is the presence of cortical Lewy bodies, abnormal intracytoplasmic inclusion deposits, on neuropathologic examination. However, multiple other pathologic features, including accumulation of tau protein, concurrent vascular and/or AD pathology, neurotransmitter abnormalities, and frontostriatal projections that have been disrupted by loss of dopaminergic neurons can all contribute to the cognitive decline associated with these diseases.

Although Parkinson disease and DLB have historically been considered related but separate clinical entities, many of the neuropathologic, clinical, cognitive, and psychiatric characteristics of the two diseases have considerable overlap. Thus recent debates have centered on whether or not Parkinson disease, Parkinson disease with dementia (PDD), and DLB should be placed along a clinical continuum representing the same underlying pathology. Currently, the differential diagnosis is based purely on the timing of the onset of the cognitive symptoms. A Parkinson patient who develops dementia after 1 year of motor symptoms is classified as "PDD," while earlier cognitive symptoms may indicate DLB.

Parkinson disease At its early stages, Parkinson disease can be difficult to differentiate from normal aging. Most patients initially present with a resting tremor. Other cardinal symptoms include bradykinesia, rigidity, and postural instability. Patients may also present with a shuffling gait, masked facies, depression, and sleep disorders. Relatively healthy older patients can present with a number of these symptoms for unrelated problems. For instance, essential tremors are not uncommon with aging, patients with arthritis often show slowed motor movements, and peripheral neuropathy, common in medical conditions such as diabetes, can impair gait.

Although motor symptoms have long been considered the defining feature of PD, a wide range of associated nonmotor symptoms are increasingly recognized as having substantial impact on functional abilities and quality of life for these patients. Of these nonmotor symptoms, cognitive dysfunction is a primary concern: dementia prevalence rates among patients diagnosed with Parkinson disease are 30% to 40%, with upwards of 80% of patients who live for 20

years or more with Parkinson disease expected to develop dementia over the course of the disease. In patients without dementia, the rate of concurrent cognitive impairment can be quite high, such that cognitive deficits, even if only slight, are now considered an inherent component of the disease. However, there is substantial variability in the nature and course of cognitive symptoms in Parkinson disease, with many patients maintaining a stable or fluctuating course and others demonstrating more rapid decline. Most patients with Parkinson disease exhibit at least some decline in attention, working memory, processing speed, or other executive functions, although the nature and degree of impairments across other domains are variable. PDD is often characterized by visuospatial deficits, impaired verbal fluency, difficulty planning or shifting to a new stimulus, slowed information processing speed, and impaired memory. Memory impairment is most frequently attributable to a retrieval deficit since recognition is often intact. Procedural learning may be impaired, a pattern atypical in normal aging or in AD. Some language skills are intact, such as vocabulary, while others that tap additional cognitive domains, such as verbal fluency, may be impaired. Mechanical aspects of speech are often impaired as well. Although PDD has been previously characterized as a "subcortical" dementia to distinguish it from cortical dementias such as AD, this characterization has been criticized more recently and may serve simply as a gross depiction of the cognitive profile. Indeed, recent research suggests that while initial mild cognitive deficits in Parkinson disease likely result from depleted dopamine in the midbrain and resulting defects in the frontostriatal loop, cortical pathology is required for the development of dementia.

Dementia with Lewy bodies As discussed above, DLB and PDD share many of the same features, including cognitive fluctuations, neuropsychiatric features, and motor symptoms. However, the timing and severity of these symptoms may differ. Visual hallucinations often occur earlier in DLB, delusions may be more common, and a differential response to antiparkinsonian medications has been reported. In terms of cognition, prominent visuospatial and executive impairments are noted, similar to PDD. However, memory impairments are more prominent in DLB. According to consensus criteria for DLB, cognition must be carefully assessed. A progressive cognitive decline, usually over the course of a number of years, must be observed to a degree that it disables the patient. In addition the patient must show some combination of fluctuations in cognition, recurrent visual hallucinations, or spontaneous parkinsonism. Many patients may also present with other psychiatric symptoms, neuroleptic sensitivity, and a history of falls and syncopal attacks. Based on these criteria, the differential diagnosis between DLB and Parkinson disease is obviously difficult. One pattern that has emerged in patients with DLB, however, is a higher likelihood of overlap with AD pathology. Indeed, unlike PDD, a substantial majority of DLB cases have concurrent AD pathology.

The differential diagnosis between DLB and AD can thus also be difficult. The presence of visual hallucinations in patients with MMSE scores greater than 20 is highly suggestive of DLB. Neuropsychological studies have identified typical cognitive profiles that may aid in diagnosis. In DLB, patients have more difficulty than AD patients in copying complex designs, assembling pieces of an object, or completing other tasks requiring visuospatial skills. In contrast, AD subjects generally show significantly more impairment on delayed recall tasks than patients with DLB. DLB patients have attentional skills that are generally equivalent to those of AD patients; however, patients with DLB exhibit significant attentional fluctuations. As a result, evaluating attention over time is more helpful than the overall severity of attention problems in the differential diagnosis. Finally, these cognitive profiles are most evident early in the course of the diseases. As the diseases progress, all cognitive functions become impaired and neuropsychological testing is less helpful for diagnosis.

Vascular Cognitive Impairment

The construct of vascular cognitive impairment (VCI) is undergoing rapid development. The recent statement for health care professionals from the American Heart Association and American Stroke Association describes VCI as an umbrella term that uses a nosology similar to AD categorization, and subsumes the conditions of probable and possible VaD and vascular mild cognitive impairment (VaMCI). An additional category of unstable VaMCI is used to refer to patients with a diagnosis of probable or possible VaMCI who revert to normal. A diagnosis or VaD requires evidence of cerebrovascular disease on neuroimaging, decline in cognitive function in two or more domains, determined through cognitive testing, and compromise in daily function that is not attributable to the physical effects of the cerebrovascular injury. Probable VaD further requires that there be no evidence of decline prior to any vascular event that suggests underlying nonvascular neurodegeneration. Possible VaD is diagnosed when there is insufficient evidence to ascertain temporal or functional contiguity between cerebrovascular abnormalities, or to exclude other neurodegenerative processes. VaMCI subtypes are diagnosed with criteria similar to AD-related MCI.

Progress in achieving a cognitive nosology is hindered by the likely heterogenous nature of these conditions, which complicates efforts to identify characteristic cognitive profiles. According to NINDS-AIREN criteria, six vascular

"subtypes" ascribe dementia to multiple large infarcts, strategic single infarcts, small vessel disease, hypoperfusion, hemorrhage, or miscellaneous vascular insult. It is likely that dementia due to small vessel disease is the most common form of vascular dementia and provides the most uniform pattern of cognitive impairment. Cognitive profiles of these patients at early stages typically reveal executive function deficits, reduced verbal fluency, and slowing, with preservation of cued memory and an absence of intrusions. Depression, irritability and lack of initiative are also common. Contrary to long-standing clinical lore, VaD does not necessarily present primarily with stepwise deterioration in cognition, rather, continuous small vessel insults can lead to slowly progressive decline in cognitive abilities. Thus, it can be difficult to differentiate VaD from AD on the basis of the clinical course of symptoms. Detailed review of cardiovascular risk factors and cognitive profile may provide better differentiation. A review of studies examining early-stage AD and VaD found that the latter group had more pronounced deficits in executive function on tests such as the Wisconsin Card Sorting Test and the executive function scale of the Mattis Dementia Rating Scale than did adults with AD. Interestingly, performance between the two groups was similar on tests of selective attention and working memory such as the Trail-Making Test and Stroop Color Word Interference test. In contrast, VaD patients had better performance than AD patients on tests of verbal learning and story recall, such as the California Verbal Learning Test and the Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R), with fewer intrusions. However, VaD can impact the structure and function of the hippocampus thus leading to more notable memory deficits in some patients, although these impairments may not occur until later in the disease process. Because memory impairment is most often the reason patients seek evaluation, adults with VaD may have more progressed dementia and greater cognitive impairment at the time of diagnosis. It is important to note that as both VaD and AD progress, the cognitive profiles become more similar, so that differentiating mid-stage disease is very difficult. In addition, recent neuropathologic studies have shown that many patients previously diagnosed with vascular dementia due to presence of vascular risk factors such as diabetes, hypertension, and radiologic evidence of ischemia have prominent AD pathology as well. Prevalence estimates of the cooccurrence of AD and vascular dementia range from 20% to 40% of patients with dementia. Few studies have attempted to differentiate between mixed AD/VaD and either form of dementia on a neuropsychological basis, although it has been suggested that mixed dementia most closely resembles VaD from a cognitive perspective. Vascular pathology increases the likelihood that patients with neuropathologic AD will show significant cognitive impairment. Finally, cognitive profiles for other forms of VaD such as multiple large vessel or single strategic infarcts are highly idiosyncratic, depending on lesion location and volume.

Frontotemporal Lobar Degeneration

Frontotemporal lobar degeneration (FTLD) is caused by a range of underlying neuropathologic conditions (including intracellular inclusions of tau or TDP-43, among others). Various clinical presentations can be caused by FTLD, primarily resulting in gradually progressive disturbances in language and/or behavior. FTLD has been estimated to account for 3% to 20% of dementia cases, although diagnosis is often difficult, so precise estimates are unknown. The following diagnostic variants are currently recognized as most likely resulting from FTLD, although the extent to which these represent distinct disorders is not currently well defined.

Behavioral variant FTLD This diagnostic category, which includes Pick disease, includes the prototypical symptoms of personality change and slowly progressive executive dysfunction. This variant most often presents initially with behavioral disturbance that includes at least three of the following: (a) disinhibition, (b) apathy, (c) diminished empathy/sympathy, (c) perseverative, stereotyped, or compulsive behaviors, (d) hyperorality, and (e) executive deficits on neuropsychological examination with relatively intact recall and visuospatial skills, although performance on these measures may be affected by severe executive impairments, such as disorganization. Neuropsychological testing generally reveals impaired selective and divided attention, difficulty shifting mental set, poor abstraction, and impaired verbal fluency, and perseverative errors are common. Unfortunately, the MMSE is not very helpful in screening for early behavioral variant FTLD (FTLDbv) since many patients score within normal limits early in the disease.

Primary progressive aphasia The diagnosis of primary progressive aphasia (PPA) requires initial prominent language dysfunction with relative sparing of other cognitive domains, and the absence of radiologic evidence of cerebrovascular or other neurologic injury that would account for the aphasia. PPA variants include (1) *agrammatic (nonfluent) PPA*, which is characterized by labored articulation and agrammatism with preserved comprehension except for complex sentences with embedded clauses; (2) *logopenic PPA*, which presents with impaired naming, spontaneous speech, and repetition; and (3) *semantic PPA (sometimes called semantic dementia)*, which involves a loss

of ability to understand words and deficits in confrontational naming, often accompanied by impairment in visual recognition of objects, dyslexia, and dysgraphia. Patients with semantic dementia may display prominent visual agnosias and may not be able to demonstrate object use accurately.

Because anomia and other language deficits may occur in a number of neurodegenerative conditions, the differential diagnosis of PPA rests on the clear demonstration that nonlinguistic cognitive and behavioral functions are intact during the initial stages of the disease. The examiner must carefully determine whether poor performance on memory and other nonlanguage tests is due to language deficits such as impaired comprehension of instructions. The onset of PPA is typically in the fifth or sixth decade of life, and its rate of progression varies greatly. As the disease progresses, however, other cognitive functions become impaired, as does the patient's ability to carry out functional activities, thus, making a diagnosis of mid-stage PPA difficult at best. Differential diagnosis is also complicated by the heterogenous etiologies of PPA demonstrated by the different subtypes. Although not consistent across all cases, agrammatic PPA is often associated with tau pathology, logopenic PPA with AD pathology (although not always in brain regions typically associated with AD), and semantic PPA with TDP-43 pathology.

FTLD movement disorders Certain movement disorders, which may also include behavioral and/or language disturbance, may be caused by or associated with FTLD.

Progressive supranuclear palsy Although Lewy bodies are found in only the minority of progressive supranuclear palsy (PSP) cases, PSP is frequently misdiagnosed as Parkinson disease. A core feature of the disorder is vertical supranuclear gaze palsy, although this symptom may not present early in the course of the disease. Patients also present with postural instability, and falls are often seen shortly after onset. Cognition is characterized by mental slowing and executive dysfunction. Memory impairments are observed, but they are not as severe as in AD. Language functions resemble those seen in PD. Visual spatial deficits and increased apathy are also observed.

Corticobasal syndrome Corticobasal syndrome (CBS) leads to asymmetric motor symptoms such as tremor, loss of coordination, rigidity, and spasms, and a higher prevalence of alien limb syndrome. Apraxia (most commonly ideomotor), a range of language abnormalities, and/or executive/behavioral dysfunction may be seen in CBS. Memory loss may be prominent in some patients. Neuropsychiatric symptoms are common.

In addition to the variants described above, FTD with parkinsonism and FTD associated with amyotrophic lateral sclerosis (FTD-ALS) involve symptoms of the combined diseases, and are often associated with specific genetic mutations.

Both the personality changes and cognitive dysfunction observed at early stages of FTLD exceed those seen in normal aging. As with other dementing conditions, the most difficult differential diagnosis is between FTLD and AD. Age of onset for FTLD is typically in the late 50s or early 60s, although there is a wide range observed. Therefore, on average FTLD patients show symptoms about a decade earlier than AD patients. As with AD, FTLD patients show insidious onset of symptoms with a gradual progression. Although comparisons of AD and FTLD groups do not always reveal significantly different cognitive profiles, in general, FTLD patients show relatively spared memory performance in comparison to their executive and language functioning, especially when memory cues are provided. Apraxia is also more common in FTLD than in AD. Often a multidisciplinary approach may be most helpful in the differential diagnosis since studies indicate that up to 75% of pathologically confirmed FTLD patients also appear to meet clinical criteria for probable AD.

Alcohol-Related Dementia

Recent epidemiologic analyses suggest that mild-to-moderate alcohol use reduces the risk for developing certain dementias, including Alzheimer disease and vascular dementia. Chronic and profound alcohol use, however, can have a negative effect on cognition and may exacerbate the cognitive symptoms of other dementias and brain injuries. Poor nutrition (thiamine deficiency in particular) resulting from alcohol abuse is a primary contributor to the onset of cognitive problems. In addition, liver disease itself can interfere with thiamine regulation in the brain and may be a factor in the multiple cognitive and motor impairments associated with long-term alcohol use.

Persistent alcohol dementia Alcohol dementia involves impairment in more than one area of cognitive function that persists after the patient stops drinking for a period of time. Visuospatial problem-solving deficits and executive problems, including apathy, decreased judgment, and reduced interest in self-care, are prominent in these patients. Memory problems, in particular anterograde amnesia, are also common, but are generally not more impaired than other cognitive domains, and recognition is often intact. Typical neuropsychological sequelae include impairments on tasks

requiring visual scanning, visuospatial organization, perceptual-motor speed, sustained attention, abstraction, and mental flexibility, while language functions are generally preserved. Perseveration and confabulation are common indicators of impaired executive function in the responses of patients with chronic alcohol use. It is also noteworthy that chronic alcohol use may potentiate the onset of AD, and produce a clinical picture of conjoint cognitive deficits.

Wernicke-Korsakoff syndrome The most severe neurologic outcome of heavy and prolonged alcohol use, and the result of critical malnutrition, is Wernicke-Korsakoff syndrome. In contrast to patients with persistent alcohol dementia, Wernicke-Korsakoff patients exhibit an acute symptom onset, often beginning with a grave confusional state, nystagmus, and significant ataxia. During this phase, symptoms progressively and rapidly worsen if treatment (immediate thiamine replacement) is not applied. This phase is almost always followed by a chronic and progressive stage that is associated primarily with impaired frontal and cerebellar functions. Unlike persistent alcohol dementia, Korsakoff patients have significant impairments in memory relative to other cognitive effects, and memory impairment includes both retrograde and anterograde amnesia for episodic events, frequently with prominent confabulation. In contrast to AD, semantic memory is relatively spared in the Korsakoff patient. Patients show a characteristic gradient of remote memory impairment, with better recall for remote events and progressively reduced recall of recent events. As with persistent alcohol dementia, executive dysfunction and visuospatial impairments are also significant symptoms of the syndrome. Cerebellar atrophy and peripheral nerve damage lead to impaired gait, decreased or abnormal reflexes, and other movement abnormalities in these patients.

Prion Diseases

The prion diseases are a group of rare fatal spongiform encephalopathies that result from mutations and polymorphisms in the prion protein gene (*PrP*), causing rapid neurodegeneration. These diseases, of which Creutzfeldt-Jakob is the most well known, produce a profound and quickly progressive dementia, and may be sporadic, familial, or infectious. Sporadic cases are the most common, and are generally diagnosed in people in their 60s, with a typical age range between 40 and 80. Early cognitive signs of the prion diseases are usually vague and nonspecific, such as poor memory, concentration, and problem solving. Initially, there are also often psychiatric symptoms, including apathy, emotional lability, impaired sleep, and appetite loss. Early frank neurologic symptoms are not common, but as the disease progresses, hyperreflexia, impaired coordination, changes in saccadic eye movements, and incontinence may occur. Given the early vague symptoms and dearth of neurologic symptoms, patients are not likely to present for evaluation until they are in the more moderate-to-advanced stages, which can occur in a matter of months. Diagnosis typically involves measuring electroencephalographic changes, hyperintensities on magnetic resonance imaging, and abnormal 14-3-3 protein deposits in the CSF. The most common differential diagnoses include depression, AD, and LBD.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) is a potentially reversible dementia that makes up about 6% of dementia cases. Abnormalities in the production, absorption, or flow of CSF result in ventricular dilatation. Patients may present with a triad of clinical symptoms that include gait or balance disturbance, urinary incontinence, and cognitive deficits. Unlike most other dementias, cognitive symptoms often present later in the course. This can make early clinical diagnosis difficult since gait abnormalities and incontinence have a variety of etiologies in geriatric populations. Radiographic evidence and intraventricular pressure measurement aid in the diagnosis. When cognitive deficits are present, they are most frequently observed in executive functioning. Although many subjects may have subjective memory complaints, memory deficits are not a prominent early symptom, and some memory declines are attributable to attention problems, which are more common. However, many of these patients may have concurrent underlying neurodegenerative disease, and thus may present with varied cognitive profiles.

When treated, a ventriculoperitoneal shunt is usually used to divert CSF for better absorption. However, surgery in geriatric populations always involves added risks, and the benefits of shunt surgery remain unclear. A wide variety of success rates have been reported, with better outcomes often reported after shorter follow-up periods. Patients with the full triad of symptoms appear to respond best to shunt surgery. Gait problems show the most frequent improvement, while cognitive function improves in the fewest patients. Recently findings from a 5-year follow-up of NPH patients with and without shunt surgery showed that at the 6-month assessment, 83% of the shunt cases improved in gait and 46% improved in memory. Of surviving shunt cases 5 years after surgery, 39% remained improved in gait, and fewer than 10% continued to show improvements on cognitive tests. Results suggested that outcomes may be improved in

younger patients.

HIV-Associated Neurocognitive Disorder

Although there is often the perception that geriatric patients are not at risk for HIV infection, the Centers for Disease Control and Prevention (CDC) reported that 10% of all HIV cases in the United States are in patients of 50 years or older, and these numbers are expected to grow. The earliest cognitive areas affected are usually speed of information processing, attention, and motor speed. A subgroup of patients progress to HIV-associated dementia which is usually characterized by impairments in executive functioning, psychomotor speed, and memory, along with slowed motor function and loss of coordination. However, progression to dementia generally occurs in the absence of treatment, and is rare when antiretroviral therapy is used.

Neurosyphilis

Neurosyphilis is an advanced syphilitic infection that may present with hallucinations, delusions, mood disturbance, personality change, strokes, ataxia, or cognitive decline. Deficits are observed in short-term memory and mental status with progressive cognitive decline in all areas of functioning. Although neurosyphilis is often classified as a reversible dementia, there is only limited evidence to support cognitive benefits with treatment. The onset of dementia in neurosyphilis often occurs several decades after contraction of the disease. Neurosyphilis should be considered in a differential diagnosis of dementia of unclear etiology in geriatric patients.

CONCLUSION

We have greatly furthered our understanding that age-related medical conditions not considered classically neurologic in nature can nevertheless impact the central nervous system and thereby affect cognition. This knowledge has led to the realization that many of the changes in cognition previously thought to be unavoidable concomitants of normal aging are in fact preventable and in some cases even reversible. The deleterious consequences of not treating such disorders have become evident, given that many common diseases such as type 2 diabetes and hypertension appear to be risk factors for dementia. In turn, early identification of dementia or the prodromal condition mild cognitive impairment will become critical as therapeutic options for delaying disease progression proliferate. Careful characterization of cognitive status through neuropsychological assessment can provide the clinician with essential information to determine whether the patient is experiencing symptoms that warrant concern or further treatment. As the field of geriatrics approaches the goal of controlling or even preventing endemic late-life chronic diseases, it will become increasingly clear that deleterious cognitive changes that occur with healthy aging are fewer and more subtle than we thought, and that they are accompanied by age-related strengths in experience and knowledge that will enable us to lead vital, productive lives well into our 80s and beyond.

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Chapter 64

Psychoactive Drug Therapy

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Learning Objectives

- Learn the appropriate indications, dosage, and adverse effect profile of commonly used psychoactive drugs in older adults.
- Understand the principles of safe prescribing of antidepressants, especially the newer second-generation selective serotonin reuptake inhibitors (SSRI), serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) in older adults with depression.
- Gain state-of-the-art knowledge about the proper indications, efficacy, safety, and results of randomized clinical trials targeting use of atypical antipsychotics for management of behavioral symptoms in patients with dementia.
- Learn about the appropriate use, side effects, and efficacy of anxiolytics and mood stabilizers in older patients with anxiety and dementia.

Key Clinical Points

1. **The use of psychotropic medications is only second to cardiovascular drugs among older patients. Nearly one in five community-dwelling older adults and over 47% older residents of nursing homes are on psychoactive medications.**
2. **In nursing homes, psychotropic drugs and anticoagulants are the most common medications associated with adverse drug reactions (ADRs).**
3. **There is a significant interindividual variation in efficacy and clearance of psychoactive medications in older adults.**
4. **The most common adverse effects of SSRIs include nausea, dry mouth, constipation, drowsiness, and sleep problems.**
5. **Use of antidepressants is associated with increased risk for falls, hip fractures, and osteoporosis.**
6. **Administration of atypical antipsychotics is associated with an increased risk for sudden death and cerebrovascular accidents in older patients with dementia.**
7. **Quetiapine is the drug of choice for older patients with Parkinson disease and Lewy body dementia due to low incidence of extrapyramidal side effects.**

INTRODUCTION

This chapter focuses on the use of psychotherapeutic medications in older adults, including antidepressants, psychostimulants, antipsychotics, mood stabilizers, and anxiolytics. These classes of drugs are used to treat psychiatric disorders across the lifespan into late life, including major depression, anxiety, psychosis, and the behavioral and psychological disturbances that frequently accompany Alzheimer disease (AD) and other neurocognitive disorders.

Mood and behavioral disturbances are commonly encountered in older adults. Late-life depression, including major

depressive disorder and dysthymia, affects 8% to 16% of older adults. These rates are found to be consistent with those in younger adults; however, older people face a disease profile that is more chronic and treatment resistant, as it is often accompanied by age-related and pathologic cognitive decline. Depression in community-living older patients frequently remains unidentified and untreated. Depression occurring in persons greater than 60 years is likely distinct from that which occurs among younger age groups. For example, late-life depression is often associated with significant vascular disease. Structural abnormalities in frontal white matter thought to be secondary to cerebrovascular disease are associated with unremitted depression.

Late-life depression leads to further deterioration in quality of life and increases the risk for dementia and suicide. Depressed elders are known to suffer greater rates of disability, mortality, and nursing home placement. Furthermore, when depression co-occurs with other medical or psychiatric illness, it negatively alters the disease process, further complicating the management of the disorder. For example, cardiac mortality is increased in depressed patients with unstable angina, postmyocardial infarction, and congestive heart failure, while comorbid anxiety impairs interpersonal function and leads to greater severity of physical symptoms. Consequently, the effects of depression result in greater strain on an already overburdened health care system.

Anxiety disorders are also highly prevalent in older adults, affecting 2% to 19% of community-dwelling elders, with the most common forms being generalized anxiety disorder (GAD) and specific phobias. Further, 20% of older individuals are known to experience subclinical levels of anxiety. Late-life anxiety can co-occur with physical illness, depression, or side effects of medication use. Some of the most commonly experienced risk factors for anxiety in elders include cognitive and physical impairments, economic difficulties, and social segregation.

Older individuals with anxiety experience greater physical disability and cognitive impairment, as well as reduced ability to carry out activities of daily life. Similar to other disorders, late-life anxiety is associated with diminished quality of life. Moreover, comorbid anxiety increases the risk of mortality and coronary artery disease (particularly in men) when present in later life. Anxious elders are prone to excessive use of medical services, with anxiety disorders comprising 38% of mental health claims as compared to 21% for affective disorders.

Behavioral instability, including agitation, aggression, and psychosis, is also frequent in late life, especially when associated with a major neurocognitive disorder (ie, dementia). Approximately 2% to 5% of individuals 60 years or older suffer from neurodegenerative diseases, while 15% to 40% of those older than 85 develop dementia. At some point in the course of dementia, most nursing home and community-dwelling patients experience behavioral dysfunction and/or psychosis. For example, studies indicate that 10% to 70% of patients with dementia experience psychotic symptoms. In a 4-year study, psychosis reportedly occurred in 51% of patients with AD. Across samples of AD patients, the most common delusional symptoms were related to theft or suspicion. Hallucinations can involve either visual or auditory stimuli, and are reported to occur in 5% to 15% of dementia patients.

Behavioral and personality disturbances can develop early in the course of a major neurocognitive disorder. Such changes include agitation, aggression, irritability, depression, apathy, emotional withdrawal, impulsivity, and disinhibition. Patients with neurocognitive disorder may become stubborn, combative, and neglectful of activities essential to daily life. As such, many caregivers have no other option, but to institutionalize their loved ones due to the degree of the patient's care needs and unsafe behaviors. Both community-dwelling and long-term care residents experiencing behavioral or psychological symptoms of dementia (BPSD) have an elevated mortality risk. Extrapyramidal symptoms (EPS) and cognitive decline are also associated with BPSD. The use of psychotropic medications are second only to the use of cardiovascular medications among older patients, including the frail and chronically ill. Nearly one in five community-dwelling elders and 47% of nursing home residents take regular psychotropic medications. However, the basic pharmacokinetic profiles and clinical evidence supporting the widespread use of psychotropic medications in late life are lacking. In fact, most psychiatric medications are tested only in young and healthy patients prior to their release.

ADRs and the inappropriate prescribing of medications to older adults are more common in later life than in younger adults. In an acute geriatric medical unit, one study found that the prevalence of ADRs was 16% on admission for those patients taking appropriate medications, and that 66% of admissions were preceded by the prescription of at least one inappropriate medication. In the long-term care setting, psychoactive medications (antipsychotics, antidepressants, and sedative/hypnotics) and anticoagulants were the most common medications associated with ADRs, and neuropsychiatric events were the most common manifestations of preventable ADRs. There is also evidence that commonly used antidepressants may have limited efficacy and more adverse effects in the oldest old and frail elderly. Moreover, atypical antipsychotic agents often used for the treatment of the psychotic and aggressive symptoms in dementia may lead to cerebrovascular events and increased mortality in nursing home residents.

As with other medications, the treatment of older patients with psychotropics is further complicated by age-

associated pharmacokinetic and pharmacodynamic variations, which are exacerbated by illness, and increase the probability of drug-drug interactions and medication nonadherence. An additional complication for psychotropics is the lack of diagnostic precision and pathophysiologic understanding of the disorders being treated. Psychotropic treatment is based on treating symptoms that have a heterogeneous etiology. The strategy for drug discovery in psychiatry has relied upon the serendipitous observation of symptomatic benefit of a known drug, the study of the mechanisms of that compound, and efforts to develop similar compounds with improved efficacy and tolerability. The limitations of this approach are evident in the treatment of "psychoses" in dementia, as if it were the same disorder as psychoses that tend to have their onset earlier in life, such as schizophrenia. Similarly, depression appearing later in life may be associated with ischemic injury or the later development of AD. For currently available psychotropics, there have been few studies of their "real-world" comparative effectiveness. One example is the Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study, which found an unfavorable risk-to-benefit ratio for use of atypical antipsychotic medications in patients with AD. One of the challenges to demonstrating efficacy includes variability in drug exposure. The recent use of population pharmacokinetic methodologies in older psychiatric patients treated with antidepressants or antipsychotics is beginning to reveal the extensive interindividual differences in drug clearance for these medications.

ANTIDEPRESSANTS

Selective Serotonin Reuptake Inhibitors

SSRIs are considered first-line pharmacotherapy for late-life depression. These drugs act on the serotonergic system by blocking the presynaptic reuptake of the neurotransmitter, serotonin. In comparison with most other antidepressants, SSRIs generally have a more favorable side-effect profile and are well tolerated. They are also markedly safer than their parent drugs, TCAs, in overdose. Over 30 randomized, placebo-controlled, clinical trials with more than 5000 older patients with SSRIs have been conducted. These studies have included patients with a variety of psychiatric and medical illnesses, including mild cognitive impairment, dementia, minor depression, schizophrenia, cardiovascular and cerebrovascular disease, or other medical conditions. In the largest clinical trial studies published, SSRI response rates (defined as $\geq$ 50% reduction in the severity of depression) ranged from 35% to 60%, in comparison with placebo, which ranged from 26% to 40%. There is not enough evidence in the current literature, however, to conclude that SSRIs increase remission rates in depressed older persons.

SSRIs are established as the preferred pharmacologic treatment of anxiety in younger adults, however, only a single placebo-controlled trial and two open-label studies have suggested efficacy of SSRIs for anxiety in later life. There is still limited evidence supporting the efficacy of SSRIs in treating dementia-related behavioral disturbances, such as agitation, disinhibition, delusions, and hallucinations. For instance, the Citalopram for Agitation in Alzheimer Disease (CitAD) study examined patients with probable AD with significant agitation. The trial found that psychosocial intervention along with citalopram significantly reduced agitation and caregiver distress when compared with placebo. One of the challenges with citalopram, however, is the risk of arrhythmia at higher doses, which may limit its practical application.

Although there is similar efficacy between each of the SSRIs, citalopram, escitalopram, and sertraline have better pharmacokinetic profiles, are less of a risk for drug-drug interactions, and appear not to interfere with cognition. As such, these drugs are generally preferable to fluvoxamine, fluoxetine, or paroxetine. Recently, however, citalopram and escitalopram were associated with dose-dependent QT interval prolongation in those greater than 60 years, increasing the risk of fatal arrhythmia and limiting the maximum recommended dose in late life. In older adults, starting dosages are administered in one daily dose, at half the amount administered to younger adults (**Table 64-1**). Dosages are typically increased every 2 to 4 weeks based on response and tolerability, but can be increased more rapidly, that is after a week of use as needed. Fluvoxamine is the only SSRI that should be given according to a twice-daily dosing regimen. Of note, concomitant use with MAOIs should be avoided due to the risk of a hypertensive crisis or the development of serotonin syndrome.

TABLE 64-1 ANTIDEPRESSANT ORAL DOSAGES AND SIDE EFFECTS

CLASS/MEDICATION	INITIAL DAILY DOSE (MG)	MAX DAILY DOSE (MG)	RISK FOR DRUG INTERACTION	SIDE EFFECTS

Selective serotonin reuptake inhibitors				
Citalopram	5–10/d	20/d	Low	GI distress, sexual dysfunction, slight weight gain, QTc prolongation, hyponatremia, SIADH
Escitalopram	5/d	10/d	Low	GI distress, sexual dysfunction, slight weight gain, QTc prolongation, hyponatremia, SIADH
Fluoxetine	10/d	40/d	High	Insomnia, slight anticholinergic effects, GI distress, sexual dysfunction, slight weight gain, EPS, hyponatremia, SIADH
Paroxetine Paroxetine CR	5–10/d 12.5/d	40/d 50/d	Moderate	GI distress, sexual dysfunction, moderate weight gain, minimal sedation, withdrawal symptoms, anticholinergic effects, hyponatremia, SIADH
Sertraline	12.5–25/d	200/d	Low	GI distress, sexual dysfunction, slight weight gain, EPS, hyponatremia, SIADH
Vilazodone	10/d	40/d	Moderate	GI distress, dizziness, insomnia, sexual dysfunction, abnormal dreams (limited geriatric data)
Vortioxetine	5/d	20/d	High	GI distress, headache, nasopharyngitis, sexual dysfunction, hyperhidrosis, somnolence, dry mouth and dizziness, hyponatremia, SIADH (limited geriatric data)
Serotonin norepinephrine reuptake inhibitors				
Duloxetine	20/d	60/d or 30 BID	Low	GI distress, dry mouth, urinary hesitancy, headaches, fatigue, drowsiness, hyponatremia, SIADH
Venlafaxine XR Venlafaxine IR	37.5/d 25–50/d	225/d 375/d	High	GI distress, minimal sedation, headaches, sexual dysfunction, serotonin syndrome, SIADH, withdrawal symptoms, adrenergic effects, dose-dependent hypertension, ECG changes, arrhythmia, acute ischemia, EPS, hyponatremia, SIADH
Desvenlafaxine	50/d	50–100/d	Low	Dizziness, dry mouth, insomnia, decreased appetite, GI distress, dose-dependent hypertension, QTc prolongation, elevated lipids, elevated liver enzymes, exacerbation of ischemic cardiac diseases, hyponatremia, SIADH (limited geriatric data)
Other second-generation antidepressants				
Bupropion XL	150/d	450/d	Moderate	Slight GI distress; CYP2B6

Bupropion SR Bupropion IR	100/d 75/d	150 BID 150 TID		inhibitors: risk for seizure, gait disturbance, falls, psychosis, headache, agitation, dizziness, insomnia, loss of appetite, weight loss
Mirtazapine	15 qhs	45 qhs	Low	Mild anticholinergic effects, hypotension, high sedation, slight sexual dysfunction, serotonin syndrome, increased appetite, xerostomia
Preferred tricyclic antidepressants				
Desipramine	10–25 qhs	50–150/d	High	Therapeutic window 150–300 ng/mL; mild anticholinergic effects, hypotension, slight GI distress, sedation, sexual dysfunction, slight weight gain
Nortriptyline	10–25 qhs	75–150/d	High	Therapeutic window 50–150 ng/mL; anticholinergic effects, hypotension, sedation, sexual dysfunction, slight weight gain

BID, twice daily; CR, controlled release; d, day; ECG, electrocardiogram; EPS, extrapyramidal symptoms; GI distress, gastrointestinal (eg, nausea, vomiting, diarrhea, constipation); IR, immediate release; qhs, once before bedtime; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; SR, sustained release; TID, three times daily; XR, extended release.

Fluoxetine Fluoxetine was the first SSRI to become available on the market in 1988. This drug ushered in a new era of treatment, providing an alternative to the TCAs. In geriatric patients, fluoxetine has demonstrated superiority as compared to placebo, and is as efficacious as amitriptyline, doxepin, escitalopram, paroxetine, sertraline, and trimipramine. Dosage recommendations for older adults indicate starting at 10 mg/day, which can be increased every 14 days by 10 mg to a maximum of 40 mg/day. This SSRI and its active metabolite norfluoxetine have mean half-lives of 4.6 and 9.3 days, respectively, rendering it an unfavorable choice for older adults. Fluoxetine and norfluoxetine inhibit the enzyme CYP2D6, and to a lesser extent CYP1A2 and CYP3A4. Norfluoxetine is cleared renally and subject to age-related declines in kidney function. Thus, it is crucial to consider interactions with other medications metabolized by these enzymes to avoid drug accumulation and toxicity (**Table 64-2**).

TABLE 64-2 CYP450 ISOZYME SUBSTRATES AND INHIBITORS

CLASS/MEDICATION	1A2	2A6	2B6	2C19	2C8/9	2D6	2E1	3A4
Selective serotonin reuptake inhibitors								
Citalopram	–	0	–	++/–	0	+/–	0	++
Escitalopram	0–	0	0	++	0	–	0	++
Fluoxetine	+/– –	0	+/–	+/– –	++/–	++/– – –	+	+/–
Fluvoxamine	++/– – –	0	–	– – –	–	++/–	0	–
Paroxetine	–	0	– –	–	–	++/– – –	0	–
Sertraline	–	0	+/– –	++/– –	+/–	++/– –	0	+/– –
Vortioxetine	0	+	+	+	+	++	0	++
Vilazodone	0	0	0	+/– –	–	+/–	0	++
Serotonin norepinephrine reuptake inhibitors								
Duloxetine	++	0	0	0	0	++/– –	0	0
Venlafaxine	0	0	–	+	+	++/–	0	++/–
Desvenlafaxine	0	0	0	0	0	–	0	+/– –
Milnacipran	0	0	0	+	+	+	0	++
Other second-generation antidepressants								
Bupropion	+	+	++	0	+	+/–	+	+
Mirtazapine	++/–	0	0	0	+	++	0	++/–
Preferred tricyclic antidepressants								
Desipramine	+	– –	– –	0	0	++/– –	–	– –
Nortriptyline	+	0	0	+	0	++/–	–	+
Atypical antipsychotics								
Aripiprazole	0	0	0	0	0	++	0	++
Clozapine	++/–	+	0	+/–	+/–	+/–	–	++/–
Olanzapine	++/–	0	0	–	–	+/–	0	–
Quetiapine	0	0	0	0	0	+	0	++
Risperidone	0	0	0	0	0	++/–	0	+/–
Ziprasidone	+	0	0	0	0	–	0	++/–
Paliperidone	0	0	0	0	0	0	0	0
Lurasidone	0	0	0	0	0	0	0	++/ –
Iloperidone	0	0	0	0	0	++	0	+/ –
Asenapine	++	0	0	0	0	+/–	0	+
Anticonvulsant mood stabilizers								
Carbamazepine	– – –	0	– – –	– – –	+/– – –	0	0	++/– – –
Valproic acid	0	+	+	+/–	+/–	–	+	–
Anxiolytics								
Buspirone	0	0	0	0	0	+	0	++

0, no metabolism; +, minor substrate; ++, major substrate; –, weak inhibitor; – –, moderate inhibitor; – – –, strong inhibitor.

Sertraline Sertraline was the second SSRI introduced, and is more specific in its effects on the inhibition of serotonin (5-hydroxytryptamine [5HT]) reuptake than fluoxetine. Its effects on the reuptake of norepinephrine and dopamine are modest. Sertraline is more effective than placebo, and is comparable to amitriptyline, fluoxetine, fluvoxamine, imipramine, nortriptyline, and venlafaxine in treating late-life depression. It is tolerated more favorably than imipramine and venlafaxine and demonstrates greater cognitive improvement than nortriptyline or fluoxetine. Dosing

in older patients is typically initiated at 12.5 to 25 mg/day, with increases of 12.5 to 25 mg/day occurring every 2 to 4 weeks to a daily maximum of 200 mg. Dose may be increased more rapidly depending on tolerability. Sertraline reaches its peak plasma concentration more rapidly when it is taken with food. One study, which included frail nursing home patients, noted an average maintenance dose of 77 mg/day. Although sertraline is a mild inhibitor of CYP2D6, its minimal effects translate to lower risk for drug interactions.

Paroxetine Paroxetine is as effective in depressed geriatric patients as amitriptyline, bupropion, clomipramine, doxepin, fluoxetine, imipramine, and nortriptyline. Again, this SSRI demonstrates superiority to placebo; however, in a study of very old long-term care patients with minor depression, paroxetine resulted in greater cognitive impairment as compared to placebo, which may be attributable to its increased anticholinergic effects relative to other SSRIs. Mirtazapine displayed marginal efficacy over paroxetine in one double-blind, randomized trial. Paroxetine elicits fewer side effects compared to the tricyclic nortriptyline. A starting dose of 5 to 10 mg/day is recommended for geriatric patients. After 1 week, dosing can increase by 5 to 10 mg to a maximum of 40 mg/day. Dose titration from 20 to 30 mg results in median half-life changes (30 and 38 hours, respectively), as well as changes in steady-state concentrations (46 ng/mL and 80 mg). Paroxetine can be given by controlled-release tablets at an initial dose of 12.5 mg/day and titrated each week up to a maximum of 50 mg/day. This drug is another potent inhibitor of CYP2D6, and thus the metabolic activity of concomitant medications must be examined prior to administration of paroxetine to minimize the risk of drug interactions. Paroxetine has the most anticholinergic activity of the SSRIs. Of note, paroxetine is clinically well known to cause significant withdrawal symptoms if stopped abruptly. It should therefore be gradually tapered over days to weeks as clinically indicated.

Citalopram and escitalopram The majority of published trials examining citalopram in depressed older individuals include those with concomitant dementia or cognitive impairment. Escitalopram is the S-enantiomer of racemic citalopram. Only one randomized, controlled trial has evaluated escitalopram in late-life depression. Citalopram has demonstrated greater efficacy over placebo in depressed older adults without dementia, and has similar efficacy as amitriptyline, and venlafaxine. While citalopram is associated with lower remission rates than nortriptyline, it is much better tolerated. In the single study comparing escitalopram, fluoxetine, and placebo, both active drugs were well tolerated. However, neither was more efficacious than placebo in reducing depressive symptoms. Geriatric dosage recommendations for citalopram indicate a starting dose of 10 mg, which can be titrated after 1 to 4 weeks. The United States Food and Drug Administration (FDA) issued a warning in 2011 that citalopram causes dose-dependent QT interval prolongation which can lead to the life-threatening cardiac arrhythmia, torsade de pointes. The warning recommended a maximum dose of citalopram of 20 mg/day and escitalopram of 10 mg/day among older adults (60 years or older), patients with hepatic impairment, patients who are CYP2C19 poor metabolizers, or patients taking concomitant medications that inhibit CYP2C19. It is also recommended that electrocardiograms be performed when starting citalopram or escitalopram and occasionally thereafter in order to monitor QT interval prolongation. With the aforementioned caveat in mind, for patients taking other medications, citalopram and escitalopram are often a good choice as neither is significantly affected by, nor do they affect, the CYP450 system. In older patients, however, the half-life of citalopram is increased, while availability and clearance are decreased. Those patients with mild-to-moderate renal function experience a 17% reduction in citalopram clearance.

Vilazodone Vilazodone is a novel antidepressant approved by the FDA for the treatment of depression. The potency for serotonin reuptake has been found to be 30-fold increase in comparison to fluoxetine. The medication should be initiated at 10 mg daily for 1 week, increased to 20 mg daily for 1 week, and then administered at a recommended dose of 40 mg daily. The adherence to the schedule is purportedly important to minimize gastrointestinal adverse events. The time to peak plasma concentration is 4 to 5 hours after a single oral dose of 40 mg/day with food, which increases the bioavailability of vilazodone by 147% to 160%. The most commonly reported adverse effects with the treatment of vilazodone are mild to moderate in intensity and consist of diarrhea, nausea, dizziness, insomnia, vomiting, and abnormal dreams. The only clinically significant pharmacokinetic interactions documented involve the concomitant use of strong CYP3A4 inhibitors. Therefore, it is recommended that doses greater than 20 mg/day should not be administered with strong CYP3A4 inhibitors. The efficacy and safety of vilazodone treatment in older adults have yet to be established, thus it is recommended that vilazodone be used with caution in older adults.

Vortioxetine Vortioxetine is a novel antidepressant that was approved recently by the FDA. This “multimodel” agent has affinity for $5HT_{1A}$ and $5HT_{3A}$ in addition to the serotonin transporter, which is hypothesized to produce a more

robust antidepressant effects with fewer adverse effects as compared to other neurotransmitter reuptake inhibition. Only one published double-blind study exists involving 453 older depressed patients, showing that vortioxetine was well tolerated among older adults and may have beneficial cognitive effects. The recommended initial dose of vortioxetine is 10 mg once daily. The dose can be gradually titrated to a maximum of 20 mg/day as tolerated. The most common adverse events associated with vortioxetine are nausea, vomiting, headache, diarrhea, nasopharyngitis, hyperhidrosis, somnolence, dry mouth, and dizziness. There may be potential significant drug interactions in the form of increased vortioxetine levels when coadministered with bupropion (CYP2D6 inhibitor and CYP2B6 substrate), fluconazole (CYP450 2C9, 2C19, and 3A4 inhibitor), and ketoconazole (CYP3A4 and P-glycoprotein inhibitor) and decreased vortioxetine levels when it was coadministered with rifampicin (CYP inducer). It may be potentially inappropriate for use in older adults due to the risk of syndrome of inappropriate antidiuretic hormone secretion (SIADH) and for those at increased risk of falls.

Adverse effects and safety Adverse effects are of particular concern in older adults, especially in the oldest old, frail, or medically ill. The most frequently reported adverse effects of SSRIs range from 1% to 17%, and include nausea, dry mouth, constipation, diarrhea anorexia, drowsiness, dizziness, lethargy, sleep disturbance, tremor, and anxiety. SSRIs have also received significant attention in the treatment of patients with ischemic heart disease, congestive heart failure, and immediately postmyocardial infarction. Evidence shows generally no increased cardiac risk, with no effects of SSRIs on blood pressure, cardiac conduction, or arrhythmias (with the notable exceptions of citalopram and escitalopram). Patients with bradycardia or those taking β-blockers may, however, experience a further reduction in heart rate. Though the SSRIs are well tolerated by older adults, caution should be exercised. Following initial treatment, some patients may experience gastrointestinal (GI) difficulties (eg, nausea), and there is slight potential for GI or postsurgical bleeding, especially when combined with nonsteroidal anti-inflammatory medications (NSAIDs) or low-dose aspirin. SSRIs may decrease platelet activation, affecting platelet aggregation, prolonging bleeding time. Proton pump inhibitors (PPIs) may lower that risk of GI bleeding when used in conjunction with an SSRI. Hyponatremia, is a possible consequence of SSRI use and should be assessed early in treatment or if there is a change in cognitive status. Concomitant use, or use within 3 to 4 weeks of cessation, of MAOIs can lead to the potentially fatal serotonin syndrome.

While Parkinson patients are able to tolerate SSRIs, SSRI use may cause EPS in some older patients. Antidepressant use is associated with risk for falls and hip fractures, and prolonged use of SSRIs may affect bone metabolism leading to an increased risk of fragility fractures. The risk of fractures was higher for new patients using SSRIs who initiated their medication in the last 30 days in comparison with continuous users. Risk for suicide in the first month of SSRI treatment may be elevated in older adults; however, there is a significant decrease in suicidal ideation in patients taking SSRIs versus placebo. This suggests that there may be a small subgroup susceptible to suicidal ideation during the first month of treatment with SSRIs.

Serotonin Norepinephrine Reuptake Inhibitors

The serotonin norepinephrine reuptake inhibitors (SNRIs) are a relatively recent class of antidepressants that are considered second-line therapy for late-life depression. The three drugs that are currently available are duloxetine, venlafaxine, and desvenlafaxine. These drugs are known to involve a dual action on both major monoamines involved in depression, which are noradrenaline and serotonin. The dual reuptake ensures efficacy that is comparable to TCAs and may be higher than SSRI, particularly in the treatment of severe depression. The use of SNRIs is associated with an increased rate of response as well as remission, decreasing the risk of relapse and recurrence of depression in late life. The absence of affinity for muscarinic, histaminic, α_1-adrenergic, opioid of GABAergic receptors, and the absence of action on monoamine oxidase limits the adverse effects, which allows for greater tolerability than TCAs. In randomized clinical trials involving older adults with late-life depression, however, there were no significant differences between the benefits in treatment with SSRIs and SNRIs, though adverse effects have been observed to be more frequent with the use of SNRIs.

Duloxetine Efficacy and tolerability of duloxetine in young adults are supported by several randomized, controlled trials in patients with major depression, pain associated with diabetic neuropathy, and stress urinary incontinence. In older adults, duloxetine is efficacious for the treatment of depression and associated pain symptoms (headaches, backaches, and arthralgias) as compared to placebo. Duloxetine was also found to improve cognitive performance and quality of life as compared to placebo among depressed older patients with medical comorbidity. Duloxetine inhibits

both serotonin and norepinephrine reuptake, and aging does not seem to affect its pharmacokinetic profile. Initial doses in older adults should be started at 20 mg/day. Increases can be made to a maximum of 60 mg/day as a single or divided dose. Duloxetine is immediately absorbed following oral administration and the presence of food tends to reduce the rates of absorption by about 10%.Duloxetine moderately inhibits CYP2D6 and CYP3A4. Although it is reported to have minimal effects on heart rate and blood pressure in healthy young adults, duloxetine's action on norepinephrine may have greater implications for older patients with heart disease. In the absence of further evidence of the safety of this antidepressant in the treatment of older adults, duloxetine should be used cautiously as it has been reported that there is a possibility of increased risk of falls.

Venlafaxine Venlafaxine is a serotonin-norepinephrine reuptake inhibitor that can be used as a first-line alternative to SSRIs for the treatment of depression among older adults and as a preferred agent in those who do not respond to SSRIs. Venlafaxine appears to be less well tolerated than sertraline, but as tolerable as citalopram. Meta-analytic data indicate that venlafaxine is as efficacious as SSRIs in the treatment of depression in younger adults with possibly greater rates of remission rates. Such benefits may be further enhanced in women of 50 years or older. Geriatric trials of this antidepressant have included patients with atypical depression, dysthymia, and poststroke depression. Venlafaxine is also effective for late-life GAD and chronic pain. Venlafaxine's effects on the serotonergic system tend to occur at lower doses. Typically, the extended-release formulation of the drug is prescribed. The initial starting dose for venlafaxine extended-release is 37.5 mg/day to a maximum daily dose of 225 mg/day. Dose adjustments are required for those with renal failure. Patients may experience a similar side effect profile as with SSRI use, including GI distress, headaches, sexual dysfunction, serotonin syndrome, the syndrome of inappropriate antidiuretic hormone secretion, and hyponatremia. Symptoms associated with the discontinuation of venlafaxine may also occur, regardless of drug preparation type. In addition, side effects associated with the adrenergic system can occur, such as dry mouth, constipation, increased ocular pressure, cardiovascular difficulties, and agitation. Hypertension results in a dose-dependent fashion, with hypotension, electrocardiographic changes, arrhythmia, and acute ischemia also possible when taking venlafaxine. Experts discourage the use of venlafaxine in patients with heart disease, and recommend close cardiac monitoring for patients on higher dosages. While venlafaxine has minimal effect on the CYP450 system, it is metabolized by CYP2D6. Thus, poor 2D6 metabolizers or patients taking other drugs inhibiting this isozyme may have higher concentrations of venlafaxine. Of note, venlafaxine is clinically well known to cause significant withdrawal symptoms if stopped abruptly. It should therefore be gradually tapered over days to weeks as clinically indicated.

Desvenlafaxine Desvenlafaxine is the major active metabolite of venlafaxine. Similar to its parent drug, desvenlafaxine is a serotonin and norepinephrine reuptake inhibitor. It is reported to have 10 times greater activity for neurotransmitter uptake compared with the norepinephrine monoamine. Desvenlafaxine was shown to reduce anxiety and improve overall functional quality-of-life outcomes. The effective doses of desvenlafaxine were found to range from 50 to 400 mg/day; however, doses greater than 50 mg/day were associated with increased adverse effects in a dose-dependent fashion with little-to-no added clinical benefit. The time to peak plasma concentration is 7.5 hours after administration and steady-state plasma concentrations are achieved after 4 days. In older patients with concurrent hepatic dysfunction or renal impairment, doses of greater than 50 mg/day should be prescribed with caution due to the limited evidence of added benefit greater than 50 mg/day. Desvenlafaxine is associated with several mild adverse effects such as dizziness, dry mouth, insomnia, decreased appetite, and with the most common side effect being nausea. The less common, but more serious adverse effects reported are hypertension, QTc interval prolongation, elevated lipids, elevated liver enzymes, and exacerbation of ischemic cardiac diseases.

Other Commonly Used Antidepressants

For older patients who are unresponsive to, or are unable to tolerate the use of SSRIs or SNRIs, antidepressants with novel mechanisms such as bupropion and mirtazapine may be used alternatively. Open-label, and small controlled clinical trials support the use of bupropion (response rate, 71%) and mirtazapine (response rate, 47%) in patients with late-life depression; however, data from rigorous placebo-controlled trials are lacking. These medications therefore should be prescribed as single agents to limit adverse effects and drug interactions; however, they are often effective adjuncts in those who partially respond to SSRIs or SNRIs.

Bupropion Nonresponders to SSRIs, or those older depressed patients who cannot tolerate SSRIs, may benefit from bupropion on its own or augmented another antidepressant. For example, bupropion is favored in patients experiencing nausea, diarrhea, severe fatigue, or sexual dysfunction with SSRI use. This antidepressant is well tolerated in medically

ill patients, including those with heart disease, those that smoke, and patients with neuropathic pain. Bupropion was shown to have similar efficacy to imipramine and paroxetine in depressed older patients. Typically, the sustained or extended-release formulations are prescribed. Starting-dose recommendations for older patients are 100 mg daily of the sustained-release tablets, or 150 mg/day of the extended-release formulation. Increases consistent with initial dosages can be made every 3 to 7 days up to a maximum of 300 mg/day. Bupropion is rapidly absorbed following oral administration with nearly 100% bioavailability. Patients with renal impairment should be initiated at a reduced dose because bupropion metabolites may accumulate in these patients. Bupropion should be avoided in patients at risk for seizures or psychotic symptoms. Although seizures are infrequent at therapeutic doses, those with an established seizure disorder or electrolyte disturbances, such as eating disorder patients, are at an elevated risk. Case reports have shown an association between the emergence of psychosis and the initiation of bupropion possibly owing to its action on the dopaminergic system. Bupropion is a moderate inhibiter of CYP2D6. As a substrate of CYP2B6, medications inhibiting this isozyme (eg, fluoxetine, paroxetine) may increase bupropion's plasma concentration.

Mirtazapine By blocking α_2-autoreceptors, mirtazapine enhances noradrenergic and specific serotonergic transmission. Patients who do not tolerate SSRIs because of sexual dysfunction, tremor, or severe nausea may respond well to mirtazapine. This drug has also shown success in the treatment of depressed oncology patients receiving chemotherapy. Mirtazapine is as effective in the treatment of late-life depression as low-dose amitriptyline and marginally superior to paroxetine, yet no placebo-controlled trials have been published. The recommended starting dose of mirtazapine in older patients should be 15 mg at bedtime to a maximum dose of 45 mg. Its concurrent use with other SSRIs raises concerns of increased risk for serotonin syndrome in older adults, however, its coadministration with SSRIs is generally well tolerated. Cognitive impairment and excess sedation in older patients are of concern, likely as a result of its antihistaminergic properties. For similar reasons, the drug is associated with driving impairment. Drug-drug interactions are of minimal concern when taking mirtazapine, as it has little effect on the CYP450 system.

Tricyclic antidepressants and monoamine oxidase inhibitors Once widely prescribed for the treatment of depression, TCAs have largely been supplanted by SSRIs as the treatment of choice. TCAs have been studied in numerous randomized, placebo-controlled, and comparator trials. They have similar efficacy to that of SSRIs in the treatment of late-life depression. Though these studies demonstrate the efficacy of TCAs in treating late-life depression, most do not account for optimal dosing strategies using serum level monitoring. MAOIs have also shown antidepressant effects similar to TCAs. Both of these drug classes require significant efforts to prevent associated adverse events, many of which can be severe and toxic. As such, TCAs and MAOIs are considered third- and fourth-line treatments of geriatric depression, when SSRIs, SNRIs, or safer alternatives are ineffective.

Common side effects of the TCAs include sedation, orthostatic hypotension (leading to dizziness, falls, and fractures), and anticholinergic effects, such as dry mouth, blurred vision, constipation, confusion, and delirium. Nortriptyline, a secondary amine TCA, is better tolerated in older adults and has a lower tendency to result in orthostasis, falls, and anticholinergic effects. The optimal serum level for therapeutic response is 50 to 150 ng/mL. Toxicity tends to occur at serum levels greater than or equal to 300 ng/mL, but can occur at lower doses in older adults. The ability to attain meaningful serum levels allows for more accurate and effective dosing. Two open trials of nortriptyline found this medication to be effective in treating depression in older adults. Three randomized, comparator trials found that nortriptyline was as efficacious as paroxetine and sertraline in alleviating geriatric depression; however, paroxetine was better tolerated than the TCA, and sertraline was associated with better cognitive improvement. Starting doses are usually 10 to 25 mg before bedtime. Serum levels are taken within 5 to 7 days, and linear dosage adjustments can be made up to target serum levels of 50 to 150 ng/mL. Though nortriptyline is preferred to the tertiary TCAs (ie, amitriptyline, clomipramine, doxepin, imipramine), it is still associated with anticholinergic effects. Cardiovascular events are also a significant concern with tricyclics as even slight overdoses can result in lethal heart block or arrhythmia. Patients with ischemic heart disease should not be given TCAs due to the increased risk of sudden cardiovascular death.

MAOI use in older populations is infrequent. While these medications are associated with fewer cardiac and anticholinergic side effects, serious hypo- and hypertension or serotonin syndrome may result from the concurrent intake of other serotonergic medications or foods containing tyramine. Thus, it is crucial for patients taking MAOIs to adhere to strict dietary restrictions, inform all health care providers of MAOI use, and have their blood pressure monitored. Any signs of headache, stiff neck, nausea, or vomiting require an evaluation of blood pressure. If blood pressure is elevated, immediate medical attention is required. Though very rarely used in older adults owing to adverse

events and dietary restrictions, phenelzine is the preferred MAOI as it is the most studied in older patients and is shown to be effective for the treatment of late-life depression. A transdermal patch form of selegiline is approved by the FDA to treat major depression. However, there is very limited geriatric experience with this medication and dietary restrictions are still recommended for higher dosages.

PSYCHOSTIMULANTS

Methylphenidate

Psychostimulants currently have a very limited role in the treatment of depression. Methylphenidate is a controlled substance used for the treatment of attention deficit disorder and for the management of somnolence in narcolepsy. Some data indicate that depressed older adults with concomitant medical complications may have symptomatic benefit with acceptable tolerability. In particular, it may improve symptoms of apathy and anergia that often occur with depression or dementia. To date, only one controlled randomized clinical trial has been published with older patients. The study reported that methylphenidate was more effective than placebo in a small group of inpatients. Methylphenidate, like other stimulants, is advantageous, as it tends to have a fast response, usually within 48 hours. Adverse effects associated with methylphenidate include anxiety, psychosis, anorexia, and hypertension, which are of greater concern in older adults. Drug interactions with warfarin should also be monitored, as methylphenidate may decrease warfarin's metabolism.

ANTIPSYCHOTICS

Atypical antipsychotic medications are first-line treatment of symptoms of psychosis including those attributable to dementia. Studies examining medication use in long-term care facilities suggest that as many as 30% to 50% of older residents are prescribed an antipsychotic. These agents are efficacious in the treatment of schizophrenia, delirium, and BPSD. However, the safety and tolerability of antipsychotics in elders remain a concern.

Typical Antipsychotics

The first antipsychotics were introduced in the 1950s. Generally, all of the typical antipsychotics share similar rates of efficacy. However, side-effect profiles can vary. Typical antipsychotics are shown to be effective for BPSDs, although placebo response rates are also high. Conventional antipsychotics are associated with EPS (eg, dystonia, parkinsonism, akathisia, tardive dyskinesia) even when administered at moderate doses. In a study comparing low and moderate doses of haloperidol to placebo, moderate doses of the antipsychotic were more effective in treating psychosis and psychomotor agitation, but associated with greater EPS. In a comparison of perphenazine to citalopram and placebo, the antipsychotic was comparable in efficacy to citalopram and superior to placebo; however, the SSRI had a more favorable side-effect profile. Similar results were demonstrated in a comparison of citalopram and risperidone, where both medications successfully reduced symptoms of agitation and psychosis in hospitalized patients with dementia, yet citalopram was associated with significantly fewer adverse events. Currently, atypical antipsychotics are preferred to typical antipsychotics in treating BPSD due to the improved adverse effect profile.

Atypical Antipsychotics

Atypical antipsychotics have replaced typical agents in the treatment of psychosis, aggression, and agitation in older patients with dementia. This was mainly as a result of greater tolerability, reduced risk for acute EPS, and tardive dyskinesia when compared with conventional antipsychotics. In comparator trials of atypical and typical antipsychotics, olanzapine and risperidone have demonstrated comparable or greater efficacy and tolerability over promazine or haloperidol in older patients with BPSD, schizophrenia, or delirium. In recent years, however, the use of atypical antipsychotics has been widely debated due to safety concerns, particularly in older patients with dementia. Indeed, the FDA added a black box warning about the possible risk for sudden death and included a warning of an increased risk for cerebrovascular adverse events (CVAEs) in all antipsychotic labels. In selecting an antipsychotic medication, it is prudent to consider both the clinical profile of the patient as well as the side effects common to that medication (**Table 64-3**).

TABLE 64-3 ATYPICAL ANTIPSYCHOTIC DOSAGES, HALF-LIFE, AND SIDE EFFECTS

MEDICATION	DOSE (MG/D)	CLEARANCE (HALF-LIFE)	SIDE EFFECTS
Aripiprazole	2–15/d	75–96 h	Sedation (limited geriatric data)
Clozapine	25–300/d	Mean 12 h	Excessive sedation, seizure, anticholinergic effects, agranulocytosis, orthostatic hypotension, sustained tachycardia, weight gain, high risk of diabetes mellitus, and dyslipidemia
Olanzapine	2.5–10/d	Mean 30 h	Sedation, dose-dependent anticholinergic effects, gait disturbance, orthostatic hypotension, high risk of weight gain, hyperglycemia, diabetes mellitus, risk of cerebrovascular events, dose-dependent EPS, EEG abnormality
Quetiapine	25–800/d	3–6 h	Sedation, orthostatic hypotension, moderate risk of weight gain, diabetes mellitus, and dyslipidemia
Risperidone	0.25–2/d	Mean 20 h	Orthostatic hypotension, dose-dependent EPS, tardive dyskinesia, hyperprolactinemia, risk of cerebrovascular events, weight gain, moderate risk of diabetes mellitus and dyslipidemia, moderate EEG abnormality, mild sedation, rare cognitive effects
Ziprasidone	20–80 BID	7 h	Prolongation of QTc interval (limited geriatric data)
Lurasidone	20–80/d	7.5–18 h	Sedation, drowsiness, dose-dependent EPS, akathisia parkinsonian-like syndrome, nausea, tachycardia, insomnia, agitation, anxiety, dystonia, somnolence, nasopharyngitis, dyspepsia, increase serum prolactin (limited geriatric data)
Paliperidone	3–12/d	23–51 h	Tachycardia, dose-dependent EPS, headache, somnolence, anxiety, dizziness, insomnia, somnolence, orthostatic hypotension, salivary hypersecretion
Iloperidone	1–12 BID	18–37 h	Sedation, dizziness, orthostatic hypotension, nausea, headache, fatigue, impaired balance, prolongation of QTc interval, anticholinergic effects (limited geriatric data)
Asenapine	5–10 BID	24 h	Akathisia, oral hypoesthesia and somnolence, anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, wheezing and rash (limited geriatric data)

BID, twice daily; d, day; EEG, electroencephalography; EPS, extrapyramidal symptoms; QTc, QT (cardiac output) corrected for heart rate.
Anticholinergic effects: dry mouth, blurred vision, constipation, confusion.

Clozapine The first atypical antipsychotic approved for use by the FDA was clozapine. It is a partial agonist of the $5HT_{1A}$ receptor, has a high affinity for the dopaminergic type 4 (D_4) receptor, and is a strong antagonist at adrenergic, cholinergic, muscarinic, and histaminergic receptor sites. Clozapine is indicated for the treatment of schizophrenia in younger adults, and is highly efficacious with relatively no risk for the development of tardive dyskinesia. Two case series provide evidence that moderate dosages of clozapine may provide symptomatic relief for older patients with

primary psychotic diagnoses, and a randomized comparator trial of clozapine and chlorpromazine supports these results. Lower dosages of clozapine (eg, 12.5–50 mg/day) are suggested as safe and efficacious in the treatment of drug-induced psychosis in Parkinson patients. There are no double-blind placebo-controlled trials evaluating the efficacy or tolerability of clozapine in the treatment of BPSD.

Data from retrospective reviews and case studies have found this atypical agent to be moderately effective, but not without significant side effects. Clozapine levels increase in a dose- and age-dependent fashion and levels may be attenuated in women. Adverse events are numerous with this drug, and range from minor to severe, and potentially fatal. Common side effects include excessive sedation, sialorrhea, and anticholinergic effects of dry mouth, constipation, and cognitive impairment. Clozapine lowers the seizure threshold more so than other antipsychotics. Agranulocytosis is a potentially serious and life-threatening adverse event that occurs in 0.38% of patients. Intensive hematologic monitoring is required, especially in older adults. Orthostatic hypotension is another common adverse effect that increases the risk for falls and fractures in older patients. Thus, the side-effect profile of clozapine limits its utility in the treatment of later life. Its use in demented older patients should be restricted to instances where other antipsychotics have failed.

Risperidone Risperidone is a strong antagonist of $5HT_2$, D_2, adrenergic α_1 and α_2 receptors, a mild histaminergic H_1 antagonist, and has little effect at cholinergic receptor sites. Most evidence for the use of antipsychotics in later life is for risperidone. Several randomized, placebo-controlled trials, randomized, comparator trials (with haloperidol, promazine and olanzapine, or olanzapine), and uncontrolled or case studies have indicated that BPSDs are treated safely and effectively with risperidone. Risperidone is also a safe and efficacious treatment of schizophrenia in older adults as compared to olanzapine and in a randomized, open-label study, where patients were switched from a typical antipsychotic to either risperidone or olanzapine. Uncontrolled data including older individuals with schizophrenia and other psychotic disorders demonstrate similar results, as does an evaluation of a long-acting injectable preparation of risperidone for older adults with schizophrenia. Risperidone like all other atypical antipsychotics, however, is not approved for use in geriatric patients with dementia-related psychosis or dementia, as it is associated with an increased risk for death. As risperidone is known to increase QTc interval, paliperidone should be avoided among patients with a history of cardiac arrhythmias or congenital long QT syndrome or in combination with other drugs that are known to prolong QTc.

Risperidone is shown to reduce the duration of delirium in late life, and it is well tolerated, as indicated by a randomized, comparator trial with haloperidol and additional supportive uncontrolled reports. While evidence supports the use of risperidone in young bipolar patients, there is a paucity of data regarding risperidone for older bipolar patients. In this case, mood stabilizers or other antipsychotics are the preferred first line of treatment. When severe mania or mania with psychosis co-occurs, a mood stabilizer is typically combined with risperidone, olanzapine, or quetiapine. Risperidone's safety and efficacy, even at low doses, is not established in patients with drug-induced psychosis in Parkinson disease or Lewy body dementia due to the aggravation of parkinsonism. High-potency antipsychotics, such as risperidone, should be avoided in patients with parkinsonism with a preference for low-potency antipsychotics, such as quetiapine and clozapine.

Risperidone, and its active metabolite 9-hydroxyrisperidone (paliperidone), appear to increase in concentration at certain dosages in an age-dependent manner. As such, in older demented patients, dosages should range between 0.25 and 2 mg/day; initial doses can start at 0.25 mg and titration should be slow. In older patients without dementia, dosages should be initiated at 0.25 mg/day, increasing by 0.25 to 0.5 mg increments every 4 to 7 days to a maximum below 4 mg/day. Since the half-life of risperidone ranges from 20 to 22 hours, once-daily dosing is acceptable. A common initial side effect is orthostatic hypotension, and EPS can occur in a dose-dependent manner. Tardive dyskinesia has been reported in patients with dementia taking an average dose of risperidone at 0.96 mg daily (SD, 0.56 mg); however, the persistence of these symptoms 1 year later was quite low. Risperidone is the atypical antipsychotic most associated with hyperprolactinemia, but leads to moderate abnormalities in electroencephalography (EEG), and its limited affinity for muscarinic receptors results in rare effects on cognition. Mild sedation has also been reported. Weight gain, diabetes, and dyslipidemia are more likely to occur with use of risperidone than with aripiprazole or ziprasidone; however, these side effects appear more frequently when taking the atypical agents clozapine or olanzapine than risperidone.

Paliperidone Paliperidone is a newer atypical antipsychotic for the treatment of schizophrenia and schizoaffective disorder. It is the main metabolite of its parent drug, risperidone with a similar mechanism of action, efficacy, and safety to that of risperidone. As a metabolite, hepatic impairment or metabolism by CYP2D6 should not impact

paliperidone's clearance. Renal function, however, will affect clearance rates. The extended-release formulation of paliperidone can be given once daily, which may be beneficial for patients with compliance issues. The safety and tolerability of paliperidone ER among older patients with schizophrenia in the dosage of 3 to 12 mg was generally comparable to those seen in younger adult populations. Paliperidone like risperidone is known to increase QTc interval. Overall, paliperidone is generally safe and well tolerated with short-term use in older patients with schizophrenia. Long-term studies are still required in order to determine further clinical effectiveness and side-effect profile in the older population.

Olanzapine The use of olanzapine in geriatric patients has also received extensive examination. This atypical agent inhibits various receptor sites, with a high affinity for $5HT_{2A/2C}$, and milder effects at $D_{4/3/2/1}$, H_1, muscarinic acetylcholine, and α_1 receptors. Randomized, placebo-controlled trials and randomized, comparator trials (with haloperidol, promazine and risperidone, and risperidone) have demonstrated that olanzapine can safely and effectively treat BPSD. Also, older patients with schizophrenia have seen effective and tolerable benefits from olanzapine treatment in two randomized, comparator trials each with haloperidol and risperidone. A large randomized, controlled trial found olanzapine and haloperidol to be similarly efficacious in the treatment of late-life delirium. Yet, evidence from other controlled trials suggests cognitive worsening in demented patients receiving olanzapine, and case reports indicate the occurrence of olanzapine-induced delirium possibly due to its strong anticholinergic properties. Olanzapine's efficacy and tolerability are uncertain in treating drug-induced psychosis in Parkinson. This agent did not reduce symptoms of psychosis beyond placebo, but did result in a worsening of parkinsonism and activities of daily living. Another randomized study found no difference between the efficacy of olanzapine and clozapine, and more toxicity with the former atypical antipsychotic. Furthermore, while a few open trials or case series have been positive, many have demonstrated that olanzapine can exacerbate motor symptoms in patients with Parkinson or Lewy body dementia. Olanzapine also appears effective for the treatment of geriatric bipolar disorder.

Dosing in patients with schizophrenia, mood disorders, or BPSD can be initiated at 2.5 mg/day with clinically indicated titration up to10 mg daily. Response should be evaluated for at least a week before doses are increased. Single daily is possible due to olanzapine's mean half-life of 30 hours. It is well absorbed with no effect of food intake. A 2004 consensus conference examining available data including younger patients with psychotic or mood disorders taking olanzapine and clozapine, found that these agents demonstrated the highest risk for diabetes, weight gain, and dyslipidemia as compared to other atypical antipsychotics. Sedation and gait disturbance are the most common complaints associated with olanzapine; however, dose-dependent EPS and orthostatic hypotension does occur, typically at doses greater than 5 to 10 mg daily. EEG abnormalities have been reported with use of this agent. Other reported effects in older adults include constipation (institutionalized dementia patients), dose-dependent decreased efficacy (patients with BPSD), negative cognitive effects versus risperidone (older patients with schizophrenic and dementia), cognitive decline (AD patients), and delirium. These adverse reactions may be attributable to olanzapine's anticholinergic effects. Dose-dependent adverse effects are of concern in older patients, women, nonsmokers, and those taking medications that inhibit CYP1A2 (eg, fluvoxamine or ciprofloxacin). Olanzapine should be avoided in older patients where cognitive impairment, constipation, diabetes, diabetic neuropathy, dyslipidemia, obesity, xerophthalmia, or xerostomia are of concern.

Quetiapine This atypical antipsychotic works to inhibit $5HT_{1A/2}$, $D_{2/1}$, H_1, α_1, and α_2 receptors. As with olanzapine, quetiapine has a higher affinity for the serotonergic receptors than the dopaminergic sites. Furthermore, quetiapine has minimal effect on cholinergic or benzodiazepine receptors. Quetiapine was found efficacious for the symptomatic treatment of BPSD in older patients with primary psychotic disorders, dementia, and delirium. However, in four trials including patients with dementia or parkinsonism, quetiapine failed to significantly alleviate agitated or psychotic behaviors above placebo, with one trial demonstrating greater cognitive decline in patients treated with quetiapine. Evidence from published studies examining quetiapine for drug-induced psychosis and Parkinson disease generally supports the efficacy and tolerability of this medication for these conditions. Quetiapine is the first-line option for older patients with Parkinson or Lewy body dementia, and those with tardive dyskinesia.

Somnolence is a common adverse effect with the initiation of quetiapine, and though most patients adjust to this relatively fast, quetiapine should be started at doses as low as 25 mg before bedtime. Dosages can range from 25 to a maximum of 800 mg daily. Generally, older patients are maintained on approximately 100 mg/day, as the lower clearance rates in older adults can result in higher concentrations of this agent. Its short half-life of 3 to 6 hours may necessitate a twice-daily dosing regimen. Complaints of sedation and dizziness can be combated with a slower dose titration, and the risk for EPS is low. Quetiapine and risperidone have a similar risk for causing weight gain, diabetes,

or dyslipidemia, but the risk for these adverse effects is lower than with clozapine or olanzapine.

Ziprasidone Ziprasidone has a high affinity for dopaminergic, serotonergic, and α-adrenergic receptors, and little affinity for muscarinic and histamine receptors. This atypical antipsychotic has limited effects on glucose, lipids, and weight, and minimal anticholinergic activity on cognition, making it an attractive option for use in older adults. Evidence for the oral preparation of ziprasidone in older patients is limited to a published case series and a pharmacokinetic analysis. Ziprasidone's propensity to prolong the QTc interval may limit its use in older patients with cardiovascular disease. Use of intramuscular ziprasidone was not associated with any adverse cardiovascular or EEG effects in two separate studies. Due to limited geriatric clinical trials, ziprasidone should be used as a second-line treatment.

Aripiprazole Among antipsychotics, aripiprazole uniquely acts as a partial D_2 agonist, though at increased concentrations, typical in elders, more complete dopaminergic inhibition results. As with ziprasidone, aripiprazole has minimal metabolic and antimuscarinic effects. However, geriatric data are limited. A single randomized, placebo-controlled trial of aripiprazole to treat BPSD had shown minimal efficacy in reducing psychosis on secondary outcome measures with an average dose of 10 mg/day, which was well tolerated. The initial daily dose of aripiprazole is 2 to 5 mg with a maximum of 15 mg. Aripirazole is associated with an elevated risk of akathisia, sedation, nausea, headache, weight gain, and increased cholesterol levels. The long half-life of this agent (75–96 hours) is also of concern in older adults. Thus aripiprazole should be used as second-line treatment in the absence of further geriatric data in a variety of conditions.

Lurasidone Lurasidone is a novel atypical antipsychotic approved by the FDA for the treatment of schizophrenia. Like many other atypical antipsychotics, the compound has potent dopamine D_2 and serotonin $5HT_{2A}$ affinity, but greater affinity than most agents in this class for serotonin $5HT_7$, $5HT_{1A}$, and α_{2c}-adrenergic receptor subtypes. It should be taken with a meal as the bioavailability increases two- to threefold with food. Phase II/phase III clinical trials indicate that doses from 40 to 120 mg/day are effective in the reduction of positive symptoms. Doses higher than 80 mg/day are associated with an increase in dose-related adverse events such as akathisia, parkinsonism, somnolence, and prolactin elevations, without additional statistically significant clinical benefit. The maximum recommended dose of lurasidone in younger adults is 160 mg/day. Thus, doses greater than 80 mg/day in older adults should be given cautiously. Common with all antipsychotics, lurasidone carries warnings for leukopenia, neutropenia, agranulocytosis, neuroleptic malignant syndrome suicide, tardive dyskinesia, and increased seizure risk. As with other antipsychotics, lurasidone is not recommend for use in patients with dementia-related psychosis because of an increased risk for sudden cardiac death, but does not appear to be associated with QT prolongation. Additional studies involving older patients are needed to further evaluate its role in psychiatric disorders of later life.

Iloperidone Iloperidone is a second-generation atypical antipsychotic recently approved by the FDA. The drug is a dopamine D_2 and serotonin $5HT_{2A}$ receptor antagonist with additional high affinity for α_{2c}-adrenergic receptors, which may theoretically result in antidepressant and anxiolytic activity, and improved cognitive function. The recommended therapeutic dose range of iloperidone is from 4 to 24 mg/day for schizophrenia or schizoaffective disorder. Due to the elevated risk of orthostatic hypotension, iloperidone should be initiated at 1 mg BID and gradually titrated to 6 mg BID by day 4. The half-life is 18 to 33 hours. Compared to other antipsychotics, iloperidone is associated with less extrapyramidal symptoms and an intermediate degree of weight gain. Common treatment-related adverse events include dizziness, dry mouth, somnolence, and dyspepsia. The dose of iloperidone should be reduced by 50% for patients taking other medications known to inhibit CYP34A or CYP2D6. The efficacy of iloperidone has yet to be determined in the geriatric population. Its propensity for QT prolongation and orthostatic hypotension limit its use in older adults.

Asenapine Asenapine is a tetracyclic antipsychotic approved for the treatment of acute schizophrenia and maintenance treatment of schizophrenia. It is administered sublingually due to its poor gastrointestinal absorption. Asenapine was efficacious in two out of four 6-week, randomized double-blind multicenter studies on the acute treatment of schizophrenia in adults. The effective dose range of asenapine was determined to be 5 to 10 mg twice daily. In clinical trials, daily doses greater than 20 mg/day were associated with an increased risk of adverse effects without offering any additional clinical benefit. The most common treatment-related adverse events reported were akathisia, oral hypoesthesia, and somnolence. Rare hypersensitivity reactions have been observed in clinical trials and

include anaphylaxis, angioedema, hypotension, tachycardia, swollen tongue, dyspnea, wheezing, and rash. Asenapine is not recommended for use in patients with severe hepatic impairment due to the risk of elevated drug levels. Similar to other antipsychotics, asenapine is not recommended for use in older patients with dementia-related psychosis as it is associated with increased risk for sudden cardiac death. The efficacy and safety of asenapine treatment in older adults has yet to be established.

Adverse Effects and Safety

Older patients are more susceptible to antipsychotic adverse effects, such as sedation, cardiovascular changes, which include tachycardia and orthostatic hypotension, anticholinergic effects, including dry mouth, blurred vision, constipation and urinary retention, neuroleptic malignant syndrome with hyperpyrexia, autonomic instability, pigmentary retinopathy, weight gain, allergic reactions, and seizures. Orthostatic hypotension, which can lead to falls and fractures in elders, is a likely consequence with low-potency typical antipsychotics such as chlorpromazine and thioridazine, and atypical agents like clozapine, risperidone, olanzapine, and quetiapine. Anticholinergic effects are most common with low-potency conventional antipsychotics, olanzapine, and clozapine. Tardive dyskinesia and EPS are also of particular concern in older adults; the low-potency atypical agents are less prone to causing EPS when compared to similar doses of high-potency typical and atypical antipsychotics (eg, haloperidol and risperidone, respectively). Approximately half of patients aged 60 to 80 taking typical agents experience EPS or tardive dyskinesia. Thus, older patients require doses of antipsychotics lower than those used in younger adults to try to limit the emergence of adverse effects.

According to published reports and an FDA-issued warning, the rate of death in older patients with BPSD treated with atypical antipsychotics is close to double that seen in patients randomized to treatment with placebo (ie, 2.6% mortality with placebo vs 4.5% with atypicals over 12 weeks), though the increased absolute risk of mortality is low. Risk of sudden cardiac death in patients taking antipsychotics is also increased, with thioridazine users at particular risk. Some studies have challenged whether the atypical agents lead to reduced incidence of falls or EPS as compared to typical antipsychotics, especially when higher drug dosages are involved. Typical antipsychotics may demonstrate decreased risk for cerebrovascular events, venous thromboembolism, or pancreatitis; yet several meta-analytic and pharmacoepidemiologic studies have suggested these drugs have similar or increased risk to atypicals for diabetes mellitus, cerebrovascular events, stroke, or death. In light of the lack of consensus with regard to the safety of antipsychotics and paucity of data concerning alternate drug classes, clinicians must consider individualized risk-benefit analysis when providing care for patients. For treatment of agitation/psychosis in dementia, it was estimated from a meta-analysis of placebo-controlled studies with atypical antipsychotics that the number needed to treat is approximately 7 to 12 and the number needed to harm is between 44 and 118. In treating a particular disorder, it is also important to consider the strength of the data available for that condition for each drug, as well as the associated adverse effect profiles of those drugs.

MOOD STABALIZERS

Randomized, controlled trials of mood stabilizers including geriatric patients are severely lacking. The available data that exist consist of case series, chart reviews, and other uncontrolled reports. This class of medications is considered to be of high risk because of their potential for toxicity, serious adverse events, and interactions with other drugs. However, lithium continues to be recommended as the treatment of choice for late-life bipolar disorder with classic mania and minimal neurologic impairment. Whether lithium should be utilized as a first-line mood stabilizer in order to treat mania in older patients remains to be determined. Anticonvulsants are also prescribed to treat agitation associated with dementia.

Lithium

Lithium carbonate is an effective acute and preventive treatment of mania in older patients. However, the use of lithium in elders necessitates special care; thus it tends to be prescribed less in later life because of concerns of tolerability, especially in the context of multiple comorbidities. Renal function declines with age and as such, so does the clearance of lithium. The elimination of half-life of lithium ranges between 28 and 36 hours for older patients, in comparison to 24 hours among younger adults. This increases older adult’s sensitivity to adverse effects and the risk for toxicity. Common medical conditions of later life, such as renal dysfunction, hyponatremia, dehydration, and heart

failure also increase the risk of lithium toxicity. Renal clearance is further complicated by use of thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEI), and NSAIDs. Thus, lower serum levels of lithium should be maintained in older patients. Trough serum levels should be measured 12 hours after dosing 4 to 5 days after the initial does of 150 to 300 mg once or divided doses daily with safe and efficacious measurements being 0.4 to 0.8 mmol/L (mEq/L).

Common side effects of lithium in older adults include cognitive impairment, ataxia or gait abnormalities, nausea, fine hand tremor, hypothyroidism, weight gain, rash or cutaneous abnormalities, worsening of arthritis, peripheral edema, and urinary frequency or renal deterioration. Neurologic side effects indicating toxicity can include coarse tremor, slurred speech, ataxia, confusion, and drowsiness. Toxicity can develop at levels between 1.5 and 2 mmol/L in adults, and can manifest with levels as low as 1.0 mmol/L in older patients. Serum levels of 1.5 mmol/L are associated with delirium, and levels below 1.0 mmol/L have resulted in cognitive impairment in older adults. Lithium toxicity necessitates immediate medical attention as it can result in death or persistent neurologic dysfunction. Regular electrocardiograms and monitoring of electrolytes and lithium levels are warranted in older adults. Lithium-induced renal impairment should be monitored via analyses of serum creatinine and urine osmolality, and lithium-induced hypothyroidism should be monitored via thyroid-stimulating hormone concentrations every 6 months. Drug interactions affecting renal clearance should also be considered to avoid toxicity (**Table 64-4**).

TABLE 64-4 DRUG INTERACTIONS WITH LITHIUM

CLASS/MEDICATION	TOXICITY RISK
ACEIs/ARBs	Lithium toxicity Toxicity via sodium depletion
Carbamazepine	Neurotoxicity (ataxia, tremors, nausea, vomiting, diarrhea, tinnitus)
Calcium channel blockers (eg, diltiazem, verapamil)	Neurotoxicity
Haloperidol	Neurotoxicity; encephalopathy (results in irreversible brain damage)
Diuretics	Decrease in renal clearance leading to toxicity
MAOIs	Fatal malignant hyperpyrexia
Metronidazole	Lithium toxicity (rare) NSAIDs: lithium toxicity
Phenothiazines	Neurotoxicity
Phenytoin	Lithium toxicity
SSRIs	Neurotoxicity (particularly fluoxetine and fluvoxamine)
Sibutramine	Serotonin syndrome
Tricyclic antidepressants	Neurotoxicity

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; MAOI, monoamine oxidase inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs.

Anticonvulsants

Anticonvulsants are increasingly being used instead of lithium to treat bipolar disorders in later life, partly due to age-related reduction in tolerance to lithium. Bipolar patients with dysphoria or rapid cycling may actually respond better to anticonvulsants than lithium. Secondary mania, defined as mania occurring in the presence of dementia or other neurologic illness, may similarly respond well to anticonvulsants.

Valproate Valproate's anticonvulsant activity is thought to be mediated by increasing concentrations of γ-aminobutyric acid (GABA) in the central nervous system. Case studies have shown tolerability of valproate by older bipolar patients and those with dementia-related agitation. Conversely, four placebo-controlled trials found that valproate did not relieve dementia-related agitation more than placebo. Valproate is prepared in several mutually exclusive formulations: valproic acid, divalproex sodium, and an extended-release preparation. Preliminary medical

work-up should be initiated before the start of valproate therapy, which includes liver enzyme levels, complete blood count with platelets, and electrocardiogram (ECG). Divalproex sodium is commonly initiated at 250 mg once to twice daily. Titrations can be made up to a maximum of 500 to 2000 mg/day as single or divided doses. Efficacious and tolerable serum levels are between 200 and 700 mmol/L (35–100 mg/mL). Common dose-dependent side effects include sedation, nausea, weight gain, hand tremor, reversible elevations in liver enzymes and blood ammonia levels, and thrombocytopenia, which may manifest at lower drug levels in older patients. Liver failure or pancreatitis may also occur in rare instances. Valproate may also occasionally cause encephalopathy, specifically in patients with a urea cycle disorder. Metabolism of valproate initially occurs via mitochondrial β-oxidation, with the CYP450 system having minimal influence on its metabolism. Administering valproate in conjunction with carbamazepine, lamotrigine, diazepam, phenobarbital, or primidone increases the concentrations of these drugs, while concomitant use of valproate with carbamazepine, lamotrigine, topiramate, or phenytoin decreases valproate levels. Valproate works synergistically with fluoxetine and erythromycin, amplifying the effects of valproate.

Carbamazepine For decades, carbamazepine has been used as an off-label alternative to lithium. The FDA has recently approved its extended-release for the management of bipolar disorder. This drug inhibits the repetitive activation of sodium channels and works well to reduce seizures. In young patients, carbamazepine was found to offer some advantage in patients with atypical bipolar disorder or secondary mania. In patients with dementia, this medication also has demonstrated efficacy in reducing agitation and aggression in comparison with placebo. It is important to indicate that before the start of carbamazepine therapy, preliminary medical work-up such as assessing liver enzymes, complete blood count with platelets, and ECG should be completed. Carbamazepine is started at 100 mg once or twice daily, and a gradual titration can be made of 100 to 200 mg every 3 to 5 days. Based on clinical data, carbamazepine could be dosed to achieve a serum level of 4 to 12 μg/mL, which is a typical dose range of 400 to 800 mg/day in two divided doses. There is a dose-dependent risk for side effects with carbamazepine, including nausea, dizziness, confusion, ataxia, neutropenia, hepatotoxicity, leucopenia, agranulocytosis, and drug interactions. Carbamazepine clearance is reduced with age. It is primarily metabolized by CYP3A4, acting as both a substrate and inducer, leading to autoinduction with repeated dosing. Its initial half-life is 25 to 65 hours, but drops to 12 to 17 hours with repeated dosing due to the induction of its own metabolism. Medications that inhibit this CYP3A4 (eg, macrolide antibiotics, antifungals, some antidepressants) can lead to toxic concentrations of carbamazepine. Conversely, those medications that induce this isoenzyme (eg, phenobarbital, phenytoin, and carbamazepine) will lower concentrations of drugs metabolized by CYP3A4. There are currently no controlled clinical trials of carbamazepine involving geriatric patients with bipolar disorder.

Gabapentin and pregabalin Gabapentin has a mild side-effect profile and works to reduce symptoms of anxiety and neuropathic pain. A retrospective case series study indicates gabapentin is effective and well tolerated for the treatment of agitated and aggressive behavior in patients with dementia. There is an absence of controlled clinical trials indicating the efficacy of this medication in treating patients with bipolar disorder or dementia, though it is used clinically in these populations. The drug is eliminated exclusively via renal excretion. Thus, renal impairment can result in ataxia, involuntary movements, disorganized thinking, excitation, and excessive sedation. It is important to ensure that the dose is adjusted for the degree of renal impairment, regardless of the patient's age. Pregabalin is the potent successor to gabapentin. The combined results of clinical trials involving older patients with mean range from 57.1 to 73.2 years indicated significant dose-related efficacy for pregabalin compared with placebo in terms of pain relief, sleep, quality of life, and patients' and clinicians' global impressions. In older patients, initial dosages for pregabalin or gabapentin are recommended at 150 mg/day (divided in two or three doses), followed by titration over 1 week to 300 mg/day (in three divided doses) as needed. Further titration to a maximum dose of 600 mg/day (in three divided doses) is recommended for those with an inadequate response to 300 mg/day. The two most common treatment-emergent adverse events with the treatment of pregabalin are dizziness and somnolence. Therefore patients taking this specific drug should be warned about the potential hazards when driving and operating machines. Geriatric evidence is still limited in determining the efficiency use of pregabalin and gabapentin, though its pharmacokinetic profile is favorable and it may be used in the treatment of neuropathic pain in older adults.

Lamotrigine The FDA has granted approval for the use of lamotrigine in the preventative treatment of the depressive, manic, or mixed episodes of bipolar disorder, but it is primarily used for the treatment or prevention of bipolar depression. In older bipolar patients, lamotrigine has demonstrated superior efficacy versus placebo. Dosing in older adults is initiated at 25 mg daily for 2 weeks, then 50 mg daily for the following 2 weeks, and then 100 mg/day for 7

days. Dosages can then be increased up to 200 mg daily. However, in patients also taking valproate, lamotrigine's titration schedule is reduced and target dosages are halved since valproate increases lamotrigine levels. Though lamotrigine does not appear to increase weight, common side effects in older adults include excessive drowsiness, headaches, and rashes. Any sign of rash or hypersensitivity related to lamotrigine use should result in its discontinuation and immediate evaluation of the patient. While rare, severe rashes such as Stevens-Johnson syndrome or toxic epidermal necrolysis have occurred in 0.3% of adults. Reducing the rate of dose titration of lamotrigine can lessen the risk for rashes.

ANXIOLYTICS

Benzodiazepines

Anxiety and insomnia in older adults are frequently treated using benzodiazepines. A meta-analysis examining the published studies of sedative-hypnotics in older adults, however, suggests that the significant adverse effects associated with benzodiazepines far outweigh the relatively minimal, short-term benefits. Side effects can include excessive daytime sedation, risk of falls and hip fractures, and impairments of cognition and psychomotor performance, even at low doses. The half-lives of benzodiazepines are longer in later life, resulting in their accumulation and an increased likelihood of adverse events. If they are to be used, intermediate-acting benzodiazepines (eg, lorazepam) are preferred. Chronic use of benzodiazepines in moderate-to-high doses followed by abrupt discontinuation can lead to symptoms of withdrawal, including anxiety, insomnia, tremor, tachycardia, delirium, psychosis, or seizure. Benzodiazepines should be avoided in older patients experiencing heavy snoring (suggestive of sleep apnea), dementia, or concurrent use of other sedatives or alcohol. Lorazepam and oxazepam do not affect the CYP450 isozymes and are not associated with drug interactions. Oxazepam exhibits variability in absorption making lorazepam the preferred sedative. Lorazepam is administered in low dosages of 0.25 to 0.5 mg/day and should not exceed 2 mg daily. Ideally, benzodiazepines, such as lorazepam, should be reserved for episodes of acute agitation or aggression, or when all other safer alternatives have failed.

Buspirone

The antianxiety medication buspirone does not lead to sedation, is not addictive, and is tolerated well by older adults. It is a partial agonist of $5HT_{1A}$ receptors with no affinity for the benzodiazepine/GABA receptors, and may be particularly useful in treating GAD in geriatric patients that are susceptible to falls, confusion, or chronic lung disease. A disadvantage of buspirone is that its onset of anxiolytic action may not be evident for 1 to 3 weeks following initial dosing. This drug may also lead to dizziness, headache, and nervousness. The initial dose of buspirone is 5 mg twice daily. Increases by 2.5 mg daily can be made weekly to a maximum daily dose of 60 mg/day. The pharmacokinetic profile of buspirone is similar in young and old adults. However, concurrent use of verapamil, diltiazem, erythromycin, or itraconazole will elevate concentrations of buspirone, and concomitant administration of SSRIs may rarely lead to serotonin syndrome.

SUMMARY

As with other classes of drugs, the use of psychoactive agents in older patients is complicated by comorbid medical illness and concomitant use of multiple medications. Consequently, older patients experience more adverse events with psychoactive medications, which tend to be more serious than those in younger groups. Clinicians must consider individual patient risk-to-benefit ratios when considering the use of psychoactive agents in later life, taking into account drug-specific adverse effect profiles, drug interactions, and patient's comorbid medical conditions. The detrimental effects of depression, anxiety, or psychosis in late-life on activities of daily living, cognition, institutionalization, and mortality cannot be ignored. These disorders exacerbate concurrent physical ailments in patients and increase the burden on the health care system. Although efficacy and tolerability data are limited in comparison with younger adults, many elders are able to achieve and maintain an improved quality of life with the use of psychoactive agents. While psychotropic use in older adults can be challenging, drug therapy is an important tool to combat many debilitating behavioral and psychiatric disorders.

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Chapter 65

Cerebrovascular Disease

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Learning Objectives

- Understand the pathophysiology and clinical presentations of different types of strokes, and specific symptoms and signs associated with the involvement of each major cerebral artery and location of infarction.
- Learn about the state-of-the-art neuroimaging techniques and other tests available to evaluate and diagnose stroke.
- Acquire latest information about the pharmacology, specific indications, and adverse effects of various drugs and surgical interventions available to treat different stages and types of strokes.
- Learn about the results of pivotal clinical trials forming the basis for latest guidelines to treat different types of strokes.
- Understand the rationale for various preventive strategies commonly used for different types of strokes.

Key Clinical Points

1. **It is important to identify the pathophysiology in each stroke patient, as it drives selection of the best treatment choice.**
2. **Magnetic resonance imaging (MRI) brain scans with diffusion-weighted imaging (DWI) are the best way of identifying cerebral infarcts acutely and accurately, while computed tomography (CT) scanning is insensitive to recent infarcts of less than 12 hours.**
3. **Imaging of the cervical and cerebral large arterial system with CT angiography (CTA) or MR angiography (MRA) should be urgently performed to assess the arterial system. CTA offers the best resolution.**
4. **Recombinant tissue plasminogen activator (rt-PA) initiated within 3 hours of symptom onset has been shown to reduce stroke-related disability. In general, use of rt-PA in older adults with stroke outweighs risks.**
5. **Benefits of using heparin in acute stroke are uncertain.**
6. **Efficacy of carotid endarterectomy for symptomatic disease with more than 70% stenosis is high. Carotid stenting is reserved for patients in whom surgery is contraindicated.**

Although stroke is the fifth leading cause of death in the United States, it remains the single most important cause of disability. Many varied pathologic processes lead to either occlusion of an extra- or intracranial artery or vein causing ischemic stroke or transient ischemic attack (TIA), or rupture of an intracranial artery causing hemorrhagic stroke. With TIAs, and ischemic or hemorrhagic stroke, the key to acute or chronic therapy is the determination of the precise diagnosis. The diagnostic formulation must not only establish that the clinical entity is indeed an ischemic stroke or TIA, or a hemorrhagic stroke, but it also must localize and characterize the precise arterial or venous pathologic process causing the stroke and elucidate the nature of the spared collateral circulation (**Figures 65-1** and **65-2**). This chapter focuses on identifying this pathologic process as the pivot on which hinges rational medical and/or surgical treatments or preventive strategies. For both ischemic and/or hemorrhagic stroke, the precise pathophysiologic process divides logically into specific stroke or TIA subtypes.

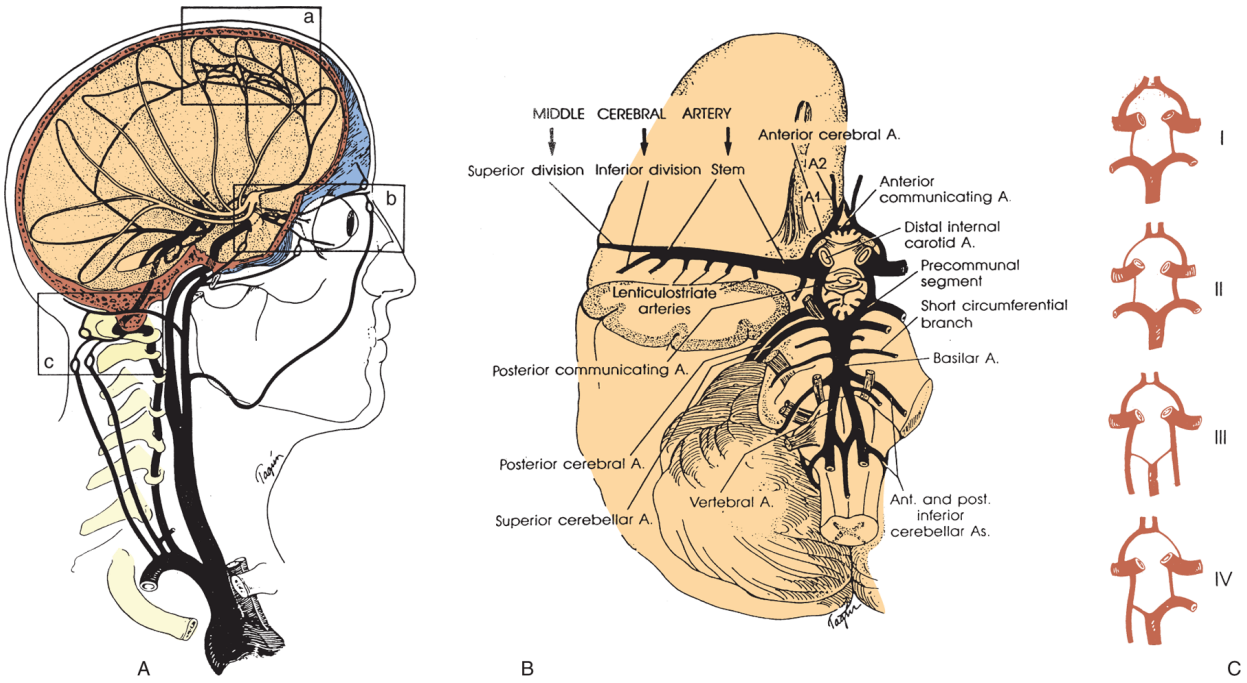


FIGURE 65-1. **A.** Arrangement of the major arteries of the right side carrying blood from the heart to the brain. Also shown are vessels of collateral circulation that may modify the effects of cerebral ischemia (a, b, and c). Not shown is the circle of Willis, which also provides a source for collateral circulation. *a*. The anastomotic channels between the distal branches of the anterior and middle cerebral artery, termed borderzone or watershed anastomotic channels. Note that they also occur between the posterior and middle cerebral arteries and the anterior and posterior cerebral arteries. *b*. The anastomotic channels occurring through the orbit between branches of the external carotid artery and ophthalmic branch of the internal carotid artery. *c*. Wholly extracranial anastomotic channels between the muscular branches of the ascending cervical arteries and muscular branches of the occipital artery that anastomose with the distal vertebral artery. Note that the occipital artery arises from the external carotid artery, thereby allowing reconstitution of flow in the vertebral from the carotid circulation. (Part A courtesy of C. M. Fisher, MD.) **B.** Diagram of the brain stem, cerebellum, inferior right frontal lobe, and temporal lobe transected. Principal branches of the vertebral basilar arterial system are pictured. Small branches of the vertebral and basilar artery that penetrate the medulla and pons are not pictured. The stem of the middle cerebral artery with its small, deep-penetrating lenticulostriate arteries and the circle of Willis with its small, deep-penetrating branches, are shown. **C.** Roman numerals I, II, III, and IV represent some of the possible variations of the circle of Willis caused by atresia of one or more of its arterial components.

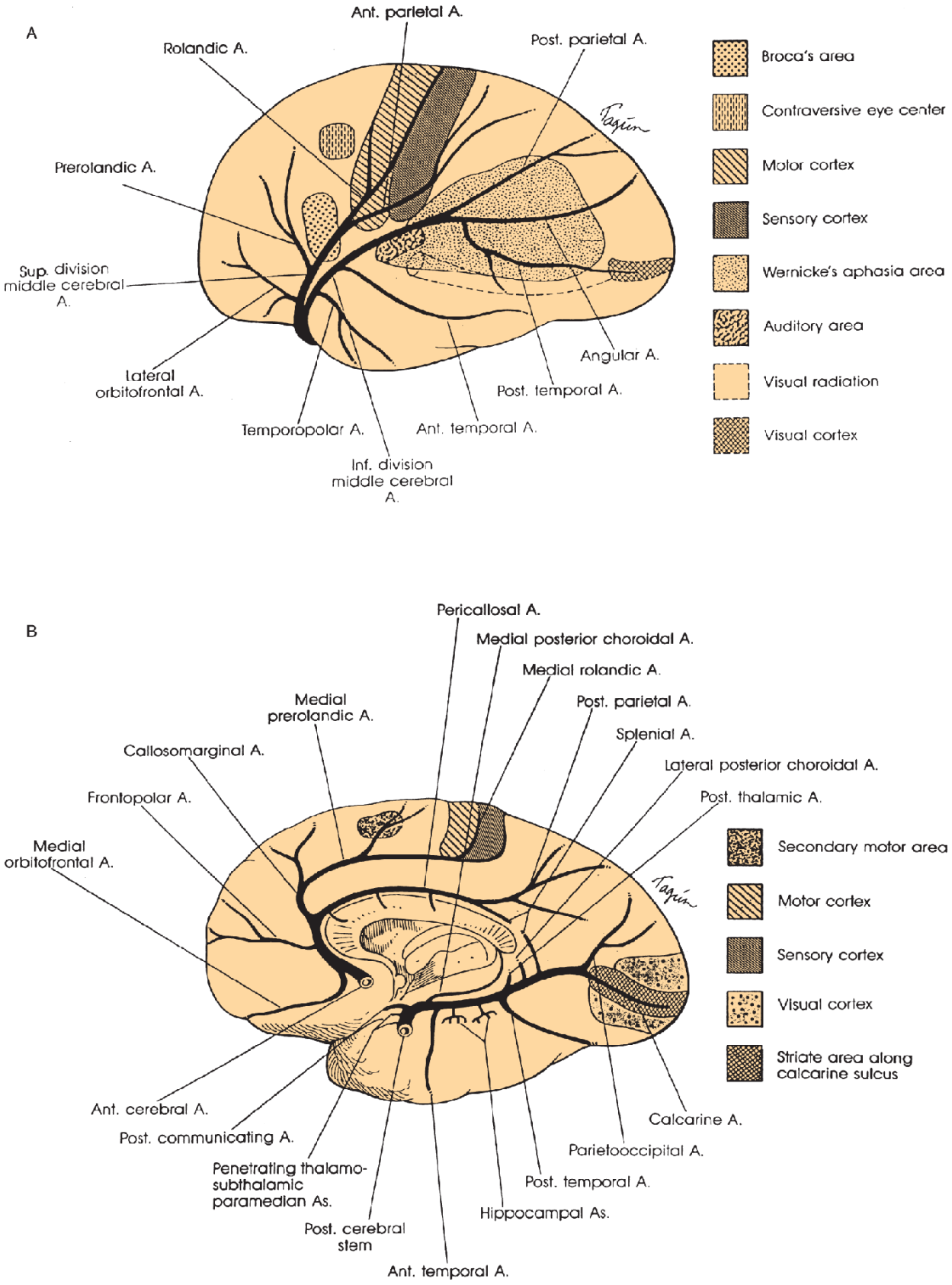


FIGURE 65-2. **A.** Diagram of a cerebral hemisphere, lateral aspect, showing the branches and distribution of the middle cerebral artery and the principal regions of cerebral localization. Note the bifurcation of the middle cerebral artery into a superior and inferior division. **B.** Diagram of a cerebral hemisphere, medial aspect, showing the branches and distribution of the anterior cerebral artery and the principal regions of cerebral localization. (Courtesy of C. M. Fisher, MD.)

ISCHEMIC STROKE OR TIA SUBTYPE

Pathophysiology and Clinical Presentation

It is important to recognize that ischemic stroke and TIA share the same pathophysiologic causation in terms of the underlying arterial pathology. The terms “stroke” and “TIA” are no more a diagnosis that dictates a specific therapeutic strategy than are the terms “fever” and “abdominal pain.” Just as the primary care physician would treat pneumococcal pneumonia giving rise to a fever, or pancreatitis giving rise to abdominal pain, so should the underlying arterial pathophysiology of the ischemic stroke or TIA be the focus of a treatment strategy. The term “cerebral vascular accident” or “CVA” should be discarded and the terms “TIA” and “ischemic stroke” should be complemented by terms defining their pathophysiologic subtype. Ischemic stroke and TIA conveniently divide into five subtypes: (1) large artery atherosclerosis (25%); (2) small-vessel lacunar (25%); (3) cardioembolic (20%); (4) cryptogenic (25%), and (5) other (5%), such as arterial dissection, venous sinus occlusion, and arteritis. The percentages of the various ischemic stroke or TIA subtypes vary with different ethnic population groups. African Americans are at relatively higher risk of lacunar stroke and atherothrombotic stroke, particularly that portion of atherothrombotic stroke caused by intracranial arterial atherosclerosis. Asians have a higher frequency of intracranial arterial atherosclerotic disease, as well.

When transient or sustained focal neurologic symptoms or signs develop in a patient, the history, general physical examination, and neurologic examination are important to diagnose stroke, localize the territory of the brain or spinal cord affected and the corresponding vascular distribution, and may even suggest the pathophysiologic subtype. Strokes and TIAs require immediate noninvasive assessment of the extra- and intracranial arterial vasculature focusing on the arteries supplying the suspected symptomatic arterial territory. Neurovascular imaging encompasses imaging the large arteries from the aortic arch to the cerebral cortex. The “parent” artery pathology, or lack thereof, and the location of the cerebral infarct then confirm the stroke subtype; namely, large artery atherothrombotic, cardioembolic, small-vessel disease, or other. Often an embolus fragments and migrates, leaving the parent vessel patent, or it enters a branch of the parent vessel not shown in the scheme outlined in **Figure 65-2**. In that case, embolism is suggested only by the specific territory of the infarction. When a small infarction occurs in the territory of a single penetrating vessel deep in the brain (as might arise from the basilar artery, the middle cerebral artery [MCA] stem, or the arteries of the circle of Willis), a small-vessel lacunar stroke is diagnosed.

To confirm the clinically suspected pathophysiologic diagnosis, CT scanning of the head alone in the acute or subacute phase is inadequate. CT has nearly perfect sensitivity for acute intracerebral hemorrhage (ICH) (approaching 100%) and good sensitivity for acute subarachnoid hemorrhage (SAH) (~ 90%). Sensitivity for ischemic infarction in the acute setting is, however, much lower. Ischemic infarction may not be demonstrable by noncontrast CT for 12 to 14 hours after symptom onset. In addition, infarction involving only the cortical surface supratentorially, or infarction in the posterior fossa, can often be obscured by bone artifact. Therefore, CTA, MRI with MRA, and/or carotid duplex ultrasound and transcranial Doppler, should be obtained to outline the parent vessels (see **Figure 65-2**), before specific treatment can be devised. Only with the precise knowledge of parent vessel pathology, or its absence, can therapy be properly addressed. The following sections outline each of the four ischemic stroke and TIA subtypes, and intracerebral and subarachnoid hemorrhage, in terms of their pathophysiologic process and clinical presentation. A discussion of a focused diagnostic approach to confirm that clinically presumed diagnosis follows. Based on the particular TIA or stroke subtype and its causative pathologic process, acute, subacute, and preventive management strategies can then be addressed.

Large-vessel, atherothrombotic stroke/TIA subtype Atheroth rombotic cerebral vascular disease accounts for approximately 25% of all ischemic strokes. The atheromatous process commonly has a predilection for four extra- and intracranial arterial locations (see **Figure 65-2**): (1) the internal carotid artery origin, (2) the carotid siphon portion, (3) the middle cerebral stem, and (4) the vertebrobasilar junction. Although the origins of the common carotid and vertebral arteries also are sites of atheromatous disease, they are less often the cause of stroke or TIA. At each of the sites of predilection, several mechanisms are possible and responsible for causing the stroke or TIA: (1) Embolism: thrombus forms on an atherothrombotic plaque and a piece of clot travels distally to occlude a more distal vessel. This is called an “artery-to-artery” embolus. (2) Thrombus propagation: this is less common, but if the thrombus propagates to occlude a distal vessel off the circle of Willis, large strokes can occur. (3) Hypoperfusion: the atherothrombotic process might occlude or narrow the vessel to such a degree that distal flow is diminished and not compensated via collateral flow via the circle of Willis. This low-flow state may result in border-zone infarctions or TIAs. In general, both artery-to-artery embolism and low-flow stroke occur when the vessel is narrowed to a degree (often $\geq$ 70% stenosis) that decreases pressure across the arterial segment. Low-flow stroke or TIA occurs less often from a cervical

lesion because the circle of Willis can provide needed distal collateral circulation when a proximal stenosis becomes hemodynamically significant. Low-flow stroke or TIA occurs more often with atheromatous disease in the intracranial vasculature as this compromises the ability of the circle of Willis to provide sufficient collateral flow. In 70% of the population, the circle of Willis is incompetent, with one or more of the connecting arteries atretic or functionally inadequate (see **Figure 65-2**). In this circumstance, low-flow TIA or stroke may arise from atherothrombosis at the internal carotid artery origin or in its petrous or siphon portions.

A TIA is said to occur if symptoms clear within 24 hours. In artery-to-artery embolic events, symptoms may last for shorter periods of time, and in low-flow transient ischemic events they may last only minutes to as long as an hour or more. Often, artery-to-artery or low-flow transient ischemic events may be associated with an MRI-proven area of infarction, notwithstanding resolution of the symptoms. When symptomatic stroke ensues in this setting, it is because the artery-to-artery embolic fragment lodges in an intracranial vessel with inadequate distal collateral supply, or because the clot propagates and occludes the vessel. A dramatic example of the latter occurs with internal carotid artery origin occlusion and propagation of the clot distally into the middle cerebral stem (see **Figures 65-1** and **65-2**).

Atherothrombotic Disease of the Anterior Cerebral Circulation (Origin of the Internal Carotid Artery, Its Major Branches, and the Common Carotid Artery) In the anterior circulation, atheroma occurs most often at the bifurcation of the common carotid artery (CCA), and usually begins on the posterior wall of the internal carotid artery origin.

- *Internal carotid artery (ICA)*: Most often, atheroma at the origin of the ICA becomes symptomatic after it has narrowed the lumen by 70%, leaving a residual lumen diameter of 1.5 mm—the point where the pressure begins to drop across the stenosis, allowing both embolic or low-flow ischemic TIA and stroke to occur. Embolism from thrombus forming in an ulcerated plaque may occur at 50% to 70% stenosis, but it is much less common, and rarely occurs with lesser degrees of stenosis. Artery-to-artery embolism can also occur if the atheromatous process occludes the ICA origin forming a thrombus at the site. At times, the occluding thrombus may also propagate without embolization, reaching the ophthalmic artery origin and producing monocular blindness, or extending even more distally to the MCA origin and producing a devastating, full-territory stroke.

  Low-flow symptoms caused by ICA origin stenosis are less common than artery-to-artery embolism, and occur only if two conditions exist: (1) the lesion has to be hemodynamically significant, that is, severe enough to provoke a drop in pressure across the lesion, which is a situation supervening at a residual lumen diameter less than 1.5 mm and (2) collateral flow distally through the circle of Willis or external carotid artery–ophthalmic artery anastomotic routes is inadequate, leading to a low-pressure state either in the MCA or in one or both of the anterior cerebral arteries. If there is internal carotid artery occlusion and little distal collateral flow then a complete middle cerebral syndrome may result. The posterior cerebral artery (PCA) territory may also be vulnerable to low flow when this artery arises directly from the ICA, that is, a “fetal PCA.” If the circle of Willis is complete, then occlusion of the ICA can be asymptomatic if it does not have an associated embolic or propagated thrombotic component.

  The signs and symptoms of artery-to-artery embolism from the ICA are variable, depending on the distal branch in which the embolism lodges, and the degree of distal collateral flow. The MCA territory is the most often affected. Transient monocular blindness (TMB) or blurring, often with a shade lowering or telescopic effect, points to ischemia in the *ophthalmic artery* territory. Symptoms associated with ischemia in the other territories are discussed, in their respective sections, below.

  Atheromatous disease in the ICA siphon occurs less often, but shares the same type of physiologic mechanisms for TIA and stroke as seen with atheromatous disease of the ICA origin.
- *MCA*: MCA territory symptoms may conveniently be divided into those involving the stem territory (M1 segment; see **Figure 65-2**) and those involving the superior or inferior territory divisions or one of their cortical surface branches (see **Figures 65-1** and **65-2**). When the stem of the MCA is occluded, a complete MCA syndrome may occur. It produces a complete contralateral hemiplegia equally involving the face, arm, hand, leg, and foot. Eye deviation toward the ischemic hemisphere occurs due to involvement of the frontal eye fields. Ischemia in the dominant hemisphere causes global or partial aphasia and ischemia of the nondominant hemisphere results in neglect and anosognosia. The degree of cortical involvement depends on the level of occlusion and the degree of cortical surface collateral flow (see **Figure 65-1**). Smaller emboli cause single superior or inferior branch of the MCA syndromes, or partial branch syndromes. Superior division infarcts, typically present with either isolated contralateral weakness or isolated expressive aphasia or a combination of the two. Inferior division syndromes include difficulty with reading, writing, auditory comprehension of language, or fluent aphasic speech with no

limb weakness. Paraphasic errors abound in both inferior and superior division syndromes. Neglect of the left visual hemifield occurs most noticeably in nondominant syndromes, but may also occur on the right with dominant syndromes.

Low-flow syndromes occur when the ICA occlusion is not supported by adequate collateralization distally. They include recurrent transient brief episodes of hip and shoulder weakness, arm and leg weakness, speech trouble, and face or tongue numbness or weakness, many of which are similar, that is, stereotyped. Cortical surface infarcts secondary to low flow tend to occur in the distal field of the MCA branches, before they anastomose with the anterior or posterior cerebral artery cortical surface branches, or in the distal field of the lenticulostriate penetrating arteries, affecting the deep white matter of the corona radiata.

- *Anterior cerebral artery (ACA)*: ACAs divide into two segments: part of the circle of Willis (A1 or stem) and the postcommunal (A2) segment distal to the anterior communicating artery (see **Figure 65-1**). The A1 segment gives rise to several deep penetrating arteries that supply the anterior limb of the internal capsule, the anterior perforated substance, portions of the anterior hypothalamus, and the posterior part of the head of the caudate nucleus. Infarction in these territories is more often caused by an embolus than by local atheromatous disease. ACA infarcts result in contralateral leg weakness. If the right and left A2 segments arise from a single anterior cerebral artery A1 segment, a normal anatomic variant, an occlusion of this single A1 segment causes bilateral frontal lobe infarction resulting in bilateral leg weakness. Other symptoms of ACA infarcts include urinary incontinence, abulia, gait apraxia, and forced grasping of the hand.
- *Anterior choroidal artery (AChA)*: This artery arises from the ICA and supplies the posterior limb of the internal capsule and its adjacent white matter, through which pass some of the geniculocalcarine fibers. The complete clinical syndrome consists of contralateral hemiparesis, hemianesthesia, and hemianopia. However, because this territory is also supplied by penetrating vessels of the MCA stem, the posterior communicating and the posterior choroidal arteries, syndromes with minimal deficits occur and patients often have an excellent recovery.
- *CCA*: All of the neurologic symptoms of ICA stenosis or occlusion can occur with proximal CCA stenosis or thrombosis. The occurrence of stroke or TIA from disease in the CCA is far less than that of the ICA. Bilateral common carotid occlusions can cause faintness on arising, recurrent loss of consciousness, bilateral dim vision, headache, atrophy of the iris, pericapillary arteriovenous malformations (AVMs), rubeosis iridis, optic atrophy, and claudication of the jaw muscles.

Atherothrombotic Disease of the Posterior Cerebral Circulation: Vertebrobasilar and Posterior Cerebral Arteries and Their Branches As seen in the anterior circulation, atherosclerosis has a predilection for certain parts of the posterior circulation—most frequently, the distal vertebral artery and the proximal to mid-basilar artery (see **Figure 65-1**).

- *Vertebral and posterior inferior cerebellar artery*: An occlusion of the distal vertebral or its major branch, the posterior inferior cerebellar artery (PICA), may be caused by either atherothrombosis or by embolism from a proximal arterial source or the heart. Atherothrombotic vertebral artery stroke is often heralded by TIA or minor stroke. Occlusion of either the vertebral artery or the PICA produces infarction in the lateral medulla, resulting in the lateral medullary syndrome. The symptoms and signs vary, but the most frequent include vertigo, nausea and vomiting, hoarseness, dysphagia, ipsilateral facial numbness associated with impaired sensation of pain and temperature over the ipsilateral face and contralateral arm and leg, ipsilateral Horner syndrome, and ipsilateral limb ataxia. The PICA also supplies the posteroinferior cerebellum that may become infarcted if collateral circulation from the superior cerebellar artery (SCA) is inadequate. The infarct resulting from vertebral occlusion does not differ anatomically from that produced by PICA occlusion, except for a greater involvement of the restiform body (inferior cerebellar peduncle) in the latter. Nevertheless, involvement of the cerebellum does not appreciably alter the clinical picture, except in cases where cerebellar edema increases the pressure in the posterior fossa enough to result in progressive obtundation and death. Although cerebellar edema can be treated with osmotic agents such as mannitol, surgical decompression via suboccipital craniectomy may be necessary.
- *Basilar artery*: TIA usually heralds atherothrombotic basilar artery occlusion and the consequent accompanying devastating brainstem infarction. The symptoms of a TIA in the territory of the distal vertebral and the basilar artery are more varied than in the carotid–middle cerebral territory because of the many different anatomic structures involved. Moreover, brainstem TIAs may be caused by disease of either of the small penetrating branches of the basilar or vertebral artery or disease of the basilar or vertebral arteries themselves. Penetrating branch disease may be atherothrombotic, involving the proximal origins of these small branch vessels, or

lipohyalinotic, involving the small vessels deeper in the brain stem (see “Lacunar stroke/TIA subtype” later in this chapter). In general, small-vessel disease is less threatening than disease of the basilar trunk. Therefore, when brainstem TIA or acute stroke occurs, it is extremely important to determine whether the problem lies in the basilar artery or in one of its smaller branches. Disease of a basilar branch produces unilateral infarction, whereas disease of the basilar artery itself usually causes bilateral infarction. Transient dizziness associated with diplopia, dysarthria, and numbness around the mouth strongly indicates the presence of basilar insufficiency. Other important symptoms occurring less often include a general profound feeling of weakness of the entire body, staggering, and/or a feeling of propulsion. Bilateral signs such as gaze paresis or internuclear ophthalmoplegia (INO) associated with ipsilateral sensory loss or weakness signify ischemic infarction in both sides of the pons, and therefore exclude single penetrating branch disease as the culprit.

Many branch syndromes have been described while others await clinical correlation. Syndromes of unilateral brainstem infarction typically involve some combination of ipsilateral signs of the head and face, from involvement of cranial nerve nuclei or their fascicles, and contralateral signs in the limbs, from involvement of ipsilateral crossed long tracts, such as the corticospinal tract or spinothalamic tract.

- *Major basilar branches—anterior inferior cerebellar artery, superior cerebellar artery, posterior cerebral artery*: These major branches of the basilar artery produce their own distinct pathophysiologic syndromes. They are most often caused by artery-to-artery embolism from an atherothrombotic source within the proximal basilar artery or the vertebral artery. Less often, an aortic or cardiogenic source is found. Rarely, primary atherothrombotic stenosis or occlusion at their origins is the cause of the stroke or TIA.
- *SCA*: Occlusion of the SCA results in one or more of the following symptoms: ipsilateral cerebellar ataxia (caused by ischemia of the middle and/or superior cerebellar peduncle, or dentate nucleus); nausea and vomiting; dysarthria and contralateral loss of pain and temperature sensation over the extremities, body, and face (caused by ischemia of the spinal and trigeminal thalamic tract); and ataxic tremor of the ipsilateral upper extremity. Horner syndrome, partial deafness, and palatal myoclonus may occur rarely. Partial syndromes occur frequently.
- *Anterior inferior cerebellar artery (AICA)*: Occlusion of the AICA produces variable degrees of infarction because the size of this artery varies inversely with that of the PICA. The territory it supplies usually includes the lateral midpons, middle cerebellar peduncle, cerebellum, and the labyrinth and cochlea. The principal symptoms may include ipsilateral deafness, facial weakness, vertigo, nausea, vomiting, nystagmus, tinnitus cerebellar ataxia, Horner syndrome, and paresis of conjugate lateral gaze. The opposite side of the body loses pain and temperature sensation. An occlusion close to the origin of the artery may cause corticospinal tract signs.
- *Paramedian and short circumferential branches of the basilar artery*: Occlusion of one of the five to seven short circumferential branches of the basilar artery affects the lateral two-thirds of the pons and/or middle or superior cerebellar peduncle, whereas occlusion of one of the 7 to 10 paramedian branches of the basilar artery affects a wedge-shaped area on either side of the medial pons. Many brainstem syndromes with cranial nerve abnormalities and crossed hemiplegia have been given eponyms.
- *PCA*: Arising from the bifurcation at the top of the basilar artery, each posterior cerebral artery divides into two segments: (1) the proximal precommunal (P1) segment, beginning at the top of the basilar artery and extending to the posterior communicating artery takeoff, with penetrating branches to the subthalamus, thalamus, and midbrain, (2) the postcommunal segment (P2), beginning at the posterior communicating artery takeoff, supplies the medial inferior temporal lobe and the medial occipital lobe. Twenty percent of the time, one or both of the right or left P1 segments are atretic and the P2 segment is supplied by the ICA via the posterior communicating artery. As discussed previously, this is referred to as a “fetal” PCA origin. The majority of ischemic syndromes, result from embolism (artery-to-artery or cardiac) and less commonly atherothrombotic disease of the posterior cerebral artery.
- *Precommunal posterior cerebral artery (P1)*: Syndromes are related to midbrain, subthalamic, and thalamic signs that vary depending on whether the embolus occludes the top of the basilar area, the right or left posterior cerebral artery precommunal segment, or the penetrating artery branches of the precommunal segment. Top of the basilar artery occlusion results in the devastating syndrome of coma and quadriplegia, resulting from infarction of the reticular activating system and bilateral corticospinal tracts within the midbrain. Branch occlusions cause third nerve palsy and contralateral motor or sensory findings. The artery of Percheron is a normal anatomic variant in which a single large medial mesencephalic artery supplies both sides of the subthalamus and thalamus and part of the midbrain. Occlusion of this artery results in bilateral ptosis, paralysis of upgaze, and decreased consciousness, caused by involvement of both thalami and bilateral midbrain. When only a single penetrating precommunal artery

territory is involved, small-vessel lacunar disease results (see "Lacunar or Small-Vessel Disease" later in this chapter).

- *Postcommunal posterior cerebral artery (P2)*: Syndromes result from involvement of cortical branches to the medial inferior temporal lobe, giving rise to memory loss and delirium, and branches to the medial occipital lobe, giving rise to contralateral homonymous visual field defects. Distal field border zone ischemia of the PCAs and MCAs give rise to visual impairment syndromes that include inability to recognize faces or pictures or to put items in a picture together to form an object (Balint syndrome).

Small-vessel, lacunar stroke/TIA subtype As defined by C. Miller Fisher through fastidious brainstem serial section, a lacunar infarct results from an occlusion of a small single penetrating artery arising from the circle of Willis, the middle cerebral stem, the basilar artery, or either distal vertebral arteries. These penetrating arteries vary in size from 100 to 400 microns in diameter, rendering the infarct size finite from 0.5 to 1.5 cm in diameter, and usually no more than 3 cm in the longest dimension. The cause is lipohyalinotic narrowing or occlusion in the mid- or distal part of the artery or atherothrombotic lesion at its origin; embolism is rarely the cause. Lacunar strokes account for 25% of all ischemic strokes. These strokes cause recognizable clinical syndromes that evolve over hours to days, and may be preceded by transient symptoms (lacunar TIAs). The location of the ischemia determines the nature and severity of the symptoms. Recovery occurs often within days, but in some with especially strategically placed infarcts, significant disability is persistent.

The most common lacunar syndromes are the following:

- *Pure motor hemiparesis* from an infarct in the posterior limb of the internal capsule or basis pontis. The face, arm, leg, foot, and toes are equally paretic or plegic, but with no sensory deficit. The weakness may be intermittent (TIA), progress in a stepwise manner, or appear abruptly. The progression may result in a complete hemiplegia. Improvement to almost normal occurs in many cases.
- *Pure sensory stroke* from an infarct in the ventrolateral thalamus. This type of infarct produces face, arm, and leg sensory involvement with numbness, tingling, and loss of pain and temperature. The patient generally recovers but often is left with an abnormal sensory sensation. On rare occasions, an intolerable pain syndrome with dysesthesia occurs in the involved extremities some months afterwards (Dejerine-Roussy syndrome).
- *Ataxic hemiparesis* from an infarct in the basis pontis or corona radiata near the genu of the internal capsule. This results in contralateral weakness and ataxia.
- *Dysarthria—clumsy hand syndrome* caused by lacunar infarction of the genu of the internal capsule or, less frequently, the corona radiata or the paramedian rostral pons, with resulting mild contralateral arm ataxia or arm weakness, and dysarthric speech.

Careful attention to antihypertensive, diabetic, and dyslipidemic therapies offers the best form of prevention of small-vessel disease. In all lacunar strokes or TIAs, it is essential to ascertain that the large arteries at the base of the brain giving rise to the penetrating small arteries are not harboring a thrombus (see "Evaluation and Therapeutic Strategies" below).

Cardioembolic stroke/TIA subtype Embolic strokes are diagnosed when a sudden or stuttering neurologic deficit appears in the territory of a large intracranial artery or in one of its major branches, and the extra- or intracranial arterial supply to this ischemic territory zone does not have a significant stenotic or thrombotic occlusive lesion. In some cases, the embolic fragment may be seen, on imaging, to occlude the vessel or a distal branch. In other cases, the suspected embolic material is not visualized because it has already been dissolved by the endogenous fibrinolytic system, but not before significant ischemia has occurred. It is most convenient, for determining appropriate preventive therapy, to divide these types of emboli into specific treatment categories: first, those with commonly accepted cardiac source of emboli where anticoagulant therapy is standard of practice, most commonly as in atrial fibrillation; second, those with commonly accepted cardiac source of emboli where anticoagulant therapy is contraindicated, as in bacterial endocarditis; third, those possible cardioaortic sources that can only be diagnosed by transthoracic echocardiogram or transesophageal echocardiogram, in which debate exists as to the best therapy, be it anticoagulant, antiplatelet, or cardiointerventional; fourth, those truly cryptogenic strokes in which a possible or definite cardiac and aortic source is excluded (**Table 65-1**). Within all of these source categories, the level of activity of the hemostatic system may be a significant determinant in the incidence of local thrombus formation and embolism. Therefore, in addition to careful evaluation of the heart, evaluation of the hemostatic system, as well as exclusion of a primary arterial source of embolism, is essential in order to plan appropriate pathophysiology-based treatment.

TABLE 65-1 EMBOLIC STROKE CLASSIFICATION

Cardiac source is definite: anticoagulant therapy generally considered standard of practice.
Left ventricular thrombi
Left atrial thrombi
Rheumatic valvular disease
Mechanical prosthetic valves
Atrial fibrillation
Nonbacterial thrombotic endocarditis
Cardiac source is definite: anticoagulation considered hazardous.
Bacterial endocarditis
Atrial myxoma
Cardiac source is possible: synonyms in the literature include “unknown source,” “cryptogenic stroke”—these diagnoses are made by transthoracic or transesophageal echocardiogram. The efficacy of antiplatelet versus anticoagulant therapy is uncertain.
Mitral annular calcification
Left ventricular dysfunction and dilated cardiomyopathy
Postmyocardial infarction with or without left ventricular aneurysm or thrombi
Left atrial spontaneous echo contrast
Patent foramen ovale
Atrioseptal aneurysm
Valvular strands
Ascending aortic atheromatous disease: mobile plaque 4 mm or greater.
Truly unknown-source embolic stroke.

The clinical presentations of embolism in the anterior and posterior cerebral circulation are similar to that of artery-to-artery embolism. The nature and severity of the symptoms depend entirely on the location of the embolic fragment occluding the artery and the spared collateral circulation to its cerebral territory. The intracranial artery occluded, depends on the size of the embolic fragment and the extracranial artery it enters. In the case of an embolic fragment entering the vertebral artery, it may migrate, stop, and then migrate again, leaving a trail of infarcted tissue from the cerebellum and lower brain stem to the upper brain stem, thalamus, and temporal and occipital lobes as it ascends (the so-called “basilar scrape” syndrome). Embolic fragments that enter the middle cerebral stem often disperse to branches of the superior and inferior division of the middle cerebral artery, giving rise to a patchy infarct in the deep or basal lenticulostriate arterial territory, and in the cortical surface branch territories.

In every case of embolic stroke, embolism from an infected heart valve should be considered because of the devastating consequences if not detected. Subacute bacterial endocarditis may have a very subtle presentation. An erythrocyte sedimentation rate (ESR) should be sent in all stroke patients.

Patent Foramen Ovale and Embolic Stroke Patent foramen ovale (PFO) is the consequence of failure of complete closure of the atrial septum primum and septum secundum immediately following birth, thereby leaving a communication between the right atrium and left atrium. PFO has been associated with stroke in epidemiologic studies, which indicate it is present in as many as 50% of patients with cryptogenic embolic stroke. Stroke may be more common in those with PFO because the atrial communication provides a channel by which a venous embolism can pass from the right-to-left side of the heart with the potential for subsequent cerebral embolism (so-called “paradoxical embolism”). Alternately, the PFO may itself be the source of thrombus formation with subsequent embolism. The PFO may be identified by transthoracic echocardiography with injection of agitated saline. Transesophageal echocardiography offers increased sensitivity. Transcranial Doppler ultrasound can also be used to detect the presence of right-to-left shunting by documenting the passage of agitated microbubbles into the cerebral circulation following a peripheral venous injection. It has equal or greater sensitivity than transthoracic echocardiography and can be used to guide the cardiac evaluation.

There is considerable controversy regarding the significance and therapeutic implications of PFO in stroke. PFOs are common and present in approximately 15% to 35% of the general population. After a thorough diagnostic work-up for stroke etiology, it is often difficult to determine if a PFO is related to the stroke or an "innocent bystander." Preventive therapy with aspirin or warfarin has been used, as well as invasive strategies to physically occlude the PFO, mostly using endovascular devices rather than open cardiac surgery. There have been three major randomized-controlled trials investigating PFO closure compared to medical therapy (RESPECT, CLOSURE, and PC). None of these trials were able to establish that PFO closure is superior to medical therapy although they trended toward benefit with PFO closure. There have also been several meta-analyses that have included these trials and although the results are slightly more variable, the majority of these analyses have also failed to demonstrate superiority of PFO closure over medical therapy. One study identified the coexistence of an atrial septal aneurysm as an additional risk factor for recurrent stroke; however, it is unclear whether this should affect the therapeutic strategy. If a PFO is identified, the patient should be screened for the presence of deep venous thrombosis, which would itself be an indication for a period of anticoagulation. The significance of identifying PFO in older patients with "traditional" risk factors is unclear. A subgroup analysis of the Warfarin versus Aspirin Recurrent Stroke Study (WARSS), enrolling mostly patients older than 60 years with vascular risk factors, found that, among the subgroup with PFO, there was no difference in recurrent stroke among those on warfarin compared to those on aspirin.

Other causes of cerebral infarction Although other causes of cerebral infarction account for only 5% of all ischemic strokes, they are extremely important because their precise pathophysiologic diagnosis can lead to effective treatment.

Dissection of the cervical cerebral arteries is, by far, the most common cause of stroke in this category subtype. A dissection is a tear in the arterial wall leading to intramural hematoma formation. A subintimal dissection occurs when an intramural hematoma is between the intima and the media layers, and may lead to arterial narrowing and thrombus formation. A subadventitial dissection occurs when an intramural hematoma is between the media and the adventitia layers, and may lead to pseudoaneurysm formation.

ICA dissections usually occur 2 cm distal to the carotid bifurcation near the base of the skull. Vertebral artery dissections occur in the cervical transverse foramen and most commonly at the base of the skull, at the C1-C2 level. Intracranial dissections are less common than cervical dissections. Trauma, either severe or trivial, are common causes of dissection, but Valsalva maneuvers associated with coughing and vomiting, weight lifting, contact sports, or chiropractic manipulations are other recognized associations. Spontaneous dissections, without clear antecedent, are not uncommon. Dissections occur at all ages, but are a frequent cause of stroke in children and young adults.

The most common symptom of arterial dissection is headache or neck pain. The clinical hallmark of carotid dissection is an ipsilateral Horner syndrome (ptosis, miosis, and anhydrosis). Artery-to-artery embolism or low-flow syndromes occur, just as they do for atherothrombotic disease of the ICA. Similar pathophysiologic circumstances exist for vertebral artery dissections; with them, cervical spine pain and occipital headache are the suggestive symptoms. The most common site of infarction in vertebral dissection is the lateral medulla, with or without concomitant involvement of the PICA territory in the cerebellum. Dizziness, ataxia of gait, nausea and vomiting with a unilateral Horner syndrome, and ipsilateral face numbness with contralateral body numbness are the hallmark symptoms. Occasionally, diplopia and a hoarse voice are evident. Artery-to-artery emboli arising from a thrombus at the site of dissection in the vertebral artery may migrate to distal branches of the basilar artery, producing brainstem, cerebellar, or thalamic infarction. The Cervical Artery Dissection in Stroke Study (CADISS) trial is investigating anticoagulation versus antiplatelet therapy in the treatment of cervical artery dissection. The nonrandomized arm of the study demonstrates no superiority of anticoagulation or antiplatelet therapy in the management of cervical artery dissections. Although not proven by randomized clinical trials, based on our experience and given the pathophysiology of stroke from dissection, we suggest immediate anticoagulation with intravenous heparin, followed by 3 to 6 months of anticoagulant therapy with warfarin, using a target international normalized ratio (INR) of 2 to 3.

Fibromuscular dysplasia (FMD) is a noninflammatory, nonatherosclerotic vascular disease that can result in arterial stenosis, occlusion, aneurysm, or dissection. FMD most frequently involves the renal artery, but can also involve the extracranial carotid and vertebral arteries. There is limited data on the prevalence of cerebrovascular FMD, but it is estimated to range from 0.3% to 3.2%. On angiography, it looks like a ruffled sock. The most common clinical manifestations are headache and pulsatile tinnitus, but neck pain, nonpulsatile tinnitus, and light-headedness are also common symptoms. More concerning is when FMD results in stroke or TIA. From the US Registry, 13.4% of patients with FMD suffered a hemispheric TIA, 9.8% suffered from stroke, 12.1% experienced cervical dissection, and 5.2% experienced amaurosis fugax. Carotid, cerebral, vertebral, and basilar artery aneurysms were present in approximately

7% of the patients. Treatment options can include medical therapy and surveillance, endovascular treatment for stenosis or aneurysms, or surgery. The approach for therapy depends on the nature and location of the lesion. Antiplatelet therapy or anticoagulant therapy is frequently used, although there is currently no data to support either approach. Revasularization is generally only reserved for patients with a symptomatic stenosis, that is, patients with retinal ischemic or recurrent hemispheric ischemic symptoms despite being on maximum medical therapy. Patients with aneurysms as a result of FMD are generally treated in the same manner as the general population.

Vasculitis is inflammation of the blood vessels. There are numerous causes such as infection, malignancy, immune diseases, and drugs. Infectious vasculitis from bacterial or syphilitic infections is no longer a common cause of cerebral thrombosis. Infectious arteritis may rarely follow infection with herpes virus, particularly if the ophthalmic division is involved. Cerebral arteritis may rarely accompany certain systemic vasculitides, including polyarteritis nodosa or Wegener granulomatosis. Necrotizing granulomatous arteritis, or primary angiitis of the central nervous system, involves the distal small branches (< 2 mm diameter) of the main intracranial arteries and produces small ischemic infarcts in the brain, optic nerve, and spinal cord. By definition, there is no systemic involvement. This rare disease is often relentlessly progressive. Presenting symptoms are varied and nonspecific, but headache is the most frequent complaint. MRI is frequently abnormal, but the findings are nonspecific. Findings include cortical and subcortical infarcts, parenchymal and leptomeningeal enhancement, intracranial hemorrhage, or mass lesions. Angiography can demonstrate areas of stenosis alternating with normal or dilated segments. Diagnosis of primary angiitis of the central nervous system can be difficult and typically requires either angiographic criteria be met or a tissue diagnosis. However, controversy exists as to how many cases meeting radiographic criteria, but without biopsy confirmation, are truly primary angiitis of the central nervous system. Spinal fluid analysis is an important aspect of diagnosis in patients with suspected vasculitis. The cerebral spinal fluid is abnormal in 80% to 90% of patients with vasculitis, typically with mild pleocytosis and mild elevation of protein. There is limited data on therapy, but in some cases, glucocorticoid therapy (prednisone, 40–60 mg/day) has been helpful, as has immunosuppressive therapy (eg, cyclophosphamide). Idiopathic giant cell arteritis involving the great vessels arising from the aortic arch (Takayasu syndrome) may cause carotid or vertebral artery thrombosis; but it is infrequent in the Western Hemisphere.

Giant cell arteritis is a relatively common affliction of older persons, in which the external carotid system—particularly the temporal arteries—is the site of a subacute granulomatous infiltration with an exudate of lymphocytes, monocytes, neutrophilic leukocytes, and giant cells. The etiology of giant cell arteritis is not entirely clear, but it is likely secondary to multiple genetic and environmental factors with numerous infectious etiologies having been suspected in the past. The pathogenesis is believed to involve an initial antigen-driven event that leads to the recruitment of T cells. Subsequent cytokine release activates local macrophages which then produce platelet-derived growth factor and vascular endothelial growth factor (VEGF) that can lead to intimal proliferation. The generation of metalloproteinases can then lead to destruction of the vessel wall with further inflammation potentially causing vascular damage and intimal hyperplasia, the end result of which can cause stenosis or occlusion.

Clinically, the chief complaint is frequently headache or jaw claudication. Systemic manifestations, through the release of inflammatory cytokines, can include fever, loss of weight, malaise, and polymyalgia rheumatica. Blindness of one or both eyes results from occlusion of the branches of the ophthalmic artery. Occasionally, an ophthalmoplegia caused by involvement of extrinsic ocular muscles occurs. In some cases, an arteritis of the aorta and its major branches, including the carotids, subclavian, coronary, and femoral arteries have been found at postmortem examination. Significant inflammatory involvement of the intracranial arteries is rare, but strokes occur occasionally on the basis of occlusion of the internal carotid, middle cerebral, or vertebral arteries.

Per the American College of Rheumatology, the diagnosis is made if three of the five following criteria are met, (1) age of onset is greater than 50, (2) new headache, (3) temporal artery abnormality (tenderness to palpation or decreased pulsation unrelated to arteriosclerosis of the cervical arteries), (4) elevated ESR (≥ 50 mm/h), (5) abnormal findings on temporal artery biopsy. The hallmark symptom is transient monocular blindness. When this occurs in patients older than 50 years, a sedimentation rate, fibrinogen level, C-reactive protein (CRP), and complete blood count should be done urgently. Corticosteroids may bring striking relief and prevent blindness, but treatment must be initiated quickly and ideally within 24 hours of vision loss because delay in treatment decreases the likelihood of restoration of vision. Prednisone is most often used, beginning with large daily doses of 80 to 100 mg/day and then tapering over 2 to 4 weeks using the sedimentation rate as a guide.

Moyamoya disease is a poorly understood occlusive disorder involving the progressive stenosis of large intracranial arteries, especially the distal ICA, the stem of the MCA, and the ACA. The lenticulostriate arteries develop a rich collateral network around the middle cerebral occlusive lesion giving the impression of a puff of smoke (“moyamoya” in Japanese) on cerebral angiography. Other collaterals include transdural anastomoses between the cortical surface

branches of the middle cerebral artery and the scalp arteries. The disease mainly occurs in the Asian population, but is becoming increasingly recognized in the western population. It should be suspected when TIAs or strokes occur in children or young adults. The etiology of Moyamoya is unknown, but is likely multifactorial as it has been associated with sickle cell disease, cranial radiation, neurofibromatosis type 1, and Down syndrome. Genetics likely play a strong role with more recent links to autoimmune or endocrine disorders. Many cases are ultimately idiopathic. Pathologic studies suggest that hyalinotic fibrous type material is associated with arterial narrowing and microaneurysm formation. The best treatment is not known. There is currently no treatment that can reverse or stop the intracranial arteriopathy. Although no formal study has been performed to determine the optimal treatment of patients with symptoms of ischemia or infarction, aspirin or other antiplatelet agents have often been used. Anticoagulation is not recommended in all symptomatic cases, but rather on a case-by-case basis. The use of antiplatelet and anticoagulant drugs must be balanced against the risk of hemorrhage (both intraparenchymal and subarachnoid) from rupture of the small, fragile anastomotic channels, or from rupture of the microaneurysms occurring in the perforating arteries from the circle of Willis. A variety of surgical revascularization procedures has been proposed to improve collateral flow and prevent brain infarction and hemorrhage. These include cervical sympathectomy, omentum transplantation, superficial temporal artery–middle cerebral artery bypass, or encephaloduroarteriosynangiosis. Although observational and retrospective studies suggest some benefit from surgical intervention, there is no consensus on the timing of surgery for asymptomatic patients or which revascularization procedure is most appropriate.

Reversible cerebral vasoconstriction syndrome (RCVS) is a reversible angiopathy that presents with severe "thunderclap" headache, often recurrent, and fluctuating neurologic symptoms and signs as well as angiographic findings of alternating areas of constriction and dilation. Brain imaging can be normal or show cerebral infarction, hemorrhage, or transient cerebral edema. The etiology is unknown. Eclampsia, the postpartum period, head injury, migraine, and sympathomimetic and serotonergic drugs have all been associated with this entity. Conventional angiography is the gold standard for establishing the diagnosis although newer imaging techniques such as CTA and MRA are proving useful. Cerebrospinal fluid (CSF) is normal in most cases and this is one of the characteristics that distinguish this entity from primary angiitis of the central nervous system. The disease is self-limited and, with adequate supportive care, partial or complete recovery occurs in the majority of cases. The headaches and arterial vasoconstriction usually resolve within a few weeks. There is no proven therapy to prevent neurologic deterioration. Vasodilators such as nimodipine, a calcium channel blocking agent, or intravenous magnesium can be considered. Maintenance of normal systemic arterial pressure and adequate hydration is important on empirical grounds.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare primary arteriolopathy affecting small penetrating vessels to the basal ganglia, thalamus, and cerebral white matter. The disease is caused by a variety of mutations in the *Notch3* gene. The clinical presentation is varied, but there are five primary symptoms including late-onset migraine headaches with aura, subcortical ischemic strokes, mood disturbances, cognitive impairment, and apathy. Migraine headaches with aura, when present, are frequently the presenting symptom of CADASIL and the mean age of migraine development is 30, although there is substantial variation. About 50% of patients with CADASIL may have atypical migraines (eg, basilar, hemiplegic, confusion, etc). Strokes/TIAs are the most frequent manifestation in CADASIL, occurring in 60% to 85% of patients. CADASIL-related strokes have been estimated to account for 11% of strokes in patients younger than 50 years. Cognitive impairment is the second most common symptom in patients with CADASIL. Executive dysfunction typically presents first with worsening cognitive decline with age. Shortly before death, patients will typically develop motor dysfunction, gait impairment, and pseudobulbar palsy. Mood disturbance is present in approximately 20% of CADASIL patients and typically presents with severe depression, but manic episodes and apathy are also common. CSF examination and cerebral angiography are normal. Abnormal findings on MRI of the brain include subcortical infarcts and leukoencephalopathy and can precede clinical symptoms by 10 to 15 years. There is no specific treatment to date. The diagnosis can be made by genetic testing with sequencing of the *Notch3* gene. Cerebral, leptomeningeal, or skin biopsy with demonstration, by electron microscopy, of typical osmophilic granular deposits in or around the vascular smooth muscle cells of the tunica media and basal lamina matrix is also diagnostic.

Binswanger subcortical leukoencephalopathy, now rare, is a syndrome seen with advanced small-vessel hypertensive disease. Diffuse vascular lesions are seen in the subcortical layers of the cerebral hemispheres and there is widespread white matter demyelination. It usually affects individuals around 50 years, and is characterized by fluctuations in mood and consciousness and perhaps even seizures. Dementia may be an early and prominent symptom preceded or accompanied by symptoms and signs of one or more small-vessel infarctions. Confusional states, memory difficulties, and abulia are prominent, and are sometimes accompanied by focal cortical-subcortical deficits such as aphasia, apraxia, or neglect. Focal neurologic deficits, or uni- or bilateral limb signs may lead to a pseudobulbar state

and gait difficulties are prominent. There is often evidence of vascular compromise in other body districts. Binswanger disease must be differentiated from disorders with prominent subcortical white matter involvement on CT or MRI such as hypertensive encephalopathy, cerebral amyloid angiopathy, and CADASIL.

Hematologic diseases such as acute and chronic leukemia, essential and secondary thrombocytosis, thrombocytopenia, and sickle cell disease can be complicated by ischemic or hemorrhagic stroke. Hypercoagulable states, such as the deficiency of protein C, protein S, antiphospholipid antibody syndrome, factor V Leiden, prothrombin gene mutation or antithrombin III, are rare causes of stroke, but are often included in the evaluation of stroke in the young.

Finally, stroke can ensue during the course of a severe attack of migraine, especially migraine with aura ("migraine-induced stroke"). It is often difficult to distinguish whether the patient developed a migraine-induced stroke, a stroke-induced headache, or had the coincidental occurrence of stroke and migraine. Since migraine-induced stroke is a diagnosis of exclusion, a thorough evaluation is required to exclude other potential causes, both common and uncommon, before making this diagnosis.

Evaluation

The initial history and physical examination are the hallmark of the evaluation to obtain the pathophysiologic stroke or TIA subtype diagnosis. Urgent brain and vascular imaging must be performed in all patients. Noncontrast head CT, for most centers, is the initial imaging evaluation as it allows rapid exclusion of hemorrhage. A head CT does not usually define the area of infarction acutely. CT scanning is insensitive to recent infarcts of less than 12 hours duration and small cortical surface embolic infarct and infarcts in the posterior fossa, because of beam-hardening artifact from the closely approximated bones of the skull. MRI of the brain with diffusion-weighted imaging (DWI) is the best way of identifying cerebral infarcts acutely and accurately. Susceptibility sequences identify subacute hemorrhagic infarcts and small areas of chronic hemorrhage (microbleeds) that might be associated with small-vessel diseases such as amyloid angiopathy or hypertensive vasculopathy.

Imaging of the cervical and cerebral large arterial system with CTA, MRA, or carotid duplex and transcranial Doppler ultrasound is also urgently required to define the arterial pathology. CTA of the head and neck is an extremely rapid, accurate way of identifying the pathology in the parent vessel from the origin of the aortic arch to the cerebral cortex (vessels shown in **Figure 65-1B**). This technique can be combined with CT-perfusion imaging, in which a contrast bolus is tracked, by serial scanning, as it passes through the tissue and the results deconvoluted into a map of perfusion times. MRA of the head and neck does not offer the same resolution of the arterial system as conventional transfemoral angiography or CT angiography. MR perfusion-weighted imaging can, in an analogous way to CT perfusion imaging, identify areas of perfusion delay that indicate tissue at risk of progression to infarction. The disadvantage of MRI imaging is the time it takes for the scan to be obtained. In addition, claustrophobia occurs in approximately 10% of patients because of the small head diameter of the imaging system. These disadvantages decrease its efficacy in the hyperacute stroke state when compared to CT and CTA. Neurosonology tests include carotid duplex ultrasound and transcranial Doppler assessment of the extra- and intracranial arterial system. Carotid duplex Doppler assesses flow in the common carotid artery, its bifurcation, and the internal and external carotid arteries. In addition, flow in the middle portion of the vertebral artery is typically assessed to identify more proximal or distal obstructive lesions. Transcranial Doppler allows assessment of flow in the intracranial carotid artery and the ophthalmic artery through the transorbital approach. The transtemporal approach permits assessment of flow in the middle, anterior, and posterior cerebral artery stems. The occipital foramen magnum approach allows determination of flow in the distal vertebral arteries and in the proximal and mid sections of the basilar artery. These tests have the advantage of being simple and noninvasive, can be used by the physician similar to the cardiologist's stethoscope examination, and are highly portable. We use neurosonology tests to follow the progression of the arterial pathology subacutely and chronically. The quantification of carotid artery atheromatous disease and its progression is an especially important use of carotid duplex Doppler combined with transcranial Doppler.

The initial electrocardiogram (ECG) and blood work should include a sedimentation rate as a screen for subacute bacterial endocarditis or vasculitis. In addition, the standard complete blood count, prothrombin time, partial thromboplastin time, and general chemistry examination is essential. Checking a fasting lipid panel and screening for diabetes with hemoglobin A_{1c} should also be performed for stroke risk factor modification. None of those laboratory assessments should interfere with the urgent timing of neuroimaging and ultrasound studies. Special clotting studies are not essential urgently, but are often useful when a hypercoagulable state is suspected or when there is embolism of uncertain origin. Such studies could include assessment of protein C, protein S, and antithrombin 3, antiphospholipid

antibodies, factor V Leiden mutation, and prothrombin *G20210A* gene mutation. The screen of thyroid function with a thyroid-stimulating hormone has helped us in identifying clinically unapparent hyperthyroidism, a condition that may be associated with atrial fibrillation or hyperlipidemia. In the initial blood evaluation, cardiac enzymes are also essential to rule out an associated myocardial infarction.

Cardiac evaluation In addition to obtaining a baseline electrocardiogram, cardiac enzymes, and sedimentation rate acutely, cardiac echocardiography and cardiac rhythm monitoring should be performed when a cardiac embolism is considered in the differential diagnosis. Echocardiography generally starts with transthoracic echocardiogram (TTE) but in cases where the diagnosis is not obvious and the suspicion for cardiac embolism remains high after TTE, transesophageal echocardiogram (TEE) is then considered. Contrast echocardiography or contrast transcranial Doppler ultrasonography can easily identify patients who have a PFO. Outpatient prolonged cardiac rhythm monitoring is very helpful if atrial fibrillation or other cardiogenic arrhythmias are to be considered and is now standard of care to look for atrial fibrillation in cases of suspected cardiac embolism. The Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) and 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) trials suggest that longer durations of monitoring, 30 days to 6 months, can increase the yield of detecting atrial fibrillation.

Therapeutic Strategies for Ischemic Stroke

With the acute onset of neurologic deficits suggesting cerebral ischemia, the essential therapeutic goal is to prevent clinical deterioration and to facilitate or reestablish blood flow to the ischemic zone. The therapeutic strategy should always be guided by the ischemic stroke pathophysiology and mechanism, whether presumed (history and physical examination) or confirmed (history, physical examination, and diagnostic data including neuroimaging, neurosonology, echocardiography, heart rhythm monitoring, and laboratory testing). The diagnosis should include not only the ischemic stroke or TIA subtypes noted earlier, but also the presence or absence of pathology in the parent vessel supplying the ischemic zone and the extent of the spared collateral flow to it. The time of onset to treatment determines the therapeutic options available. Three phases exist: (1) the hyperacute (1–4.5 hours) to acute (4.5–12 hours) phase, (2) the subacute phase (12 hours–2 weeks), and (3) the chronic/preventative phase.

After the pathophysiologic diagnosis has been determined and the patient has been evaluated for therapies designed to facilitate or reestablish cerebral perfusion and prevent subsequent strokes, further management efforts are directed at preventing common complications, such as deep venous thrombosis and aspiration pneumonia, and assisting with neurologic recovery through rehabilitation.

Hyperacute/acute In the hyperacute/acute phase, the goal is to open the occluded parent artery. For patients in whom treatment can be initiated within 3 hours of symptom onset, intravenous rt-PA (alteplase), at a dose of 0.9 mg/kg with 10% given as an immediate bolus and the remainder infused over 1 hour, has been shown to reduce stroke-related disability. In the pivotal National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial, patients treated with rt-PA had a 12% greater absolute chance of a good outcome, defined as minimal or no stroke-related disability. This benefit was present despite a 6% risk of intracranial hemorrhage in the rt-PA group, of which more than half were fatal. There is incomplete evidence regarding which stroke pathophysiologic subtypes respond best to rt-PA. Posthoc analysis of the trial did not show statistical evidence that the treatment effect varied by presumed stroke subtype, although the power to detect differences was modest. More recently, a trial of rt-PA given to patients with acute ischemic stroke within 3 to 4.5 hours showed a significant benefit of rt-PA as compared to placebo. In this study, the European Cooperative Acute Stroke Study (ECASS) III, the mean time to administration of rt-PA was 3 hours 59 minutes. Patients receiving IV rt-PA had a 7.2% absolute chance of a better outcome, defined as a modified Rankin score of 0 or 1 at 90 days. Mortality did not differ between the two groups. The rate of any intracranial hemorrhage was, as expected, higher in the rt-PA group (27% vs 17.6%) as was the rate of symptomatic intracranial hemorrhage (2.4% vs 0.3%), though lower than in the NINDS rt-PA trial. It is important to note that in ECASS III patients were excluded if aged more than 80, if they had a severe stroke, or if they had a history of previous stroke and diabetes mellitus. Further, both in NINDS and in ECASS III, the earlier patients received rt-PA, the better their outcomes. Therefore it is of utmost importance to initiate thrombolytic therapy in patients with acute ischemic stroke as soon as possible, that is, aiming for shorter “door-to-needle” times.

Because of the risks of hemorrhage, the decision to give rt-PA should be based on an individual assessment of the benefits and risks for the specific individual, with careful attention to the treatment inclusion and exclusion criteria. Patients with acute neurologic disabling deficits without hemorrhage or established infarct on initial head CT should be

considered for IV rt-PA. Exclusion criteria must be reviewed carefully prior to IV rt-PA administration. The decision not to give rt-PA should be made carefully, however, because data suggest that some patients with mild or improving stroke may have stroke recurrence or extension of the infarct. The ability to predict which patients will have subsequent worsening is unfortunately limited. There has been concern about treatment of the older adults because age may be a risk factor for rt-PA–related hemorrhage; however, the NINDS trial data show that this increased risk does not outweigh the potential benefit in older persons. Age is not an exclusion criterion to rt-PA use at our institution when given up to 3 hours. We have treated patients with IV rt-PA in their 90s at our hospital. Intravenous rt-PA is best administered by experienced stroke teams with expert neuroradiologic consultation available 24 hours a day. The Joint Commission on Accreditation of Hospital Organizations (JCAHO) offers an accreditation program to certify hospitals as "primary stroke centers," which includes documentation of competency in administering rt-PA.

Intra-arterial therapy (IAT) has been employed, in selected centers, in patient with moderate-to-severe neurologic deficits within 6 to 8 hours of stroke onset. Patients with a basilar thrombus up to 12 hours after stroke onset are also sometimes treated because in the posterior circulation, particularly the brain stem and cerebellum, a rich collateralization can delay the progression to infarction for longer periods of time. IAT is sometimes used after intravenous rt-PA in cases where there was no immediate response to the intravenous rt-PA because of persistent arterial occlusion. Intra-arterial treatment options include direct administration of thrombolytics, wire manipulation, angioplasty or stenting, or clot retrieval. Most of these approaches had not been proven effective in randomized trials until very recently. Early observational studies suggested, however, that recanalization of arterial occlusions of the proximal branches of the circle of Willis was feasible. Intra-arterial infusion of prourokinase was shown to produce better outcomes than placebo in the Prolyse in Acute Cerebral Thromboemoblism II (PROACT II) study, but the evidence was not sufficient to prompt the United States Food and Drug Administration (FDA) to grant approval for the drug. Subsequently, intra-arterial clot retrievers, used alone or in combination with IV thrombolytic therapy, led to a new series of studies.

In the 2005 nonrandomized Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, an embolectomy device, the Merci Retriever, was shown to effectively recanalize intracranial large-vessel occlusions in patients ineligible for rt-PA up to 8 hours after stroke onset. Subsequently, in the single-arm multicenter Multi-MERCI study, a second-generation embolectomy device was used up to 8 hours in patients who had persistent arterial occlusions despite receiving intravenous rt-PA. Arterial recanalization was achieved in 57.3% of patients treated with the newer-generation device, and in 69.5% after adjunctive therapy. While demonstrating promising rates of arterial recanalization, these studies did not definitively demonstrate clinical benefit, as there were high rates of clinically significant procedural complications and intracranial hemorrhage. Newer devices were brought to market, all with even more promising designs. Subsequently, clinical trials were undertaken to assess if treatments with similar or newer devices could demonstrate clinical improvement in randomized-controlled studies. In the Interventional Management of Stroke (IMS) III trial, patients with acute ischemic stroke who received IV rt-PA up to 3 hours after stroke onset were randomly assigned to no additional therapy, or to intra-arterial clot retrieval, to be completed within 7 hours of stroke onset. The study was stopped prematurely due to futility; favorable outcomes at 90 days, mortality and symptomatic intracranial hemorrhage did not differ between the groups, despite significantly better recanalization rates in the intervention group. Subgroup analyses indicated that endovascular therapy could lead to clinical benefit if started earlier (ie, up to 90 minutes after intravenous rt-PA administration). In the MR-RESCUE study, assessment of the ischemic penumbra by MRI perfusion for selection of patients likely to benefit from endovascular clot retrieval did not lead to improved clinical outcomes. Most of these studies, however, were criticized for the use of older generation and less effective clot retrieval devices than the ones marketed at the time of their scientific publication. These negative study results led to increased clinical equipoise, and halted the indiscriminate use of off-label endovascular clot retrieval. This prompted the design of newer clinical trials focusing on improved patient selection, optimization of early intravenous rt-PA, and earlier endovascular clot retrieval.

In early 2015, the pivotal Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) showed that in anterior circulation ischemic stroke patients who received intravenous rt-PA without significant clinical improvement, endovascular revascularization (mainly with stent retrievers) up to 6 hours after stroke onset led to improved clinical outcomes at 90 days, as compared to no additional therapy. Shortly thereafter the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial results were published. The ESCAPE trial randomized anterior circulation acute ischemic stroke patients to best medical therapy versus best medical therapy and endovascular clot retrieval with available endovascular devices—mostly stent retrievers. Patients were very well selected for this study, which included subjects with a proximal anterior circulation vessel occlusion without tandem

cervical carotid lesions, a small infarct core, as assessed by noncontrast head CT, and good collateral circulation. Furthermore, intra-arterial therapy was started very early on, with mean time to first arterial reperfusion of only 84 minutes. The trial was stopped prematurely due to favorable results in the intervention arm: 53% versus 29% favorable 90-day outcomes, significantly reduced mortality (10.4% vs 19%), and no significant difference in the rate of symptomatic intracranial hemorrhages. These much-awaited results have given a new impetus to the field of interventional acute ischemic stroke management. It is expected that the FDA will approve stent retrievers for acute ischemic stroke management in the near future. Newer clot retrieval devices and interventional patient selection algorithms continue to be fashioned, with a strong focus on approaches to optimize ultra-early arterial revascularization.

Intravenous and low-molecular-weight heparins, as well as heparin-like anticoagulants, have been tested in a number of clinical trials with conflicting results. Current guidelines acknowledge that the benefit of using heparin for acute stroke is uncertain. On the other hand, it is possible that heparin could prevent clot propagation in the parent vessel (although clot lysis is unlikely), or prevent early recurrent stroke especially from a high-risk arterial source. To that end, intravenous heparin has been empirically used in specific clinical scenarios, first, in large-vessel atherothrombotic disease, to prevent clot propagation, or to prevent further embolization from the atherothrombotic site. This strategy is most commonly used in critical or hairline stenoses of the extracranial internal carotid artery, in anticipation of an imminent arterial revascularization procedure. It is also commonly used in vertebrobasilar atherothrombosis. Second, in embolic stroke from a cardiac or aortic source where the embolus remains in the stem of one of the parent vessels (ie, the middle cerebral artery, the internal carotid artery, or the basilar artery), and the deficit is submaximal, that is, the deficit could worsen if the embolus propagates as a thrombus. Third, intravenous heparin may be of benefit in patients who have carotid or vertebral artery dissections. Many centers use heparin in the acute setting of arterial dissection in order to prevent clot propagation and artery-to-artery embolus. This strategy, however, has not been proven in a clinical trial, and case-control studies have not shown a significant benefit of anticoagulation as compared to antiplatelet therapy for secondary stroke prevention in cervical artery dissection. If the arterial dissection extends into the intradural segments of the arteries, heparin should be avoided as it may increase the risk of subarachnoid bleeding in that setting. Fourth, in sinovenous thrombosis, in this disease the efficacy of intravenous unfractionated heparin and of subcutaneous low-molecular-weight heparin has been proven in small randomized clinical trials. It is common practice to anticoagulate patients with sinovenous and cortical vein thrombosis, even if a hemorrhagic venous infarction is present prior to initiation of anticoagulation. Lastly, in patients with a high-risk cardioembolic source or arterial source of embolism, heparin may reduce the risk of early recurrent stroke in the acute phase.

Heparin use is associated with an increased risk of hemorrhagic transformation of ischemic stroke, and this risk is greater when the infarct volume is large. The risk of hemorrhage is, however, much lower than with rt-PA. In our practice, heparin is not given if the stroke is large (greater than one-third of the middle cerebral artery territory or the complete posterior cerebral artery territory), particularly if the stroke involves the deep penetrating branches to the basal ganglia. In patients who have received thrombolytics, full-dose heparin should not be given within 24 hours of treatment.

Subacute In the subacute phase of stroke, patients should be admitted to the hospital in order to monitor for neurologic deterioration and cardiovascular or systemic complications and to complete investigations to determine the ischemic stroke mechanism. Maintaining cerebral perfusion pressure is still a key component of therapy in this phase. Therefore, if the ischemic stroke patient has not received thrombolysis, blood pressure is allowed to autoregulate with permissible systolic blood pressure (SBP) up to 220 mm Hg in the first 24 hours, subsequently aiming to gently lower blood pressure (with SBP goals of 160–180 mm Hg) within 24 to 72 hours of ischemic stroke onset. Close attention must be paid to the neurologic examination, as abrupt blood pressure drops may lead to hypoperfusion of an arterial territory at risk of infarction.

Common medical complications of stroke include aspiration pneumonia, deep venous thrombosis, and pulmonary embolism. When in-dwelling bladder catheters are used, urinary tract infection is an additional concern. All stroke patients with evidence of dysarthria, aphasia, cough, or aspiration should have a formal swallowing evaluation before being allowed to take food, liquid, or medicines by mouth. Some patients may require placement of a percutaneous gastrostomy feeding tube, which, in most cases, can be removed in several months when the ability to swallow improves. Deep venous thrombosis can be prevented by the administration of subcutaneous heparin or the use of pneumatic compression boots, followed by ambulation as soon as possible. Attention should be made to avoidance of hyperglycemia and hyperthermia, which may lead to poorer stroke outcomes.

Stroke-specific management in this phase is dependent on the presumed stroke mechanism, as explored below.

Extracranial Large-Artery Atherosclerosis Surgical therapeutic options can be considered in this subacute phase. Carotid revascularization procedures may be applied in two distinct clinical settings: (1) symptomatic disease and (2) asymptomatic disease. The efficacy of carotid endarterectomy for symptomatic disease is high when there is a 70% to 99% stenosis, but modest when there is a 50% to 69% stenosis. Carotid endarterectomy for mild-to-moderate stroke or TIA in the territory of the internal carotid artery has been proven effective by the North American Symptomatic Carotid Endarterectomy Trial (NASCET) study, for patients with both 70% to 99% and 50% to 69% stenosis. Patients with severe stroke in the middle cerebral artery territory are not appropriate for carotid endarterectomy in the subacute phase. If the patient with severe stroke improves in rehabilitation to the point where worsening of the deficit would be problematic from recurrent stroke, then endarterectomy can be reconsidered. The surgical benefit for patients with symptomatic moderate stenosis was statistically significant but small, with only 1.5% absolute risk reduction per year, and therefore surgery should only be considered in centers with low perioperative rates of surgical morbidity. The decision to perform carotid endarterectomy for symptomatic moderate carotid stenosis should be made on an individual basis, taking into account the patient's surgical risk, center-specific perioperative complication rate (which should be < 2%), and the patient's life expectancy. Because the surgical risk occurs upfront during the perioperative period, the benefit from surgery accrues with increased years of life. For the older adults, the risks and benefits must be carefully weighed, and surgery should be withheld for patients with life expectancy fewer than 5 years. When there is symptomatic severe stenosis (70%–99% luminal narrowing) the surgical benefit is, by contrast, quite high, and most patients will benefit from surgical rather than medical management.

Carotid artery stenting (CAS) with angioplasty and stenting of the internal carotid artery plaque has gained ground as an alternative to carotid endarterectomy. Advantages include shorter hospital stay, lack of a neck incision, avoidance of general anesthesia, and a lower incidence of cranial neuropathy as a complication. A significant concern, however, is the risk of distal embolization of thrombus or fragments of atheroma dislodged during arterial access, balloon inflation, or stent deployment. An evolving array of embolization protection devices, deployed distal to the stent, are designed to limit this risk. Stenting is still an option for patients at high risk for complications from endarterectomy, including those with medical comorbidities, unfavorable neck anatomy, and restenosis at previous endarterectomy site. Randomized trials have addressed whether stenting can produce results as good as endarterectomy. Two trials, Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) and Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE), showed that, in symptomatic patients with greater than 60% internal carotid artery stenosis, stenting was worse than endarterectomy with regard to 30-day rates of major complications such as stroke and myocardial infarction. By contrast the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial, which included only patients who were deemed poor operative candidates for endarterectomy, showed equivalency between stenting and endarterectomy, with slightly lower complication rates in the stenting group. The Carotid Revascularization Endarterectomy versus Stent Trial (CREST) randomized patients with recent hemispheric TIA, ocular TIA or minor stroke, with at least 50% to 70% carotid stenosis. There were no significant differences between endarterectomy and stenting for the composite outcome of stroke, myocardial infarction or death over a 4-year follow-up period. However, during the 30-day periprocedural period there were significantly higher risks of stroke in patients undergoing stenting, and of myocardial infarction in patients undergoing endarterectomy. Of interest, an interaction between age and treatment efficacy was detected ($p = 0.02$), with a crossover at an age of approximately 70 such that carotid artery stenting tended to show greater efficacy at younger ages, and carotid endarterectomy at older ages. It is still our practice to prefer carotid endarterectomy for patients with symptomatic carotid stenosis as above, and reserve stenting for patients in whom surgery may be contraindicated. At this time we do not see any clinical situation in which carotid stenting is clearly superior to endarterectomy. For symptomatic lesions that are poorly amenable to surgery, because of poor anatomic factors or medical comorbidities, stenting is a reasonable, possibly safer alternative.

The timing of carotid revascularization for ischemic stroke is of major importance. If the ischemic stroke is small, then early intervention, up to 2 weeks poststroke, is preferable. In more extensive strokes, however, the risk of cerebral reperfusion injury after a revascularization procedure is high, especially in severe or critical intracranial carotid stenosis. In this circumstance, carotid revascularization procedures should be deferred to a later date to allow the infarcted territory to heal and to allow normalization of the local cerebral blood volume. Precise assessment of the degree of severity of the stenosis and its effect intracranially is extremely helpful when determining the urgency of timing of surgery. In addition, an image through CTA or MRA is also helpful in identifying the pathology not only in the internal carotid artery origin, but also in the arteries distally and in those arteries providing collateral flow.

Cardioembolic Stroke For patients with nonvalvular atrial fibrillation, anticoagulant therapy with warfarin has been proven by randomized clinical trials to reduce the risk of recurrent cerebral or systemic embolism by close to 70%, as compared to aspirin. The INR goal is 2 to 3. Novel oral anticoagulants (NOACs) such as the direct thrombin inhibitor dabigatran, and direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban have been shown to be noninferior to warfarin in prevention of cerebral or systemic embolism in nonvalvular atrial fibrillation. Further, NOACs as a group have a significantly lower risk of intracranial hemorrhage as compared to warfarin, despite a significantly higher risk of major systemic bleeding, mainly gastrointestinal. Despite this, there appears to be a net therapeutic benefit of NOACs over warfarin therapy. An additional advantage to these novel anticoagulants is that they do not require routine hematologic monitoring. Their current major disadvantage, however, is the lack of specific antidotes to counter bleeding from these medications. Anticoagulation is relatively contraindicated in infective endocarditis and in left atrial myxomatous syndromes because of associated cortical surface mycotic and myxomatous aneurysm with the risk of hemorrhage in the early phases of these diseases.

In patients with ischemic stroke presumed due to paradoxical embolism via a PFO, the risk of a recurrent stroke is relatively low, but can increase significantly with an associated atrial septal aneurysm. The optimal treatment in this condition is still uncertain. Multiple trials have randomized subjects with cryptogenic stroke to aspirin, warfarin, or percutaneous PFO closure and antiplatelet therapy. The CLOSURE I trial (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) followed patients with cryptogenic stroke or TIA who had a PFO, for a period of 2 years. Closure with the STARflex septal occluder device did not offer greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA. Critics of the study have expressed concerns regarding the short follow-up time, large number of patients with TIA as the initial event, insufficient rates of septal closure in the patients assigned to closure with the STARflex occluder, and the relatively high risk of device thrombosis in the study. The more recent Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial randomized cryptogenic ischemic stroke patients to aspirin, warfarin, or PF closure with the Amplatzer PFO occluder and followed them for a mean of 2.6 years (follow-up data are also available for many patients after 7 years of randomization). RESPECT did not demonstrate a significant benefit of PFO closure over medical therapy alone in the intention-to-treat analysis. However, the study also performed prespecified per-protocol and per-treatment analyses, given the expected high patient crossover rates. In these secondary analyses, PFO closure was superior to medical therapy alone, with a low rate of associated risks. Additional subgroup analyses further demonstrated benefit of PFO closure in patients with a substantial PFO shunt, associated atrial septal aneurysm, and superficial infarcts. At this time, the FDA has not approved PFO closure for secondary stroke prevention in cryptogenic embolism. In our institution, we may offer PFO closure for patients with cryptogenic stroke in whom the PFO-attributable stroke risk is higher, such as in young patients without associated cardiovascular risk factors.

In advanced congestive heart failure, the risk of ischemic stroke or systemic embolism may be elevated due to the formation of intracardiac clots, especially in extensive anterior wall myocardial infarction with an apical aneurysm. Anticoagulation may be recommended early on in this setting to prevent initial or recurrent embolism. The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) study enrolled patients with left ventricular ejection fraction less than 35% and who were in sinus rhythm. Patients were randomized to aspirin 325 mg daily or warfarin with goal INR 2 to 3, and were followed up to 6 years, with mean follow-up of 3.5 years. There was no significant overall difference in the risk of ischemic stroke, hemorrhagic stroke, or death between treatment with warfarin and treatment with aspirin. A reduced risk of ischemic stroke with warfarin was seen, but this was offset by an increased risk of major systemic hemorrhage. Thus, there is currently no clear evidence for anticoagulation of patients with congestive heart failure past the acute to subacute phases of ischemic stroke.

Lacunar Infarction The mainstay of early therapy in lacunar infarctions is mostly supportive, aiming to avoid clinical decompensation which can occur in the form of a stuttering lacunar syndrome in up to 30% of patients. Antiplatelet therapy should be instituted early on, blood pressure allowed to autorregulate, and glucose closely monitored. The choice of antiplatelet is mainly individual as all are equally effective for secondary ischemic stroke prevention, as discussed later in this section. Dual antiplatelet therapy (DAPT) with aspirin 325 mg and clopidogrel 75 mg daily was not superior to aspirin therapy alone for reduction of recurrent lacunar stroke risk in the Secondary Prevention of Small Subcortical Strokes (SPS3) trial. Further, this combination promoted harm, leading to a significantly higher risk of bleeding and death. There is also no clear evidence that anticoagulation can improve clinical outcomes in lacunar stroke. Therefore, dual antiplatelet therapy and anticoagulation are not recommended for patients with lacunar stroke.

Intracranial Atherosclerosis For patients with symptomatic severe intracranial stenosis, warfarin was also shown in a

randomized trial to be no more effective than aspirin in preventing recurrent stroke. A more recent trial, the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial randomized patients with severe (> 70%) symptomatic intracranial stenosis to intensive medical therapy alone, versus intensive medical therapy and intracranial stenting with the Wingspan device. All patients received aspirin 325 mg daily and clopidogrel 75 mg daily for 90 days. Intensive medical therapy consisted of management of primary and secondary risk factors, aggressive blood pressure control, and intensive lipid lowering (target LCL-C < 70 mg/dL). The trial was stopped prematurely as the rate of stroke or death was significantly higher in the stenting group as compared to the patients receiving medical management only. Therefore, it has been our practice to withhold angioplasty and stenting for ischemic strokes attributed to intracranial atherosclerosis. We routinely treat patients with dual antiplatelets for 90 days, and thereafter transition to antiplatelet monotherapy.

Cryptogenic Embolism In cryptogenic embolism, debate exists as to the efficacy of anticoagulant therapy. Aspirin or other antiplatelet agents have been prescribed in lieu of anticoagulant therapy, but their efficacy also has not been proven by randomized clinical trials. Stroke and TIA subtypes were not identified in those studies in which aspirin was compared to placebo or to another antiplatelet agent for the secondary prevention of recurrent stroke or TIA after a previous minor primary stroke or TIA. One study in which the primary and secondary stroke subtypes were accurately identified was WARSS, which compared the efficacy of warfarin to aspirin in secondary stroke prevention. When all of the stroke subtypes were combined, there was no difference in the risk of stroke with warfarin compared to aspirin. When the data for primary individual stroke subtypes were analyzed in terms of secondary stroke prevention, there was a trend in favor of anticoagulant therapy for patients with cryptogenic embolism. However, in WARSS the stroke risk reduction with warfarin was small (8%) and therefore warrants additional investigations, which are currently under way.

Management of malignant cerebral infarction Hemicraniectomy may be considered when progressive cerebral edema in the nondominant hemisphere becomes severe enough to compromise cerebral perfusion or cause brain herniation. This operation can prevent herniation and death by relieving intracranial pressure (ICP), but is unlikely to restore significant neurologic function because it is typically performed in the setting of extensive brain infarction. A pooled analysis of three small trials confirms that hemicraniectomy prevents severe dependency or death in patients younger than 60 years. Among patients of 61 years or older with a malignant middle cerebral artery infarction, hemicraniectomy increased survival without severe disability. However, the majority of survivors required assistance with most bodily needs.

In cerebellar ischemic strokes larger than 2 to 3 cm in diameter, decompressive posterior fossa craniectomy may also be performed if the patient shows signs of clinical deterioration, to avoid brainstem compression and upward herniation.

PREVENTIVE

There are two important aspects of preventive therapy. First, the control and prevention strategies related to the primary risk factors for all stroke subtypes and, second, preventive strategies directed toward the specific stroke or TIA subtype in the particular patient.

Preventive Strategies for Controlling Primary Risk Factors Treatment of hypertension is, by far, the most important aspect of risk factor control. Achieving and maintaining blood pressure treatment targets are probably more important than class effects of the drugs. Control of lipids is also important. Following the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATPIII) guidelines for prevention of myocardial infarction, the primary goal is lowering the low-density lipoprotein (LDL). Risk factor adjustment including diet, exercise, weight reduction, cessation of smoking, and diabetes management are all important first steps. Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (“statins”) are associated with reduction in the risk of stroke, as well as reduction in the risk of myocardial infarction. The Stroke Prevention with Atorvastatin to Reduce Cholesterol Levels (SPARCL) trial showed that, among patients with large-vessel atherothrombotic or lacunar stroke subtypes and LDL greater than 100 mg/dL, high-dose atorvastatin (80 mg every day) was superior to placebo in reducing subsequent stroke. Our practice is to treat all patients with large-vessel atherothrombotic or lacunar stroke with statins to lower the LDL to less than 70 mg/dL.

Preventive Therapy Directed Toward the Specific Stroke/TIA Subtype Therapy directed toward preventing the

specific stroke subtypes consists of two aspects: (1) antiplatelet versus anticoagulant therapy and (2) surgical strategies.

- *Anticoagulant versus antiplatelet therapy*: Anticoagulant therapy is accepted as standard of practice for cardiac conditions outlined in **Table 65-1**. In addition, we may on occasion manage carotid or vertebral dissection with warfarin, when there is presence of a luminal clot and the dissection is extradural. The INR goal in all of these conditions is 2 to 3. Generally, for dissection, we continue warfarin for 3 to 6 months; then if neuroimaging suggests the arteries are open, and the patient is symptom free, we switch to aspirin. If the artery has not healed, then one must consider whether to continue warfarin for a period of time and repeat the noninvasive imaging or, at some point, consider switching to aspirin.
- *Choice of antiplatelet therapy*: Many studies have compared the efficacy of aspirin to other antiplatelet agents, typically without consideration of the pathophysiologic stroke subtype. Two randomized trials show that the combination of aspirin with sustained-release dipyridamole at a dose of 200 mg twice daily (marketed as Aggrenox) confers an absolute risk reduction of 1% to 1.5% per year compared to aspirin alone. This must be balanced against a risk of throbbing headache that led to higher dropout rates in the aspirin plus dipyridamole group. Clopidogrel was shown in a randomized trial to be slightly better than aspirin (0.5% absolute risk reduction per year) in preventing a combined end point of stroke, coronary events, and peripheral vascular disease; when stroke end points alone were considered, the difference was no longer significant. Three large trials have looked at the combination of aspirin and clopidogrel for chronic prevention of cardiovascular diseases and found that the combination has a relatively high rate of bleeding complications compared to single-agent therapy, without better efficacy. Recently, however, a trial of patients with minor ischemic stroke or high-risk TIA had a lower risk of recurrent embolism when they received DAPT for the first 21 days after stroke. This combination should, therefore, be avoided except in specific circumstances where the benefit is well accepted. As an example, DAPT may be required after stenting to avoid in-stent restenosis.

Stroke Recovery Patients with stroke-related disability should be evaluated by specialists in physical therapy, occupational therapy, or speech therapy as appropriate. A substantial number of patients may benefit from inpatient rehabilitation following their acute hospital stay. There is evidence from observational studies that patients treated in dedicated stroke units, with experienced physician, nursing and rehabilitation staff, have better outcomes than those treated in general medical or surgical wards.

Stroke recovery may require 6 months to a year, or even longer, because of the slow nature of neuroplastic changes following brain injury. Late complications of stroke include spasticity, contracture, pressure ulcers, shoulder joint dislocation, and depression. The injection of botulinum toxin in affected muscles has been shown to improve symptoms of stroke-related spasticity. Recently, a recovery trial has shown that early use of fluoxetine with physical therapy enhanced motor recovery in stroke patients with moderate-to-severe deficits, independent of the drug's effect on mood. More studies are ongoing to confirm these results.

INTRACRANIAL HEMORRHAGE

Intracranial hemorrhages are classified according to the site of origin. The diagnosis, treatment, and secondary prevention of intracranial hemorrhage depends on the assessment of the underlying specific pathophysiology, analogous to the way in which ischemic stroke diagnosis and treatment depend on identifying the ischemic stroke subtype. There are four locations of origin: intracerebral, subarachnoid, subdural, and epidural. Subdural and epidural hemorrhages are predominantly traumatic and are not considered a form of hemorrhagic stroke. This section will therefore be concerned with intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Hemorrhagic stroke accounts for approximately 15% of all strokes. ICH may be further divided by location into deep ICH (arising in the deep hemispheric portions of the brain, including the basal ganglia, thalamus, brain stem, and cerebellum) and lobar ICH (arising in the cortex or at the junction of the cortex and the white matter). Hypertension is the most common cause of spontaneous ICH, while cerebral amyloid angiopathy (CAA) is the most common cause of spontaneous lobar ICH in the older adults.

Intracerebral Hemorrhage

Deep hemispheric hemorrhage Hypertension is by far the major cause of hemorrhage in deep brain locations. The most common sites are the putamen, thalamus, pons, and cerebellum. A penetrating artery arising from one of the

major intracranial arteries (middle cerebral stem or M1 segment), basilar artery, or posterior cerebral artery) is generally the source of the hemorrhage. These same vessels are also frequently affected by lipohyalinosis and when occlusion occurs rather than rupture, lacunar infarction is the outcome.

Clinical Presentation Each of the four sites of deep ICH produces a characteristic clinical syndrome. In *putaminal hemorrhage*, there is contralateral hemiplegia and conjugate deviation of the eyes toward the hemorrhage side. Stupor is evident at the onset in most cases. *Thalamic hemorrhage* typically presents with contralateral sensory loss and gaze abnormalities. Involvement of the internal capsule results in contralateral hemiparesis. Aphasia can occur in left thalamic ICH and visuospatial abnormalities can occur in right thalamic ICH. Involvement of the reticular activating system results in reduced consciousness and sleepiness. *Pontine hemorrhage* produces coma, quadriplegia, decerebrate rigidity, impairment of horizontal eye movements, and pinpoint pupils. *Cerebellar hemorrhage* typically presents with headache, vertigo, nausea, vomiting, and instability of gait. Facial weakness and gaze palsies can also occur. Coma may result from brainstem compression or upward or downward herniation of cerebellar structures.

Lobar hemorrhage Lobar hemorrhages occur spontaneously in the supratentorial white matter and cerebral cortex of all lobes of the brain. The manifestations are dependent on the area involved. Frontal hemorrhages may present with contralateral hemiparesis, expressive aphasia, and gaze deviation toward the hemorrhage. Parietal hemorrhages may result in contralateral neglect and sensory loss, while occipital hemorrhages could present with contralateral homonymous hemianopia. Temporal hemorrhages of the dominant hemisphere may present with receptive aphasia. Headache is sometimes present and may be most severe near the location of the hemorrhage. If the hemorrhage is large, then depressed consciousness may be present. The symptoms usually evolve over minutes or hours, in contrast to embolic ischemic stroke where the onset of symptoms is abrupt. A precise cause of lobar ICH is found in a significant number of cases: CAA and vascular malformations are the most common; metastatic disease is less frequent, but well known. A proportion of lobar ICH is likely caused by hypertension. Lobar ICH is more readily accessible for surgical evacuation because of its superficial location. A subgroup analysis of the Surgical Trial for Intracerebral Hemorrhage (STICH) trial showed a benefit for surgery, compared to initial conservative management, for ICH less than 1 cm from the cortical surface. At our institution, we consider surgical evacuation for not moribund lobar ICH patients who are deteriorating from mass effect caused either by hematoma expansion or accumulation of perihematomal edema on a case-by-case basis.

CAA is a common cause of both single and recurrent lobar hemorrhages in the older population, and is diagnosed conclusively only by postmortem demonstration of amyloid in the media of cortical and leptomeningeal arterioles and capillaries. Sporadic amyloid angiopathy is caused by the deposition of β-amyloid only in the cerebral arteries, without systemic amyloidosis. But the clinical history of repeated supratentorial lobar hemorrhages and the demonstration of small, 1- to 2-mm areas of hypointensity on MRI susceptibility-weighted sequences, indicative of prior small asymptomatic hemorrhages (cerebral microbleeds), strongly suggest the diagnosis. These small, silent hemorrhages may be the cause of recurrent focal symptoms sometimes seen in these patients. A clinical-pathologic correlation study suggests that CAA is the cause of approximately 70% of primary lobar ICH in persons aged greater than 55 years. Other than avoidance of anticoagulants, treatment options remain elusive. There is a high recurrence rate of 10% to 14% per year in sporadic lobar ICH, mostly caused by CAA, which is significantly higher than the recurrence rate of 2% to 4% per year observed in survivors of deep ICH. Careful control of associated hypertension, if present, seems prudent.

A small number of cases are associated with vascular or perivascular inflammation that frequently responds to a pulse of steroids, although late relapses may occur. Inflammatory CAA typically presents with cognitive impairment, seizure or focal neurologic signs rather than hemorrhagic stroke. Asymmetric white and gray matter hyperintensities, often with small silent hemorrhages on susceptibility sequence, are observed on MRI. Biopsy is usually indicated to exclude other causes of vasculitis.

Lobar Hemorrhages Caused by Metastatic Disease Cerebral metastases, particularly malignant melanoma, may give rise to cerebral hemorrhage. Usually, the metastases are multiple and can easily be demonstrated by contrast MRI or CT scans.

Evaluation of ICH: Noncontrast head CT scan has excellent sensitivity for ICH and is the initial modality of choice in ICH diagnosis. There are no clinical signs or symptoms specific for ischemic stroke compared to hemorrhagic stroke, making CT mandatory in all patients presenting with potential stroke. Vessel imaging with CTA or MRA should be performed for the diagnosis of cerebral aneurysm or vascular malformation. Venous imaging with CT venography (CTV) or MR venography (MRV) should be performed if concern for venous sinus thrombosis exists.

Catheter angiography should be performed if suspicion remains high for vascular abnormality despite negative CTA or MRA. Contrast-enhanced CT or MRI should be performed when suspicion of underlying mass lesion exists. A "spot sign" on CTA is the finding of contrast extravasation into a hematoma and is associated with hemorrhage expansion and poor outcome. MRI also has excellent sensitivity for detecting ICH. Hemorrhage on special T2-weighted sequences such as gradient recalled echo (GRE) or susceptibility-weighted imaging (SWI) appears as hypointensity or low signal compared to surrounding brain. Cerebral microbleeds are small areas of hypointensity that represent chronic small hemorrhage. Their location often points to an underlying etiology with deep microbleeds mainly due to hypertension and lobar microbleeds due to CAA. Older patients with a history of hypertension and hemorrhage in a typical location do not need angiographic assessment. In contrast, younger patients and those with an atypical-appearing hemorrhage should have angiography. When hemorrhages occur in atypical locations or in the absence of a history of hypertension, a follow-up MRI brain scan with and without contrast is performed in 3 months, following ICH resorption, to screen for an underlying lesion such as a vascular malformation or tumor. Acute laboratory assessment should include platelet count, prothrombin time, partial thromboplastin time, and INR to exclude bleeding diathesis. An ESR, CRP, and blood cultures should be considered in patients at risk for septic embolism from bacterial endocarditis. The history, physical examination, and imaging should exclude secondary causes of hemorrhage such as coagulopathy, brain tumor, aneurysm rupture, and hemorrhagic transformation of ischemic infarction.

The size and location of the hematoma determine the treatment and prognosis. Supratentorial hematomas greater than 5 cm in diameter have a poor prognosis. Infratentorial hematomas greater than 3 cm in size are generally fatal if they are in the pons. Other factors associated with poor prognosis are the presence of intraventricular blood and worse level of consciousness at presentation.

Treatment of ICH: All patients with ICH should be initially managed in an intensive care unit. General supportive care should be provided. Eunatremia, normoglycemia, and normothermia are mainstays of treatment. Seizures may occur and should be treated with anticonvulsant medications when they occur. Seizure prophylaxis is generally not recommended. Patients taking warfarin at the time of ICH must have the INR aggressively corrected emergently with vitamin K and vitamin K–dependent factors and the warfarin discontinued. Patients with ICH on antiplatelet medications should have these antiplatelet medications discontinued. There is currently not enough evidence to recommend platelet transfusions in this scenario. Blood pressure management is important after ICH. Current guidelines state that it is likely safe to reduce SBP to less than 140 mm Hg acutely when the presenting SBP is between 150 and 220 mm Hg. Elevated ICP can result either from hematoma or associated cerebral edema. Patients with Glasgow Coma Scale (GCS) less than or equal to 8, evidence of transtentorial herniation or hydrocephalus, or significant intraventricular hemorrhage should have ICP monitoring and treatment. Osmotic agents such as mannitol or hypertonic saline are frequently used to lower ICP. Ventriculostomy with an external ventricular drain is often used in obstructive or communicating hydrocephalus.

The surgical indications for ICH depend mainly on the location of the ICH. Patients with cerebellar hemorrhages greater than 3 cm and neurologic deterioration or brainstem compression and/or hydrocephalus should have early hematoma evacuation. For other locations, surgical evacuation is controversial. The STICH trial failed to find a benefit for surgical evacuation over medical management. In STITCH, patients with ICH less than 1 cm from the cortical surface had a trend toward favorable outcome with early surgery. Current guidelines call for surgical hematoma evacuation for patients with lobar ICH greater than 30 mL and within 1 cm of the cortical surface. Surgical evacuation for deep ICH accompanied by decreasing level of consciousness caused by increasing mass effect is also considered. Less invasive surgical methods are currently being developed and could be used widely in the future.

Vascular malformations Increasingly recognized with advances in neuroimaging techniques, vascular malformations are classified into four types: venous malformations, capillary telangiectasias, AVMs, and cavernous malformations or angioma. Vascular malformations may cause hemorrhage in either deep or lobar locations.

Venous malformations, also known as venous angiomas or developmental venous anomalies, consist of anomalous veins that, while not associated with arterial feeders, nevertheless provide functional venous drainage, and are usually asymptomatic.

Capillary telangiectasias are small, often punctate, lesions composed of small clusters of dilated capillaries with normal intervening parenchyma. Small capillary telangiectasias in basal ganglia or in the brain stem are usually asymptomatic (ie, discovered at autopsy), but may rarely rupture and produce a hematoma.

Arteriovenous malformations and *cavernous malformations* are clinically significant because of their potential for producing hemorrhage and neurologic deficits.

Arteriovenous malformations (AVMs) consist of a tangle of abnormal vessels forming an abnormal communication

between the arterial and venous systems. Most are developmental arteriovenous fistulas in which the constituent blood vessels enlarge and grow with the passage of time. They vary in size from a small blemish a few millimeters in diameter to a huge mass of tortuous channels composed of an arteriovenous shunt of sufficient magnitude to raise the cardiac output. Hypertrophic dilated arterial "feeders" approach the main lesion and then disappear into a network of thin-walled blood vessels, which are the source of rupture. Some AVMs harbor berry aneurysms. AVMs occur in all parts of the brain, brain stem, and spinal cord, but larger ones are most frequently located in the hemispheres.

The chief clinical symptoms and signs are headache, seizures, and findings associated with rupture. When headache occurs without bleeding, it may be hemicranial, throbbing like migraine, or diffuse. Hemiplegia may accompany the headache, resembling the syndrome of hemiplegic migraine. Focal seizures that become generalized occur in approximately 30% of cases and are sometimes difficult to control with antiepileptic drugs. In half of the cases, arteriovenous malformations manifest with an ICH. In most of these cases, the hemorrhage is mainly intraparenchymal with a small amount of spillage into the subarachnoid space. Blood is usually not deposited in the basal cisterns, thus symptomatic vasospasm is rare. When the hemorrhage occurs, it may be large leading to death or small, giving rise to focal symptoms. Headache at the onset of rupture is common, and may be difficult to distinguish from that associated with nonruptured arteriovenous malformations.

Large supratentorial arteriovenous malformations may be associated with an audible bruit. The bruit is sometimes even self-audible, particularly when the malformation involves the dural vessels (also called arteriovenous dural fistula). *Cavernous malformations* represent approximately 10% of all intracranial vascular malformations. Located within the brain parenchyma without site of predilection, they are composed of thin-walled, dilated vessels like a mulberry, devoid of intervening normal brain and often surrounded by a ring of hemosiderin, a residuum of prior hemorrhages. Cavernous malformations may be multiple in as many as 3.6% of patients. In some families, multiple cavernous malformations are inherited as an autosomal dominant trait. Three gene loci have recently been identified: CCM1 (caused by mutation of the *Krit1* gene), CCM2 (caused by mutations of the *Malcavernin* gene), and CCM3 (caused by mutations of the *PDCD10* gene).

The symptoms of cavernous malformations are similar to those of arteriovenous malformations: seizures, headaches, or neurologic deficits associated with rupture. Hemorrhages are usually small and circumscribed, but on occasion can be quite large, or clinically devastating because of their critical location, for example, in the pons. The reported risk of symptomatic hemorrhage varies widely across studies, from as low as 1% per year to as high as 20% annually. The hemorrhages are typically less disabling than primary ICH, but when there are multiple recurrences, progressive neurologic disability occurs.

The management of patients with vascular malformations is best accomplished by an experienced team comprised of neurosurgeons and physicians who can consider both surgical and endovascular approaches, sometimes in combination. Radiosurgical obliteration may also be an option in some cases (ie, deep, inaccessible lesions associated with repeated hemorrhages or progressive neurologic deficits). Each case requires a unique approach that takes into account the extent and location of the vascular malformation, and the feasibility and safety of the various therapeutic approaches.

Subarachnoid Hemorrhage

The most common cause of atraumatic subarachnoid hemorrhage is rupture of a berry aneurysm. Other less-common causes include blood dyscrasia or leukemia, tumors (such as ependymoma or meningioma, glioblastoma, renal cell, or metastasis), vascular malformation, or, rarely, venous sinus disease or meningitis.

Ruptured saccular "berry" aneurysms occur at the branch points of arteries at the base of the brain and following rupture, give rise to subarachnoid hemorrhage, or sometimes ICH. Histologic examination shows interruption of the internal elastic lamina with an aneurysmal outpouching that appears like a berry. Although usually single, aneurysms can be multiple in 15% to 20% of cases. The most common sites are the anterior communicating artery, junction of the posterior communicating artery with the internal carotid artery, middle cerebral stem bifurcation, top of the basilar artery, origin of the major branches of the basilar artery, and at the origin of PICA. Intracranial aneurysms can be associated with coarctation of the aorta and are more common in autosomal domination polycystic kidney disease.

Prodromal symptoms and signs, prior to rupture occur in as many as a third of cases. These symptoms may include headache, diplopia, or blurred vision. Pinpoint pain behind the eye with or without a third nerve palsy is the most common and indicates the presence of an aneurysm at the posterior communicating artery–internal carotid artery junction. It represents a medical emergency. Juxtaclinoid aneurysms compress the optic nerve, leading to amblyopia. Supraclinoid aneurysms can be confused with suprasellar tumors, sometimes producing a hypothalamic syndrome.

Aneurysms in the vertebrobasilar system can produce occipital headaches and cerebellar or long-tract signs as well as cranial nerve deficits.

The most common symptom of aneurysmal rupture is a sudden, severe headache, often characterized as the "worst headache of my life." Other symptoms may include loss of consciousness, nausea and vomiting, and meningismus. Focal neurologic signs occur infrequently. Focal signs occur when the hemorrhage ruptures into the brain parenchyma and help in localization of the rupture site. For example, anterior communicating artery aneurysmal rupture produces a slowed or abulic state with contralateral weakness of the leg while middle cerebral artery aneurysm rupture produces contralateral hemiparesis and aphasia if the dominant hemisphere is involved.

Evaluation of SAH: A noncontrast head CT is the initial modality of choice and has excellent sensitivity for SAH. At our institution a CTA of the head, to look for a cerebral aneurysm, is also performed at the time of the noncontrast head CT. If the head CT is negative for SAH, but high suspicion remains, a lumbar puncture (LP) must be performed. The main findings consistent with SAH on the LP are elevated red blood cell count, xanthochromia, and elevated opening pressure.

Delayed clinical syndromes mainly consist of re-rupture syndromes, hydrocephalus, and the syndromes resulting from cerebral vasospasm. *Re-rupture* is most frequent during the first 72 hours after the initial rupture. Early surgical or endovascular intervention now precludes many re-ruptures. *Fever* ($\geq$ 38°C) in the absence of a discernible infective etiology is common in subarachnoid hemorrhage, and in some instances, may be confused with florid meningitis. *Hydrocephalus* may be acute in the first day or two after the subarachnoid hemorrhage and requires ventricular drainage. Delayed hydrocephalus presents several days to weeks after the subarachnoid hemorrhage and may require ventriculoperitoneal shunting. Worsening stupor is a sign of both early and delayed hydrocephalus. *Cerebral vasospasm* usually develops between days 4 and 14 following the subarachnoid hemorrhage. Its location and severity have been related to the extent and location of the subarachnoid blood, with thick clot typically present around the artery developing spasm. In 30% of cases, the spasm is severe enough to give rise to ischemic symptoms and infarction may ensue. In middle cerebral artery stem vasospasm, the resulting infarction may cause devastating cerebral edema. The extent and location of blood in the basal cisterns postoperatively, may represent patients likely to have severe vasospasm to develop signs of ischemia or infarction.

Management of the patient with subarachnoid hemorrhage from a ruptured berry aneurysm should focus on (1) medical stabilization, with aggressive treatment of elevated blood pressure and good supportive neurocritical care, (2) early surgical clipping or endovascular coiling in non-moribund patients to prevent re-re-rupture, and (3) prevention and treatment of delayed ischemia caused by vasospasm. The International Subarachnoid Aneurysm Trial (ISAT) showed that, for aneurysms equally accessible for surgical clipping or endovascular treatment with detachable coils, the endovascular strategy was associated with less death or dependency at 1 year. Volume expansion and blood pressure elevation together with calcium channel blockers are often used to prevent symptomatic ischemia from vasospasm. Oral nimodipine, 60 mg given every 4 hours, has been shown in multiple clinical trials to reduce mortality and the incidence of delayed ischemia. For refractory cases local intra-arterial infusion of vasodilators such as nicardipine, or angioplasty of the affected arteries, may alleviate arterial stenosis caused by vasospasm.

Given the above complications and expertise necessary to perform highly technical neurosurgical and endovascular approaches to obliterate aneurysms, the patient should be managed at a center capable of carrying out these maneuvers.

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Chapter 66

Dementia Including Alzheimer Disease

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Learning Objectives

- Describe the current diagnostic criteria for dementia, Alzheimer disease (AD), and mild cognitive impairment (MCI) and how these conditions differ from normal cognitive aging.
- Understand the effects of age and other genetic and nongenetic risk factors on risk of developing AD.
- Identify key neuropathologic features and mechanistic pathways associated with AD.
- Recognize common reversible causes of cognitive dysfunction.
- Describe an effective dementia care management plan across care settings and stages of disease, integrating use of pharmacologic and nonpharmacologic interventions, education, and community resources.

Key Clinical Points

1. **AD is the most common neurodegenerative disorder affecting older adults with prevalence rates increasing with advancing age.**
2. **While aging is the most established risk factor for late-onset AD, various other genetic, lifestyle, and environmental factors also influence dementia risk.**
3. **The diagnostic evaluation for dementia, AD, and MCI depends heavily on a careful assessment of an individual's change in functional status, a structured cognitive assessment, a thorough clinical examination, and exclusion of other competing causes of cognitive decline.**
4. **As there are no proven preventive or disease-modifying therapies for AD, current standard-of-care management plans integrate use of pharmacologic therapies to delay symptom progression; nonpharmacologic strategies to optimize function, behavior, and safety; and education and support for patients and their care partners.**
5. **Advanced care planning prior to loss of decisional capacity is of critical importance in developing patient-centered goals of care in persons with cognitive impairment.**

AD is the most common neurodegenerative disorder affecting older adults, projected to affect more than 13 million Americans and 115 million individuals worldwide by 2050. Compared to projections in high-income countries, the number of individuals with AD in low- and middle-income nations is increasing at an even greater rate. The disease is characterized by diffuse functional and structural abnormalities in the brain that lead to progressive cognitive and behavioral deficits and functional decline. AD is associated with significant morbidity and mortality and is among the 10 most common causes of death in the United States. The physical, psychological, functional, and socioeconomic impact of AD substantially affects the well-being and quality of life of patients and their caregivers. Caring for patients with AD places heavy financial burden on patients, families, communities, and the health care system at large. In the United States in 2015, the average annual health care and long-term care cost for an older adult with AD ranged from $28,000 to $75,000, depending on whether the person lived in the community or a residential facility. The total cost of caring for Americans with AD exceeds $225 billion annually. Evidence is just beginning to emerge on the economic impact of dementia care in low- and middle-income countries as most of the costs in these nations are

related to informal care.

Recognizing the enormity of the burden of AD, international collaborations between clinicians, researchers, policy makers, patient advocacy groups, the media, and many others have increased public awareness of the global impact of the disease and have laid the foundation for the development of effective preventive and therapeutic strategies as well as improvements in care management for patients with AD. An example of such a coordinated effort is the 2011 United States National Alzheimer's Project Act (NAPA), a law designed to create and maintain an integrated national plan to address AD. The plan encompasses federal coordination of AD research and services and aims to improve early diagnosis and coordination of care, accelerate development of effective treatments, promote health equity in AD care among ethnic and racial minority populations, and stimulate coordination with international groups to address AD globally. Such national and international collaborations will help accelerate optimal diagnosis and care of patients at risk for AD and related dementias.

DEFINITION

In defining AD features, it is widely recognized that the clinical cognitive and behavioral signs and symptoms do not always correlate with the degree of AD neuropathologic changes noted in the brain. The discrepancy between the neuropathologic changes and the individual clinical expression of disease is likely related to additional unidentified physiologic, metabolic, or genetic factors that either accelerate or slow cognitive decline. For example, some older adults with normal cognitive function just prior to death have been found to have significant AD neuropathology on autopsy. These individuals may have unrecognized neuroprotective factors that help preserve cognitive function despite notable neuropathologic changes. Thus, in order to disentangle the clinical syndrome from the neuropathologic changes the current AD core clinical criteria are distinct from the AD neuropathologic guidelines, yet encourage clinicians and researchers to postulate the most likely neuropathology underlying the clinical presentation of disease.

In 2011, the National Institute on Aging and the Alzheimer's Association (NIA-AA) released cosponsored revised clinical diagnostic guidelines for dementia, dementia due to AD, MCI, and a theoretical framework for defining the preclinical stages of AD. Core clinical diagnostic criteria for dementia, AD, and MCI were designed for use in all clinical settings and are summarized in **Tables 66-1** and **66-2**. In 2013, the American Psychiatric Association published the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Within this edition, the term "dementia" was replaced with "major neurocognitive disorder" and the term "mild cognitive impairment" with "mild neurocognitive disorder." While the DSM-5 and NIA-AA terminologies differ, the diagnostic criteria for major neurocognitive disorder and dementia as well as those for mild neurocognitive disorder and MCI are nearly identical (see **Tables 66-1** and **66-2**) and, thus, in most circumstances are interchangeable. For simplicity, this chapter uses the terms "dementia" and "MCI."

TABLE 66-1 NIA-AA CORE CLINICAL DIAGNOSTIC CRITERIA FOR ALL-CAUSE DEMENTIA AND DEMENTIA DUE TO ALZHEIMER DISEASE

DEMENTIA
The patient has cognitive or behavioral symptoms that: • Interfere with the ability to function at work or at usual activities • Represent a decline from previous levels of functioning and performing • Are not explained by delirium or major psychiatric disorder Cognitive impairment is detected and diagnosed through a combination of: • History-taking from the patient and a knowledgeable informant • An objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing The cognitive or behavioral impairment involves a minimum of two of the following domains[a]: • Impaired ability to acquire and remember new information • Impaired reasoning, judgment, and handling of complex tasks • Impaired visuospatial abilities • Impaired language functions • Changes in personality, behavior, or comportment

PROBABLE DEMENTIA DUE TO ALZHEIMER DISEASE[b]
The patient meets criteria for dementia *and* has the following characteristics: • Insidious onset over months to years, not sudden over hours or days • Clear-cut history of worsening cognition by report or observation • Initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: *Amnestic presentation* (most common presentation)—Deficits should include impairment in learning and recall of recently learned information, plus cognitive dysfunction in at least one other cognitive domain. *Nonamnestic presentations*[c]: *Language presentation*—The most prominent deficits are in word finding, but deficits in other cognitive domains should be present. *Visuospatial presentation*—The most prominent deficits are in spatial cognition, but deficits in other cognitive domains should be present. *Executive dysfunction*—The most prominent deficits are impaired reasoning, judgment, and problem solving, but deficits in other cognitive domains should be present. The diagnosis of probable AD dementia ***should not*** be applied when there is evidence of: • Substantial concomitant cerebrovascular disease (defined by a history of a stroke temporally related to onset or worsening of cognitive impairment or presence of multiple or extensive infarcts or severe white matter hyperintensity burden) • Core features of dementia with Lewy bodies • Prominent features of behavioral variant frontotemporal dementia • Prominent features of primary progressive aphasia • Active neurologic disease or a medical comorbidity or use of medication that could have a substantial effect on cognition

[a]Diagnostic criteria for DSM-5 "major neurocognitive disorder" require a significant cognitive decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition).
[b]The diagnosis of "probable AD dementia with increased level of certainty" is made when there is a documented cognitive decline and/or evidence of a causative genetic mutation (APP, PSEN1, or PSEN2, not APOE4) in addition to the above diagnostic criteria.
[c]Diagnostic criteria for DSM-5 "major neurocognitive disorder due to Alzheimer disease" require that one of the affected cognitive domains be memory and learning.
Based on McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:263–269.

TABLE 66-2 ■ NIA-AA CORE CLINICAL DIAGNOSTIC CRITERIA FOR MILD COGNITIVE IMPAIRMENT

MILD COGNITIVE IMPAIRMENT[a]
The patient, an informant who knows the patient well, or a clinician observing the patient notes a concern regarding a change in cognition in comparison to the patient's previous level.
There is evidence of lower performance in one or more cognitive domains (memory, executive function, attention, language, and/or visuospatial skills) that is greater than would be expected for the patient's age and educational background.
The patient maintains preserved independence in functional abilities, although they may take more time, be less efficient, and make more errors at performing such activities than in the past.
The patient does ***not*** meet criteria for dementia.

[a]DSM-5 "mild neurocognitive disorder" criteria also state that these deficits do not occur exclusively in the context of a delirium or other mental disorder (eg, major depressive disorder, schizophrenia). Identification and exclusion of other neurologic, psychiatric, and medical disorders is implied in the text of the NIA-AA MCI diagnostic criteria.
Based on Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7:270–279.

EPIDEMIOLOGY

AD is the most common cause of dementia in older adults, currently affecting more than 5 million Americans. Worldwide more than 44 million individuals currently have AD or a related dementia. Unless effective preventive

strategies are identified, it is anticipated that the prevalence of AD will double every 20 years. The United Nations predicts that the major rate of increase in the prevalence of AD will likely occur in developing countries that may not possess the essential resources, public health support system, or medical expertise to care for patients with AD. There is clear evidence that a number of risk factors significantly enhance the overall risk for developing AD. These risk factors relate to both genetic and nongenetic markers and are discussed below.

Aging

Age is the single most important and validated risk factor for AD. Epidemiologic studies indicate that the incidence and prevalence of AD both increase with age. Based on data from the 2010 US Census, the prevalence of AD was approximately 3% among adults between the ages of 65 to 74, 17% in persons aged 75 to 84, and 32% in individuals over age 85. With the average human lifespan increasing, the prevalence of AD is expected to accelerate at an even greater rate in coming decades. Although not clearly understood, converging research findings provide clues concerning the potential molecular pathway(s) underlying the association between aging and AD. Increases in the pathologic hallmarks of AD, notably amyloid plaques and neurofibrillary tangles, have been noted in the brains of older adults.

Age-related changes in molecular pathways involving insulin-like growth factor 1 receptor (IGF1-R), neurotrophin signaling, β-site amyloid precursor protein cleaving enzyme 1 (BACE1), and amyloid precursor protein (APP) metabolism may account for some of the increase in incidence and prevalence of AD with aging. Additionally, aging and IGF1-R signaling are both associated with cerebrovascular dysfunction, which may play a key role in the development of AD. An increased exposure time to age-dependent vascular risk factors or an interaction between aging and vascular risk factors may in part account for the effects of aging on the pathobiology of AD.

Apolipoprotein E Genotype

Late-onset AD is the most common form of the disorder, accounting for greater than 95% of all AD cases. Although some cases of younger-onset AD have strong links to the genes coding for amyloid precursor protein (*APP*) and presenilin 1 (*PSEN1*) and 2 (*PSEN2*) proteins, many cases of late-onset AD are seen in individuals without any clear genetic predisposition. A common polymorphism in the apolipoprotein E (*APOE*) gene is the major determinant of risk in families with late-onset AD. Of the three allelic forms ($\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$), AD risk is increased fourfold in individuals with at least one $\varepsilon 4$ allele and 12-fold in persons with two copies of the $\varepsilon 4$ allele. While $\varepsilon 4$ genotype modifies an individual's risk of the disease, by itself it is neither necessary nor sufficient for the development of AD. In the Framingham Study, 55% of $\varepsilon 4$ homozygote carriers, 27% of $\varepsilon 4$ heterozygote carriers, and 9% of noncarriers developed AD by age 85. *APOE* $\varepsilon 4$ genotype may contribute to AD by influencing processes related to the development of AD, including altering the rate of production, clearance, or aggregation of amyloid β-peptide and/or influencing cerebral cholesterol metabolism and inflammation.

Vascular Risk Factors

Midlife vascular risk factors, including hypercholesterolemia, hypertension, diabetes mellitus, metabolic syndrome, obesity, and physical inactivity, have all been associated with a greater risk of developing AD in later life. High midlife total cholesterol and blood pressure levels are associated with a two- to nearly threefold increased risk of developing AD decades later and may convey an even greater risk than that caused by *APOE* $\varepsilon 4$ allele. Abnormal cholesterol metabolism is related to *APOE* $\varepsilon 4$ allele, suggesting that some of the adverse effects of this genotype on AD risk may be partially mediated through lipoprotein dysregulation. In a community-based cohort study, higher glucose levels were associated with an increased risk of dementia in populations both with and without diabetes mellitus. Metabolic syndrome is also associated with increased risk for AD, although this cluster of risk factors is more consistently related to greater risk of vascular dementia. Midlife obesity (RR 1.60, 95% CI 1.34–1.92) and physical inactivity (RR 1.82, 95% CI 1.19–2.78) are interrelated and both independently increase the risk for developing AD in late life. With more than 35% of current US adults meeting criteria for obesity, there is concern that this risk factor could further accelerate projected increases in AD incidence rates over the coming decades.

Studies support that vascular factors exert an independent additive effect on AD risk. The presence of multiple cardiovascular risk factors at midlife substantially increases the risk of late-life dementia in a dose-dependent manner. The positive corollary to these findings is that about a third of AD cases worldwide might be attributable to potentially modifiable risk factors, thus, providing a target for preventive strategies. Vascular risk factors exert their adverse

effects on AD pathology through a variety of mechanisms, including modulation of β-amyloid (Aβ) metabolism, effects on insulin receptors, blood-brain barrier integrity, endothelial dysfunction, and cerebral blood flow. These vascular-mediated changes subsequently lead to tissue hypoxia, increased oxidative stress, inflammation, and cognitive decline.

Traumatic Brain Injury

There is increasing epidemiologic evidence that moderate or severe traumatic brain injury (TBI) is a risk factor for AD in late life and may precipitate earlier onset of the disease. In longitudinal studies, the magnitude of AD risk increases with TBI severity. Compared to controls, World War II veterans with moderate TBI were twice as likely to develop AD, whereas the risk was fourfold in veterans with severe TBI with loss of consciousness. Neuropathologic examination of brains from patients with a history of head trauma generally reveals changes of diffuse amyloid plaques together with tau pathology, inflammatory response, and loss of cholinergic neurons. These pathologic changes may be related to transient upregulation of β-site amyloid precursor protein cleaving enzyme 1 (BACE1) together with increased generation of Aβ. These features are accompanied by tau hyperphosphorylation and increased caspase-mediated cleavage of APP. Thus, head trauma may lead to AD by triggering accelerated neurodegeneration.

Newer evidence demonstrates that recurrent mild TBI, including both concussive and subconcussive injuries, may also contribute to future risk of cognitive decline. However, it has been difficult to establish risk estimates of the impact of repetitive mild TBI on risk for AD due to a variety of methodologic challenges. The high frequency of concussive and subconcussive injuries, the variability in definitions and measurements of mild TBI, the heterogeneity of injuries among various cohorts (ie, military combat veterans vs contact sport athletes), and selection and recall biases have complicated research of this area. Repetitive concussive injuries may also lead to chronic traumatic encephalopathy (CTE), a condition that is neuropathologically distinct from AD. Symptoms of CTE frequently include headaches and disturbances in attention or concentration and depression; however, clinical criteria have not yet been defined. Research is underway to clarify the varying types and severity of TBI and the effects of such injuries on risk for posttraumatic neurodegeneration.

Depression

More than 30% of patients with AD develop depression during the course of their illness, and some may present with depressive symptoms as their first clinical manifestation of underlying AD. While depression has long been recognized as a common psychiatric condition in older adults that may mimic dementia, depression is likely also a risk factor for AD. Findings of a meta-analysis involving over 20 population-based prospective studies supported an increased risk of AD in patients with a history of late-life depression (pooled risk OR [95% CI] 1.65 [1.42–1.92]). To date, the precise mechanisms underlying the association between depression and enhanced AD risk are unknown. Several potential mechanisms have been proposed that are common to both AD and depression, including elevated levels of cytokines, increased vascular risk factors, and the potential role of *APOE4* allele. More research is needed to better understand the biological basis of increased risk of AD in patients with a history of depression.

Race and Ethnicity

The assessment of differences in AD prevalence rates across geographic regions worldwide and among various racial and ethnic groups has proven to be challenging. Differences in education, literacy, life expectancy, access to health care, nutrition, social stressors, vascular risk factors, and cultural beliefs in what is considered normal aging can all influence AD prevalence estimates. In the Indianapolis/Ibadan studies, the incidence and prevalence of AD were significantly lower among Africans in Ibadan, Nigeria, than among age-matched African Americans in Indianapolis, suggesting that differences in environmental factors may play a larger role than race in influencing the development of AD. The significant influence of environmental factors on AD risk is also supported by data showing that migrant populations tend to have dementia rates that fall between those seen in their homeland and adopted countries. Standardized approaches to case ascertainment of dementia and statistical comparisons across nations have been implemented to better assess variations in prevalence rates among low-, middle-, and high-income countries. These approaches have produced age-adjusted dementia prevalence estimates of approximately 5% to 9% in people over age 60 across global regions.

Studies assessing ethnic and racial variations in dementia rates within countries have identified some group differences in AD incidence and prevalence. In a population-based study in the Washington Heights and Inwood

communities of New York City, the cumulative incidence of AD was increased twofold among individuals of African-American and Caribbean Hispanic origin. The group differences in AD incidence did not change following corrections for differences in years of education or history of vascular risk factors. In a study in Houston, Texas, both the incidence and prevalence of AD were higher among older African-American and Hispanic individuals compared to non-Hispanic white adults. In Singapore, ethnic Malays and Indians had higher rates of dementia compared to ethnic Chinese, independent of vascular risk factors. While some research suggests there may be biological or genetic differences driving variations in AD risk, other studies support that these racial and ethnic group differences will not persist after rigorously accounting for important social, cultural, and environmental factors influencing risk of dementia.

Education

Low educational attainment, poor educational quality, and illiteracy have been shown to be associated with increased risk for AD. In a meta-analysis of 13 cohort and six case-control studies, low education had a pooled relative risk (RR) estimate for AD of 1.80 (95% CI 1.45–2.27) compared to high education, although the estimate from cohort studies (RR 1.59 [95% CI 1.35–1.86]) was significantly lower than the estimate based on case-control studies (2.40, [1.32–4.38]). Prospective cohort studies likely provide a more accurate assessment of the association between education and dementia since they allow for documentation of a decline from a previous level of cognitive performance. Some studies have found that education may be a marker of cognitive reserve as it modifies the association between AD neuropathology and level of cognitive function. For the same degree of brain pathology, persons with higher education demonstrate less cognitive impairment. In addition, higher levels of education may help individuals cope more effectively with cognitive changes. Access to higher levels of education may also be a marker of socioeconomic status, coexisting chronic diseases, access to health care resources, and premorbid intellectual abilities. Thus, while low educational attainment is associated with increased AD risk, it is not clear to what extent low education contributes to AD or whether early educational interventions will protect against the development of dementia.

Gender

There is some evidence that AD is more common among women, although study results are conflicting. In population-based studies, more than half reported a greater risk of AD in women, while the others found no difference. Some data support that estrogen deficiency following menopause may contribute to the development of AD; however, the effect of hormone replacement therapy on cognition remains controversial. The discrepant findings between studies assessing sex-based variations in dementia risk are likely due to methodologic differences in accounting for potential gender-related variability in life-expectancy, education, occupation, and lifestyle factors that can directly affect AD risk.

PATHOPHYSIOLOGY

Genetics of Alzheimer Disease

Based on the onset of symptoms, AD is normally divided into two groups: younger-onset (< 65 years) and late-onset (> 65 years) disease. Younger-onset patients include individuals with familial AD which accounts for between 1% and 5% of all AD cases and to date has been linked to mutations in the genes for the amyloid precursor protein (APP; gene name *APP*) on chromosome 21, presenilin 1 (PS1; gene name *PSEN1*) on chromosome 14, and presenilin 2 (PS2; gene name *PSEN2*) on chromosome 1. Among these genes, more than 250 different mutations have so far been identified, accounting for approximately 40% of all cases of familial AD, yet only 0.5% of AD cases overall. Most of the mutations (~ 200) are found in the *PSEN1* gene and account for 78% of the familial AD mutations. *APP* mutations (~ 33) account for about 18% of younger-onset autosomal dominant cases and *PSEN2* (~ 22 mutations) for about 4%. Familial AD is characterized by younger onset of cognitive symptoms (typically in the late 40s or early 50s), but is clinically indistinguishable from late-onset AD.

Late-onset AD, also called sporadic AD, accounts for greater than 95% of all cases of the disease. *APOE* is the only established susceptibility gene consistently found associated with late-onset AD in both case-control and genetic studies. *APOE* maps to chromosome 19 in a cluster with the genes encoding translocase of outer mitochondrial membrane 40 (*TOMM40*), apolipoprotein C1, and apolipoprotein C2. The *APOE* gene exists as three major alleles (ε2, ε3, and ε4) that encode three different ApoE isoforms: ApoE2, ApoE3, and ApoE4. Interestingly, these isoforms only differ in amino acid sequences at either position 112 or 158 of the protein. The inheritance of the ε4 allele confers an

increased risk for developing AD, while the ε2 allele confers protection. For example, presence of one copy of the ε4 allele increases risk of AD fourfold, whereas inheritance of two copies enhances the risk by 12-fold. However, unlike genetic mutations associated with familial AD, the presence of *APOE ε*4 alone is insufficient to cause AD without additional factors. Even though the first report of an association between *APOE ε*4 and AD was published decades ago, the precise molecular mechanisms underlying this association still remain elusive. It is currently unknown if the *APOE4* allele influences the rate of production, clearance, or aggregation of Aβ peptide or whether it influences cholesterol metabolism and inflammation that reportedly play a major role in the pathobiology of AD.

With the advent of genome-wide association studies (GWAS), a number of new genetic loci with genome-wide significance have been identified. In addition to *APOE4*, more than 40 other polymorphisms have been associated with increased risk for late-onset AD. However, none of these associations has been uniformly confirmed in every population group studied to date. Over 20 genetic loci have been associated with late-onset AD, leading to four main mechanisms: Aβ metabolism, lipid metabolism, immune response, and cell signaling. Further research is needed to clarify the impact of other genetic changes on AD risk, genetic-environmental interactions, and the impact of such genetic factors on mechanisms of neurodegeneration and neuroprotection.

Neuropathology of Alzheimer Disease

The neuropathologic hallmarks of AD include amyloid plaques, neurofibrillary tangles, and neuritic plaques (**Figure 66-1**). The latter are a subset of amyloid plaques that are closely associated with neuronal injury and occur with dystrophic neurites. Cerebral amyloid angiopathy (CAA) frequently co-occurs with amyloid plaques, resulting from deposition of Aβ into cerebral vessels. Sporadic CAA is observed in 80% to 90% of AD patients and may cause lobar intracerebral hemorrhages and microbleeds. Together these processes contribute to loss of neurons and synapses in the neocortex, hippocampus, and other subcortical regions of the brain. The predominance of amyloid plaques versus neurofibrillary tangles or amyloid angiopathy can differ from one patient to another. However, neuronal/synaptic loss is a constant feature and eventually the direct cause of dementia. The distribution of the disease pathology seems to follow a region-specific pattern with amyloid plaques being more prevalent in the neocortex and neuronal/synaptic loss being more prevalent in the hippocampus, posterior cingulate, and corpus callosum—areas of the brain closely involved with memory formation and higher cortical activities. Finally, brains of persons with AD are also characterized by a diffuse and widespread invasion of reactive astrocytes, mostly concentrated in the hippocampus and around areas of neuronal loss. These astrocytic changes are not specific to AD and can be observed in other neurodegenerative disorders associated with inflammation and neurotoxic insults.

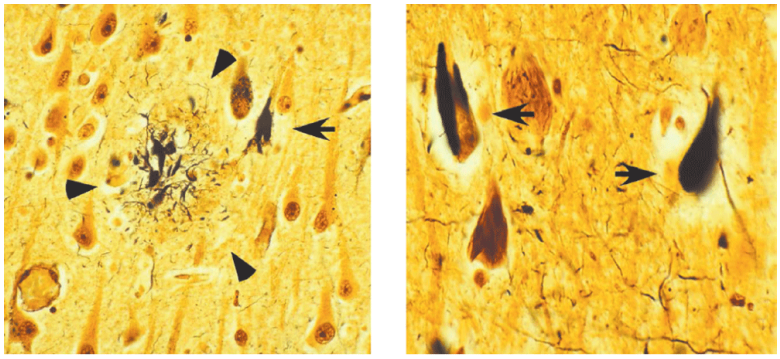


FIGURE 66-1. Small section of the neocortex from a patient with Alzheimer disease showing two classical neuropathologic lesions of the disease. **A.** The modified silver staining shows one dense senile (amyloid) plaque indicated by three arrowheads. The plaque consists of aggregated extracellular deposits of amyloid β-peptide (Aβ) fragments surrounded by silver-positive dystrophic neurites. The arrow indicates a neuron containing neurofibrillary tangles, which appear as dark masses of abnormal filaments occupying most of the cytoplasm. **B.** The image shows higher magnification of two neurons containing neurofibrillary tangles (*indicated by arrows*). (Photograph courtesy of Shahriar Salamat, MD, PhD, University of Wisconsin School of Medicine and Public Health, Department of Pathology and Laboratory Medicine.)

The dominant component of the amyloid plaque core is Aβ organized in fibrils of approximately 7 to 10 nm intermixed with nonfibrillar forms of the peptide. Neuritic plaques are characterized by a dense core of aggregated fibrillar Aβ, surrounded by dystrophic dendrites and axons, activated microglia, and reactive astrocytes. In addition, diffuse deposits of Aβ, likely representing a prefibrillary form of the aggregated peptide, are found without any surrounding dystrophic neurites, astrocytes, or microglia. These diffuse plaques can be found in limbic and association

cortices, as well as in the cerebellum.

The other neuropathologic hallmark of AD is the presence of neurofibrillary tangles found exclusively in the cytoplasm of neurons (see **Figure 66-1**). The tangles appear as paired, helically twisted protein filaments composed of highly stable polymers of cytoplasmic proteins called tau. Tau comprises a group of alternatively spliced proteins found in the cytoplasm that possess either three or four microtubule-binding domains and can assemble with tubulin, thus helping the formation of cross bridges between adjacent microtubules. Tau proteins can be phosphorylated in multiple sites, and the degree of phosphorylation is inversely correlated with binding to microtubules. As a result, highly phosphorylated tau proteins dissociate from microtubules and polymerize into filaments forming neurofibrillary tangles. In addition to AD, the abnormal accumulation of filamentous tau is observed in frontotemporal forms of dementia, progressive supranuclear palsy, corticobasal degeneration, and Pick disease. Contrary to prior belief, tau proteins themselves can cause dementia, and multiple mutations in the *tau* gene have been found in frontotemporal dementia with parkinsonism. The precise role of tau proteins in the pathogenesis of AD and their potential interaction with Aβ are still unclear.

In 2012, NIA and the Alzheimer's Association published revised criteria for AD neuropathologic change. These criteria recommended reporting on the presence and extent of hallmark lesions for AD observed at autopsy independent of the individual's cognitive state. These new guidelines took into account several well-established neuropathologic scoring criteria and integrated them into an "ABC score" based on three parameters (*A*myloid, *B*raak, *C*ERAD): criterion "A" ranks the Aβ plaque score (based on criteria from Thal et al.), criterion "B" measures the neurofibrillary tangle stage (modified from Braak criteria), and criterion "C" assesses the neuritic plaque score (modified from the Consortium to Establish a Registry for Alzheimer's Disease [CERAD]). For reporting, these ABC scores are then transformed into one of four levels of neuropathic change: none, low, intermediate, or high. While CAA is not considered in the "ABC" score, the guidelines recognize that these changes frequently co-occur with parenchymal Aβ plaques and recommend neuropathologists comment on such changes separately within the neuropathology report.

Amyloid Precursor Protein Processing and Generation of Aβ

Aβ is a 39 to 43 amino acid hydrophobic peptide proteolytically released from a much larger precursor, APP. Although APP is the major source of toxic Aβ, it also exerts several important functions in the nervous system, including serving as a cell-surface receptor, growth factor, protease inhibitor, cell-cell interaction molecule, coreceptor/partner in the endocytic/lysosomal network, coagulation inhibitor factor, cell-surface scaffold protein, kinesin-interacting molecule for axonal transport, and transcription factor. The generation of Aβ from APP (**Figure 66-2**) requires the sequential recruitment of two enzymatic activities: β-secretase, also called BACE1, and γ-secretase, a multimeric protein complex containing presenilin, nicastrin, Aph-1, Pen-2, and CD147. The β-cleavage is the rate-limiting step and occurs before the γ-cleavage. It liberates a large N-terminal fragment of the protein (sβAPP) that is released in the extracellular milieu and a small (~12 kDa) membrane-anchored fragment called β-APP-CTF (or C99). The release of the large N-terminal domain allows subsequent γ-cleavage, and liberation of Aβ and the signaling of active intracellular domain (AICD) of APP (see **Figure 66-2**). Generation of Aβ40 and Aβ42 results from γ-cleavage of Aβ at positions 40 and 42, respectively. The release of Aβ in the extracellular milieu is followed by oligomerization and aggregation in the form of fibrils and amyloid plaques. Additionally, small Aβ aggregates are also found in the soma of the neurons suggesting that the Aβ fragments can escape secretion and aggregate in the intracellular environment. The molecular mechanisms underlying the toxicity of Aβ are still being investigated and currently incompletely understood. However, research seems to indicate that small Aβ aggregates (oligomers), which represent the "preplaque" neurotoxic species of Aβ, act as the proximate cause of neuronal injury and synaptic loss associated with AD. Additionally, the C-terminal tail of APP can undergo further processing at amino acid 664 of APP695 liberating two small cytosolic fragments, Jcasp and C31. Both of these fragments are generated only after γ-cleavage, require caspase-mediated processing of APP, and can activate proapoptotic pathways in a variety of cellular systems.

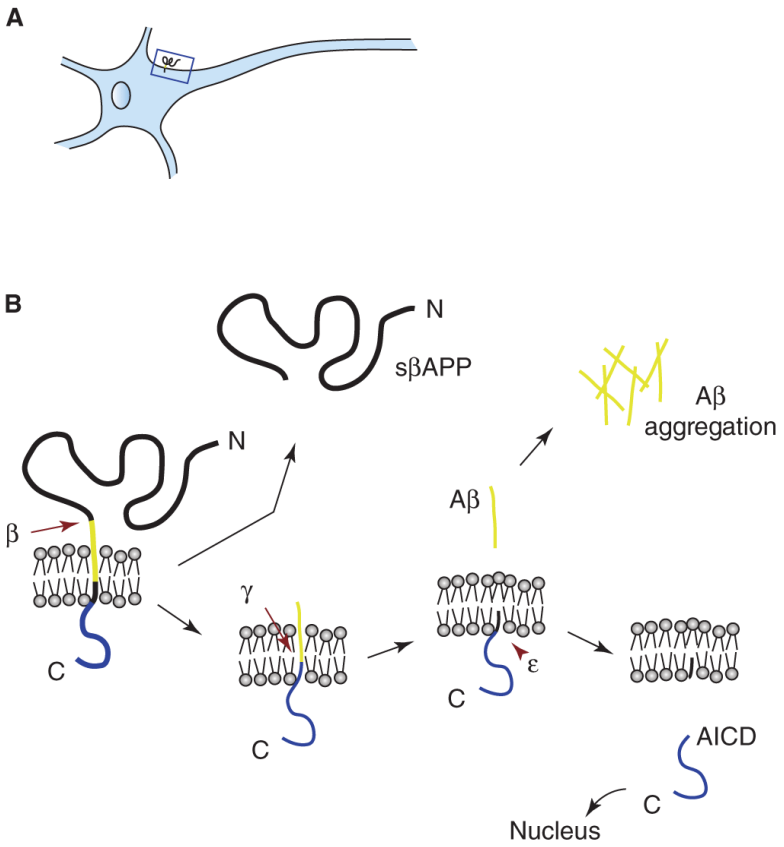


FIGURE 66-2. Generation of amyloid β-peptide (Aβ) from amyloid precursor protein (APP). APP is a type 1 membrane protein with a large extracellular domain, a single membrane-spanning domain, and a short cytoplasmic tail. The Aβ region of APP (*in yellow*) includes the first 12 to 14 amino acids of the membrane domain. **(A)** Shows a schematic image of APP on the cell surface of a neuron, whereas **(B)** provides a closer view of APP processing. The initial enzymatic step for the generation of Aβ requires proteolysis of APP at β-site (amino acid 1 of the Aβ region). This event liberates a large N-terminal fragment (sβAPP) that is rapidly secreted into the extracellular milieu and a small C-terminal fragment (β-APP-CTF) of 99 amino acids (also called C99). The removal of sβAPP most likely induces a conformational change that allows subsequent cleavage by γ-secretase. Once generated, the Aβ peptides aggregate in the brain in the form of plaques. Further cleavage of β-APP-CTF at the site liberates the signaling active APP intracellular domain (AICD). In addition to the above β/γ pathway, APP can also be cleaved at the α-site (between amino acids 16 and 17 of the Aβ region) precluding the generation of Aβ.

The most critical clinical link between Aβ and AD came from the observation that patients with Down syndrome (trisomy 21) had a higher propensity for developing a clinical and pathologic phenotype resembling AD, thereby suggesting a potential association between AD and chromosome 21. This observation was further strengthened by the fact that Aβ was the major component in plaques from both patients with Down syndrome and AD, and that its genesis was related to a gene (*APP*) located on chromosome 21, close to the obligate Down syndrome region. Following the identification of APP, several groups found mutations in the *APP* gene that were linked to familial forms of AD. Given that the duplication of the *APP* locus could result in early AD and that Down syndrome patients with partial trisomy 21 developed AD only when the trisomy was proximal to the *APP* locus, the potential direct relationship between APP metabolism and AD seems strong. Furthermore, causative mutations in the genes that encode for PS1 and PS2, which are also implicated in the metabolism of APP, have been found and are associated with familial forms of AD, thereby conferring additional strength to the linkage between APP/Aβ metabolism and AD.

Although the generation of Aβ from APP seems to be a pivotal step in the pathobiology of AD, it does not explain all the neuropathologic changes observed in patients with AD. For example, examination of the brain of transgenic mice expressing human APP harboring one or more familial AD-associated mutations reveals the presence of amyloid plaques and some synaptic loss and cognitive deficits, but absence of tau pathology and astrocytosis. This suggests that additional biochemical/molecular events are required to develop the full pathologic spectrum of AD. To circumvent this issue, several new animal models have been generated where human APP is accompanied by additional genes. These genes include the *presenilins* (harboring familial AD-associated mutations), *tau*, and *APOE*. Recently, several transgenic mice models harboring three or five familial AD-associated mutations (respectively called 3X and 5X mice) in two or more genes have been generated. All of these models demonstrate that Aβ is an essential element for the development of AD-like neuropathology and revealed a close relationship between Aβ and the

phosphorylation/aggregation state of tau. However, none of the mouse models fully reproduce the classical AD phenotype, thereby again suggesting that Aβ seems to be necessary but not sufficient to produce the entire spectrum of AD neuropathology. Transgenic mice expressing the human microtubule-associated protein tau develop the typical tau-related pathology found in individuals suffering from frontotemporal dementia with parkinsonism; however, they do not develop amyloid plaques, suggesting that tau is not required for the formation of plaques. Crossing these mice with APP transgenic mice potentiates tau-related pathology and neuronal loss but does not aggravate plaque pathology, suggesting that Aβ acts upstream of tau in the classical AD phenotype. However, studies from patients with AD, mouse models, and ex vivo cellular systems indicate that Aβ and tau can interact synergistically, thereby fostering their respective aggregation and neuronal loss. Thus, the true relationship between Aβ and tau is more complex than previously thought and likely involves additional molecular and biochemical pathways acting upstream of both Aβ and tau production in the AD brain.

CLINICAL PRESENTATION

The most common clinical onset of AD is an amnestic presentation, characterized by slowly progressive memory loss for recent events. Patients with AD frequently have problems remembering recent conversations, dates, appointments, and may misplace items. Many patients are not aware of these deficits and are brought to medical attention by their family members or friends. For some patients, memory loss symptoms are first noted by others during a stressful life event, such as the patient's hospitalization or the death of a spouse; however, a thorough interview frequently reveals that the cognitive deficits preceded such an event by months to years. The memory deficits of AD are generally differentiated from those caused by normal aging by the fact that AD-related deficits are progressive and interfere with the individual's usual daily activities. Memory loss leading to a change in functional status is not a part of normal aging and warrants further evaluation.

Nonamnestic presentations of AD are also common and may include prominent initial impairments in language abilities, visuospatial skills, and executive function. As these presentations are less commonly recognized by patients, families, and clinicians alike as being early symptoms related to AD, individuals with nonamnestic presentations are frequently misdiagnosed or experience a delay in diagnosis. In addition to the more common amnestic presentation, nonamnestic presentations are specifically identified in the NIA-AA diagnostic criteria for AD (see **Table 66-1**). Patients who initially present with language impairment frequently will complain of marked word-finding problems with subsequent progression to paraphasic errors and circumlocution. AD patients with a visuospatial presentation may have prominent deficits in spatial cognition, including poor object and face recognition, an inability to perceive multiple visual elements simultaneously, and difficulty understanding written language. Executive dysfunction is another common initial presenting symptom of AD, leading to impairments in reasoning, judgment, problem solving, and an inability to complete complex demanding tasks. Deficits in concentration and attention frequently occur in patients with AD, but these changes may also be notable in persons with depression, attention deficit disorder, sleep disorders, or adverse medication effects.

As the disease progresses, changes in personality are commonly seen in patients with AD and may include increased passivity, lack of interest, agitation, restlessness, and/or overactivity. AD patients may exhibit increased irritability when confronted with memory loss symptoms, such as when struggling to find a word, being reminded of a prior conversation or event, or searching for a misplaced item. More than 30% of persons with AD develop symptoms of depression, which may be the first clinical presentation of the disease. Early signs of depression in patients with AD include increased irritability, alterations in appetite or sleep, trouble concentrating or making decisions, low energy, social withdrawal, and a decline in physical function. Worsening of behavior and cognitive symptoms in the evening is also common in patients with AD and may be related to changes in circadian rhythm from loss of sunlight.

In the later stages of the disease, individuals may have increased confusion, dysphagia, impaired gait, and repeated falls. In some patients with AD, disruptive behaviors may increase with aggression, agitation, and physical or verbal hostility; in others, these behavioral symptoms lessen with disease progression. The majority of patients become increasingly frail and dependent for self-care and activities of daily living with many patients developing bowel and bladder incontinence. Persons in the late stages of AD may become immobile and bed-bound, which increases their risk of developing pressure sores, malnutrition, and dehydration. The most common causes of death in patients with AD include pneumonia, urinary sepsis, dehydration, pressure sores, fractures, and malnutrition. The median survival period from the time of diagnosis to death generally ranges from 7 to 10 years, although some patients, especially those with familial AD, die earlier.

EVALUATION

For many older patients with cognitive complaints, their evaluation, diagnosis, and management may be effectively completed within a primary care setting. If available, utilization of multidisciplinary team members from nursing, social work, psychology, and/or pharmacy can greatly aid a primary care physician in the diagnosis and management of patients with cognitive concerns. A smaller subset of patients will need more in-depth neuropsychological assessment and clinical evaluation from a dementia specialist. The NIA-AA clinical diagnostic criteria for dementia, AD, and MCI (see **Tables 66-1** and **66-2**) were designed to be used across all clinical settings, including primary care, specialty clinics, and long-term care. The clinical diagnoses of MCI and dementia are primarily ascertained through completion of a focused interview with the patient and an informant who knows the patient well, a thorough review of the patient's medical history and medication use, a comprehensive physical examination, a formal assessment of cognitive function, basic laboratory tests, and neuroimaging (**Table 66-3**). While the differential diagnosis for AD is extensive (**Table 66-4**), a systematic approach to dementia diagnosis can help primary care clinicians identify common confounding medical and psychiatric conditions and medications that can adversely affect cognition. In addition, a structured evaluation may facilitate accurate diagnosis of the most common causes of dementia—AD and AD mixed with vascular dementia as well as predementia syndromes such as MCI. Integrating various established diagnostic criteria, **Figure 66-3** shows a primary care diagnostic algorithm developed to guide clinicians in their assessment of patients with cognitive complaints.

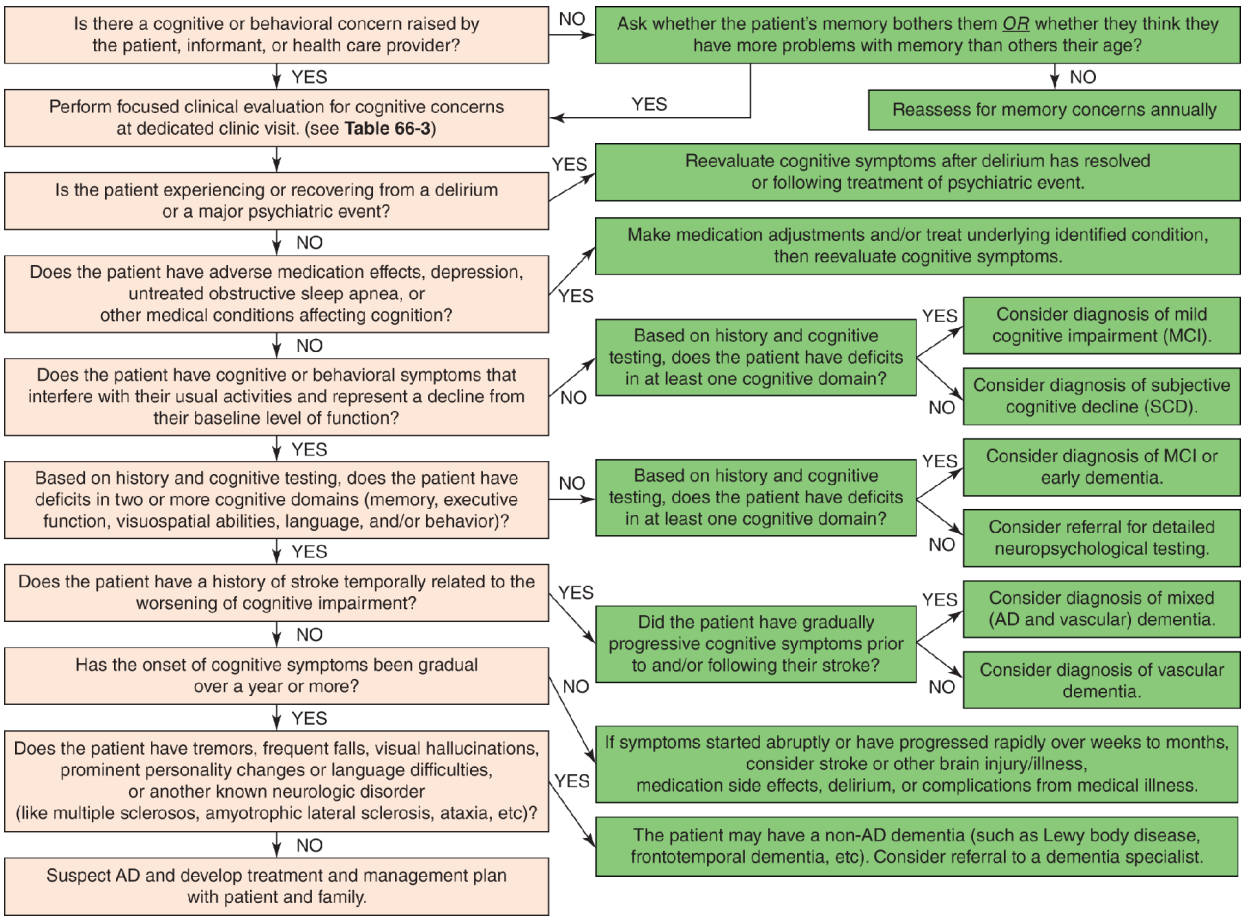


FIGURE 66-3. Algorithm for the clinical diagnosis of Alzheimer disease.

TABLE 66-3 EVALUATION OF THE PATIENT WITH COGNITIVE CONCERNS

History of cognitive changes
Primary symptom(s) at onset (memory loss, language/spelling errors, impaired reasoning, difficulties in multitasking, personality changes, etc)

Date of onset and time course of cognitive decline (gradually progressive, stepwise, fluctuating, abrupt, rapidly progressive, etc) and whether or not it was associated with delirium

Past and present function at higher level tasks (including tasks at work, hobbies, daily household chores including instrumental activities of daily living [IADLs])

Safety concerns (medication management, driving, kitchen safety, use of firearms or heavy equipment, wandering, financial scams, etc)

Other associated symptoms (depression, tremor, frequent falls, visual hallucinations, stroke and/or transient ischemic attack symptoms, ataxia, urinary incontinence, agitation, personality changes, etc)

Past medical and psychiatric history

Vascular risk factors (including how well they have been controlled over time)

Strokes and/or transient ischemic attacks (assess whether cerebrovascular event was associated with onset of cognitive symptoms)

Atrial fibrillation, carotid artery disease, patent foramen ovale, and/or other risk factors for stroke

Coronary artery bypass surgery (assess whether surgery was associated with onset of cognitive symptoms)

Other major central nervous system (CNS) event (traumatic brain injury with loss of consciousness, anoxic brain injury, postoperative cognitive dysfunction, etc)

Hearing and/or vision loss

Obstructive sleep apnea (including how well it is treated with continuous positive airway pressure [CPAP] or other modalities)

Alcohol or other substance abuse

Depression, anxiety, posttraumatic stress disorder, or other psychiatric illness

Parkinson disease, parkinsonism, amyotrophic lateral sclerosis, or multiple sclerosis

Seizure disorder

History of malignancy with or without prior treatment with chemotherapy

Medication review

Prescription and nonprescription medications and supplements (especially those with anticholinergic or sedating side effects)

Timing of onset of cognitive symptoms with medication/supplement initiation or dose change

Social history

Family, friends, and other social support

Use of community resources (including home aides, senior centers, meal services, etc)

Educational history (including formal years of education and/or technical training, any interruption in schooling or repeated grades, any suspected or diagnosed learning disabilities or attention deficit disorder, etc)

Work history (including types of responsibilities associated with occupation)

Military history (including exposure to combat or blast injuries)

Hobbies and other daily activities

Substance use history (including any prior history of heavy alcohol use)

Family history

History of AD or other dementias (including age of onset of symptoms in affected family members)

History of other neurodegenerative disorders, strokes, psychiatric illnesses, etc

Physical examination

General appearance (attention, comprehension, cooperation, personal hygiene and grooming, social appropriateness, psychomotor slowing, word-finding difficulties)

Mental status (behavior, attitude, mood, affect, insight, judgment, thought content, thought process, speech, language)

Cranial nerves (facial symmetry, visual acuity, pupillary responses, eye movements, visual fields, hearing impairment)

Motor function and integration (strength, tone, cogwheeling, simulation of motor actions to test for apraxia)

Sensory function and integration (sensation to light touch, identification by touch of an object placed in the hand or a number written on the hand, ability to perceive simultaneous bilateral tactile stimuli)

Coordination (rapid alternating movements, finger-to-nose testing, heel-shin testing)

Deep tendon reflexes

Gait
Screening Cognitive Tests (time to administer)
Mini Mental State Examination (MMSE) (5–10 min)
Montreal Cognitive Assessment (MoCA) (10 min)
Saint Louis University Mental Status (SLUMS) Examination (5–10 min)
Mini-Cog (3 min)
Memory Impairment Screen (MIS) (3–4 min)
General Practitioner Assessment of Cognition (GPCOG) (4 min)
Depression screen
Geriatric Depression Scale—Short Form (GDS-SF) (5–7 min—may be self-administered)
Informant assessment
Eight-Item Interview to Differentiate Aging and Dementia (AD8) (3 min)
GPCOG Informant Questionnaire (2 min)
Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (10–15 min)
Laboratory evaluation
Vitamin B_{12}, thyroid-stimulating hormone (TSH), 25-OH vitamin D, complete blood count, glucose, blood urea nitrogen and creatinine, basic metabolic profile, liver enzymes
Neuroimaging
Noncontrast head CT
MRI

TABLE 66-4 DIFFERENTIAL DIAGNOSIS FOR ALZHEIMER DISEASE

Depression	Lewy body dementia
Adverse medication effects	Vascular dementia/vascular cognitive impairment
Delirium	Frontotemporal dementia
Acute alcohol intoxication	Parkinson disease dementia
Substance use disorders	Progressive supranuclear palsy
Obstructive sleep apnea	Corticobasal degeneration
Other sleep disorders	Prion-related diseases (Creutzfeldt-Jakob, bovine spongiform encephalopathy)
Chronic hypoxia and/or hypercapnia	Normal pressure hydrocephalus (NPH)
Recurrent hypoglycemia	Huntington disease
Thyroid diseases	Alcohol-related dementia
Other metabolic-endocrine disorders	Wernicke-Korsakoff syndrome
Vitamins B_1 (thiamine), B_{12}, and/or D deficiencies	Traumatic brain injury
Uremia	Chronic traumatic encephalopathy (CTE)
Hepatic encephalopathy	Mass lesions (neoplasms, benign tumors, hematomas)
Environmental toxicity (lead, mercury, polychlorinated biphenyls [PCBs], dioxins, etc)	Central nervous system rheumatologic/autoimmune disorders (systemic lupus erythematosus, sarcoidosis, vasculitis, multiple sclerosis, etc)
Lyme disease	Paraneoplastic syndromes
HIV-associated neurocognitive disorders (HAND)	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
Progressive multifocal leukoencephalopathy (PML)	Carotid artery disease
Chronic meningitis/encephalitis	Postoperative cognitive dysfunction

Neurosyphilis	Seizure disorder

Identification of a cognitive concern is the first step in the evaluation. While early cognitive changes in some patients may be readily identified by the individuals themselves, their families, and/or their clinicians, such symptoms may not be as apparent in other patients due to a variety of factors, including poor insight, attribution of such changes to normal aging, cultural views of dementia, or lack of corroborative history from others. Whether all older adults should undergo routine screening for dementia remains controversial. The United States Preventive Services Task Force recommends against routine screening for dementia in asymptomatic older adults based on insufficient evidence that such widespread screening impacts individual or societal outcomes. However, the US Medicare Annual Wellness Visit requires that clinicians assess cognitive function by "direct observation," although no cognitive screening tool is endorsed. In an effort to operationalize the Medicare Annual Wellness Visit requirements, the Alzheimer's Association recommends using self-reported memory concerns, clinician observations, or concerns from a person who knows the patient well to trigger a formal memory assessment. Screening questions such as "Does your memory bother you?" or "Do you think your memory is worse than others of your age?" also may be used to determine which older patients need a formal evaluation of cognitive performance. Identifying memory concerns through self-report or screening questions may reduce the number of unnecessary formal cognitive screening tests administered to asymptomatic adults at low risk for dementia. However, individuals without a close informant may need structured cognitive tests to identify memory concerns. When a cognitive concern is identified, a separate clinic visit should be arranged to investigate the underlying cause (see **Figure 66-3**, **Table 66-3**).

Within a dedicated primary care clinic visit, an optimal cognitive assessment includes gathering information not only from the patient's perspective, but also independently in a separate interview from an informant who knows the patient well. Depending on available time and resources, an independent informant interview may be accomplished through utilizing a variety of health care team members, such as social workers, medical assistants, nurses, or psychologists to conduct a brief structured informant interview or a full detailed assessment. Important historical elements include establishing when the cognitive symptoms began and the very first symptoms noted (such as problems with memory, language, executive function, apraxia, or personality changes). A careful delineation of the time course of progression will narrow the differential diagnosis and will help identify whether there are multiple contributing factors or one underlying process. Frequently, an inciting event that disrupts coping skills, such as a hospitalization or the death of a spouse, will draw the attention of family members to a patient's memory problems. The family may give a history of an acute onset of memory impairment following the inciting event, but careful questioning may identify cognitive problems preceding that time period and point to a gradually progressive course.

A key component to the interview is establishing the patient's baseline cognitive and functional performance, taking into account past educational opportunities, estimated baseline intellectual function, occupational history, and prior established skills and abilities. Understanding the patient's baseline function will put neuropsychological test results into context in order to prevent over- or underdiagnosing dementia in patients who present with cognitive concerns. Changes in the person's ability to carry out tasks related to their occupation, hobbies, household management, and other volunteer activities should then be ascertained.

There are common reversible causes of cognitive dysfunction that next should be addressed. One of the first steps should be a careful review of prescription and nonprescription medications. Drugs with known anticholinergic properties (such as antihistamines, tricyclic antidepressants, bladder antispasmodic agents, etc) or sedating side effects (such as high-dose gabapentin, other antiepileptic medications, narcotic analgesics, benzodiazepines, sleeping aids, etc) should be carefully reviewed to see if the benefit of the offending medication outweighs the adverse cognitive effects. Patients should be included in shared decision making with any medication adjustments as the value placed on various symptoms is likely to differ between individuals.

Clinicians should carefully evaluate their older patients for depression, anxiety, or other mood disorders that can affect cognitive performance. Depression may be a prodromal syndrome prior to dementia onset, but also commonly co-occurs with this syndrome. Pointed questions assessing for changes in sleep duration and/or quality, interest in activities, feelings of guilt, loss of energy, impaired concentration, changes in appetite, psychomotor slowing, and suicidal thoughts should be assessed. A brief screening tool such as the Geriatric Depression Scale (GDS) can be administered by a health care team member or self-administered while the patient is waiting for the clinician. Older patients with depression frequently complain of problems with poor concentration and forgetfulness and may perform poorly on tests of attention, speed of processing, and memory. In such patients, it is important to differentiate a loss of interest related to depression from a lack of initiative due to a neurodegenerative disorder. Treating depression and anxiety may lead to improvements in cognitive performance as well as mood.

Hearing loss may mimic cognitive dysfunction as patients who cannot hear well may not be able to properly encode new information from conversations or other auditory-received information. Questions on hearing loss symptoms and use and fit of any prescribed hearing aids can alert the provider as to whether hearing loss is contributing to cognitive symptoms or if further hearing evaluation is needed (see Chapter 39 for approach to screening for hearing loss).

A careful assessment of alcohol use should be completed in all patients, especially if cognitive performance varies widely from visit to visit or if the patient lives alone. Risk for obstructive sleep apnea should be assessed with several screening questions assessing the patient's snoring, witnessed apneic episodes, excessive daytime sleepiness, or nonrestorative sleep. In patients with diagnosed sleep apnea, their ability to effectively and regularly use their continuous positive airway pressure (CPAP) device should be assessed and any difficulties should be reported to the sleep medicine and/or respiratory therapy team to seek out other mask options for better fit and tolerance. Obstructive sleep apnea with its related hypoxia can cause profound effects on cognition.

Vascular disease may contribute to cognitive impairment through a variety of mechanisms. In addition to stroke causing acute cognitive decline, chronic low cerebral blood flow leading to subclinical hypoperfusion may also contribute to cognitive impairment and AD. Thus, a careful assessment of vascular risk factors should be completed to make sure they are well treated. Carotid bruits or a history of sudden cognitive changes should prompt work-up for cerebrovascular disease with neuroimaging (computed tomography [CT] or preferably magnetic resonance imaging [MRI]) and either carotid ultrasound or magnetic resonance angiogram (MRA).

Delirium is associated with an acute or subacute onset of fluctuating cognitive dysfunction and may be caused by a wide variety of medical conditions and medications. In patients with delirium, a careful history frequently can tease out the temporal relationship between the onset of potentially reversible cognitive symptoms and contributing underlying medical problems or medications. Patients who have had a significant medial illness may exhibit signs of delirium for weeks to months following the inciting illness. Care should be made to avoid making a diagnosis of dementia in the presence of a resolving delirium. Since dementia is a risk factor for delirium, however, the presence of a delirium may suggest an underlying neurodegenerative disorder.

Additional information on safety should be obtained, including inquiries on medication management, driving, kitchen safety, use of firearms or heavy equipment or power tools, wandering, and susceptibility to financial scams. A review of systems should include questions on depression, tremors, falls, visual hallucinations, symptoms of stroke or transient ischemic attack, ataxia, dysphagia, urinary incontinence, waxing and waning level of consciousness, agitation, and personality changes.

The patient's past medical history should be reviewed for medical and psychiatric conditions affecting cognition, including cardiovascular and cerebrovascular disease and associated risk factors, surgical procedures including coronary artery bypass surgery, significant hearing loss, depression, Parkinson disease, traumatic brain injury, seizures, and/or heavy alcohol use. A thorough medication review should be conducted to assess all prescription and nonprescription medications and the association of any medication initiation and/or dose adjustment with changes in cognitive symptoms. Patients should be encouraged to bring in all pill bottles to the clinic visit. The social history should assess the patient's education and occupational baseline, their social support network, and their use of community resources. An accurate assessment of prior or current alcohol or illicit drug use and a sexual history with special attention to sexually transmitted disease (notably syphilis and HIV) risk factors are critical to a correct diagnosis. An assessment of family history of dementia should include age of onset and time course of any symptoms of family members with memory loss.

The physical examination should include assessment of general appearance and a mental status examination (see **Table 66-3**). Careful observation upon interviewing a patient can provide rich information as to their ability to care for themselves, their organizational ability, their ability to provide detail within their conversation, and their comprehension of posed questions and the appropriateness of their response. Ears should be checked for any cerumen accumulation and/or hearing loss. A neurologic examination should screen for focal deficits, gaze palsies, increased muscle tone, cogwheeling, tremors, and ataxia. A detailed review of a comprehensive mental status and neurologic examination in older adults is described in Chapter 11. Cardiac arrhythmias, carotid bruits, or abdominal or femoral bruits may suggest a vascular contribution. The remainder of the physical examination should focus on ascertaining any major medical conditions that could have significant cognitive effects, such as hypoxia or significant active infection.

While there is no consensus as to which is the best cognitive screening tool, there are a variety of cognitive screening tests that have been validated in a primary care setting. Clinicians should identify several with which they are comfortable so that they can be used consistently over time with their patient population. The Mini Mental State

Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Saint Louis University Mental Status Examination (SLUMS) have been widely used in primary care settings. The Alzheimer's Association recommends use of the General Practitioner Assessment of Cognition (GPCOG), the Mini-Cog, or the Memory Impairment Screen (MIS) for cognitive screening related to the Medicare Annual Wellness Visit, as these tests take less than 5 minutes to administer, have good psychometric properties, and can be administered by a variety of health care team members. Informant assessment of changes in patient performance may include the GPCOG informant questionnaire, the Eight-Item Interview to Differentiate Aging and Dementia (AD8), or the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (see **Table 66-3**). If time and resources allow, additional interview time with an informant may identify specific areas of safety concerns and help tailor the management plan.

In adults with high baseline cognitive function, these screening tests may be normal in the presence of obvious functional impairment necessitating referral to a neuropsychologist for more detailed cognitive testing. In individuals with lower educational levels or learning disabilities, cognitive screening tests may suggest impairment, but the history may not suggest any changes in functional status. Thus, it is critical to use age- and education-adjusted norms, and integrate historical information on baseline function to decide if further neuropsychological testing is warranted or if abnormal testing actually reflects the patient's baseline cognitive performance.

Laboratory data can assist in identifying factors that may be contributing to cognitive decline. Rarely do these factors alone account for the overall cognitive changes that lead to the presentation of a patient with significant memory loss. Nevertheless, treating such factors may improve cognitive symptoms in patients with pronounced laboratory abnormalities, numerous comorbid illnesses, or an underlying neurodegenerative process. Recommended laboratory tests include vitamin B_{12}, folate, thyroid-stimulating hormone (TSH), electrolytes, complete blood count, liver enzymes, and 25-OH vitamin D. If symptoms are atypical or if there are specific risk factors, then an HIV test or serologic test for syphilis may be performed. In patients with assumed heavy alcohol use, thiamine (vitamin B_1) levels should be checked. In some European countries, routine assessment of cerebrospinal fluid (CSF) for β-amyloid and tau levels is done as part of the clinical evaluation. While CSF β-amyloid and tau levels may increase diagnostic accuracy of MCI and dementia due to AD, in general they are not recommended for widespread clinical practice as in most cases they do not change a patient's management plan. CSF collection may be used in memory specialty clinics, though, to differentiate between different dementias, including Creutzfeldt-Jakob disease, normal pressure hydrocephalus (NPH), or other less-common causes of neurodegeneration (see **Table 66-4**). Genetic testing for *APOE ε4* genotype is not recommended in routine clinical practice. Testing for *PSEN1*, *PSEN2*, or *APP* genes should be reserved for specialists evaluating cases in which there is a suspicion for familial AD.

In patients with documented cognitive impairment, it is recommended that either a CT or MRI scan of the brain be obtained. If neuroimaging was obtained for another indication prior to the onset of cognitive symptoms, in most cases the patient should be reimaged. Typical findings for AD on neuroimaging can range from a fairly normal scan to focal or diffuse cerebral atrophy. A CT of the head without contrast is usually sufficient to screen for significant cerebrovascular disease, brain tumors, subdural hematoma, or NPH. MRI can provide more information if lacunar infarcts are suspected. MRA may be helpful in identifying significant stenosis that could cause hypoperfusion. In persons with suspected seizure disorder or Creutzfeldt-Jakob disease, an electroencephalogram (EEG) may be considered. Use of FDG positron emission tomography (PET) and amyloid PET imaging to differentiate frontotemporal dementia from AD should be reserved for specialty clinic use. Tau PET imaging is a novel research tool that is not yet approved for clinical practice.

Formulating a Diagnosis

Once a cognitive concern is recognized and delirium is ruled out, the clinician should identify and document any impaired cognitive domains (such as memory, executive function, language, or visuospatial skills) on cognitive testing and any functional loss in the individual's daily activities. Each potentially reversible cause of cognitive impairment should be outlined (ie, medication side effects, alcohol, sleep apnea, depression, or other medical comorbidities) and a plan to address these conditions should be developed. Objective cognitive impairment in the context of a supportive clinical history plus a decline in the individual's daily functional abilities are key elements necessary to differentiate normal cognitive aging and subjective cognitive decline from MCI and dementia. With normal aging, individuals may experience a decline in mental processing speed and may have more difficulty learning new material, but these cognitive changes should not affect their usual function within their daily activities. For example, a healthy older adult may have more difficulty recalling an acquaintance's name or learning a new computer program, but their cognitive testing should be normal and daily functional activities should remain intact. Subjective cognitive decline (SCD) is a

newer term used primarily in research settings to broadly describe symptoms within a pre-MCI stage of neurodegeneration. SCD is currently defined as a self-identified persistent decline in cognitive capacity compared with the individual's previous normal status in a person who still performs in the normal range on standardized cognitive tests. An example would be a business manager with normal performance on cognitive testing who has noticed a subjective decline in her efficiency in managing numerous projects simultaneously despite maintaining a similar work load for many years. It is not yet known what percentage of patients presenting with SCD progress on to MCI and eventually AD. However, identification of patients with SCD allows clinicians to complete a thorough evaluation for other medical, psychological, and medication factors that could contribute to cognitive decline. Patients with SCD should be screened for cognitive dysfunction annually to evaluate for objective evidence of a decline in cognitive performance.

Once a person with SCD develops deficits in at least one cognitive domain, they may meet criteria for MCI (see **Table 66-2**), a symptomatic predementia syndrome noted in up to 15% to 20% of older adults. Individuals with MCI may present with cognitive complaints and describe a variety of methods they use to compensate for these cognitive changes, such as increasing use of lists, calendars, alarms, and other reminders. They maintain their level of function, but are less efficient in doing so. For example, a cabinetmaker who demonstrates impairment in executive function on testing may complain that in order to complete a cabinet work order with his same level of quality workmanship, it now takes him 2 to 3 weeks, whereas a few years ago he could complete such an order in 1 week. Once an individual's cognitive impairment progresses to the point that they can no longer maintain their baseline level of function, they may meet criteria for dementia. In the previous example, as the cabinetmaker's cognition declines he may no longer be able complete a cabinet order at all or may finish it with poorer-quality workmanship. At that point he may have progressed to a dementia.

Approximately 12% to 15% of persons with MCI will progress each year to AD or other forms of dementia. MCI patients who have impairment in memory performance (single-domain amnestic MCI) or in memory plus another cognitive area (multidomain amnestic MCI) are more likely to progress to AD. Older individuals with nonamnestic MCI may be more likely to progress to other forms of dementia, such as frontotemporal dementia, dementia with Lewy bodies, or vascular dementia. Once a diagnosis of dementia is suspected, the clinician must differentiate between various causes of dementia. AD is the most common form of dementia in the United States, accounting for 50% to 90% of all dementia cases. Dementia with Lewy bodies, vascular dementia, and frontotemporal dementia are other common forms of dementia (**Table 66-5**). Details of the clinical and pathologic features of these dementias are covered in Chapter 68. Differentiating AD from other causes of memory loss can help clinicians choose effective therapies, anticipate behavior changes and other potential complications, and provide patients and caregivers information on prognosis.

TABLE 66-5 CLINICAL FEATURES OF COMMON DEMENTIAS

TYPE OF DEMENTIA	ALZHEIMER DISEASE	VASCULAR DEMENTIA	DEMENTIA WITH LEWY BODIES	FRONTOTEMPORAL DEMENTIA
MUST FIRST MEET DIAGNOSTIC CRITERIA FOR DEMENTIA (SEE **TABLE 66-1**)				
Typical Course	Insidious onset and gradually progressive	Acute onset of cognitive impairment with some stabilization (if only one vascular event) and/or stepwise deterioration (if multiple infarcts)	Progressive cognitive decline with fluctuating cognition, attention, and alertness	Insidious onset and gradually progressive
Cognitive Symptoms	Memory is the most commonly affected cognitive domain May also have impairments in executive function, language, and/or visuospatial skills	Various cognitive domains may be affected depending on the location of the clinical stroke(s) and/or severe subcortical cerebrovascular disease	Cognitive symptoms may fluctuate May have prominent impairment in visuospatial ability, attention, and/or executive function	Will have early behavioral disinhibition and apathy (frontal lobe predominance) or early prominent language abnormalities (temporal lobe predominance) Deficits are chiefly noted in executive tasks

				with relative sparing of memory and visuospatial skills
Other Associated Symptoms/Signs	Some patients may have agitation and/or behavioral changes	May or may not have focal neurologic signs on examination Should have evidence of relevant cerebrovascular disease by brain imaging	May have recurrent well-formed visual hallucinations (usually people or animals), parkinsonism (including tremor, rigidity, and postural instability), recurrent falls and syncope, rapid eye movement (REM) sleep behavior disorder, neuroleptic sensitivity, and/or delusions	In behavioral variant frontotemporal dementia, may have early behavioral disinhibition, apathy, loss of empathy, perseverative behaviors, and hyperorality

If a patient does not meet the criteria for AD yet clinical suspicion remains, the clinician may consider obtaining more detailed neuropsychological testing or repeating screening cognitive testing in 6 to 12 months to clarify the diagnosis as the symptoms become more apparent. Persons with suspected MCI should be reassessed on an annual basis to evaluate for progression to dementia. If the symptoms or course of the disease are atypical for AD, the level of functional decline is out of proportion to neuropsychological testing results, or if there are significant behavioral issues that need to be addressed, then referral to a geriatrician, neurologist, or psychiatrist with expertise in dementia is recommended.

Future Diagnostic Tools

Novel biomarkers are continually being investigated for use in the diagnosis of AD and other types of dementia, as well as in identifying predementia syndromes. Many of these tools are still used chiefly in research settings, but are being studied to evaluate their potential role in clinical practice. Current investigations are focusing on specific neuroimaging modalities and biomarkers (including blood and CSF) with strong relationships to clinically relevant outcomes that could be used not only for diagnosis of dementia, but also for identifying asymptomatic persons at risk for cognitive decline. Neuroimaging modalities have shown great promise in documenting not only the late effects of neuronal damage in AD (regional and global cerebral atrophy), but also in identifying preclinical pathology (such as in vivo amyloid and tau imaging on PET) and the functional consequences of such pathology (such as changes in activation patterns on functional MRI or glucose uptake on FDG-PET). CSF levels of Aβ and tau have been shown to predict risk for progression to AD in older adults and persons with MCI. With the recent advances in the safety and acceptability of lumbar punctures, CSF markers may eventually find their way into the widespread clinical diagnostic work-up of preclinical AD. Identification of reliable blood biomarkers has been difficult due to extensive protein binding of Aβ in the periphery. Future research is focusing on how novel biomarkers may be used in combination with cognitive tests to identify which individuals are at greatest risk for AD, who would benefit most from preventive therapies, and how effective these therapies are in modifying the underlying disease process in asymptomatic and symptomatic individuals.

MANAGEMENT

Managing patients with AD involves presentation of the diagnosis, initiation of medical therapy, assessment and treatment of concomitant depression and/or behavioral concerns, identification of a social support network, education of patients and caregivers, provision of caregiver support, and initiation of appropriate safety measures.

Presenting the Diagnosis

Presenting the diagnosis of AD to a patient is difficult, as it may generate significant emotional responses from the patient and their family and trigger fear of future demise. Frequently, patients and family members suspect the diagnosis before it is presented, but how they respond to the news depends on personal coping mechanisms, cultural

influences, family dynamics, and their preconceived understanding of AD. Clinicians may help patients and families adjust to this diagnosis by using an empathetic, yet honest approach and by providing them with educational and support resources, including those provided by agencies such as the Alzheimer's Association and the National Institute on Aging Alzheimer's Disease Education and Referral (ADEAR) Center. In addition, the clinician should emphasize the goals of diagnosing AD in order to take steps to protect the patient's memory, delay the progression of the disease, and to maintain the person's safety. It is widely recommended to tell both the patient and family the diagnosis using the term "Alzheimer disease," thus, providing patients and families with a starting point for education. Encouraging both persons with the disorder and caregivers to utilize resources such as local support groups, community resources, and national Alzheimer organizations is an important part of the patient management plan.

Drug Therapy and Nonpharmacologic Therapy

Acetylcholinesterase inhibitors (AChEIs) are the mainstay of therapy for AD. AChEIs increase the levels of the neurotransmitter acetylcholine in neuronal synapses, thereby enhancing cholinergic activity in the affected brain regions. Although 18% to 48% of persons may experience improvements in cognition after taking these medications, the majority of patients do not have any noticeable improvement, but instead experience a plateau or slowing of their rate of cognitive decline. While prior studies raised questions as to the cost-effectiveness of treating AD patients with AChEIs, newer studies integrating generic drug cost estimates have demonstrated that these drugs are cost-effective. Delaying the progression of cognitive decline may lead to improvements in quality of life, reduced caregiver burden, and decreased economic cost associated with long-term care. AChEIs have not been shown to be effective in delaying progression from MCI to AD and, thus, are chiefly recommended for use in patients who already have a diagnosis of dementia.

Three FDA-approved AChEIs are actively prescribed in the United States: donepezil (Aricept), galantamine (Razadyne), and rivastigmine (Exelon) (**Table 66-6**). While all three of these compounds are available as generic medications, some specific long-acting formulations and solutions of these drugs are still under patent (see **Table 66-6**) and, thus, are not yet available in generic form. In general, the most common adverse effects associated with AChEI use are nausea, anorexia, and diarrhea. Bradycardia, atrioventricular (AV) nodal block, and syncope are additional potentially serious adverse side effects. Thus, it is recommended that patients are started on a low dose of the medication with dose increases approximately every 2 months until a therapeutic dose is achieved (see **Table 66-6**). Gastrointestinal side effects may be alleviated by taking the medications with food. Sleep disturbances are also common, and may improve with altering the dosing schedule.

TABLE 66-6 FDA-APPROVED MEDICATIONS FOR THE TREATMENT OF ALZHEIMER DISEASE[a]

MEDICATION	INDICATION	AVAILABLE FORMULATIONS	DOSE RANGE AND TITRATION	ADVERSE EFFECTS
ACETYLCHOLINESTERASE INHIBITORS				
Donepezil (available as generic donepezil or Aricept)	Mild-to-moderate AD	• 5- and 10-mg tablets • 5- and 10-mg oral disintegrating tablets	• 5–10 mg once daily at bedtime • May be taken with or without food • Oral disintegrating tablets should be dissolved on tongue and followed with water • Begin at 5 mg once daily for 4–6 weeks, then increase to 10 mg daily as tolerated • Effective dose: 5–10 mg daily	• Bradycardia or heart block, syncope, nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia
Donepezil (available as generic donepezil in 10-mg tablets or Aricept in 10- or 23-mg tablets)	Moderate-to-severe AD	• 10- and 23-mg tablets • 10-mg oral disintegrating tablets	• 10 mg once daily at bedtime • If the clinician thinks there is a strong indication for increased dosing, a patient who has been on 10 mg for 3 mo may increase to the 23-mg tablet daily • 23-mg tablets should not be split, crushed, or chewed • Effective dose: 10 or 23 mg daily	• Bradycardia or heart block, nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia

Galantamine (available as generic galantamine, galantamine ER, Razadyne, or Razadyne ER)	Mild-to-moderate AD	• 4-, 8-, and 12-mg immediate-release tablets • 4 mg/mL immediate-release oral solution • 8-, 16-, and 24-mg extended-release capsules	**Immediate-Release Tablets or Oral Solution:** • 4–12 mg twice daily • Should be taken with meals • Begin at 4 mg twice daily for at least 4 wk then increase to 8 mg twice daily for at least 4 wk then 12 mg twice daily as tolerated • For patients with moderate hepatic or renal impairment (creatinine clearance 9–59 mL/min), dose should not exceed 16 mg/d • Should not be used in patients with severe hepatic or renal impairment (creatinine clearance < 9 mL/min) **Extended-Release Capsules:** • 8–24 mg once daily • Should be taken in the morning with food • Begin at 8 mg once daily in the morning for at least 4 wk then increase to 16 mg once daily in the morning for at least 4 wk then 24 mg once daily as tolerated • Conversion from tablets (or oral solution) to extended release should occur at the same daily dosage with the last dose of the tablets (or oral solution) occurring in the evening and the extended-release formulation starting the next morning • Effective dose: 16–24 mg daily	• Nausea, vomiting, diarrhea, dizziness, headache, decreased appetite, weight loss
Rivastigmine (available as generic rivastigmine capsules or Exelon capsules, oral solution, or transdermal patch)	Mild-to-moderate AD	• 1.5-, 3-, 4.5-, and 6-mg capsules • 2 mg/mL oral solution • 4.6 mg/24 h and 9.5 mg/24 h patches	**Capsules or Oral Solution:** • 1.5–6 mg twice daily • Should be taken with meals • Oral solution may be taken directly or mixed with beverage • Begin at 1.5 mg twice daily for minimum of 2 wk then increase to 3 mg twice daily for minimum of 2 wk then 4.5 mg twice daily for minimum of 2 wk then 6 mg twice daily as tolerated • Patients with mild or moderate hepatic impairment or moderate-to-severe renal impairment may be able to only tolerate lower doses • Effective dose: 6–12 mg daily **Patch:** • Begin at 4.6 mg/24 h patch daily for 4–6 wk then increase to 9.5 mg/24 h patch daily as tolerated • Apply patch on intact skin for 24-h period; replace with a new patch every	• Nausea, vomiting, anorexia, dyspepsia, weakness

			24 h • Effective dose: 9.5 mg/24 h	
Rivastigmine patch (available as Exelon transdermal patch)	Mild, moderate, and severe AD	• 4.6 mg/24 h, 9.5 mg/24 h, and 13.3 mg/24 h patches	**Patch:** • Begin at 4.6 mg/24 h patch daily for a minimum of 4 weeks then increase to 9.5 mg/24 h patch daily as tolerated; may increase to maximum of 13.3 mg/24 h after minimum of 4 wk • Apply patch on intact skin for 24-h period; replace with a new patch every 24 h • Consider dose adjustments in mild-to-moderate hepatic impairment and low (< 50 kg) body weight • If switching to an Exelon patch from rivastigmine capsules (or oral solution), a patient on a total daily dose of < 6 mg of oral rivastigmine can be switched to the 4.6 mg/24 h patch while a patient on a total daily dose of 6–12 mg can be switched to the 9.5 mg/24 h patch • If switching, apply the first patch on the day following the last oral dose • Effective dose: 9.5 mg/24 h or 13.3 mg/24 h	• Nausea, vomiting, diarrhea
N-METHYL-D-ASPARTATE (NMDA) RECEPTOR ANTAGONIST				
Memantine (available as generic memantine tablets or Namenda tablets or oral solution)	Moderate-to-severe AD	• 5- and 10-mg tablets • 2 mg/mL oral solution	**Tablets or Oral Solution:** • 10 mg twice daily • May be taken with or without food • Begin at 5 mg once daily for 1 wk then increase to 5 mg twice daily for 1 wk then 10 mg in the morning and 5 mg in the evening for 1 wk then 10 mg twice daily as tolerated • In patients with severe renal impairment (creatinine clearance 5–29 mL/min) target dose is 5 mg twice daily • Effective dose: 20 mg daily	• Dizziness, headache, confusion, constipation
Memantine extended release (available as Namenda XR)	Moderate-to-severe AD	• 7-, 14-, 21-, or 28-mg capsules	• Patients on memantine 10 mg twice daily may be switched to Namenda XR 28 mg daily the day following the last dose of 10-mg memantine • Patients with severe renal impairment (creatinine clearance of 5–29 mL/min) may be switched from memantine 5 mg twice daily to Namenda XR 14 mg once daily • May be taken with or without food • Capsules can be taken intact or may be opened and sprinkled on applesauce • Effective dose: 28 mg daily	• Headache, diarrhea, dizziness

COMBINATION THERAPY (ACETYLCHOLINESTERASE INHIBITORS AND NMDA RECEPTOR ANTAGONIST)				
Namzaric (memantine HCl ER and donepezil HCl) capsules	Moderate-to-severe AD	• 14-mg memantine HCl ER/10-mg donepezil HCl or 28-/10-mg capsules	• Once patient stabilized on a daily dose of memantine ER (10 mg twice daily or 28 mg ER once daily) and donepezil 10 mg daily may switch to Namzaric 28-/10-mg capsule once a day in the evening • Patients with severe renal impairment on memantine HCl (5 mg twice daily or 14 mg ER once daily) and donepezil HCl 10 mg daily may be switched to Namzaric 14-/10-mg capsule once a day in the evening • May be taken with or without food • Capsules can be taken intact or may be opened and sprinkled on applesauce • Capsules should not be divided, chewed, or crushed	• Headache, diarrhea, dizziness, anorexia, vomiting, nausea, ecchymosis

[a]Information obtained from prescribing information documents.

Memantine (Namenda) is an FDA-approved medication for use in moderate-to-severe AD. Memantine is an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. At high concentrations, memantine can inhibit mechanisms related to learning and memory, but at lower concentrations, it can preserve or enhance memory in animal models of AD. Memantine can protect against the excitotoxic destruction of cholinergic neurons and may inhibit β-amyloid production. In persons with moderate-to-severe AD, memantine may slow the progression of cognitive decline. In addition, studies support that use of memantine was well tolerated and led to better outcomes on measures of cognition, activities of daily living, and behavior. Additional studies are needed before memantine can be recommended for earlier stages of AD. In patients with moderate-to-severe AD, combined treatment with a cholinesterase inhibitor and memantine has not been shown to be superior to treatment with either agent alone with regards to cognitive, functional, and behavioral outcomes. In patients who do not tolerate cholinesterase inhibitors due to gastrointestinal side effects or bradycardia, memantine may be used as first-line therapy. With use of either AChEIs or memantine, clinicians should educate families on what to expect with use of the medications, namely that they work to delay the progression of symptoms and not to significantly improve cognition. Consideration should be given to the modest expected benefit and monthly cost of both types of medications.

Currently there are no FDA-approved disease-modifying therapies available, but research is under way to identify pathways that could serve as targets for such therapies. Numerous disease mechanisms are under investigation to identify novel therapeutic targets for AD. Agents targeting different steps of β-amyloid metabolism are in various stages of development and include β-secretase inhibitors, γ-secretase inhibitors and modulators, α-secretase activators, and agents that work against β-amyloid aggregation. Many active and passive anti–β-amyloid vaccine clinical trials are underway, although none have yet shown beneficial results in slowing disease progression in AD patients. In addition to targeting β-amyloid pathways, novel research is focusing on the effects of inhibitors of tau phosphorylation and aggregation and the stabilization of microtubules. Other potential therapeutic agents are directed toward inflammation and oxidation, insulin signaling, mitochondrial function, and nerve growth factor signaling.

Clinical trials have not conclusively shown that treating vascular risk factors delays the development or progression of AD. However, aggressive treatment of vascular risk factors in many patients with memory complaints, including those associated with AD, may be warranted. Vascular risk factor modification has known cardiovascular benefits that may lead to reduction in cerebrovascular disease, stroke, myocardial infarction, and coronary artery bypass grafting—factors strongly linked to cognitive decline. Trials are under way to clarify if vascular risk factor reduction and improved cerebral perfusion modify the course of AD. Until the completion of such trials, clinicians should follow established cardiovascular prevention guidelines for patients presenting with memory complaints, taking into account the patient's comorbid illnesses, quality of life, treatment costs, and life expectancy.

Evidence also supports that encouraging AD patients to engage in nonpharmacologic interventions, including

physical activity and exercise, mentally stimulating activities, and social activities, may lead to cognitive benefits. Depending on an individual's physical abilities, comorbid illness, social situation, and interests, clinicians should encourage AD patients and persons with cognitive impairment to seek out opportunities for exercise and activities that promote use of their intact areas of cognitive function. For example, an AD patient with prominent language deficits but intact visuospatial skills may find crosswords or word search puzzles very frustrating, but may enjoy playing checkers or painting birdhouses. Such activities may need to be adjusted over time to account for progressive cognitive changes.

Behavioral Management

Noncognitive neuropsychiatric symptoms of dementia include aggression, agitation, depression, anxiety, delusions, hallucinations, apathy, and disinhibition. Such behaviors may be more distressing to family and caregivers than the actual memory decline. Neuropsychiatric symptoms may be managed by nonpharmacologic as well as pharmacologic interventions. Nonpharmacologic therapies should in general be explored prior to using pharmacologic therapy, unless the person's agitation threatens his or her safety or living situation.

In order to assist clinicians in identifying nonpharmacologic treatment options for challenging behaviors, a stepwise algorithm was developed by the Detroit Expert Panel utilizing the mnemonic DICE: *D*escribe, *I*nvestigate, *C*reate, and *E*valuate. This algorithm encourages caregivers to *describe* to the clinician the presenting behavior in great detail, including antecedents to the behavior, the environment, patterns of occurrence, contributing factors, and the degree of distress to the patient and the caregiver. The provider then *investigates* possible underlying causes of the problem behavior (ie, medication side effects, pain, poor sleep, boredom, etc) and works with the caregiver and health care team members to *create* a treatment plan (ie, change medications, control pain, optimize sleep hygiene, identify meaningful tasks for the patient, etc). This is followed by an *evaluation* phase to see if the plan has been implemented by the caregiver and whether it is effective.

Other nonpharmacologic interventions that may decrease behavioral problems include increasing activity (that highlight preserved capabilities and previous interests), music therapy, exercise, removing extraneous noise (eg, television) and clutter from the environment, simplifying tasks, and developing a daily routine (including a set sleep-wake time). Communication strategies to optimize behavioral response should be provided to caregivers, such as allowing the patient sufficient time to respond to questions, providing simple one-step commands, offering simple choices (two at a time), and promoting use of a reassuring tone. Wandering symptoms typically do not respond to pharmacologic therapy. Taking patients for a walk or giving them busy tasks to do may help reduce wandering. Additional safety measures for patients who wander include use of more complex door latches, door alarms, and the Safe Return Program through the Alzheimer's Association/MedicAlert.

After nonpharmacologic measures have been tried, consideration may be given to use of pharmacologic interventions, taking into account potential risks associated with these medications. Selective serotonin reuptake inhibitors (SSRIs) may reduce symptoms of agitated depression and/or sexual inappropriateness. Low-dose trazodone (25–50 mg nightly as needed) may help establish better sleep-wake cycles. Atypical antipsychotics may reduce agitation, but are not FDA approved for use in dementia patients and have been associated with increased risk of stroke and death. Randomized controlled trials evaluating antipsychotics for agitation associated with dementia suggest only modest efficacy in symptom reduction with active treatment compared to placebo. Several individual trials have yielded negative results and others have suggested that side effect burden may negate the clinical effectiveness of these agents. Studies supporting the use of carbamazepine, divalproex, or valproate for management of agitation in dementia have demonstrated only modest benefits at best and these drugs are associated with significant side effects. Referral to a multidisciplinary memory disorder clinic or a geriatric psychiatrist is appropriate for patients with significant behavioral concerns. More information is dedicated to this topic in Chapter 74.

Safety Management

Reviewing common safety concerns in persons with dementia may help identify significant risks and provide an opportunity for educating family members and caregivers on what areas to monitor closely and what safeguards to take to protect the person with AD. Some patients may require further evaluation to assess driving safety, which can be done through some occupational therapy departments, local driving schools, state Department of Motor Vehicles, or other similar agencies. Pill boxes, electronic reminders, or other similar medication planners may facilitate correct administration of medications and allow family or caregivers to help in setting up the medications properly. Other safety concerns, such as proper use of the stove, woodworking equipment, and access to firearms, should be discussed

and appropriate supervision and/or limitations be arranged.

Caregiver Support

Evidence is accumulating that the effects of AD are felt not only by the patient but also by the caregivers. Caregivers have increased depression, work absence, and health problems compared to those not caring for a family member with dementia. Clinicians and health care team members should direct caregivers toward educational resources on the disease, practical tips on helping someone with AD optimize their function, effective communication strategies, legal and financial planning, and the importance of caregiver health and social support. Use of respite services from family, friends, neighbors, home health agencies, and local adult day centers may allow for caregivers to take the appropriate time needed to maintain their own health and social connections. Local support groups allow for caregivers to share ideas and experiences. Other initiatives such as memory cafés, dementia-friendly communities, and online resources may provide caregivers important support and interaction.

PREVENTION

Currently there are no established preventive therapies for AD and no approved medications to treat MCI. Evidence supports that therapies that either delay or prevent the onset of AD may need to be started in midlife in high-risk populations in order to significantly influence the onset and course of the disease. As the underlying pathologic changes that eventually lead to clinical AD begin decades before the onset of symptoms, primary prevention trials with conversion to AD as their primary outcome will be costly and time consuming. Integrating biomarkers with strong relationships to clinically relevant outcomes into such primary prevention trials may allow for earlier identification of disease-modifying effects of potential preventive therapies. Given the multifactorial nature of AD, future preventive strategies will most likely target a variety of mechanisms related to disease progression, similar to those used in cardiovascular disease prevention. Some potential prevention therapies currently under investigation include antiamyloid therapies, vascular risk factor modification, anti-inflammatory medications, antioxidants, and lifestyle interventions such as exercise, social engagement, and cognitive stimulation.

SPECIAL ISSUES

Comorbidity

Managing comorbid illnesses in a person with AD can be challenging. Patients may forget to take important medications for comorbid conditions which, in turn, may exacerbate confusion. Persons with AD may not be able to remember symptoms related to other comorbid illnesses, such as recent episodes of chest pain, shortness of breath, or localization of arthritis pain. Thus, it is important to educate families and caregivers on how they can best assist their loved one in managing their comorbid illnesses. For example, a caregiver of an AD patient with diabetes may need to directly observe insulin administration and meal intake to maintain good glucose control. An AD patient with significant chronic pain may need their caregiver to write down the time of day that they become more agitated with the goal of optimizing the timing of their pain medications. Each management plan will need to be tailored to the AD patient's comorbid illnesses and social situation, utilizing community resources as available.

Persons with dementia are more likely to experience delirium in response to medical illness or surgery. Thus, educating families that acute episodes of confusion may suggest a harboring infection or other illness may help families seek out appropriate medical care when watching for behavioral changes. Caregivers should be forewarned that an AD patient is at increased risk for delirium following surgical procedures and that interventions such as avoiding anticholinergic and sedative hypnotic medications, maintaining good sleep-wake cycles, optimizing pain control, using hearing aids and glasses as appropriate, and establishing daytime activities may help reduce risk of escalating postoperative delirium (see also Chapter 47).

Care Settings

Ensuring a safe living environment is a high priority for patients with any form of dementia including AD. Patients living in their own house or independent apartment may need additional safety measures implemented around their home, such as by posting emergency numbers on the wall, using timers to remind them to turn the stove off, using

medical alert systems, and optimizing use of home care services to assist with tasks such as bathing, cleaning, meal preparation, transportation, and medication administration. Once patients can no longer identify what to do in an emergency situation, then 24-hour supervision is recommended. Through partnering with family and friends and use of community resources, some individuals with AD are able to stay in their own home their entire lives. However, a variety of social circumstances, medical or behavioral issues, or economic limitations may necessitate that a person with AD move to a more structured, supervised setting. The choice of setting (eg, assisted living facility, skilled nursing facility, or locked dementia unit) varies from patient to patient and depends on the degree of cognitive impairment, cultural preferences, comorbid illnesses, economic resources, and behavioral and safety concerns.

Palliative and End-of-Life Care

Upon diagnosis of AD, many patients and families have questions as to what to expect in the years ahead. Since the course of AD progression may depend not only on genetic and environmental factors but also comorbid medical conditions, the rate of decline is difficult to predict. Once an AD patient is medically treated and after all potentially reversible contributing factors have been addressed, obtaining repeat cognitive testing may give the clinician an idea of the trajectory of the individual's decline and help inform the family on what to expect in the years ahead. Providing information to family and caregivers early in the disease course on end-of-life planning may help smooth this difficult transition later in the illness. Use of respite services, home health aides or family members, or palliative care may help the person with AD stay in the home longer. If their social network cannot support the patient as care needs increase, then nursing home placement or hospice care may be necessary. Caregivers of AD patients may go through feelings of guilt when a loved one is moved from home to a facility, so appropriate support should be provided. Capacity for decision making should be assessed regularly throughout the course of the illness with appropriate activation of advanced care planning when the patient is no longer able to make their own health care decisions.

Advanced dementia is associated with poor nutritional intake, urinary incontinence, skin breakdown, and infections such as pneumonia. Palliative and end-of-life care services are increasingly being used for patients with end stages of AD and other forms of dementia. As the disease progresses, patients may reach a point when they are no longer able to express their needs. When patients are at a stage of disease where they no longer are able to engage meaningfully in social interactions or participate in self-care, then consideration should be given to discontinuing cholinesterase inhibitors and/or memantine therapy. At that point, medication regimens may be simplified to focus on therapies that optimize patient comfort. As swallowing difficulties develop, modified diets and one-on-one feeding may be needed to maintain a patient's nutritional status. Feeding tubes are not recommended in end-of-life for patients with advanced AD as they do not prolong survival or increase comfort and have not been shown to reduce the risk of pressure sores, infection, or aspiration.

Hospice care can help with symptom management late in the course of the illness. Caregiver involvement in Alzheimer support groups can provide comfort during the unique grieving process related to dementia, as family and caregivers watch the cognitive and personality transformations in their family member with AD.

SUMMARY

AD is the leading cause of dementia with 44 million individuals currently affected worldwide. Unless effective preventive strategies are identified, it is anticipated that the prevalence of AD will double every 20 years. Given the widespread prevalence of AD and its impact on the well-being and quality of life of patients and their caregivers, it is critical for clinicians to be well-trained in identifying early cognitive changes, differentiating AD from other common medical and psychiatric conditions, diagnosing the disorder, and developing an effective management plan with their patients and families. Knowledge and use of educational and community resources can provide additional culturally tailored support to AD patients and their caregivers. In most situations, AD can be effectively diagnosed and managed within a primary care setting, through careful history-taking, a physical examination, and brief cognitive testing. Ancillary laboratory tests and neuroimaging can help differentiate between various causes of memory loss and different types of dementia. AD treatment involves not only pharmacologic therapy with cholinesterase inhibitors and NMDA receptor antagonists, but also careful assessment of safety, behavioral concerns, and education for the patient, family, and other caregivers. While preventive therapies have not yet been established, novel therapies are under investigation to delay or preferably arrest the development and progression of AD. Clinicians are encouraged to be active champions of educational and research efforts to improve early diagnosis, treatment, and prevention of AD by promoting clinical research participation among willing patients and families. Annual updates on large-scale initiatives

such as the United States National Alzheimer's Project Act (NAPA), Alzheimer's Disease International's World Alzheimer Report, the Alzheimer's Association's Facts and Figures, and other international collaborations and publications will keep clinicians informed on global efforts to optimize early diagnosis and effective care of patients at risk for AD and related dementias.

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Chapter 67

Parkinson Disease and Related Disorders

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Learning Objectives

- Learn the epidemiology, pathobiology, clinical manifestations, and genetics of Parkinson disease (PD).
- Understand the latest terminology and major clinical differences between parkinsonism and Parkinson disease.
- Learn the common presenting features of diseases, such as progressive supranuclear palsy, corticobasal degeneration (CBD), and multiple system atrophy that mimic and require differentiation from Parkinson disease.
- Acquire new knowledge about the latest tests to diagnose Parkinson disease and indications and adverse effects of cutting-edge therapies, including dopaminergic and nondopaminergic agents and surgical treatments for Parkinson disease.
- Understand the significance of exercise, physical activity, and supportive care for management of patients with Parkinson disease.

Key Clinical Points

1. **Parkinsonism includes a constellation of motor and nonmotor symptoms, and Parkinson disease is the most common cause of parkinsonism. Other causes include medications, structural lesions of the brain, and diseases that present with extrapyramidal manifestations**
2. **The gold standard of making a diagnosis of Parkinson disease remains autopsy that shows Lewy bodies in substantia nigra.**
3. **Parkinson disease affects more than 1 out of every 100 individuals over the age of 60, and is more common in men.**
4. **Patients with Parkinson disease almost always respond to dopaminergic medications, while those with parkinsonism generally do not. The symptoms most responsive to treatment include bradykinesia and rigidity.**
5. **Besides symptoms, dopamine transporter single-photon emission computed tomography (SPECT) imaging helps to diagnose Parkinson disease and differentiate it from essential tremor.**
6. **Amantadine improves symptoms in approximately two-thirds of patients and is the only effective treatment for dyskinesia.**
7. **Deep brain stimulation (DBS) surgery is typically indicated for patients with difficult motor complications and medication-refractory tremors.**

DEFINITION AND TERMINOLOGY

Parkinsonism is the unifying term that describes a constellation of motor and nonmotor neurologic features. Parkinsonism can be defined as a variable combination of six specific, independent motor features: bradykinesia (slowness of movement), tremor at rest, rigidity, loss of postural reflexes, flexed posture, and freezing of gait (where the feet are transiently “glued” to the ground). Of these features, bradykinesia—either affecting the arms or legs

("appendicular bradykinesia") or midline structures including the trunk, head and neck, oropharynx, or eyes ("axial bradykinesia")—is the most central element of parkinsonism and is caused by loss of dopaminergic neurons in a midbrain structure called the substantia nigra pars compacta (SNpc) responsible for innervating a group of critical motor nuclei within the deep portions of the brain collectively labeled the basal ganglia.

There are multiple causes of parkinsonism. The most common and extensively studied is idiopathic Parkinson disease (PD), which is estimated to affect approximately 1% to 2% of people over the age of 60. PD is a complex disorder with a wide variety of clinical presentations whose exact pathogenesis is incompletely understood. The eponymous name "Parkinson disease" was coined following the publication of "An Essay on the Shaking Palsy" by the British surgeon James Parkinson in 1817. In more recent years, the term "Parkinson disease" has been favored over "Parkinson's disease" given that Dr. Parkinson neither personally contracted nor "owned" the disease that over time has been associated with his surname.

There are numerous causes of parkinsonism, almost all of which becoming increasingly common with advancing age. These include (a) secondary parkinsonism caused by toxins, medications, or structural lesions in the brain; (b) atypical parkinsonian conditions including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal syndrome (CBS), and dementia with Lewy bodies (DLB); and (c) more rare neurodegenerative conditions with heterogeneous manifestations that can include parkinsonism such as juvenile Huntington disease, spinocerebellar ataxia type 3, and Wilson disease (**Table 67-1**).

TABLE 67-1 CLASSIFICATION OF THE PARKINSONIAN STATES

Primary parkinsonism (Parkinson disease)
Sporadic
Known genetic etiology (see **Table 67-2**)
Secondary parkinsonism (environmental etiology)
Drugs
Dopamine receptor blockers (most commonly antipsychotic medications)
Dopamine storage depletors (reserpine)
Postencephalitic
Toxins—Mn, CO, MPTP, cyanide
Vascular
Brain tumors
Head trauma
Normal pressure hydrocephalus
Parkinsonism-plus syndromes
Progressive supranuclear palsy (PSP)
Multiple system atrophy (MSA)
Corticobasal syndrome (CBS)
Dementia with Lewy bodies (DLB)
Heredodegenerative disorders
Alzheimer disease
Wilson disease
Huntington disease
Frontotemporal dementia on chromosome 17
X-linked dystonia parkinsonism

It should be noted that there are a variety of overlapping and often outdated names frequently used to describe certain parkinsonian conditions that can be confusing to the nonspecialist. For example, the term olivopontocerebellar atrophy (OPCA) was formerly used to describe a collection of neurodegenerative conditions including MSA and some other progressive neurodegenerative cerebellar disorders. Similarly, the terms Lewy body dementia (LBD) and DLB

are used interchangeably to refer to the same disorder. Finally, the term “diffuse Lewy body disease” is also used loosely by both clinicians and pathologists to describe the topographical distribution of postmortem findings that can be seen in DLB.

EPIDEMIOLOGY

Like other insidiously developing progressive disorders of aging, there are inherent challenges in identifying the true prevalence of PD. The diagnosis of PD is typically made on the basis of clinical examination. There are numerous adjunctive clinical diagnostic measures, including a documented favorable response to a trial of dopaminergic medications, that can enhance certainty in the diagnosis of PD but these may not be used in large epidemiologic studies. The gold standard for making the diagnosis of PD remains autopsy where characteristic intracellular cytoplasmic inclusions of α-synuclein called Lewy bodies are seen in the SNpc and other brain and nervous system regions. Longitudinal clinical postmortem studies suggest that 10% to 20% of patients thought to have PD in life will have alternative diagnoses on autopsy. Interestingly, midbrain Lewy bodies are also seen on autopsy in about 20% of older individuals without a known history of parkinsonism suggesting that PD may be either underdiagnosed or not yet have manifested the typical motor manifestations of the disease during life. Alternatively, these individuals may have so-called prodromal DLB.

Many epidemiologic studies of PD identify cases through medical records rather than through door-to-door examinations of well-defined populations. Incidence rates of PD vary not only by age but also by gender. Estimates across all possible ages and genders tend to range from 4.5 to 19/100,000 person-years reflecting differences in ascertainment methods and biological susceptibility. Among individuals over the age of 60, incidence rates range from 27.2 to 107.2 cases/100,000 person-years. The median age of onset is in the early 60s and there is increasing risk for PD seen with each successive decade of life.

Since most people with PD live many years before death, prevalence rates of PD are higher than the incidence rates. Across all age ranges and genders, PD is thought to affect between 100 and 200 out of every 100,000 people. For people over the age of 60, PD is thought to affect slightly more than 1 out of every 100 individuals. Parkinson disease is about 1.5 times more common in men than in women for reasons that may reflect differences in underlying biological susceptibility.

In most cases, PD is not a direct cause of death and frequently goes unmentioned on death certificates. Death in individuals with PD is occasionally due to secondary acute comorbidities seen in patients with mobility restrictions including aspiration pneumonia, traumatic falls, deep vein thrombosis, and pulmonary embolus. Mortality rates in PD are slightly higher in comparison to age- and gender-matched populations, although differences in life expectancy are most profound in individuals with early-onset PD. Individuals with PD and dementia also have a higher risk of death. PD patients who follow with a neurologist have a lower likelihood of death compared to those whose PD is managed exclusively by primary care physicians.

PD is caused by a complex interaction between genetic and environmental risk factors. Nevertheless, to date, relatively few environmental risk factors for sporadic PD have been identified. Exposure to pesticides containing the pyridine compound 1-methyl-4-phenyl-1,2,3,6-tetrahydropyradine (MPTP), industrial solvents, and heavy metals including manganese have all been suggested to associate with a higher risk of incident PD. Higher incidence in rural areas has been associated with farming-related exposures to pesticides and/or drinking from well water. There are several factors that have been consistently demonstrated to have an inverse relationship with PD risk including cigarette smoking, caffeinated coffee consumption, high plasma levels of uric acid, and endogenous estrogen exposure. The biological principles that mediate these associations are incompletely understood.

Although over 90% of cases of PD are considered sporadic, there is a growing understanding of the influence of primary monogenetic genetic causes of PD. Mendelian inheritance is implicated in several PD risk factor genes, all of which share a common naming schema as *PARK* genetic loci. To date, there are 20 *PARK* genes (**Table 67-2**). The most notable of these include *PARK1* or α-synuclein mutations, which were the first genetic variant identified to cause familial parkinsonism. There are now several identified autosomal dominant and autosomal recessive causes of PD some of which show variable penetrance depending on the underlying mutation. More recently, common haplotypes of genes known to play a role in other neurodegenerative conditions have been recognized as incremental risk factors for PD. These include the *MAPT* gene encoding the tau protein implicated in neurofibrillary tangles of Alzheimer disease (AD). Allelic variations including point mutations and deletions in the *GBA* gene, whose loss of function is implicated in causing impaired lysosomal activity in Gaucher disease, have also been linked to cases of early-onset PD,

particularly among individuals of Ashkenazi Jewish ancestry.

TABLE 67-2 GENETIC FORMS OF PRIMARY PARKINSONISM

NAME	GENE SYMBOL	PROTEIN	CHROMOSOME
Autosomal Dominant Transmission			
PARK1/PARK4	*SNCA*	α-Synuclein	4q21.3
PARK3	Unknown	Unknown	2p13
PARK5	*UCH-L1*	Ubiquitin C-terminal hydrolase-L1	4p14
PARK8	*LRRK2*	Leucine-rich repeat kinase 2	12p12
Dopa-responsive dystonia		GTP cyclohydrolase 1	14q22.1–q22.2
PARK13	*HTRA2*	High-temperature requirement protein	2p13
PARK17	*VPS35*	Vacuolar protein sorting 35	16q11
PARK18	*EIF4G1*	Eukaryotic translation initiating factor 4 gamma	3q27
Autosomal Recessive Transmission			
PARK2	*PRKN*	Parkin (ubiquitin ligase)	6q25
PARK6	*PINK1*	PTEN-induced kinase 1 (PINK1)	1p36
PARK7	*DJ-1*	DJ-1	1p36
PARK9	*ATP13A2*	ATPase	1p36
PARK10			1p32
PARK14	*PLA2G6*	Phospholipase A2, group 6	22q13
PARK15	*FBX07*	F-box protein 7	22q12
PARK19	*DNAJC6*	DNAJC6	1p32
PARK20	*SYNJ1*	Synaptojanin 1	21q22
Other Associated Genes			
	GBA	β-Glucocerebrosidase	1q21
PARK10	Unknown	Unknown	1p32
PARK11	*GIGYF2*	Unknown	2q36
PARK12	Unknown	Unknown	Xq21
PARK16	Unknown	Unknown	1p32

Atypical parkinsonian conditions including PSP, MSA, and CBS manifest with a prevalence rate that is roughly 5% to 10% of PD prevalence. DLB is more common than the other atypical parkinsonisms, although prevalence estimates of DLB are confounded by its significant clinical and pathologic overlap with other common neurodegenerative conditions including PD and AD. Risks for developing PSP and CBS have been linked to allelic variation in the *MAPT* gene, and mutations in the *GBA* gene are seen with increased frequency in both PD and DLB.

PATHOPHYSIOLOGY

PD is most strongly associated with two specific postmortem hallmarks: (a) the development of cytoplasmic, eosinophilic inclusions of the misfolded synaptic protein α-synuclein called Lewy bodies and (b) the loss of SNpc

dopaminergic neurons innervating the striatum.

Nigrostriatal dopaminergic denervation is seen as part of the spectrum of normal aging, albeit to a more mild degree than is seen in PD. It is estimated that with every year of life after the third decade, we lose 0.5% to 1% of nigrostriatal nerve terminals, including the dorsal putamen a structure charged with mediating speed and precision of motor movements. By the time motor symptoms of PD are present, however, the posterior putamen has undergone profound denervation equating to the loss of over 60% to 80% of dopaminergic terminals. Although in this way, PD could be conceptualized as an accelerated form of nigrostriatal aging, the nerve terminal loss in PD has a particular predilection for the posterior and dorsal putamen compared to more anterior and ventral striatal regions. In contrast, normal aging is associated with more mild and diffuse striatal losses of nerve terminals.

Within the striatum, dopaminergic innervation is organized into two broad conceptual pathways: the direct pathway and the indirect pathway. Although this model is continually updated, it has formed the scientific basis accounting for a number of advances in neurobiology including the development of deep brain stimulation. In this conceptual model, the striatum is viewed as a series of interconnected relay nuclei that upregulate or downregulate inputs from both the cortex and deep nuclei of the brain stem and spinal cord, yielding a well-regulated motor output to the cortex, thalamus, and brainstem pedunculopontine nucleus, which is part of the mesencephalic locomotor center.

The “direct pathway” is a monosynaptic, D1 receptor–mediated excitatory connection between the striatum and the globus pallidus pars interna (GPi) and substantia nigra pars reticulata (SNpr). When stimulated, these latter two nuclei lead to an increase in motor output via thalamocortical afferents. The “indirect pathway” is a polysynaptic pathway that depends on inhibitory D2 receptors affecting the globus pallidus pars externa (GPe) and the subthalamic nucleus (STN), which then innervate the GPi/SNpr. The net effect of the indirect pathway is to suppress motor output via thalamocortical afferents. Like many models of complex biological phenomena, the direct and indirect pathway model is an oversimplification of more nuanced network and has been challenged and revised over time. It nevertheless provides a useful conceptual framework to think about the pathologic changes in PD. Since D1 receptors are excitatory and D2 receptors are inhibitory, loss of dopamine in PD has the net effect of reducing transmission through the direct pathway (less stimulation of voluntary motor activity) and increasing transmission via the indirect pathway (more inhibition of motor activity) leading to an output that is characterized by a paucity of movement.

Significant advances in neurobiology over the last 20 years have improved our understanding of cellular pathology in PD. Abnormal processing of misfolded α-synuclein is now thought to occupy a central role in PD pathogenesis. α-Synuclein itself is an endogenously produced neuronal protein involved in synaptic vesicle trafficking. The breath of mendelian genetic mutations linked to inherited forms of PD have given rise to several theories about the pathogenesis of sporadic PD, many of which coexist and contribute in additive fashion toward cell death in at-risk neuronal populations including the SNpc. These possibilities include (1) damage to the protein degradation properties of lysosomes leading to α-synuclein accumulation and aggregation; (2) effects from oxidative stress, such as the reaction of oxyradicals with nitric oxide; (3) impaired mitochondrial function leading to both reduced ATP production and accumulation of electrons that aggravate oxidative stress, with the final outcome being apoptosis and cell death; and (4) inflammatory changes in the nigra producing cytokines that augment apoptosis.

A description of contemporary models of PD pathogenesis would be incomplete without discussing the developing hypothesis that pathogenesis and disease progression of PD may be mediated through a prion-like cell-to-cell spread of misfolded α-synuclein. Prion proteins whose unusual morphology allows the induction of pathologic changes in adjacent cells by promoting misfolding of endogenous proteins, thereby transmitting cell death to adjacent neurons in an infectious-like fashion. In vitro and in vivo experiments in preclinical models of PD have shown the ability of misfolded α-synuclein to induce similar changes in adjacent neurons leading to neurodegeneration.

The “Braak model” of PD pathogenesis is a temporal and topographic schema of Lewy body or Lewy neurite deposition based on findings in a cohort of older individuals with Lewy bodies found on autopsy. In the originally proposed model, Lewy body formation begins in the medulla oblongata and then progresses in a rostral fashion to involve the upper brain stem followed by the diencephalon and cortex. Coincidentally, with the brainstem medulla deposition, this model posits also early deposition in the olfactory tubercle, which then may progress to adjacent regions. Lewy body deposition in the original Braak stage 3 (of total six stages) involves the nigra and is thought to correspond with the onset of motor features of PD. Braak stages 1 and 2 correspond with premotor features of PD, including olfactory, sleep, and autonomic symptoms that can often predate the diagnosis of PD by several years. Similarly, cortical Lewy body formation seen in Braak stages 5 and 6 correspond with cognitive impairment and dementia seen later in the disease course in PD. More recent revisions of this model suggest even earlier involvement of Lewy body deposition in peripheral autonomic nerve terminals, including the intestines, stomach, and myocardium antedating the motor symptoms of PD decades before.

Unlike PD, both PSP and CBS are not thought to be disorders of α-synuclein but instead are attributable to misfolded tau. The parkinsonism seen in these disorders is attributable to tau-based neurodegeneration of the SNpc and basal ganglia. MSA is characterized by the development of argyrophilic cytoplasmic inclusion bodies that are positive for α-synuclein in glial cells rather than typical neuronal Lewy bodies. DLB has neuropathologic overlap with PD with dementia (PDD) in that both disorders are characterized by Lewy body formation in the cortex. PDD is clinically defined by the so-called 1-year rule where motor symptoms antedate cognitive symptoms for over 1 year, whereas motor and cognitive symptoms coincide within a year in DLB. Although different in the temporal profile of the emergence of cognitive and neurobehavioral symptoms, typical features of DLB and/or PDD include hallucinations, especially visual, fluctuations in cognition and dream enactment behavior. DLB, however, also features significant cerebral amyloidopathy more characteristic of AD. Although DLB is often characterized as representing an overlap between PD and AD neuropathology, neurofibrillary tangles are less common in DLB compared to prototypical AD.

PRESENTATION AND EVALUATION

The diagnosis of PD is of prognostic importance, as well as of therapeutic significance, because PD almost always responds somewhat to dopaminergic medications whereas the atypical parkinsonian conditions often do not. In general, the features of PD that tend to improve the most with levodopa or dopamine agonists include bradykinesia, especially fine motor distal motor dexterity, and rigidity in the arms and legs. In some individuals, features of rest tremor can improve significantly with levodopa, especially in the presence of more prominent bradykinesia. Axial motor features including hypophonia, dysphagia, and postural instability are often medication refractory and signify the influence of nondopaminergic changes superimposed on top of nigrostriatal dopaminergic denervation.

While it may be difficult to distinguish between PD and Parkinson-plus syndromes in the early stages of the illness, with disease progression over time, the clinical distinctions of the Parkinson-plus disorders become more apparent with the development of other neurologic findings, such as loss of downward ocular movements in PSP or cerebellar ataxia and autonomic dysfunction (eg, postural hypotension, loss of bladder control, and impotence) which can be seen to a mild-moderate degree in PD but are often very prominent in MSA.

PD begins insidiously and gradually progresses. Three of the most helpful clues that one is likely dealing with an alternative cause of parkinsonism other than idiopathic PD are (1) a symmetrical onset of symptoms (PD often begins asymmetrically on one side of the body), (2) a lack of a substantial clinical response to adequate levodopa therapy, and (3) the absence of rest tremor—though this latter feature is less specific and is present to variable degrees in PD. There are two commonly cited clinical criteria for diagnosing PD: the UK Brain Bank Clinical Diagnostic criteria and the Gelb criteria. Both criteria emphasize that bradykinesia, the most prevalent motor feature of PD, must be present and that other causes of parkinsonism should preferably be excluded. The UK Brain Bank criteria use the presence of postural instability as an inclusion criteria for PD whereas the Gelb criteria deemphasize this feature—given that it can also be seen in atypical parkinsonian conditions—and suggest that asymmetry of motor presentation should be the key inclusion criteria for PD. Clinical features suggesting an alternative parkinsonian diagnosis, so-called “red flags,” are listed in **Table 67-3** and a comparison of diagnostic features for PD and atypical parkinsonian conditions is presented in **Table 67-4**. One common misdiagnosis is tremor due to essential tremor, which can even be unilateral, although it more commonly is bilateral. Helpful in the diagnosis is that the tremor caused by PD is a predominant rest tremor, whereas essential tremor is not typically present at rest, but appears with holding the arms in front of the body (postural tremor) and increases in amplitude with activity of the arm (kinetic or action tremor), such as with handwriting or performing the finger-to-nose maneuver. The presence of mixed and asymmetric tremor syndromes can be particularly challenging as sometimes PD and essential tremor may coexist in the same patients.

TABLE 67-3 CRITERIA TO EXCLUDE THE DIAGNOSIS OF PARKINSON DISEASE IN FAVOR OF ANOTHER CAUSE OF PARKINSONISM

	LIKELY DIAGNOSIS
History of:	
Encephalitis	Postencephalitic
Exposure to carbon monoxide, manganese, or other toxins	Toxin induced
Recent exposure to neuroleptic medications or metoclopramide	Drug induced
Onset of parkinsonian symptoms following:	

Head trauma	Posttraumatic
Stroke	Vascular
Presence on examination of:	
Cerebellar ataxia	MSA, primary ataxic disorders
Loss of downward ocular movements	PSP
Pronounced postural hypotension not because of concurrent medication	MSA
Pronounced unilateral rigidity with or without dystonia, apraxia, cortical sensory loss, alien limb	CBS
Myoclonus	CBS, MSA
Falling or freezing of gait early in the course of the disease	PSP
Autonomic dysfunction not because of medications	MSA
Excessive drooling of saliva	MSA
Early dementia or hallucinations from medications	DLB
Dystonia induced with low-dose levodopa	MSA
Neuroimaging (MRI or CT scan) revealing:	
Lacunar infarcts	Vascular parkinsonism
Capacious cerebral ventricles	Normal pressure hydrocephalus
Cerebellar atrophy	MSA, primary ataxic disorders
Atrophy of the midbrain or other parts of the brain stem	PSP, MSA
Effect of medication:	
Poor response to levodopa	PSP, MSA, CBS, vascular, NPH
No dyskinesias despite high-dose levodopa	Same as above

CBS, corticobasal syndrome; CT, computed tomography; DLB, dementia with Lewy bodies; MRI, magnetic resonance imaging; MSA, multiple system atrophy; NPH, normal pressure hydrocephalus; PSP, progressive supranuclear palsy.

TABLE 67-4 COMPARISON OF DIAGNOSTIC FEATURES FOR PD AND OTHER ATYPICAL PARKINSONIAN CONDITIONS

DISEASE	RELATIVE INCLUSION CRITERIA	CRITERIA SUPPORTIVE OF THE DIAGNOSIS	RELATIVE EXCLUSION CRITERIA
PD	• Bradykinesia • Rigidity • Rest tremor • Asymmetric onset (++)	• Gradually progressive course • Good response to dopaminergic therapies (++) • Motor fluctuations (+++) • Dyskinesias (+++) • Motor symptom duration > 5 y	• Focal brain lesions within the basal ganglia • Recent history of neuroleptic medication use • Severe dysautonomia unrelated to medications • Supranuclear gaze palsy • Prominent postural instability at initial presentation (–) • Prominent cerebellar atrophy on MRI (–) • Freezing of gait developing within 3 y of motor symptom onset (–)
PSP	• Supranuclear gaze palsy (+++) • Slowing of vertical eye movements/saccades (+++) • Tendency to fall in the first year following the onset of motor symptoms (++)	• Gradually progressive course • Symmetric parkinsonism • Increased neck tone and axial rigidity (++) • Early dysphagia • Early cognitive features including apathy, decreased verbal fluency, and pseudobulbar effect • Early frontal release signs on neurologic examination • "Hummingbird sign" on sagittal brain MRI (++)	• Alien limb syndrome • Hallucinations • Early cerebellar signs • Early dysautonomia
CBS	• Asymmetric motor findings	• Cortical sensory deficit (++)	• Rest tremor

	at presentation (+) • Limb dystonia at presentation (+) • Limb myoclonus (++) • Alien-limb phenomenon (+++)	• Frontal lobe cognitive symptoms including executive dysfunction, behavioral/personality changes, aphasia (++) • Focal cortical parietofrontal atrophy on brain MRI	• Good response to dopaminergic medications • Hallucinations • Cerebellar signs • Prominent dysautonomia
MSA	• Cerebellar features on examination (++) • Prominent dysautonomia (+++) • Hyperreflexia and other pyramidal tract findings (+)	• Relatively few cognitive features • Respiratory stridor (++) • Orofacial dyskinesias • "Hot cross bun" sign on axial brainstem MRI	• Dysautonomia only in relation to medications • Hallucinations
DLB	• Hallucinations (+++) • Fluctuations in level of alertness (++) • Dementia within 1 y of the onset of motor features of parkinsonism	• REM sleep behavior disorder (+) • Sensitivity to medications, especially neuroleptics (++)	• Active delirium explained by concurrent medications or an alternative process

+/– denotes strength of association between a particular feature and a specific disorder. PD, Parkinson disease; PSP, progressive supranuclear palsy; CBS, corticobasal syndrome; MSA, multiple system atrophy; DLB, dementia with Lewy bodies; REM, rapid eye movement.

The above table presents a summary of published diagnostic criteria. The lists of inclusion and exclusion criteria for any given disorders are not exclusive/exhaustive of all possibilities. For any given disease, not all inclusion criteria are required to make an affirmative diagnosis. Similarly, the presence of a single exclusion criterion does not represent an absolute contraindication to diagnosing a specific disorder.

Although the diagnosis of PD rests largely on the clinical history and examination, there are adjunctive diagnostic measures that can be useful in making the proper diagnosis. A history of a positive response to levodopa or other dopaminergic medications, for example, is seen in almost all patients with PD. That having been said, many patients with atypical parkinsonian conditions—in particular MSA and DLB—will also describe a generally milder improvement in certain motor features from dopaminergic medications. Dopamine transporter imaging through SPECT (I-123 ioflupane SPECT or DaTscan) scan provides molecular imaging evidence to confirm the loss of nigrostriatal dopaminergic nerve terminals, consistent with parkinsonism (**Figure 67-1**). It cannot, however, differentiate between PD and other causes of neurodegenerative parkinsonism, such as DLB, PSP, or MSA; all of these conditions will have evidence of nigrostriatal losses on dopamine transporter imaging. Dopamine transporter SPECT imaging has been approved to distinguish essential tremor from PD in patients with atypical tremor manifestation. This imaging modality can also be helpful to distinguish PD from drug-induced parkinsonism. Impaired performance on olfactory identification testing has also shown good correlation with postmortem findings of PD in patients presenting for suspected parkinsonism but can also be seen in other neurodegenerative conditions, such as AD or DLB. Scratch-and-sniff tests for odor identification are available commercially and can be completed and scored in the clinic relatively quickly.

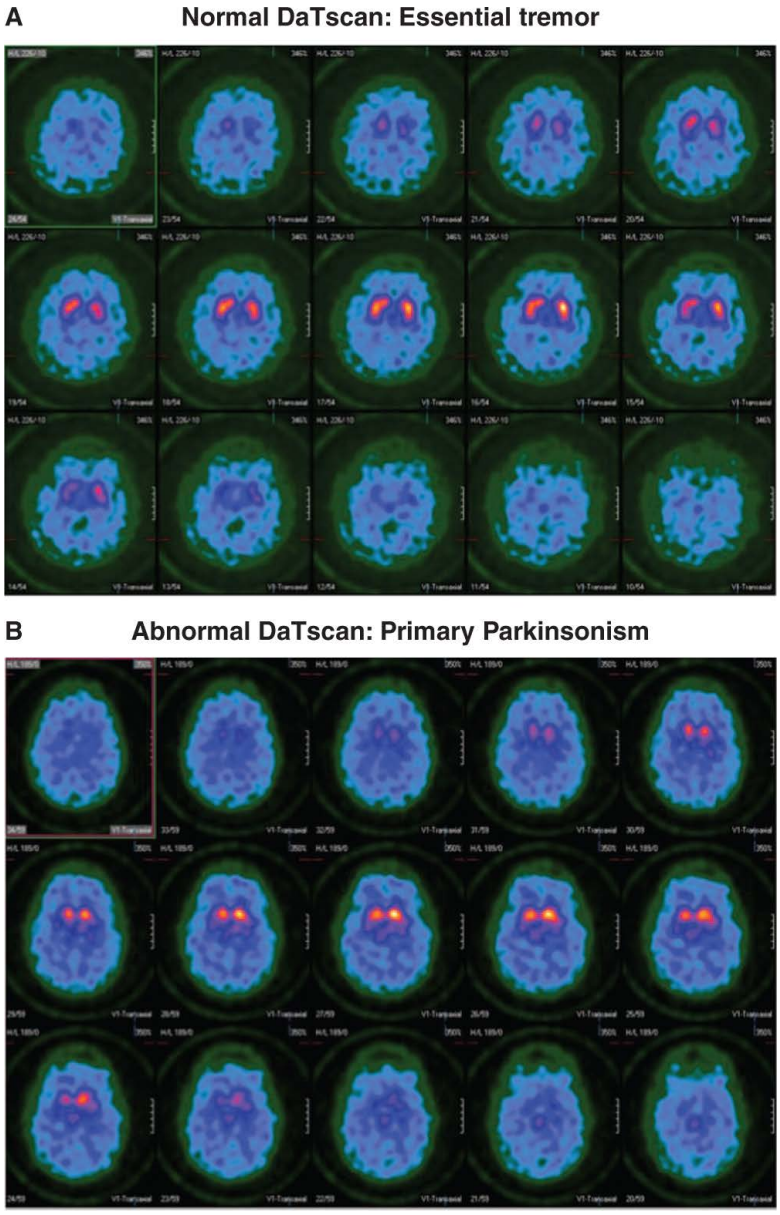


FIGURE 67-1. **A.** Normal dopamine transporter imaging through single-photon emission computed tomography (DaT SPECT scan) in a patient with essential tremor. **B.** Asymmetric loss of putaminal dopaminergic nerve terminals affecting the right striatum more than the left consistent with a primary neurodegenerative parkinsonian condition.

Although there are many motor features seen in early PD, the scope of nonmotor features associated with early PD is even larger. These can include (but are not limited to) olfactory impairment, sleep difficulties, depression, anxiety, chronic constipation, limb pain, apathy, erectile dysfunction, cognitive impairment, drooling, rhinorrhea, and other autonomic features. Although some of these features can be a secondary development due to disability accrued from PD, almost all of them are aggravated by primary Lewy body–related neuronal changes seen in various areas of the nervous system ranging from the enteric nerves of the gastrointestinal tract to the cholinergic nerves arising from the basal forebrain, which innervate the cerebral cortex. Although many of these features become increasingly common with age, the concomitant development of three or more of these features in an older individual without a clear alternate explanation should prompt a work-up for a parkinsonian condition.

Early cognitive changes seen in PD include difficulty with memory, attention, and executive dysfunction, the latter of which refers to planning, multitasking and decision-making capacity. In some patients, these cognitive features may be stable for many years, whereas in others they may progress to dementia. It is estimated that about 50% of individuals with PD will develop dementia (PDD) within 10 years of their initial diagnosis.

MSA is a parkinsonian disorder characterized by aggressive α-synuclein–related cellular loss in the brain stem, cerebellum, and basal ganglia. The median age of onset is in the sixth decade of life with a mean time to severe disability of approximately 5 years from the time of diagnosis. Progressive cell death occurs not only in dopaminergic

cells but in many different neuronal systems including the basal ganglia, substantia nigra, locus coeruleus, pontine nuclei, cerebellar Purkinje cells, and the intermediolateral cell column of the spinal cord. MSA is typically grouped into two clinical categories: MSA-P, where parkinsonism is seen, and MSA-C, where cerebellar features including ataxic gait, dystaxic limb movements, and ataxic speech predominate. Other characteristic features of both MSA-P and MSA-C that differ from PD include severe autonomic symptoms including orthostatic light-headedness, blood pressure fluctuations, and urinary dysfunction. Patients with MSA can also experience nocturnal stridor characterized by laryngeal obstruction secondary to vocal fold hypokinesia, which manifests with a high-pitched inspiratory noise. Unlike obstructive sleep apnea, nocturnal stridor can be acutely life threatening. While emergency tracheostomies have been performed in MSA for life-threatening stridor, this may be inconsistent with overall goals of care for such patients. Following with an otolaryngologist on an annual basis can be an effective method for monitoring this symptom overtime and some patients may benefit from nasal continuous positive airway pressure (CPAP). Unlike other atypical parkinsonian conditions, cognitive impairment is not a typical feature of MSA but may be present in a small subset.

PSP and CBS are both tauopathies associated with parkinsonism. PSP tends to present in the sixth and seventh decades of life with early oculomotor findings including downgaze impairment, axial rigidity, and postural instability. Patients with PSP also develop a frontal-predominant cognitive syndrome characterized by apathy, executive dysfunction, and pseudobulbar effect. CBS is the clinical diagnosis given for patients with suspected CBD, the latter of which refers specifically to neuropathologic findings. CBS is associated with several distinct histopathologies, including CBD, other forms of tau-related frontotemporal lobar degeneration such as progressive supranuclear palsy, and Alzheimer disease. Motor manifestations of CBS also tend to occur in the sixth or seventh decade of life and are characterized by progressive asymmetric rigidity, myoclonus, parkinsonism, and an unusual motor phenomenon termed “alien limb” during which patients experience adventitious semipurposeful movements of one limb. CBS is one of the exceptions to the general rule that asymmetric limb motor involvement favors a diagnosis of PD. Early cognitive changes include praxis difficulties and language impairment. Cortical sensory loss can also be seen. The variable presence of these clinical features and their overlap with features seen in PSP, PD, and frontotemporal dementia (FTD) has led clinicians to use the term CBS to describe clinically probable, though not pathologically confirmed, CBD.

MANAGEMENT

Treatment of patients with PD can be divided into three major categories: medications, physical (and mental health) therapy, and surgery. Although the pharmacologic strategies described below apply primarily to PD, they can also be tried in atypical parkinsonian conditions. MSA, PSP, and CBD, however, are typically associated with a more limited response to medications, underscoring their overall worse prognosis.

Dopaminergic Therapies

Dopamine replacement therapy is the primary medical approach to treating PD, and a variety of dopaminergic agents are available (**Table 67-5**). The most powerful oral drug is levodopa, the immediate precursor of dopamine. Levodopa, an amino acid precursor molecule of dopamine, can enter the brain, whereas dopamine is blocked by the blood-brain barrier. Levodopa is usually administered combined with a peripheral decarboxylase inhibitor (carbidopa or benserazide) to prevent formation of dopamine in the peripheral tissues, thereby increasing levodopa’s bioavailability and also markedly reducing gastrointestinal side effects. The brand name Sinemet is a combination of carbidopa and levodopa; the brand name Madopar is a combination of benserazide and levodopa. Such combination drugs are available in standard (ie, immediate-release) and extended-release formulations. The former allows a more rapid and predictable “on,” and the latter allows for a slightly longer plasma half-life, but with a slower and less predictable “on.” The combination of the two release formulations can be administered in an attempt to smooth out and extend plasma levels of levodopa. A version of carbidopa/levodopa that dissolves under the tongue (Parcopa) and enters the stomach via swallowing saliva is also available. This orally dissolving formulation has particular usefulness for patients who have swallowing difficulties.

TABLE 67-5 ■ DOPAMINERGIC AGENTS

Dopamine precursor: levodopa
Peripheral decarboxylase inhibitors: carbidopa, benserazide

Dopamine agonists: pramipexole, ropinirole, rotigotine, apomorphine
Catechol-*O*-methyltransferase inhibitors: entacapone
Dopamine releaser: amantadine
Peripheral dopamine receptor blocker: domperidone
MAO type B inhibitor: selegiline, selegiline, rasagiline

MAO, monoamine oxidase.

Although levodopa is the most effective drug to treat the symptoms of PD, over half of patients develop troublesome complications of disabling response fluctuations ("wearing-off") and/or dyskinesias after 5 years of levodopa therapy.

Besides being metabolized by aromatic amino acid decarboxylase (commonly known as dopa decarboxylase), levodopa is also metabolized by catechol-*O*-methyltransferase (COMT) to form 3-*O*-methyldopa. Entacapone is a currently available COMT inhibitor. This agent extends the plasma half-life of levodopa with and also increases its peak plasma concentration, and thereby prolongs the duration of action of each dose of levodopa. Its clinical indication is to help reduce motor fluctuations, that is, increase "on" time and reduce "off" time. Because entacapone enhances levodopa's efficacy, it can increase dyskinesias and the dosage of levodopa may need to be lowered. Entacapone is very short acting, and each 200-mg tablet is taken simultaneously with levodopa. Entacapone is also available in a combination pill with carbidopa/levodopa (Stalevo). Tolcapone (100- and 200-mg tablets) is more potent and has a longer duration of action, but it is encumbered by a greater risk of diarrhea and hepatotoxicity, the latter of which has led to its removal from the market in the United States. After levodopa, the next most powerful oral drugs in treating PD symptoms are the dopamine agonists. Several of these are available. The ergot compounds of pergolide, bromocriptine, and cabergoline have the potential to induce fibrosis (cardiac valvulopathy and retroperitoneal, pleuropulmonary, and pericardial fibrosis), so these agents are not recommended; indeed pergolide has been withdrawn from the US market. Pramipexole and ropinirole appear to be equally effective at therapeutic levels. Dopamine agonists are more likely than levodopa to cause hallucinations, confusion, and psychosis, especially in the older adults. Thus, it is safer to utilize levodopa in patients older than 70 years. On the other hand, clinical trials have shown that dopamine agonists are less likely to produce dyskinesias and the wearing-off phenomenon than levodopa. These differences are most likely due to the relatively lower potency/efficacy and longer half-life of dopamine agonists compared to levodopa. Slow-release preparations of ropinirole and pramipexole are also available. Other problems more likely to occur with dopamine agonists than levodopa are sudden sleep attacks, including falling asleep at the wheel, daytime drowsiness, ankle edema, and impulse control problems such as hypersexuality and compulsive gambling, shopping, and binge eating. The newest dopamine agonist is rotigotine which is applied via a dermal patch to the upper torso or arms. It is useful for those with swallowing difficulties and may help smooth out motor fluctuations and nocturnal akinesia, when the last prebedtime dose of levodopa does not last throughout the night. Apomorphine may be the most powerful dopamine agonist, but it needs to be injected subcutaneously (or taken sublingually or infused subcutaneously in Europe). It is used to provide faster relief to overcome a disabling "off" state.

Amantadine is adjunctive antiparkinsonian drug with several pharmacologic actions; it has mild antimuscarinic effects, but more importantly, it can activate release of dopamine from nerve terminals, block dopamine uptake into the nerve terminals, and block glutamate NMDA receptors. Its dopaminergic actions make it a useful drug to relieve symptoms in approximately two-thirds of patients, but it can induce livedo reticularis, ankle edema, visual hallucinations, and confusion. Its antiglutamatergic action is useful in reducing the severity of levodopa-induced dyskinesias, and in fact, is the only established effective antidyskinetic agent. The dose of amantadine for its anti-PD effect is usually 100 mg twice daily, but its antidyskinetic effect requires higher dosages, usually 300 to 400 mg/day. Unfortunately, the antidyskinetic effect tends to lessen over time. Older individuals often do not tolerate amantadine well because of mental adverse effects of confusion and hallucinations.

Domperidone is a peripherally active dopamine receptor blocker and is useful in preventing gastrointestinal upset from levodopa and the dopamine agonists. It is not available in the United States, but is available in other countries including Canada. Monoamine oxidase type B (MAO-B) inhibitors (selegiline, rasagiline) offer mildly effective symptomatic benefit and are without significant hypertensive diet-linked side effects seen with MAO-A inhibitors, and therefore can be used in the presence of levodopa therapy. Although there has been considerable debate about possible protective or disease-modifying benefit of MAO-B inhibitors, numerous well-powered trials have failed to

convincingly demonstrate a neuroprotective benefit. The results of these trials have been interpreted variably, however, given that selegiline and rasagiline appear to have a symptomatic benefit, which has contributed to some methodological concerns regarding specific trial designs. Selegiline, but not rasagiline, is metabolized to L-amphetamine and methamphetamine. Both of these drugs can reduce the severity of motor fluctuations with levodopa.

Motor Complications of Dopaminergic Therapies

Many patients on levodopa therapy develop motor complications (**Table 67-6**). These motor complications, also referred to as "motor fluctuations," usually begin as mild wearing-off, which can be defined as when an adequate dose of levodopa does not last at least 6 hours and motor symptoms of bradykinesia, rigidity, or tremor emerge or worsen. Typically, in the first couple of years of treatment, there is a long-duration response so that the timing of doses of levodopa is not important. Over time, the long-duration response becomes lost, and only a short-duration response occurs; patients then develop the wearing-off phenomenon. The "off" episodes tend to be mild at first, but over time become more frequent or severe with more severe parkinsonism. Simultaneously, the duration of the "on" response becomes shorter. Eventually, some patients develop random, sudden "offs" in which the deep state of parkinsonism develops over minutes rather than 10s of minutes, and they are less predictable in terms of synchrony with the dosing of levodopa. Many patients who develop response fluctuations also develop abnormal involuntary movements, that is, dyskinesias.

TABLE 67-6 PATTERN OF DEVELOPMENT OF RESPONSE FLUCTUATIONS, DYSKINESIAS, AND OTHER COMPLICATIONS

Dyskinesias (chorea and dystonia)
Peak-dose dyskinesias
Diphasic dyskinesias (beginning and end-of-dose dyskinesias)
Fluctuations
Wearing-off
Delayed "ons"
Dose failures
Sudden, unpredictable "offs" (on-offs)
Early morning "off" dystonia
"Off" dystonia during day
Alertness
Drowsy from a dose of levodopa
Reverse sleep-wake cycle
Behavioral and cognitive
Vivid dreams
Mild hallucinations
Severe hallucinations
Delusions
Punding
Apathy
Paranoia
Delirium
Dementia

Treatment of "wearing-off" The wearing-off phenomenon, when mild, may be ameliorated slightly with the addition of selegiline or rasagiline (0.5 mg once daily, and increasing to 1 mg once daily, as necessary). Both MAO-B inhibitors potentiate the action of levodopa. A higher dose of levodopa may be necessary but more frequent dosing of levodopa may be the simplest approach to manage this motor complications. Many patients can require six or more

doses per day, and then, eventually, can develop dose failures owing to poor gastric emptying. These patients are often considered for duodoneal infusion of levodopa or deep brain stimulation (see Surgical Therapy later)

Continuous-release carbidopa/levodopa (Sinemet CR) can also be effective in patients with mild wearing-off in some patients or use the combination of both immediate- and extended-release formulations. Dopamine agonists, which have a longer biological half-life than levodopa, can also be used in combination with immediate-release or continuous-release versions of carbidopa/levodopa. The addition of a dopamine agonist tends to make the "off" state less severe when used in combination with carbidopa/levodopa. COMT inhibitors have been found useful for treating wearing-off. Because of the short half-life of entacapone, it is given with each dose of carbidopa/levodopa, and is about as equally effective as rasagiline in reducing the amount of daily "off" time. For those patients who have "offs" at a specific time of day, entacapone can be strategically given just with the dosage of carbidopa/levodopa that precedes this "off" period.

Behavioral or sensory "offs" can also occur as do motor "offs," often in the absence of any motor "off," which means a return of parkinsonism. Behavioral and sensory "offs" tend not to be easily recognized, because visibly the treating physician sees no motor changes. Behavioral/sensory "offs" can consist of pain, akathisia, depression, anxiety, dysphoria, or panic, and usually a combination of more than one of these. Sensory "offs," like dystonic "offs" are very disabling. It is often the presence of one of these sensory and behavioral phenomena, more so than motoric parkinsonian or dystonic "offs," that drives the patient to take more and more levodopa, leading a few patients to develop an addictive relationship with dopaminergic medications, so-called dopamine dysregulation syndrome.

Treatment of dyskinesias Dyskinesias are involuntary movements and occur in two major forms—chorea and dystonia. Choreiform movements are irregular, nonrhythmic, unsustained dance-like movements that seem to flow from one body part to another and can appear like benign fidgeting. Dystonic movements are more sustained, twisting contractions. Many patients have a combination of choreiform and dystonic dyskinesias.

Peak-dose dyskinesias occur when the plasma concentrations of levodopa or dopamine agonists are at their peak, and the synaptic brain concentration of dopamine is too high. Reducing the individual dosage can resolve this problem of peak-dose dyskinesias. However, the patient may need to take more frequent doses at this lower amount. An alternative approach is to add amantadine, which suppresses the severity of dyskinesias, possibly because of its antiglutamatergic action. Start with a dose of 100 mg BID and increase up to 200 mg BID if necessary. Buspirone in dose up to 20 mg/day may also of benefit in treating dyskinesias in some patients.

Some patients may develop "off" dyskinesias. In the absence of so-called early morning "off" dystonia, which responds well to dopaminergic therapies, such patients are encouraged to consider deep brain stimulation (see later under Surgical Therapy). Depending on their distribution within the body and the disability associated with them, dystonic dyskinesias can also be treated with local injections of a chemodenervation agent such as botulinum toxin. This treatment can be associated with a significant improvement in quality of life but will also weaken a muscle group and thereby can impact a patient's function, particularly if the dystonic movements are occurring in the hands.

Diphasic dyskinesias are dyskinesias that occur at the beginning and end of dose, not during the time of peak plasma and brain levels of dopaminergic medications. They tend to particularly affect the legs with a mixture of chorea and dystonia.

Dopamine medication–related nonmotor complications In addition to motor features, a number of nonmotor problems can also occur as complications from dopaminergic therapy. Mental changes of psychosis, confusion, agitation, hallucinations, paranoid delusions, punding, impulse control disorders, and excessive sleeping are probably related to activation of dopamine receptors in anteroventral striatal regions, or nonstriatal regions, particularly the cortical and limbic structures.

Drug-induced hallucinations tend to be mild, visual in nature rather than auditory, and not frightening. Consideration should be given to reducing the total dose of dopaminergic medication to whatever degree is tolerable for the patient. A complete review of medications is indicated as well to identify any other symptomatic treatments that might be worsening encephalopathy, including benzodiazepines, anticholinergics, and opioids. Adjunctive treatment can begin with the addition of quetiapine, starting with 25 mg at bedtime. The dose should be increased steadily until the hallucinations are brought under control. If quetiapine is ineffective or if the hallucinations are frightening, clozapine, a stronger antipsychotic that will not worsen motor features of PD, should be considered. As mentioned previously, the reason clozapine is not the first drug of choice in dopaminergic-induced hallucinations is because clozapine causes agranulocytosis in approximately 1% to 2% of patients. Patients must have their blood counts monitored weekly for this potential complication, and then discontinue the drug if leukopenia develops. Both

quetiapine and clozapine often cause drowsiness, so bedtime dosing is recommended.

If the psychosis is severe or if the patient is in an acute delirious state, hospitalization may be necessary, with immediate initiation of antipsychotic medications, and some reduction in anti-PD medication. These medications could even be withdrawn temporarily to overcome the psychosis, but this should be done stepwise over a 3-day period to avoid the neuroleptic malignant-like syndrome that could occur with sudden withdrawal of levodopa.

Dopamine agonist medications are associated with sleep attacks and impulse control disorders. Both of these issues can also be seen with levodopa but are much less common and less severe. Sleep attacks often manifest with a sudden wave of sleepiness that comes on with little warning and can be particularly dangerous for patients who are driving at the time. Impulse control disorders consist of behavioral changes such as compulsive gambling, shopping, and eating, and hypersexual behaviors. Not surprisingly, these changes can often have significant detrimental effects on family relationships. Both of these side effects are, to some degree, dose dependent and typically necessitate reducing the dose of the dopamine agonists or stopping them altogether. Memantine, an NMDA receptor antagonist, has shown to be of benefit in some patients with dopamine agonist–induced impulse control disorders in PD.

Nondopaminergic Therapies

Nondopaminergic agents (**Table 67-7**) are useful to treat both motor and nonmotor symptoms of PD. Antimuscarinic drugs have been used since the 1950s to treat parkinsonian tremor, but have limited efficacy and frequently lead to cognitive impairment and hallucinations in the elderly population. For this reason antimuscarinics should be avoided in patients older than 70 years.

TABLE 67-7 ■ NONDOPAMINERGIC AGENTS

Parkinsonian motor symptoms:
Antimuscarinics (for tremor): trihexyphenidyl, benztropine
Antiglutamatergics (to reduce dyskinesia): amantadine
Muscle relaxants: cyclobenzaprine, diazepam, baclofen
Nonmotor symptom control:
Depression: selective and nonselective serotonin reuptake inhibitors, tricyclics, ECT
Psychosis (hallucinations, paranoia): clozapine, quetiapine
Insomnia: mirtazapine, trazodone, quetiapine, zolpidem
REM sleep behavior disorder: clonazepam, melatonin
Excessive daytime sleepiness: modafinil
Dementia: donepezil, rivastigmine
Orthostasis: fludrocortisone, midodrine, droxidopa
Restless legs: dopamine agonists, levodopa, gabapentin, opioids

Depression is common in patients with PD, and often precedes the motor symptoms of PD. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other antidepressants including bupropion and tricyclic antidepressants are useful antidepressants. If insomnia is a problem for the patient, using an antidepressant that is also a soporific can be doubly advantageous: medications such as the tricyclic nortriptyline (which has fewer anticholinergic effects than amitriptyline) or an SNRI, such as low-dose mirtazapine, are good options.

Benzodiazepines including clonazepam are effective in reducing symptoms of dream enactment behavior attributable to rapid eye movement (REM) sleep behavior disorder (RBD). Nevertheless, they should be used with caution given their potential for cognitive side effects, increased risk of falls, rebound anxiety, and their addictive potential.

Psychosis induced by levodopa and the dopamine agonists can usually be controlled by quetiapine and clozapine without worsening the parkinsonism. Other antipsychotic agents—be they typical or atypical neuroleptic mediations—are more likely to worsen the parkinsonism; therefore, they should be avoided. Clozapine is more effective than quetiapine, but because clozapine treatment requires weekly blood cell counts due to risk of agranulocytosis, low-dose quetiapine should be tried first.

Insomnia in PD requires a detailed history to distinguish specific causes of impaired sleep that may require different management approaches. Common causes of insomnia in PD include restless legs, persistent tremor, nocturnal akinesia, dream enactment behavior, bladder dysfunction, and early morning motor "off" symptoms or dystonia. Both sleep-onset insomnia and sleep-maintenance insomnia occur in PD, though sleep-maintenance insomnia may be more common and troublesome. Sleep-onset insomnia is treated conventionally with low doses of hypnotics and sedating antidepressants such as low-dose mirtazapine or trazodone. In demented patients, low nighttime doses of the atypical antipsychotic quetiapine may be useful if neurobehavioral disturbances occur at night. Sleep maintenance insomnia is due often to motor dysfunction. Bradykinesia with difficulty moving in bed or adjusting bedclothes is a common cause of sleep maintenance insomnia in PD. Levodopa has a relatively short serum half-life and a common experience is loss of levodopa effect in the middle of the night with worsening bradykinesia and nocturnal arousals. Medication schedule manipulations such as instituting or increasing a bedtime dose of levodopa may be useful. Similarly, use at bedtime of extended-release levodopa preparations, adjunctive agents that lengthen the levodopa half-life, or dopamine agonists that possess relatively long half-lives may ameliorate this form of sleep-maintenance insomnia. An additional common source of sleep-maintenance insomnia in more advanced PD is bladder dysfunction, which in men with PD may coexist with prostate enlargement. Specifically, autonomic dysfunction leading to urinary frequency, urgency, and incontinence is common in more advanced PD. Conventional approaches to treating bladder dysfunction may be useful. Nocturnal use of gabapentin can also be of benefit in some patients.

RBD is common in patients with PD, DLB, and MSA and often precedes the appearance of these disorders. RBD manifests with complex, nonstereotyped dream-enactment behavior and is usually associated with vivid or frightening dream content. Normally, dreaming in REM sleep is associated with muscle paralysis to all skeletal muscles outside of the eyes and diaphragm. This normal REM-associated muscle paralysis is reduced in RBD. RBD in PD, as in other settings, does not seem to cause daytime sleepiness but can result in injuries or disrupt bed partner rest. Infrequent and mild episodes of RBD probably do not require treatment but more severe episodes can be of dangerous to the bed partner or patient. Withdrawal of antidepressants that can precipitate or exacerbate RBD may be worthwhile. Safety measures within the sleeping room may be necessary. These can include use of separate beds, placement of mattresses on the floor, efforts to sleep on the first floor, and removing dangerous objects from the bedroom. The mainstay of medical treatment is use of hour-of-bedtime clonazepam (0.5–2 mg), which appears to be effective and is tolerated well by the majority of patients. Melatonin—though less effective—may be tried first and can be combined with clonazepam. In some patients, cholinesterase inhibitors may also help RBD symptoms. Dopaminergic therapy probably has little or no effect on RBD.

Periodic leg movements of sleep (PLMS) and restless legs syndrome (RLS) are estimated to be twice as common in PD as in matched populations. Despite this association, the relationship between PD and RLS is complex. While both RLS and PLMS may contribute to insomnia in PD, one study has shown no significant worsening in daytime sleepiness seen in PD patients with RLS compared to those without. No evidence exists that RLS predisposes patients to develop PD later in life. Though dopaminergic dysfunction may play a role in both PD and RLS, imaging studies of subjects with RLS without PD have not shown convincing evidence of a nigrostriatal dopaminergic deficit. These findings suggest that RLS may not in fact be a precursor to the cardinal motor symptoms of PD and may not be a "secondary" symptom of PD, but rather a separate disease entity that can be exacerbated by PD. Assessment and management of RLS in PD involves an evaluation for iron deficiency and iron supplementation when appropriate, and use of low doses of dopaminergic agents such as long-acting dopamine agonists or L-dopa. In patients with poor or complicated responses to dopaminergic agents, gabapentin, clonazepam, or low-dose opiates may be useful.

Fatigue is an increasingly noted nonmotor symptom in PD of unclear etiology but has shown to be correlated with poor sleep and depression. Clinicians should attempt to differentiate fatigue from excessive daytime sleepiness, the latter of which is often due to poor quality of sleep at night or adverse effects associated with excess dopaminergic medications, necessitating a different approach to diagnostic work-up and management. Many patients describe fatigue as their first presenting symptom. Management should be aimed at underlying causes, such as depression. If needed, medications such as modafinil or nonprescription therapies such as liberalizing caffeine consumption can provide some benefit.

Mild cognitive symptoms can be seen in some PD patients with early disease and worsen with increasing disease duration. Early features typically include impaired attention, verbal memory, and executive dysfunction summarized as a subcortical-frontal syndrome. Dementia in PD is often associated with the development of significant visuospatial impairments, memory difficulties, and hallucinations—the latter of which may also be seen in response to dopaminergic or anticholinergic drugs. PDD and DLB patients are at a particularly high risk for developing delirium, either in association with new medications or because of underlying acute medical illnesses. Symptoms of delirium

often involve profound disorientation and psychosis that can sometimes take weeks to resolve. Cholinergic deficits affecting subcortical and cortical structures are thought to play a significant role in PD cognitive impairment. Cholinesterase inhibitors, including donepezil and rivastigmine, are useful therapies for improving cognitive symptoms at all stages of PD. They are, however, limited in their efficacy due to limited central nervous system (CNS) bioavailability.

Orthostatic hypotension is common in PD and can be due to the disease itself or to dopaminergic medications, the latter of which lower blood pressure. It can also represent an early manifestation of an atypical parkinsonian condition, namely MSA. Fludrocortisone, midodrine, or droxidopa can overcome this symptom to some extent.

Constipation is common in PD. It may be further aggravated by anticholinergic medications. Besides changing dietary habits by increasing intake of more fiber and dried fruits, polypropylene glycol or lubiprostone can be effective. For those who have bloating because of suppression of peristalsis when they are "off," keeping them "on" with levodopa can be beneficial.

Exercise and Physical Activity

An active exercise program encourages patients to have ownership over their own care, allows muscle stretching and full range of joint mobility, increases aerobic capacity, muscle strength, motor skills, and improves a patient's mental attitude toward fighting the disease. Preclinical studies have shown that exercise slows the degeneration of dopamine neurons following local toxin, theoretically because exercise leads to an increase in brain neurotropic factors. There is also increasing evidence to suggest that sedentary behaviors, irrespective of the amount of formal exercise one performs, may have a deleterious impact on not only physical condition but also metabolic functions. These changes increase the risk for frailty among patients with PD subjects leading a decline in health. Encouraging patients to reduce the amount of time they spend seated each day is a good way to empower patients to regulate their own PD prognosis.

A regular routine of physical exercise, be it cardiovascular training or weight-based exercises, should be implemented as soon as the diagnosis is made, but is useful in all stages of disease. Stretching exercises may help to compensate for the tendency of patients to have a reduced range of motion. In moderate-to-advanced stages of PD, formal physical therapy is more valuable by keeping the joints from becoming frozen, and by providing guidance how best to remain independent in mobility, particularly with gait training and prevent injurious falls. One of the nonmotor symptoms of PD is the tendency toward apathy and conservative decision making with decreased motivation. Encouraging activity may help fight these symptoms.

Surgical Therapy

DBS surgery for PD is an increasingly available treatment option associated with significant gains in quality of life for PD patients who are good surgical candidates. DBS surgery is typically indicated for PD patients with difficult-to-manage motor complications (fluctuations and/or dyskinesias) or with medication-refractory parkinsonian tremor. DBS involves placement of an impulse pulse generator (IPG) in the chest that looks much like a pacemaker. A lead from the IPG is tunneled under the skin surface to a specific region of the brain, either the STN or the GPi.

When stimulation is optimized, patients will experience an "on" state without disabling "off" features. Patients are also able to reduce their dose of dopaminergic medications, and in this way, are able to reduce dyskinesias as well. With the exception of tremor, motor features that generally do not improve with dopaminergic medications (eg, postural instability, other axial motor features, some gait freezing) also do not improve with DBS. DBS typically has little effect on the nonmotor features of PD unless they are directly related to on-off fluctuations seen with dopaminergic medications.

Patients with significant speech, gait, depression with suicidal ideation or cognitive difficulties are usually not good candidates for DBS, not only because these symptoms do not respond to stimulation, but also because in some patients, these features may become notably worse after DBS, including the risk of suicide. The selection of appropriate candidates for DBS is often best done under the guidance of an experience movement disorder neurologist. DBS is not suggested for patients with atypical parkinsonian conditions since the majority of these motor features do not respond to dopaminergic medications.

CARE CONSIDERATIONS

No two patients with PD are alike in their clinical presentation or their rate of disease progression. In addition, not all

motor features of PD have the same clinical or prognostic significance. Gait and cognitive difficulties for example, play a more significant role in patient autonomy, disease staging, and overall disability. Different motor phenotypes in PD have been distinguished, such as tremor-predominant or imbalance-predominant (so-called postural instability and gait difficulties [PIGD]) subtypes. PIGD features, however, tend to be less responsive to common medication strategies including dopaminergic therapies and can worsen at variable rates for reasons that appear to have little to do with dopaminergic neurotransmission.

There is an increasing body of literature implicating nondopaminergic or extranigral brain changes seen with aging as a mediator of disease progression in PD. Cerebral amyloid deposition and a decline in cerebrovascular integrity occur as part of brain aging. In individuals without PD, when these progressive changes exceed a critical threshold, patients who develop clinical symptoms are diagnosed with specific disorders including Alzheimer disease and vascular dementia. When these changes are milder, however, most people are able to use existing neuronal reserve to compensate and prevent the development of clinically significant disability. In PD, where the severe loss of striatal dopaminergic neurons is seen from the earliest stage of diagnosis, neuronal compensation mechanisms are relatively impaired, leading to the development of clinically significant disease features in the presence of even low levels of age-related comorbid brain pathologies (**Figure 67-2**). Longitudinal studies of PD have suggested that the severity of medical comorbidities is a chief determinant of progression to a disability, dementia, and death. For this reason, we recommend that all patients with PD attend carefully to common chronic medical conditions including cardiovascular risk factor reduction through physical exercise, appropriate diet, and medication management of comorbidities like hypertension and diabetes mellitus. The longitudinal role of a geriatrician or primary care doctor is hence indispensible for individuals with PD.

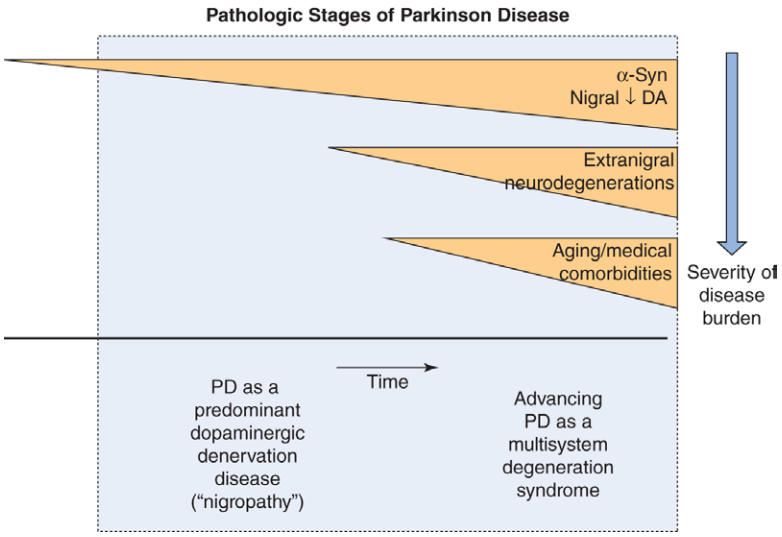


FIGURE 67-2. Schematic diagram depicting the natural history of progressive changes in Parkinson disease (PD) attributable to both dopaminergic and nondopaminergic ("extranigral") pathologies. With advancing disease duration, medical comorbidities and other neuropathologies exert additive/synergistic effects on overall motor and nonmotor disease burden in PD.

Recent data suggest that specialist care through a neurologist specifically is associated with reduced mortality in PD. Neurologists who are familiar with PD can be instrumental in making medication adjustments over time and can serve as an access point for newly approved medications and for DBS once patients have progressed from early-stage to mid-stage PD characterized by motor fluctuations. Patients with late-stage PD or with significant disability from atypical parkinsonian conditions often benefit from consultations with palliative care physicians. This is particularly helpful for later-stage patients who are either confined to a wheel chair or who are considering nursing home placement because of inability to perform activities of daily living. Progressive dysphagia can be seen in some patients with advanced PD or atypical parkinsonian conditions and may necessitate a discussion about feeding tube placement. Discussing goals of care with patients at risk for loss of autonomy can empower patients to have control over a difficult disease.

CONCLUSION

Parkinsonian conditions including PD are common sources of disability in older individuals and are typically responsive to a wide variety of treatments. Longitudinal care with skilled geriatric and neurology providers is perhaps the most important step to ensure an individualized medical approach that prioritizes quality of life.

ACKNOWLEDGMENTS

We wish to thank Dr. Stanley Fahn, the previous author of this chapter.

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Chapter 68

Other Neurodegenerative Disorders

Victor Valcour, Bruce Miller

Learning Objectives

- Learn about the epidemiology, common clinical presentations, diagnosis, and treatment of non-Alzheimer type of neurodegenerative diseases.
- Gain new knowledge about recent discoveries related to the genetics, pathology, and pathobiology of common tau- and α-synucleopathies in older adults.
- Learn about the specific behavioral and nonbehavioral symptoms, clinical signs, diagnostic criteria and common neuroimaging, genetic and laboratory tests used to diagnose non-Alzheimer type diseases of dementia.
- Understand the scientific rationale, indications and limitations of currently available and emerging therapies for common non-Alzheimer–type neurodegenerative diseases.

Key Clinical Points

1. **The evaluation of neurodegenerative disorders includes careful attention to the cognitive, behavioral, and motor symptoms along with a thorough neurologic examination.**
2. **In older age, it becomes increasingly common for there to be more than one type of pathology causing a dementia syndrome.**
3. **The characteristic features of Lewy body dementia include cognitive impairments with profound fluctuation, spontaneous parkinsonism, random eye movement (REM) behavior sleep disorder, and visual hallucinations.**
4. **About 30% of patients with Parkinson disease develop dementia. In these patients, unlike Alzheimer disease, the motor and other symptoms of Parkinson disease generally predate dementia by many years.**
5. **The dominance of behavioral and personality changes in the absence of memory and perceptual symptoms is highly suggestive of the behavioral variant of frontotemporal dementia (FTD).**
6. **History of falls and dysphagia with abnormalities in vertical gaze and preserved oculocephalic reflex is suggestive of a diagnosis of progressive supranuclear palsy (PSP).**

Alzheimer disease (AD) is the most common neurodegenerative disorder encountered by the practicing geriatrician, however, a sizable number of other neurodegenerative diseases will be seen in a typical practice, rendering a working knowledge of these disorders critical for clinicians. Furthermore, there is increasing evidence that with greater age, many individuals die with mixed pathology—with AD, vascular changes, frontotemporal lobar degeneration (FTLD), and Lewy body changes often seen in a single brain. This chapter provides an overview of the more common neurodegenerative disorders with emphasis on those that influence behavior and cognition early in the course. We begin by reviewing the clinical approach to neurodegenerative cognitive disorders and then review the clinical presentation, epidemiology, and examination findings of the more common neurodegenerative syndromes. We attempt to link clinical presentation to anatomy and neuropathology whenever possible.

APPROACH TO THE EVALUATION OF COGNITIVE AND BEHAVIORAL DISORDERS IN ADULTS

The evaluation of neurodegenerative disorders is multifaceted, requiring careful attention to the cognitive, behavioral, and motor history combined with a comprehensive neurologic examination aiming to identify the brain regions involved. Isolating anatomy in patients who present with slowly progressive neurodegenerative disorders greatly facilitates the determination of the correct diagnosis.

Emphasis should be placed on the earliest presenting symptoms, whether cognitive, behavioral, or motor in origin. These early features may be critical to the identification of the pathologic substrate. As diseases progress, signs and symptoms merge between the different disorders, making diagnosis more difficult. An early history of repeated falls, for example, should warrant concern for progressive supranuclear palsy (PSP), vascular dementia, or Parkinson disease. This finding is valuable when it is present early in the illness, although most dementias are associated with basal ganglia involvement later in their disease course, diminishing the value of falls for diagnosis in the later stages. Likewise, inappropriate behavior and disinhibition are commonly seen in patients with advanced dementia syndromes, regardless of disease etiology, however, when these findings are a prominent presenting feature in the relative absence of amnestic symptoms, FTD should be considered more likely.

Cognitive histories should be comprehensive and must include evaluation of memory, language, visuospatial function, executive functioning, behavior, and attention (**Table 68-1**). The comprehensive history should probe for autonomic symptoms and sleep patterns, with emphasis on symptoms associated with disorders of REM sleep behavior and sleep apneas.

TABLE 68-1 ■ ASSESSMENT OF MAJOR COGNITIVE DOMAINS IN NEURODEGENERATIVE DISORDERS

Memory: repetitive statements, misplacing items, missed appointment or medications, recalling recent/remote events
Language: speech fluency, comprehension, reading, writing, articulation, word-finding, content of speech, output, spelling
Visuospatial: getting lost, driving, object perception, completing household repairs, parking
Executive: planning, flexibility/rigidity in thinking, organization, multistep tasks
Motor: gait, falls, tremor, dysphagia, weakness, handwriting, coordination
Autonomic: light-headedness, bowel/bladder function, impotence, hypotension

The assessment of behavioral symptoms can be particularly helpful and sometimes critical in non-Alzheimer neurodegenerative disorders. Behavioral variant frontotemporal dementia (bvFTD) is the most common cause of dementia in patients younger than age 60. Behavioral symptoms or personality change are commonly the presenting symptoms of this disorder (see discussion later in this chapter). Recent research criteria for bvFTD require three of the following six symptoms to meet “possible” criteria: early disinhibition, early apathy, early loss of sympathy or empathy for others, early repetitive motor behaviors, early hyperorality, and deficits in frontal executive function with relative sparing of visuospatial abilities. For probable bvFTD, in addition to meeting the “possible” criteria just listed, frontotemporal atrophy or the presence of a known mutation is required. The emergence of predominant behavior and personality changes in the absence of episodic memory and perceptual complaints localizes disease to the frontal or anterior temporal lobes.

The neurologic examination is a critical component to the assessment of neurodegenerative disorders and typically confirms the clinical impression obtained from the history. The motor examination identifies both pyramidal and extrapyramidal signs as well as features characteristic of FTD, dementia with Lewy bodies (DLB), corticobasal degeneration (CBD), and PSP. Examination of cranial nerves includes an assessment of eye movements and range of gaze. Abnormalities in vertical gaze with a preserved oculocephalic reflex are a characteristic finding in PSP, while horizontal gaze abnormalities are more typical of CBD. Abnormalities in saccadic eye movements can be seen in a number of neurodegenerative disorders ranging from AD to PSP. Saccadic movements are tested by asking the patient to focus on an object in front of them (such as a pen tip held by the examiner) then to quickly refocus on an item in their peripheral field (such as the examiner’s finger) while the examiner watches carefully for saccadic latency (delay in initiation of movement), incomplete saccades (gaze palsy), and interrupted or jerky saccadic movement. Saccades should be tested in all four directions. The examiner should test ocular pursuit by having the patient track an object, such as the examiner’s finger, in both horizontal and vertical directions.

The examination should probe for changes in cognition, behavior, and movement with emphasis upon the earliest abnormalities. It is important to realize that early symptoms reflect where the illness began, and this is usually helpful in the determination of disease etiology. Confirmatory imaging and laboratory work and standard laboratory tests to exclude treatable etiologies of cognitive impairment can then be completed (**Table 68-2**).

TABLE 68-2 SOME LABORATORY TESTS COMMONLY USED IN THE EVALUATION OF COGNITIVE DISORDERS

Chemistries, including liver function tests and renal function tests
Complete blood count
Vitamin B_{12}
Homocysteine
Methylmalonic acid
Syphilis serology
HIV
Thyroid function

DISORDERS ASSOCIATED WITH α-SYNUCLEIN DEPOSITION

Dementia With Lewy Bodies

The precise role of α-synuclein in health and disease is not fully understood. High concentrations of α-synuclein in synaptic regions suggest a role in synaptic plasticity. In DLB, α-synuclein accumulates with the brain stem, basal ganglia, and cortex, resulting in a progressive neurodegenerative cognitive, behavioral, and motor disorder. The prevalence of DLB is still uncertain, and the coassociation of Lewy body and AD pathology is extremely common in aging dementia populations. Indeed, even with classical AD associated with apolipoprotein E4 genotype, more than 50% of subjects show Lewy bodies, and genetic disorders that predispose to Lewy bodies often show the coassociation of Aβ-42. Based on autopsy studies, DLB is often misdiagnosed during life.

The reported mean onset of disease is 75 years with a range from 50 to 80 years, and there is a slight predominance of DLB in men compared to women. The clinical and pathologic overlap between DLB and AD and with Parkinson disease dementia (PDD) is well recognized, resulting in some diagnostic challenges. Accurate diagnosis has clinical implications, as patients with DLB compared to AD tend to have robust response to cholinesterase inhibitors, and patients with DLB often have sensitivity to neuroleptic medications.

The characteristic features of DLB are cognitive impairment with profound fluctuation, spontaneous parkinsonism, REM behavior sleep disorder (the physical enactment of dreams), and visual hallucinations that are often complex. The typical neuropsychological profile differs somewhat from that of AD. DLB often involves greater parietal-occipital lobe deficits and lesser medial temporal lobe deficits. This manifests in testing as better performance on episodic memory tasks, and recognition memory when compared to AD patients. Invariably, memory becomes impaired over time. Combined cortical and subcortical deficits are common, and deficits in attention are a core feature of the disease.

The degree of cognitive fluctuation can be so profound as to affect Mini Mental State Examination (MMSE) scores up to 50% from day-to-day, and many patients repeatedly move in and out of delirium. Unfortunately, eliciting a history of fluctuation can be difficult, and this symptom may not be well described by caregivers. Clinicians should consider several different approaches, including questions focused on marked alteration in attention, staring spells, daytime sleepiness, and episodes of incoherent speech. On occasion, the fluctuation can be so severe as to result in emergency room evaluation for a transient ischemic attack (TIA) or delirium. Several structured scales exist to assist in assessment of fluctuation, including the One Day Fluctuation Assessment Scale and the Clinical Assessment of Fluctuation.

A common feature of neurodegenerative disorders with α-synuclein pathology is REM sleep behavior disorder (RBD) defined as vivid and often frightening dreams that are frequently acted out verbally or motorically. RBD occurs in 85% of DLB cases, compared to 15% of Parkinson disease patients and 60% of patients with multiple system atrophy (MSA). It is uncommon in other forms of dementia where α-synuclein pathology is absent. In the DLB diagnostic criteria, RBD is considered a suggestive feature. Autonomic dysfunction is also common and can be profound. When REM behavior occurs in association with severe autonomic symptoms, MSA rather than DLB should

be considered. Unexplained loss of consciousness is another supportive feature of DLB and significant depressive symptoms occur in up to 40% of cases.

About two-thirds of DLB cases will exhibit visual hallucinations, misperceptions or, less frequently, delusional misidentification. When delusional misidentification, such as mistaking the spouse, friend, or relative as an impostor, occurs as the first symptom of a dementia, DLB is highly likely. The visual hallucinations of DLB can be vivid with distinct colors and the inclusion of human figures and animals. In contrast to the hallucinations sometimes seen with more advanced AD, visual hallucinations occur early in DLB. In one pathology-based study, visual hallucinations corresponded to a greater number of Lewy bodies in the anterior/inferior temporal lobes and to larger deficits in acetylcholine. Visual hallucinations often respond to boosting brain acetylcholine with cholinesterase inhibitors.

Spontaneous parkinsonism is a hallmark feature of DLB, occurring in up to 70% of cases. Common findings include bradykinesia, axial and appendicular rigidity, postural instability, slowed response times, and hypomimia. In contrast to Parkinson disease, the parkinsonism of DLB is more commonly bilateral and less frequently includes tremor. Parkinsonism rarely occurs in isolation as an early finding in DLB although early features of the cognitive syndrome are commonly overlooked. Response to levodopa treatment is less frequent than the response seen in Parkinson disease; however, efficacy data may be biased. Clinicians are more likely to avoid such drugs in DLB patients for fear of adverse effects or aggravations of hallucinations.

Parkinsonism contributes substantially to the disability in DLB and alters the clinical course. Mean survival among postmortem confirmed cases of DLB is 10 years, with a rate of disability at approximately 10% per year, often exceeding that of Parkinson disease. Cases of rapid progression to death in 1 to 2 years have been described. Risk factors for higher mortality include older age, hallucinations, greater degrees of fluctuation, and neuroleptic sensitivity.

Diagnostic criteria for DLB assist in identification of disease and are particularly useful for research purposes (**Table 68-3**). In the revised schema, core features include prominent fluctuation, recurrent visual hallucinations, and spontaneous features of parkinsonism such as rigidity, bradykinesia, and hypomimia. Supportive and suggestive features are also defined. To meet diagnostic criteria for probable disease, two core features or the combination of one core feature and one supportive feature are required. If suggestive features are present in the absence of core features, the term “possible DLB” is used.

TABLE 68-3 MCKEITH CRITERIA FOR DLB[a]

Central features
Progressive cognitive decline with functional impairment
Prominent memory impairment may not occur early but is usually evident with progression
Deficits in attention, executive functioning, and visuospatial ability may be prominent early
Core features
Fluctuating cognition with prominent variations in attention and alertness
Recurrent visual hallucinations
Spontaneous parkinsonism
Suggestive features
REM sleep behavior disorder
Neuroleptic sensitivity
Low dopamine transporter uptake in the basal ganglia (SPECT, PET)
Supportive features
Repeated falls
Transient, unexplained loss of consciousness
Severe autonomic dysfunction
Systematized delusions
Depression
Hallucinations in nonvisual modalities
Relative preservation of medial temporal lobe structures on CT/MRI
Generalized low uptake on SPECT/PET with reduced occipital activity

Abnormal MIBG scintigraphy
Prominent slow wave activity on EEG with temporal lobe transient sharp waves

[a]Probable DLB requires two core features or one core feature and at least one suggestive feature.

Possible DLB requires one or more suggestive features. Probable DLB should not be based on suggestive features alone.

CT, computed tomography; DLB, dementia with Lewy bodies; EEG, electroencephalogram; MIBG, metaiodobenzylguanidine scintigraphy; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

Adapted from McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology. 2005;65(12):1863–1872.

The pathologic hallmark of DLB is the presence of neuronal spherical intracytoplasmic inclusions of α-synuclein, termed Lewy bodies (**Figure 68-1**). The Lewy bodies seen in DLB are very similar in appearance to those that are seen in Parkinson disease; however in DLB, the distribution extends beyond the substantia nigra and locus coeruleus to involve the neocortex and limbic system. Cortical Lewy bodies lack the typical dense core with pale halo appearance that is seen in Parkinson disease. Other intraneuronal aggregates of α-synuclein (Lewy neurites), cortical senile plaques, and sparse tau pathology are all described in DLB.

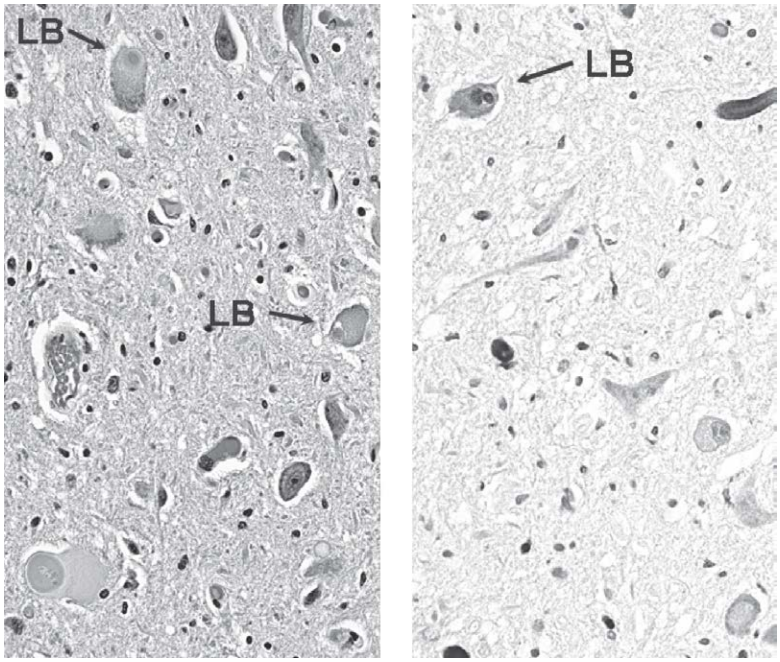


FIGURE 68-1. Lewy bodies (LB) seen with hematoxylin and eosin staining (*left*) and α-synuclein staining (*right*).

Currently, imaging studies do not add substantially to differentiating DLB from other neurodegenerative disorders and are only included as supportive features in diagnostic criteria. Structural magnetic resonance imaging (MRI) often identifies less atrophy of the medial temporal lobes in cohorts of DLB compared to AD and variably identifies greater atrophy in the basal ganglia structures and the dorsal midbrain. In group studies, single-photon emission computed tomography (SPECT) with ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO) tends to show decreased regional cortical brain activity in parietal-occipital regions of DLB compared to AD patients. DLB patients exhibit decreased dopamine transport in the putamen and caudate by dopaminergic SPECT and decreased postganglionic sympathetic cardiac innervation by I-metaiodobenzyl guanindine (MIBG) SPECT imaging. The modest performance characteristics of these tests limit their clinical utility.

The clinical course of DLB is often faster than that seen in AD and a drop of four to five points on MMSE per year is common. Patients with DLB should be tried on cholinesterase inhibitors. Often this results in responses that exceed those seen in AD. Social stimulation and physical exercise to maximize balance and strength should be recommended. Symptomatic treatment with levodopa can be used, if indicated for parkinsonian symptoms, once fluctuation and visual hallucinations are stabilized with a cholinesterase inhibitor. Patients should be advised to avoid anticholinergic medications, including many common over-the-counter cold remedies. RBD, if severe, can be treated with clonazepam. Atypical neuroleptic medications should be cautiously considered only if intolerable behavioral disturbances emerge.

Parkinson Disease Dementia

The temporal relationship between the onset of dementia and the development of parkinsonism is the primary clinical feature distinguishing DLB from PDD. In PDD, cognitive deterioration occurs in well-established Parkinson disease, typically years to decades after motor systems are identified. In contrast, research criteria for DLB require cognitive symptoms that predate parkinsonism by 12 months; although this "1-year rule" is often difficult to apply in the clinical setting. This temporal distinction is arbitrary, and many believe that the two disorders represent different points in the spectrum of the same disease, and abnormalities in α-synuclein accumulation underlie both disorders.

Approximately one-third of older Parkinson disease patients will develop sufficient cognitive symptoms during the course of their illness to impair function. Indeed, the diagnosis of Parkinson disease puts a patient at high risk with mild cognitive impairment (MCI) and then PDD following in many patients. In pure PDD, the prominent findings include motor and psychomotor slowing, decreased response times, and alterations in concentration and attention. The recognition that medications used to treat Parkinson disease can affect cognition and the understanding that, because of age, a substantial number of Parkinson patients will develop concurrent AD result in a scenario where cognitive symptoms in this population can be multifactorial. Possible predictors for dementia in Parkinson disease include older age at onset of motor symptoms, bradykinesia, nontremor prominent Parkinson disease, bilateral onset of motor signs, and declining response to levodopa. Depression and visual hallucinations may increase the risk as well. Patients with DLB typically exhibit a faster clinical decline than do patients with PDD.

Multiple System Atrophy

MSA is a sporadic disease marked by degeneration of multiple neurologic systems and resulting in relentlessly progressive clinical course. Death typically occurs within 6 to 10 years with an estimated 10-year survival of 40%. Relatively infrequent, the incidence is estimated to be 0.6/100,000 person-years or between 1.86 and 4.9/100,000 population. The incidence increases to 6/100,000 person-years among patients older than 50 years. The mean age of onset is 54. While currently speculated to have a combination of environmental and genetic predispositions, neither has been definitively established. Epidemiologic studies suggest a potential risk associated with exposure to pesticides. MSA is about three times more frequent in men than women and limited epidemiologic data suggest that it may be less frequent among smokers.

The term MSA was first used in 1969 and encompasses diseases previously labeled as striatonigral degeneration (now termed MSA-P for parkinsonism), Shy-Drager syndrome, and olivopontocerebellar degeneration (now termed MSA-C for cerebellar). The MSA subtypes are indicative of the predominant neurologic component involved. Patients with prominent orthostatic features tend to have decreased survival. Several derivations of diagnostic consensus statements exist with mixed sensitivity.

The presenting symptoms of MSA are variable and include cerebellar findings, autonomic failure, pyramidal findings, and parkinsonism. Parkinsonism (MSA-P) is prominent in the majority of cases (80%) with cerebellar symptoms (MSA-C) more prominent in about 20% of cases. The more common presenting parkinsonian features are akinesia, rigidity, and postural (rather than resting) tremor. Autonomic symptoms precede motor symptoms in most cases. Gait instability is common, but falls occur less frequently in early stages than in PSP. In early stages, MSA can mimic Parkinson disease but more symptoms evolve within 5 years. Gait ataxia, limb kinetic ataxia, and dysarthria are the more frequent presenting symptoms in patients with cerebellar-dominant MSA. The dysarthria caused by cerebellar dysfunction has a characteristic appearance of jerky, intermittently explosive, and slurred output often associated with poor separation of syllables.

Autonomic symptoms include orthostasis, erectile dysfunction, constipation, and urinary incontinence. While orthostasis is common, syncope occurs infrequently. Diagnostic criteria for the orthostatic component of MSA require a 30 mm Hg drop in systolic blood pressure; although in practice, a 20 mm Hg drop in systolic blood pressure or 10 mm Hg drop in diastolic blood pressure is thought to be significant in the absence of appropriate increased heart rate. Occurrence of symptoms suggestive of MSA in an individual younger than 30 years or in an individual with a family history of similar disease should raise suspicion for alternative diagnoses.

Most MSA patients complain of sleep problems, commonly sleep fragmentation (53%), early waking (33%), and insomnia (20%). As with other synucleinopathies, RBD is common, occurring in up to 60% of MSA patients. Nocturnal stridor and obstructive sleep apnea are also frequent in MSA. Stridor is associated with decreased survival and risk of sudden death.

Brain MRI changes occur in some patients but lack sensitivity and specificity for definitive diagnosis. These findings include hypointensity and atrophy of the putamen on T2-weighted images with a slit-like marginal

hypointensity just lateral to the putamen on axial images. A characteristic "hot cross bun" sign has been described in the pons and middle cerebral peduncles thought to be caused by degenerative changes in pontocerebellar fibers. This finding lacks sensitivity and is sometimes seen in Parkinson disease, limiting specificity. Atrophy of the brain stem, middle cerebellar peduncles, and cerebellum may also be seen. Volumetric analyses of the striatum and brain stem, where atrophy is very severe in mean systemic arterial pressure (MSAP) but not in simple Parkinson disease, demonstrate some promise in discriminating these two disorders. Electromyography (EMG) abnormalities at the anal sphincter can be seen in MSA, although the clinical utility for distinguishing MSA from Parkinson disease in early stages of disease has not been established.

The hallmark pathology of MSA is cell loss, gliosis, and glial inclusions in multiple neurologic systems including the spinal cord and cortex. Prominent abnormalities are also seen in the basal ganglia, substantia nigra, and olivopontocerebellar pathways, as suggested by the terminology, with anatomy reflecting symptoms. On gross inspection, the putamen is shrunken and displays a green-gray discoloration that can appear cribiform when disease is severe. As with DLB and Parkinson disease, there is an accumulation of α-synuclein as half-moon–, oval-, or conical-shaped argyrophilic glial cytoplasmic inclusions.

Treatment is generally symptomatic with about one-third of patients responding to levodopa in the early stages of the disease. Patients should be encouraged to sleep in a lateral decubitus rather than supine position to minimize airway obstruction. Use of positive airway pressure devices should be considered. Invasive means of controlling stridor and apneas have included tracheotomy, but should be approached cautiously within the full context of ethical and quality-of-life considerations. RBD may respond to low-dose clonazepam at night. Labile blood pressures may develop and should raise concern when symptomatic. Avoiding alcohol, heavy meals, or straining at micturition and defecation is recommended. Elastic stockings and elevating the head of the bed may provide some relief. Pharmacologic approaches designed to increase sympathetic tone (midodrine) or volume expansion (fludrocortisone) may be required. Patients with MSA-C tend to maintain function for a longer time than those with MSA-P.

NEURODEGENERATIVE DISORDERS ASSOCIATED WITH TAU, TDP-43 OR FUS PATHOLOGY

Frontotemporal Lobar Degeneration Syndromes

FTLD is the term used to capture a neuropathologically linked group of non-AD dementing conditions associated with frontotemporal and basal ganglia pathology. FTD subsumes three clinical syndromes, bvFTD, semantic variant primary progressive aphasia (svPPA), and nonfluent variant primary progressive aphasia (nfvPPA). Recent evidence indicates that FTLD is closely related to several other neurodegenerative disorders: CBD, PSP, and motor neuron disease (**Figure 68-2**).

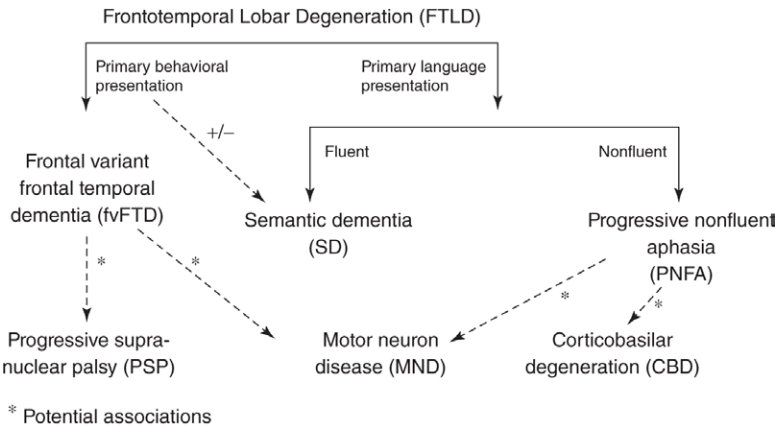


FIGURE 68-2. Frontotemporal lobar degeneration (FTLD) and potential associations to other neurodegenerative syndromes.

The core anatomic feature of FTLD is the focal, often asymmetric cortical degeneration of frontal and anterior temporal regions with general sparing of posterior cortical structures. The resultant brain atrophy can be severe, sometimes described as "knife-edge," and the brain can weigh as little as 750 g (**Figure 68-3**). Patients present with a primary behavioral or language deficit that typically corresponds to the region of greatest brain atrophy and

dysfunction. Patients presenting with primary behavioral deficits are classified as suffering with bvFTD. bvFTD overlaps considerably with the two syndromes that present with predominant language deficits, svPPA and nfvPPA. In most centers bvFTD accounts for more than 50% of all cases with the others divided between svPPA and nfvPPA. The neuropathologic basis for nearly one-half of these diseases is the abnormal accumulation of tau protein with a similar percentage associated with abnormal aggregates of TDP-43. Less than 10% show aggregates of the FUS protein. Many FTD patients are misdiagnosed as having AD during life. In addition to changes in personality and behavior, features that should alert physicians to the possibility of FTD include early abnormalities in social conduct, loss of sympathy and empathy for others, repetitive motor behaviors, or hyperorality. When cognitive testing is completed, suspicion should be raised when abnormalities in executive functioning occur in the absence of prominent amnestic complaints or cognitive features localizing to posterior structures, such as problems with calculations and visuospatial tasks.

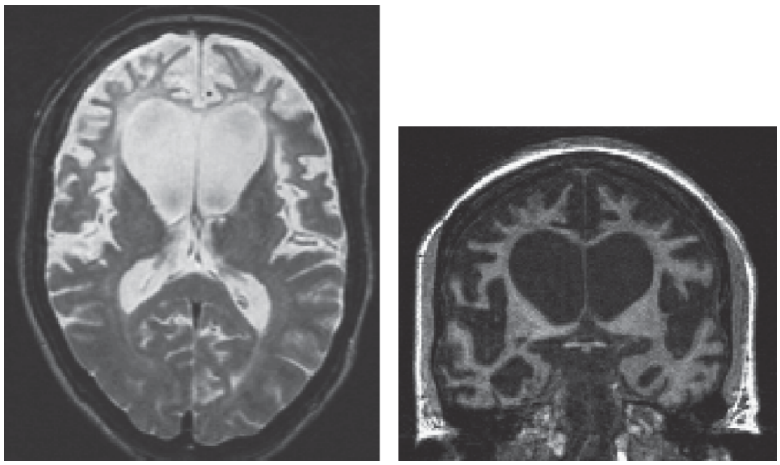


FIGURE 68-3. T2-weighted axial (*right*) and T1-weighted coronal (*left*) brain magnetic resonance imaging (MRI) in a 59-year-old woman with pathology-confirmed Pick disease.

Patients who present with isolated language symptoms that exist for at least 2 years in the initial stages of cognitive decline are termed to have primary progressive aphasia (PPA). As a group, patients with PPA have greater atrophy on the left than the right of the perisylvian region, the anterior temporal lobes, and the basal ganglia. Inferior parietal lobule atrophy has also been described in PPA and is associated with predominantly word-finding deficits. Called logopenic aphasia by Gorno-Tempini and colleagues, this form of PPA is usually due to underlying AD pathology. As the syndrome progresses, patients presenting with nfvPPA go on to develop features of PSP or CBD or even amyotrophic lateral sclerosis (ALS). Thus, careful attention to the development of motor symptoms is necessary to help with the prediction of the underlying pathology. The emergence of artistic behavior has been described in some patients with primary language difficulty.

Efforts to distinguish the various PPA syndromes from each other may have clinical ramifications. Based on apolipoprotein epsilon 4 expression in clinical studies, it appears likely that the logopenic variety of PPA is a language presentation of AD; although pathologic confirmation of this correlation is lacking. As the term implies, these patients have decreased speech output. They typically have slow speech with impaired syntactic comprehension and naming. The logopenic variety is associated with short-term phonologic memory deficits. These patients exhibit profound echoic memory deficits manifested as forgetting portions of longer phrases during repetition tasks. As pathologic studies become available, if confirmed to be AD in etiology, these patients may be amenable to treatment with cholinesterase inhibitors or emerging amyloid-directed treatment strategies.

Nonfluent Variant Primary Progressive Aphasia

Patients with nfvPPA typically have apraxic, labored speech with errors in grammar, and difficulty with more complex syntax. Speech apraxia is the inability to produce speech caused by difficulty in programming the sensorimotor commands for the positioning and movement of muscles used to produce speech. This leads to difficulty with initiation of speech, sound substitutions, omissions, transpositions of syllables, and a slower rate of expressing sentences punctuated with inappropriate starts and stops. The errors produced in apraxic speech are typically inconsistent. Patients may display difficulty with articulating multisyllabic words. Speech apraxia is localized to the left opercular and anterior insular region.

Anomia is variably present and phonemic paraphasias are frequently observed. Speech output is decreased and dropped words, often articles such as “the” occur. In patients with nfvPPA, sentences tend to have more nouns than verbs. In contrast to patients with svPPA, these patients maintain single word comprehension and semantic knowledge. Thus, nfvPPA is not likely in a patient who has preserved articulation, preserved grammar, and deficits in semantic knowledge. Insight into the condition can be exquisitely preserved with nfvPPA, and patients often develop depression. Behavioral problems are uncommon in early stages of disease.

The evaluation of brain MRIs in 11 patients with nfvPPA using voxel-based morphometry (VBM) identified regions of atrophy that are typically asymmetrically left-dominant with preferential involvement of the inferior frontal lobe, the insular region, and the caudate. Hypometabolism of the left frontal region can be observed on FDG positron emission tomography (PET). The majority of patients show tau pathology at autopsy with CBD followed by PSP and Pick changes. Approximately 20% show TDP pathology, usually TDP-43 type A.

Semantic Variant Primary Progressive Aphasia

In contrast to patients with nfvPPA, patients with svPPA have fluent speech that is grammatically accurate, but they exhibit the hallmark loss of semantic knowledge. Semantic memory is the encyclopedic knowledge of people, objects, facts, and words. Unlike episodic memories, individuals are not aware of where or when they learned these facts. Eventually individuals lose all knowledge about the fact or word and exhibit features of a multimodality agnosia. Therefore, even when they are provided with the name of the object, the object is not recognized. Early in the disease, patients are often aware of word-finding difficulties but are unaware of comprehension difficulties. Semantic paraphasias are frequent, with supraordinate substitutions of words and common use of nonspecific grouping words such as “stuff” and “things.” Repetition and prosody are preserved as is syntax and verb recognition.

Patients with svPPA display surface dyslexia manifest by difficulty pronouncing irregularly spelled words, such as “gnat,” “heir,” or “pint,” when pronunciation does not follow standard phonologic rules. On neuropsychological testing, patients with svPPA have difficulty with category fluency and confrontational naming, particularly with low-frequency words. Often, svPPA patients have difficulty naming famous people. In contrast to AD, many svPPA patients have greater deficits for remote compared to recent memory, when memory deficits become involved.

Of all the PPA syndromes, svPPA has the greatest propensity to include behavioral problems, which are included as supportive evidence in diagnostic criteria. As with FTD, the behavioral issues seen with svPPA often involve hyperorality, disinhibition, and aberrant motor behavior. Diagnostic criteria include behaviors such as loss of sympathy and empathy, narrowed preoccupations, and parsimony (excessive frugality, stinginess). Rigidity in thinking can be striking. svPPA patients can develop compulsions and have been described to have visual hypervigilance, such as recognizing that a hair is subtly out of place on an examiner or quickly seeing a coin on the street. They may exhibit difficulty in the interpretation of emotions, particularly negative emotions such as sadness, anger, and fear. Emergence of behavioral symptoms correlates with duration of illness but can also be an early finding. The presence of early behavioral issues in a patient with a PPA syndrome should alert to the possibility of svPPA.

Anatomic studies may explain why svPPA patients often exhibit behavioral abnormalities. The disorder begins in the amygdala and anterior temporal lobes. When it starts on the left side, language deficits predominate, while right-sided presentations are characterized by loss of empathy for others or deficits in the recognition of familiar people. These patients sometimes meet research criteria for bvFTD while others are more typical of svPPA. While svPPA begins in the anterior left temporal lobe, it typically spreads anteriorly to involve the frontal regions. Eventually it spreads to the right medial frontal lobe, the right orbitofrontal lobes, and the right insular region, areas associated with behaviors such as disinhibition and apathy. The absence of behavioral problems in the logopenic variety of PPA and in nfvPPA may be due to the general sparing of these same structures in those diseases.

Patients with svPPA often have TDP-43 type C–positive, tau-negative inclusions at autopsy. The etiology for svPPA and for TDP type C aggregates is unknown. Rarely are these cases familial. Recent work suggests that a significant subset of these patients have a history of autoimmunity and increased levels of tumor necrosis factor (TNF) in the serum.

Behavioral Variant Frontotemporal Dementia

bvFTD presents with the insidious onset of change in personality and inappropriate behaviors. The mean age of onset is in the mid-fifties. Most commonly, symptoms include disinhibition, poor impulse control, loss of sympathy or empathy for others, overeating, compulsive behaviors, and deficits in executive controls or multitasking (**Table 68-4**). Patients can develop stereotyped behaviors, defined as repetitive, invariant behaviors that lack purpose. Examples

include counting, pacing, organizing, or the repetitive use of catch phrases. Socially inappropriate activities can include shoplifting and other criminal behavior, public urination, offensive speech, and public masturbation. Perseveration is common. Cravings for sweets are often observed. When associated with the decreased sense of satiety that can occur, large, unhealthy weight gain results. Hyperorality and oral exploratory behavior can occur.

TABLE 68-4 BEHAVIOR SYMPTOMS SEEN IN FRONTAL VARIANT FTD

Antisocial behavior
Apathy
Change in beliefs (hyperreligiosity, change in attitude)
Cravings (sweets, weight gain)
Criminal behavior (theft, assault, public urination)
Delusions
Disinhibition
Euphoria (inappropriate jocularity)
Hyperorality (oral exploratory behavior in late disease)
Hypersexuality (offensive statements, masturbation)
Impotence and decreased sexual drive
Impulsivity
Loss of empathy (coldness, self-centered)
Obsessive-compulsive behavior
Perseverative behavior
Poor insight
Stereotyped behavior (counting, pacing, repetitive use of catch phrases)

Patients with bvFTD are often misdiagnosed as having psychiatric illness. In other instances, any patient with an atypical dementia syndrome is considered to have bvFTD. Delusions can occur, often with bizarre or grandiose overtones. Patients exhibit lack of empathy and can have a cold, blunted effect. When the anterior cingulate and medial frontal lobes are involved, apathy can be particularly prominent. Some patients undergo large changes in their beliefs and attitudes, including religious sentiments. In contrast to AD, depression is uncommon in bvFTD.

Neuropsychological testing demonstrates abnormalities in executive functioning, working memory, and social cognition with general sparing of visuospatial skills and verbal memory. Consequently, the MMSE score can be quite high even among patients with marked functional disability. bvFTD patients also display problems with set-shifting, concept formation, and abstract reasoning. They may demonstrate disinhibition, impulsivity, and poor judgment during testing. These behaviors can falsely lower verbal memory scores. When closely scrutinized, poor scores on such tests are accompanied by frequent intrusions of novel words and endorsement words that were not part of the original list learned (false positives on recognition testing).

Behavioral symptoms are a common late finding in most dementia syndromes. Thus the emergence of behavior and personality symptoms in a patient with well-established dementia should be looked upon with caution when considering a change in diagnosis to bvFTD. The importance of the first symptom (often the presenting symptom) in the evaluation of patients with neurodegenerative disorders cannot be overstated.

Patients with bvFTD will typically have profound, usually bilateral, frontal, anterior insular, and anterior temporal lobe atrophy. Patients with greater atrophy on the right frontal lobe than left have more severe behavioral symptoms. Stages of atrophy have been described with the earliest stage involving only mild atrophy of the orbital and superior medial frontal lobes and hippocampus. As the disease progresses, the anterior frontal and temporal cortices and basal ganglia are increasingly involved. The severity of atrophy increases as disease advances. William Seeley has demonstrated that in many instances, the first neurons afflicted in bvFTD are von Economo neurons that sit in the anterior insular and cingulate cortex. SPECT and FDG-PET techniques have been used to differentiate FTD from AD with PET receiving Food and Drug Administration (FDA) approval for this indication. Both SPECT and FDG-PET demonstrate bilateral frontal hypometabolism/perfusion in patients with FTD. Amyloid imaging is extremely valuable in separating AD from bvFTD, particularly in patients under the age of 70 in whom the presence amyloid is not highly

prevalent.

Pick Disease

Pick disease is a pathologic diagnosis and occurs in approximately 20% of clinical cases presenting with signs and symptoms of bvFTD. Less commonly it presents as nfvPPA. First described in 1892 by a German neurologist, Arnold Pick, the pathologic hallmark of Pick disease are argyrophilic cellular inclusions known as Pick bodies and swollen achromatic tau-positive neurons termed Pick cells. This is invariably associated with loss of large pyramidal neurons, resulting in a spongiform histologic appearance with selective atrophy of the frontal and anterior temporal lobes. Pick bodies are localized to the limbic cortex, paralimbic cortex, and predominantly the ventral aspect of the temporal lobe. The pre- and postcentral gyri are notably spared. The largest concentration of Pick bodies is found in the hippocampus and amygdala. Pick bodies are composed of randomly arranged tau filaments. In AD, tau pathology (neurofibrillary tangles) can spare the dentate gyrus; however, in Pick disease, this region is heavily involved.

Other FTLD Neuropathologies

FTLD is associated with tau pathology in about half of cases. The tau gene product has six isoforms, half of which result in three microtubule-binding repeats (3Rtau) and the other half result in four microtubule repeats (4Rtau). Pick disease is usually associated with 3Rtau. PSP and CBD, in contrast, are associated with 4Rtau. The clinical features and neuropathology of PSP and CBD are described later in this chapter.

Among FTLD cases that do not stain for tau protein, the histopathology will typically indicate a variable pattern of neuronal loss and gliosis without characteristic features such as neurofibrillary tangles or Pick bodies. Historically, the term “dementia lacking distinctive histology” (DLDH) was employed; however, new discoveries led to the reclassification of many such cases to FTLD-U (ubiquitin), and because DLDH is extremely rare, the term is disappearing. FTLD-TDP account for around 50% of all non-tau FTLD cases. In these cases, neuronal inclusion bodies with prominent ubiquitin staining are seen. These inclusion bodies stain negative for tau and are localized throughout the neocortex and within anterior horn cells. This pathology has been identified in patients with and without concurrent motor neuron disease.

More recently, TDP-43 neuropathology has been subdivided into four types, TDP-A to TDP-D, depending on the pattern of the TDP inclusions within the nucleus and cytoplasm. TDP type A is often associated with mutations in the progranulin gene, although sporadic cases have been seen. Type B is often associated with motor neuron disease, and the most common genetic mutation associated with familial FTD-ALS, *C9orf72*, often shows type B changes. TDP-C is the pattern associated with svPPA, while type D is seen with the rare FTD-causing mutation in valosin.

The Genetics of FTD

Our understanding of the genetics of FTLD is evolving. In 1998 it was discovered that a mutation in the microtubule-associated protein tau (*MAPT*) was responsible for a familial form of FTD associated with Parkinson disease (FTDP-17). This mutation appears to be more common in Southern Europe and France than in Northern Europe, and a few mutations have been reported in China and Japan. The disease onset with mutations is variable with several variants presenting in the third of fourth decade. Mean disease onset is approximately 52 years. The mechanism for disease pathogenesis with tau mutations appears to be variable. In some cases, a mutation in an intron adjacent to exon 10 leads to an excess of the 4R form of tau with abnormal aggregation of tau. In other mutations, abnormal microtubule-binding or excessive formation of oligomers appears to be the mechanism for neurodegeneration.

A mutation in the progranulin (*GRN*) gene (only 1.7 Mb away from the tau gene) was identified in 2006. This mutation appears to account for up to 11% of sporadic and 25% of familial FTD cases. Disease onset tends to be later than with tau, and approximately 10% of gene carriers remain asymptomatic after age 70. There are genes that modify progranulin expression that may be partially responsible for this clinical variability. The onset of disease can range from 35 to 80 years. The phenotype is more variable than with *MAPT*, and syndromes vary from bvFTD, nfvPPA, CBD, and Parkinson disease to AD. Asymmetry is common with one hemisphere massively atrophic and the other relatively normal. The pathomechanisms associated with *GRN* mutations are also debated: loss of neuronal growth attributed to low levels of the progranulin protein versus excessive inflammation associated with low progranulin levels or a relative increase in the granulins proteins cleaved from progranulin. All of the hypothesized mechanisms probably contribute to illness. Autoimmunity is seen in more than 10% of gene carriers and can precede neurologic disease.

In 2011 a mutation in the *C9orf72* gene was discovered as the major cause for familial forms of FTD, ALS, and FTD-ALS. A huge expansion of a hexanucleotide repeat in the intron of C9 leads to massive overproduction of RNA and the production of dipeptides generated from the RNA in a non-ATG manner. The clinical onset is typically in the sixth decade but patients in the fourth and eighth decades have been described. The illness often begins as a psychiatric illness with highly variable symptoms ranging from borderline personality disorder, bipolar illness, depression, and conversion disorder to drug addiction. Similarly, whether a gene carrier is diagnosed with bvFTD or ALS is also variable, and in some instances, both syndromes emerge together. The mechanism for disease seems to reflect RNA-mediated neurodegeneration caused by large nuclear RNA aggregates that interfere with nuclear functions, the toxic effects of dipeptides, and possibly gene haploinsufficiency.

Other isolated cases of FTLD-related mutations have been described, including valosin-containing protein gene (*VCP*) and charged multivesicular body protein 2B (*CHMP 2B*). Patients with the *VCP* mutation develop a rare disease with inclusion body myopathy, early Paget disease of bone, and FTD (IBM-PDB-FTD). Additionally, predominantly ALS but sometimes bvFTD phenotypes can occur with mutations in the TDP-43 and FUS proteins.

Treatment of FTLD

Treatment approaches for FTD and related disorders are generally aimed at symptom management, as there are no known disease-modifying therapies. Selective serotonin reuptake inhibitor (SSRI) medications may be beneficial for behavioral symptoms, including carbohydrate craving and compulsions. If delusions are problematic, atypical neuroleptics can be considered. There is no theoretical basis for the use of cholinesterase inhibitors, which can aggravate agitation. Attention to caregiver issues is important as the stressors often differ from those seen in typical AD and can be particularly burdensome. The different social and behavioral issues presented to FTLD compared to AD caregivers and the younger age of both patients and caregivers in FTLD can result in a feeling of isolation in typical AD support groups.

Disease-modifying approaches are being led by Adam Boxer at UCSF. Tau-lowering strategies are emerging for tau forms of FTD including tau mutations, Pick disease, PSP, and CBD. Monoclonal antibodies that target tau appear to show efficacy in animal models and have potential to diminish the brain's tau burden. With progranulin mutations, histone deacetylase (HDAC) inhibitors appear to double the progranulin production by the healthy gene. Clinical trials are beginning in symptomatic gene carriers with the hope that normalization of progranulin levels will slow progression or possibly provide symptomatic relief. While no trials are yet underway for *C9orf72* gene carriers, recent laboratory efforts have focused around developing small molecules that can turn off gene expression.

AMYOTROPHIC LATERAL SCLEROSIS (LOU GEHRIG DISEASE)

ALS was first identified in 1869 by the French neurologist, Jean-Martin Charcot who described a progressive neurodegenerative disease with mixed upper and lower motor neuron signs and symptoms. The disease's name is derived from myelin pallor identified in the lateral aspects of the spinal cord representing axonal degeneration from upper motor neurons as they descend to the limbs. In the United States, the disease is best known as Lou Gehrig disease, named after the famous baseball player who died of the disease in 1941. It occurs with an incidence of approximately 1 to 2/100,000 patients each year with a nearly 2:1 male-to-female predominance. About 5000 people develop ALS annually. As with FTLD, peak incidence occurs in midlife; however disease can be seen in advancing ages.

Patients with ALS typically present with complaints of weakness in one or more limbs, resulting in unexplained tripping or dropping of items. Clumsy fine finger movements lead to difficulty with tasks such as buttoning clothes or writing. Patients often complain of cramping. Bulbar symptoms such as speech slurring, difficulties with swallowing, and hoarseness occur in many patients. Bulbar symptoms are presenting symptoms in about 25% of cases and more commonly occur in older patients. Patients may complain of difficulty chewing or swallowing. Up to 45% of patients will develop a pseudobulbar effect characterized by episodes of uncontrolled laughter or crying, often in inappropriate settings. Many patients have symptoms of a slowly progressive behavioral syndrome including apathy, lack of insight, and loss of empathy.

The neurologic examination identifies both upper and lower motor neuron abnormalities. Muscle atrophy is seen, usually in the hands and often noted at the thenar or hypothenar eminence. Fasciculations and weakness are noted as lower motor neuron findings. Upper motor neuron findings include mild spasticity, hyperreflexia, and abnormal plantar responses. EMG is diagnostic for ALS.

The clinical course is relentlessly progressive with only a 50% survival at 3 years. Mild muscle weakness progresses to inability to walk, difficulty with speaking, and dysphagia. The FDA has approved riluzole for treatment of ALS, which extends survival and delays the need for ventilation support. Treatment is otherwise directed at symptom control and quality of life. This is best achieved with a multidisciplinary approach, including ancillary services such as physical therapy, respiratory therapy, and social work.

The neuropathology of ALS includes neuronal cytoplasmic inclusions of a ubiquinated protein, most commonly seen in lower motor neurons. These inclusions were shown to contain the 43-kDa TAR DNA-binding protein (TDP-43), the same protein that has been identified in FTLD-ALS or pure FTLD. This finding is consistent with a previously recognized association between ALS and FTD.

CORTICOBASAL DEGENERATION

Manifestations of CBD range from bvFTD, nfvPPA, executive and motor deficits to asymmetric parkinsonism, often with a rigid akinetic arm. Often a bvFTD or nfvPPA syndrome is present for many years before the onset of motor symptoms. The mean age of disease onset for CBD is in the mid-sixties. A few series suggest that women may be more commonly affected than men. CBD is generally sporadic in occurrence, although familial cases have been described in association with both tau and progranulin mutations. Many cases are not correctly diagnosed during life.

When parkinsonian features emerge, they are often, but not always, asymmetric. Severe upper limb dystonia can result in internal contracture of the limb with the fingers clutching the thumb with flexion at the wrist. An alien limb phenomenon sometimes occurs with the limb not only levitating, but often hooking onto clothing or grabbing other body parts and behaving as if it were no longer under the control of the patient. On occasion, the alien limb will conflict with actions of the other hand. Simple levitation of the lower extremity is described as well, but is less specific to CBD. Focal reflex myoclonus that is typically present first in the fingers, then in the hand, can be elicited with distal percussion.

Concurrent cortical sensory loss is seen without deficits to peripheral sensory modalities. This is discriminated by testing for agraphesthesia, agnosia, or problems with two-point discrimination. Bilateral limb apraxia is common, and apraxia of opening or closing the eyes can occur. Close evaluation of eye movements will often reveal saccadic latency with normal velocity, often in the horizontal plane. Supranuclear vertical gaze palsy can occur.

CBD shares many neuropathologic abnormalities with FTD and PSP, suggesting the possibility that they represent a spectrum of similar diseases linked by underlying tau pathology. Ballooned neurons throughout the neocortex associated with neuronal loss and astrocytic tau-staining plaques are the diagnostic histologic features of CBD. Unlike Pick disease, the distribution of ballooned neurons is extensive and involves both the primary sensory and motor regions. Pick bodies are absent. Commonly, the superior frontal lobes and the parietal lobes are most heavily affected and are reflected in patterns of neuropsychological testing. Secondary degeneration of the corticospinal tracts occurs. Grossly, asymmetric atrophy of the parasagittal superior frontal gyrus and superior parietal lobule are common, with relative sparing of the temporal and occipital regions.

The treatment of CBD is symptomatic as disease-altering therapies are not known. Levodopa is beneficial in the minority of patients. Muscle relaxants and physical therapy with range-of-motion exercises can be useful. Clonazepam may be instituted for myoclonus. There is no theoretical basis for the use of cholinesterase inhibitors in this disease.

PROGRESSIVE SUPRANUCLEAR PALSY

PSP, also referred to as Steele-Richardson-Olszewski syndrome, is a progressive neurodegenerative disease with prominent extrapyramidal motor findings and supranuclear ocular abnormalities. Patients with PSP present to both movement disorder clinics for motor abnormalities and behavioral clinics for cognitive or psychiatric complaints. The frequency of PSP in the general population is around 1 in 100,000, increasing to 7 in 100,000 among people older than 55 years. Diagnosis typically occurs in the sixth to seventh decade of life. There are only a few published reports of familial cases, suggesting that an autosomal dominant gene plays only a small role in the disease.

The initial descriptions of PSP emphasized abnormalities in movement with nearly all patients exhibiting early gait abnormalities, and 60% presenting with falls as the first manifestation of disease. Patients often pivot with turns and have a tendency to fall backward. Increased tone (axial more than appendicular) and dysphagia (affecting 46% in the first 5 years) are other common motor findings while bradykinesia is seen in only about a quarter of autopsy-proven

cases. Spastic dysarthria results in slurred speech. Ultimately patients become mute.

Eye movement abnormalities are the hallmark feature of the disease, with vertical supranuclear palsy a critical feature for diagnosis. While vertical gaze palsy can be upward or downward, downward gaze palsy has greater specificity for PSP. The oculocephalic reflex for vertical movement is preserved early in disease despite the vertical gaze palsy. Square wave jerks and both latency and hypometria of eye movements are often seen, typically greater with command (saccadic movements) rather than pursuit. A decreased blink rate and furrowed brow can be noticed when interviewing the patient.

Cognitive or psychiatric features are often present, even in the early stages of illness. The pattern of cognitive dysfunction is characterized by abnormalities localizing to the frontal and temporal lobes and subcortical structures. Thus, slowing of cognitive performance and below expectation performance in verbal fluency and executive functioning tasks are often documented, typically with retained verbal and visual memory performance. Behavioral symptoms of apathy, compulsions, perseveration, and utilization behavior are common. This pattern of neuropsychological and behavioral findings is similar to what is seen in FTD, consistent with the overlapping pathology of the two entities.

Treatment of PSP is focused on control of symptoms. Occupational therapy to address speech and visual limitations can be successful. Prevention of falls is critical but often challenging as impulsivity and lack of insight can limit the effectiveness of therapeutic interventions. Levodopa can be helpful in some patients with PSP, but eventually loses its efficacy. Survival is between 6 and 10 years at the time of diagnosis.

SPINOCEREBELLAR ATAXIA SYNDROMES

Spinocerebellar ataxias (SCAs) are a heterogeneous group of disorders with prominent, progressive cerebellar involvement. The current classification system corresponds to the order to which gene mutations have been identified. A comprehensive database, including scientific reviews and a listing of laboratories that will evaluate for mutations, is available at www.geneclinics.org.

Many of the SCA genetic mutations that have been identified to date are associated with expansion of repeated trinucleotides and are inherited in an autosomal-dominant manner. However, penetrance can vary greatly. The length of the polyglutamine repeat appears to be a major determinant of age for disease onset in an inverse manner. Genetic analyses are estimated to identify only 40% to 60% of familial and less than 25% of sporadic cases. The likelihood that a gene mutation will be identified decreases with older age (> 40). The prevalence of SCAs is between 1 and 4/100,000 with variation by region caused by founder effects [SCA 2 (Cuba), SCA 3 (Azores), and SCA 10 (Mexico)]. These disorders most commonly present in the third decade of life with some presenting in youth; however, the range of age extends into older ages for many SCAs.

Phenotypic overlap is common in SCA syndromes, but progressive cerebellar disability often presenting early in disease is a common feature. SCA syndromes often affect the noncerebellar portions of the nervous system, particularly as the disease progresses, with neuropathology identified in the brain stem, basal ganglia structures, and cortex. Such clinical symptoms include oculomotor features (SCA 1, 2, 3), retinopathy (SCA 7), seizures (SCA 10, 17), peripheral neuropathy (SCA 1, 2, 3, 4, 8, 18, 25), or cognitive and behavioral deterioration (SCA 17, dentatorubral pallidoluysian atrophy [DRPLA]).

Other neurodegenerative disorders should be considered in patients with progressive cerebellar dysfunction, including mitochondrial diseases, Huntington disease, leukodystrophies, Frederick ataxia, MSA, prion disease, and the premutation associated with fragile X syndrome. Paraneoplastic processes should be considered in patients presenting with subacute cerebellar dysfunction. While scattered clinical reports describe benefits for some SCAs, treatment is generally aimed at symptom management, physical and occupational therapy, and genetic counseling.

CONCLUDING REMARKS ON NON-ALZHEIMER DISEASE NEURODEGENERATIVE DISORDERS

Scientific advances have remarkably altered our understanding of non-AD neurodegenerative disorders in the past decade. Yet, large gaps remain. In many cases, neuropathology can now be identified, facilitating the process of linking disease syndromes to pathologic substrate and supporting a deeper understanding of disease. In such cases, clinical researchers can begin to accurately describe the clinical presentation of pathology-proven cases to provide

clinicians with clues to neuropathology. When combined with emerging noninvasive diagnostic tools, such as PET imaging with novel ligands such as the Pittsburg compound B, which binds to the protein in amyloid plaques, or the tau protein such as T807 or PBB3, we can achieve the ultimate goal of promoting pathology-driven treatment approaches.

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Chapter 69

Traumatic Brain Injury

Sterling C. Johnson, Christopher R. Nicholas

Learning Objectives

- Understand the epidemiology, pathophysiology, clinical manifestations, and adverse outcomes of traumatic brain injury (TBI) in older adults.
- Learn the specific neuropsychological deficits and psychiatric diseases associated with TBI.
- Acquire cutting-edge knowledge about chronic traumatic encephalopathy (CTE) and the risk of developing dementia following traumatic insults to the brain.
- Learn about various strategies and treatments used to address cognitive deficits associated with TBI.

Key Clinical Points

1. **Older adults have several age-related risk factors or diseases that increase their vulnerability to TBI and its consequences.**
2. **Falls are a major risk factor and the underlying cause in more than half of older patients with TBI.**
3. **The adverse outcomes of TBI in the older population include cognitive, psychiatric, and functional deficits with long-term dependence.**
4. **The selective vulnerability of the frontal and temporal lobes to injury underlies the preponderance of neuropsychological deficits involving frontal systems, including executive function, attention, and working memory.**
5. **History of TBI increases risk for CTE—a chronic neurodegenerative disease characterized by tau pathology in the brain and a constellation of clinical symptoms, including cognitive, mood, and motor impairments.**

DEFINITION

Traumatic Brain Injury (TBI) is craniocerebral trauma associated with decreased consciousness, cognitive or neurologic abnormalities, skull fracture, or intracranial injuries. TBI is common among older adults mainly through the association with falls. TBI in older adults presents special issues for the clinician to consider in the management of these patients, including a higher risk of poor recovery and physiatric and neuropsychiatric comorbidity. This chapter will review the epidemiology of TBI, mechanisms of injury, features on brain imaging, cognitive and psychosocial outcomes, and postacute management, with particular attention to research and practice with geriatric patients.

EPIDEMIOLOGY

More than 5.3 million Americans have disabilities related to TBI. With approximately 1.7 million incident cases per year, resulting in 1.3 million emergency department visits, 275,000 hospitalizations, and 52,000 deaths, TBI is a common cause of morbidity and mortality. Approximately 468/100,000 population are evaluated in the emergency

department for TBI. In adults aged 65 and older, there are an estimated 141,997 TBI-related emergency department visits each year, with the highest rates of TBI-related hospitalization and death occurring in adults aged 75 and older as shown in **Figures 69-1** and **69-2**. The incidence of mild TBI across all ages (not resulting in hospitalization or death) is 392 TBI-related emergency department visits per 100,000 population.

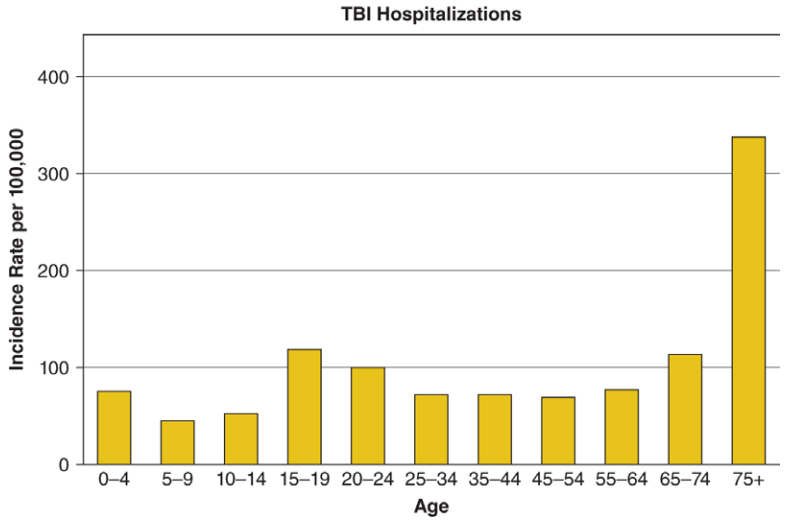


FIGURE 69-1. When TBI occurs in the older adult, it results in a greater rate of hospitalization compared with other age groups.

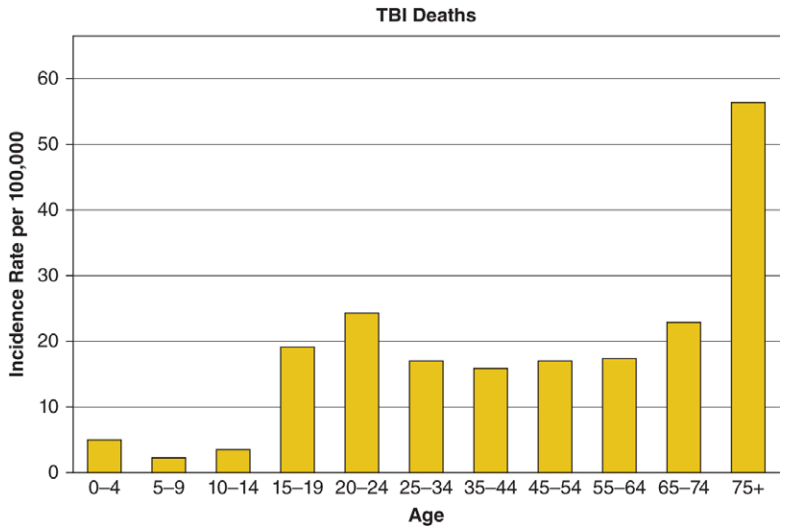


FIGURE 69-2. When TBI occurs in the older adult, it results in a greater rate of death compared with other age groups.

The economic consequences of TBI are alarming. The annual costs of TBI in the United States are approximately $60 billion. Estimates for the cost of lifetime care for a person with severe TBI range between $600,000 and $1.9 million. These estimates do not account for lost income of the patients, and time and lost earnings of family members who care for patients with TBI. Nor do these include the opportunities these victims have lost and their reduced quality of life.

ETIOLOGY

The older patient may have a number of age-related existing risk factors or conditions that increase vulnerability to both TBI and unfavorable outcome. These risks include, but are not limited to, cognitive slowing/impairment, orthopedic/mobility issues, visual acuity, balance difficulty, and neurologic and cardiac diseases. These issues increase risk for falls, being struck by/against, and motor vehicle accidents, the three major etiologies for TBI. These and other etiologies of injury are categorized in **Figure 69-3**. It is estimated that in adults 65 years and older, 60% of TBIs are because of falls, followed by motor vehicle accidents (7.9%), being struck by or against an object (5.7%), assault (1%),

and unknown/others (24.7%). In the general population, men are twice as likely to sustain TBI as women, although this difference is negligible in older adults.

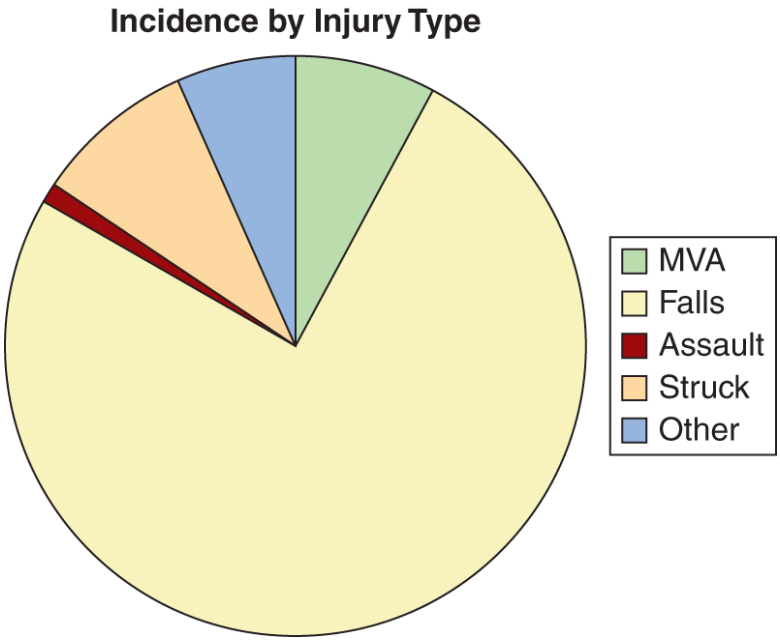


FIGURE 69-3. Etiology of TBI. Falls, being struck by/against, motor vehicle accidents, and assaults are the main known causes of injury in adults age 65 years and older.

Falls

Up to 60% of nursing home residents fall each year as do one-third of older adults in the community. It is significant to note that more than half of all TBIs in older adults are attributable to falls. In addition to being the most common mechanism of TBI, falls produce the highest rates of TBI hospital admissions in older adults. People aged 65 to 74 are three times as likely to be hospitalized from a TBI-related fall as young adults. The risk ratio doubles for ages 75 to 84 (7.6 relative risk) and doubles again for adults 85 years and older (16.4 relative risk). Similarly, the length of hospital stay is longer in the older adult, and the likelihood of being discharged to home is poorer. In adults older than 85 years, the rate of home discharge is 30%; for patients aged 75 to 84, the rate is 41%; at age 65 to 74, the rate is 54%; and in adults younger than 65 years, the rate of home discharge is 86%.

Because falls account for the majority of injuries, an assessment of risk for falls is an important part of the geriatric evaluation. Risks such as the following should be considered: chronic neurologic, sensorial, or musculoskeletal disease; alcohol use, acute illness and delirium, episodic hypotension, medication effects on alertness; as well as activity and environmental risks. Falls and their prevention are covered in Chapter 48.

Motor Vehicle Accident

Motor vehicle accident is the most common etiology of injury in the young adult. In the older adult, motor vehicle accident is the second most frequent etiology. Collisions are often at lower speeds but may still result in substantial injury. Key risks for motor vehicle accident include visual acuity and cognitive ability, particularly in the domain of attention—distractibility.

Mortality

TBI-related death in older adults is increasing. A Centers for Disease Control and Prevention (CDC) study found that for persons older than 75 years, the rate is 56.6/100,000 population. Falls, being struck by/against, and motor vehicles were the most common known causes. In hospitalized older patients with TBI, the rate of mortality is highest for subdural hematoma (33%), followed by contusions (25%) and diffuse axonal injury (11%).

Comorbidities

The presence of comorbidities may increase the risk of TBI and negatively impact outcome following a TBI. A retrospective study found that in adults 55 or older with a TBI, hypertension was the most common preexisting condition (41.4%), followed by alcohol abuse (25.3%), cardiac arrhythmias (11%), coronary artery disease (9.9%), diabetes (9.3%), chronic pulmonary disease (8.6%), myocardial infraction (7.4%), and rheumatoid arthritis (7.4%). History of myocardial infarction was the only comorbidity associated with in-hospital mortality risk following a TBI.

PATHOPHYSIOLOGY AND TYPES OF BRAIN INJURY

The circumstances, location, severity, and outcomes after brain injury are quite variable. However, some broad categorizations can be made regarding the mechanisms of injury and these are shown in **Table 69-1**. Gennarelli indicates that there are two principal mechanisms of primary brain tissue damage in TBI: contact and acceleration/deceleration. Contact-related injury is the result of the head coming in forceful contact with an object (such as the floor or windshield), or contact between the brain and the inner surface of the skull. Contact injuries tend to result in cerebral contusions and hematoma at the point of contact. Not infrequently *contre coup* lesions occur opposite to the site of contact as the brain rebounds from the initial impact against the skull. Acceleration/deceleration injuries are the result of tensile shearing and straining forces acting on the tissue at the sudden moment of the impact. Such forces may tear blood vessels surrounding the brain, resulting in epidural or subdural hematoma or in widespread (diffuse) shearing of axons and microvasculature within the brain, which is termed diffuse axonal injury. The incidence of hematoma is very common in older patients with TBI, as a result of the fact that the proportion of brain volume relative to inner cranial volume is significantly smaller in the older adult due to age-related atrophy, and the microvasculature is more brittle. These two factors may combine to yield more brain movement within the cranium at impact and higher incidence of hematoma due to strain on the vessels, even with seemingly mild impact.

TABLE 69-1 TRAUMATIC BRAIN INJURY MECHANISMS

Primary injury
Skull fracture
Cortical contusions and arachnoid-pial layer lacerations
Intracranial hematoma
Diffuse axonal injury
Diffuse microvascular injury
Cranial nerve injury
Secondary injury
Hypoxia and ischemia
Edema
Increased intracranial pressure
Infection

Focal effects of trauma can be observed in variable locations throughout the brain, depending on the specifics of the injury. However, contusions are more frequently observed in the polar, inferior, and lateral frontal and temporal lobes. For example, the lesion in **Figure 69-4** is large, but focal to the frontal lobe. Another mechanism for the increased rate of contusions in these areas is actual movement of the brain over the bony anterior and middle fossa and forward motion frontal impact sustained in, for example, motor vehicle accidents.

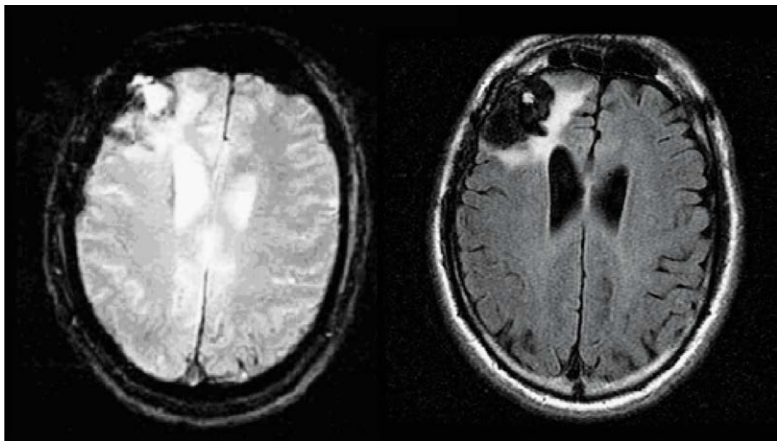


FIGURE 69-4. A 52-year-old man 14 months postinjury. The patient was involved in a low-speed motor vehicle accident and sustained a skull fracture with right frontal epidural and subdural hematomas (that were subsequently evacuated surgically) and right frontal contusions. The $T2^*$-weighted scan in the left panel is negative for diffuse axonal injury. The image on the right is FLAIR T2 and highlights the right frontal lesion with associated gliosis and encephalomalacia around the edges.

Extra-axial hemorrhages (epidural, subdural, and subarachnoid hematomas) are common in TBI, particularly in older adults, and the presence of hemorrhage may impact the quality of outcome. A classic lucid period may be described in which the patient exhibits an impact-related alteration in consciousness, followed by a period where consciousness is regained, followed by secondary deterioration of consciousness as the hematoma evolves. Older adults have a higher rate of secondary hematoma even though the initial impact/injury may be mild. On computed tomography imaging, an epidural hematoma is an extra-axial biconvex ovoid mass of blood. Its biconvex shape is caused by blood accumulation in the epidural space, compressing the dura mater onto the brain, causing mass effect. Acute subdural hematoma involves blood accumulation between the dura and brain parenchyma. On computed tomography, subdural hematoma has a characteristic crescent shape. The inner boundary of subarachnoid hematoma is more irregular—characterized on imaging with blood accumulation that conforms to the sulcal and gyral pattern of the brain. Between 40% and 80% of patients with acute subdural hematoma have an initial Glasgow Coma Scale (GCS) in the severe range (8 or less). In severe cases of high-speed or penetrating injury, lacerations of the meninges may be present, owing to depressed skull fracture, rotational forces of the injury, or a penetrating object.

The diffuse effects of moderate-to-severe TBI can be seen throughout the white matter, indexed on gradient-echo magnetic resonance imaging (MRI) by small punctate hypointensities reflecting paramagnetic hemosiderin in the parenchyma, caused by microvascular shearing (**Figure 69-5**).

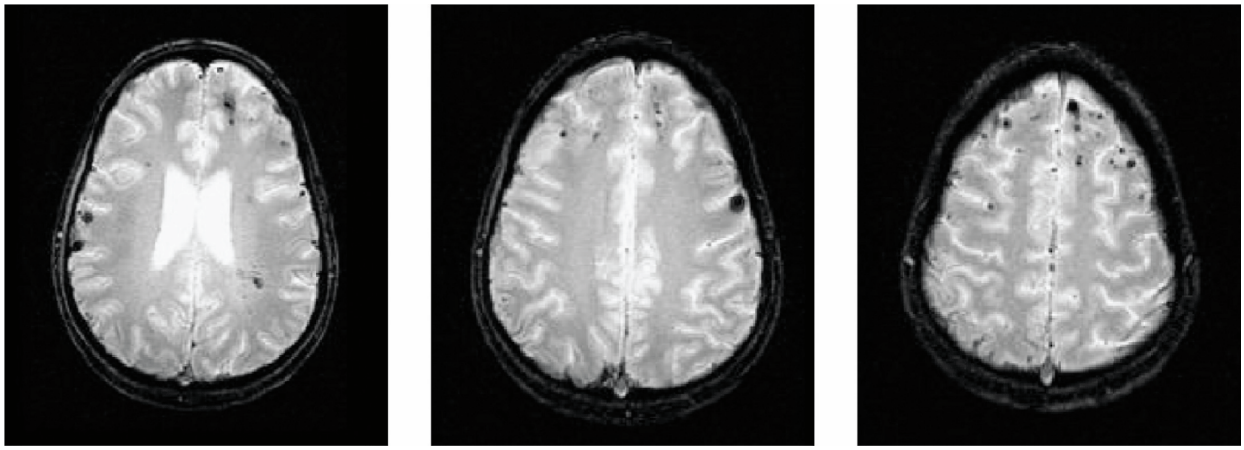


FIGURE 69-5. Diffuse axonal injury. The patient was involved in a high-speed motor vehicle accident 3 months prior to this scan. The patient's initial Glasgow Coma Scale (GCS) at the scene was 5 and 3 following intubation. After 24 hours, the GCS was 7. At 3 weeks postinjury, the GCS was 11. By 4 weeks, the patient's GCS was finally at 15. Day of injury imaging indicated a small left frontal epidural hematoma, left frontal contusions, and prominent diffuse axonal injury. This gradient-echo T2-weighted axial series of images highlights areas of hemosiderin deposition, a blood by-product containing iron, and therefore results in punctuate areas of signal loss (dephasing) on the image. The multifocal pattern of hemosiderin suggests microvascular shearing and diffuse axonal injury. The multifocal lesions mainly appear at gray-white matter junctions.

Secondary injury from diffuse axonal injury may involve a cascade of events, including defective axonal transport, swelling, and separation of proximal and distal segments of the axon for more than 12 to 24 hours. Further secondary injury may result from increased intracranial pressure, causing increased hypoxia and ischemia, and poorly regulated, excitotoxic release of glutamate and other excitatory neurotransmitters.

Severity of Injury

The GCS was developed by Jennett and Teasdale in 1974 and is still in wide use today to characterize the depth of coma, a major indicator of injury severity. The GCS is scaled from 3 to 15 (**Table 69-2**), with 3 being completely nonresponsive and 15 being completely alert, oriented, and following commands. Often the patient is necessarily intubated, making an accurate assessment of GCS difficult.

TABLE 69-2 GLASGOW COMA SCALE

Best eye response (E)	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Best motor response (M)	Obeys commands	6
	Localizes to pain	5
	Withdraws from pain	4
	Flexion response to pain	3
	Extensor response to pain	2
	None	1
Best verbal response (V)	Oriented and coherent	5
	Confused conversation	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1

The total GCS score is E+M+V (range 3–15).

Duration of loss of consciousness and that of posttraumatic confusion are also important markers of injury severity, which may help predict eventual outcome (see outcomes section below). Guidelines to appraise injury severity are given in **Table 69-3**.

TABLE 69-3 CHARACTERIZING INJURY SEVERITY

SEVERITY	GCS	LOC	PTA
Mild	13–15	< 30 min	< 24 h
Moderate	9–12	½–72 h	1 d to 1 wk
Severe	8 or less	> 72 h	> 1 wk

GCS, Glasgow Coma Scale; LOC, loss of consciousness; PTA, posttraumatic amnesia.

OUTCOMES

TBI may result in a variety of adverse outcomes along several overlapping dimensions, including dependence, cognitive, neuropsychiatric, psychosocial, and medical comorbidity. There are several factors that affect these various outcomes after TBI, and many of these are listed in **Table 69-4**, including characteristics of the injury and those of the patient. These factors may interact. For example, an older patient in the prodromal phase of Alzheimer disease (AD) may exhibit progressive symptomatology of AD, which may have been instigated by the TBI but cannot readily be

attributed to brain injury alone. This concept is especially relevant to age-associated brain disorders in older adults. Studies of people at risk of AD indicate that amyloid deposition and neuronal loss may occur gradually and be fairly asymptomatic until a certain threshold is reached. A brain injury, even if mild, may be sufficient to lower the threshold. Additional information on this topic is provided in the section on dementia and TBI later.

TABLE 69-4 FACTORS INFLUENCING OUTCOME

Injury parameters
Severity of injury (GCS, length of coma)
Comorbid injury
Location and extent of brain tissue injury
Secondary brain injury; ICP/swelling, excitotoxicity, and hypoxia
Physics and speed of the impact
Patient parameters
Age
Sex
Genetic risk for neurocognitive disease
Preinjury personality and cognitive status
Social support
Access to care
Access to social and rehabilitation services

GCS, Glasgow Coma Scale; ICP, intracranial pressure.

Global TBI Outcome and Age

TBI can result in long-standing cognitive, personality/emotional, and interpersonal deficits that often interfere with successful rehabilitation, resumption of employment or other responsibilities, interpersonal relations, and quality of life. A common finding is that older adults have *poorer* global outcome from the injury than their younger counterparts with similar injuries. The Glasgow Outcome Scale (GOS), a simple five-point scale ranging from death to good recovery (**Table 69-5**), is the predominant outcome instrument for global outcome. However, this measure is quite coarse. Despite its limitations, this scale has been used in the largest number of patients and trials. In a recent pooled analysis of the International Mission for Prognosis and Clinical Trial (IMPACT) data involving more than 8700 patients with GOS outcome scores, results indicated that age is one of the most powerful prognostic indictors of GOS outcome, as is acute GCS motor score, pupil response, and computed tomography findings. In the case of severe injury, the chance of a GOS good recovery is unlikely in the geriatric patient. Three studies have found that among patients older than 65 years who sustained severe injury (GCS $\leq$ 8), none exhibited a good recovery on the GOS. Another study found that only 6% of patients older than 65 years exhibit good recovery after severe TBI. A fifth study suggested that good recovery was possible after severe injury if the patient regained consciousness within 72 hours. Even when the injury is mild or moderate, older adults have poorer GOS outcome.

TABLE 69-5 GLASGOW OUTCOME SCALE

OUTCOME	SCALE	DESCRIPTOR
Death	1	
Vegetative state	2	Unable to interact with environment; unresponsive.
Severe disability	3	Conscious, but dependent—in need of supervision/assistance every day as a result of physical and cognitive impairments. Ranges from total dependency to assistance with one or more ADLs.
Moderate disability	4	Independent but with a disability. Basic ADLs are intact, but the patient is impaired in occupational and/or social functioning. Able to work in a supported environment.

Good recovery	5	The patient has mild to no residual deficits and has the capacity to resume independent occupational and social activity.

ADLs, activities of daily living.

With regard to rehabilitation outcomes, an important study of TBI model systems data found that patients older than 55 years experienced a doubling in the length of rehabilitation stay and associated costs, while only attaining half the rate of functional recovery of their younger counterparts. These patients also had greater cognitive impairments at discharge and higher rates of nursing home placement.

Less research has been done with fine-tuned neuropsychological assessment of outcome, and studies tend to be much smaller. A review of major cognitive domains that are affected in TBI follows.

Cognitive Outcomes: Executive Dysfunction

The selective vulnerability of the frontal and temporal lobes to injury gives rise to a preponderance of neuropsychological deficits involving frontal systems, including executive functions, working memory, speed of processing, episodic memory, and aspects of personality. All have been shown to be related to severity of injury. The precise definition of executive function is itself a matter of debate and some confusion. The executive functions are those that promote self-directed action. Self-monitoring, self-regulation, inhibition, introspective reflection, decision making, and planned and goal-directed activity are executive functions. Working memory and attentional capacity such as imperviousness to distraction and sustained attention are necessary components, but not sufficient by themselves for executive function. However, these capacities are conveniently operationalized into a quantifiable psychometric instrument (such as digit span, n-back, or serial 7s), and there is a great deal of research on these components of executive function. Executive functions and components are best assessed with a comprehensive neuropsychological evaluation, although some bedside tests such as clock draw, verbal fluency, digit span, and go-no-go tests may be useful to get a feel for the extent of the problem.

Speed of Processing

Speed of information processing is one of the most frequently observed deficits after TBI. For example, one study found patient's reaction time in a simple motor choice paradigm to be significantly slower than that of matched young adults. Another study assessed speed of information processing and attention in a group of 60 patients with severe TBI and controls. When speed of processing was statistically controlled, differences between patients and controls in focused and divided attention became nonsignificant, suggesting that slowed information processing was accounting for most of the difference. A similar finding was observed for planning and flexible problem solving in patients with severe TBI in the chronic stage of recovery. When speed was controlled, performance was equivalent between patients and controls. A factor analysis of a battery of neuropsychological test scores in survivors of TBI indicated that the most prominent factor was decreased perceptual and motor speed. Speed of processing also declines with age, and thus the older patient with TBI may have unusually slow cognitive processing speeds, greatly limiting their range of activities and quality of social interactions.

Attention/Distractibility

The ability to allocate attention between multiple tasks, and working memory is affected in TBI. For example, Baddeley's original model of working memory, which has been frequently proposed to help explain executive difficulties, states that a central executive process or supervisory attentional system within the prefrontal heteromodal cortex regulates the allocation of limited attentional resources. This system appears to be facilitated by D_2 dopamine networks within the dorsolateral frontal lobe and is particularly vulnerable to trauma through either direct contact (contusion to the lateral frontal lobe) or disconnection via acceleration/deceleration injuries.

Memory Dysfunction

Memory complaints from patients are extremely common following TBI, and measured impairment seen on neuropsychological tests is frequently observed, including difficulty at the encoding or acquisition stage, as well as difficulty in retrieval of information. Whether these complaints and deficits are secondary to the more salient attentional, processing speed and executive deficits or whether these are a primary result of hypoxic and excitotoxic injury to the hippocampus is still somewhat unresolved and may vary depending on the nature and severity of the

injury.

Personality/Emotional Functioning

The personality changes accompanying TBI vary depending on the injury location, severity, and preinjury personality factors. Prigatano has summarized the literature in detail on this point. Common overlapping descriptors of personality in patients with TBI include irritability/anger, impatience, impulsivity, poor social judgment, inappropriate social behavior, rapid mood swings, loss of drive, fatigability, and/or depression. Major ways of relating to the world following TBI have been described as "childishness" (self-centered behavior, insensitivity to others, or immature behaviors), "helplessness and dependence" (requiring supervision and inability to make important decisions or set goals), and "lack of insight/awareness" of any of the above difficulties. These patterns frequently overlap and have been collectively labeled "frontal lobe personality."

Self-Awareness

TBI results in very abrupt changes that may not be easily (and often only gradually) accommodated into one's stable sense of self. Characteristics of impaired self-awareness can be varied depending on injury location and severity. Acutely, patients with TBI may be unaware that they have deficits from the injury. Later, the patient may admit to some deficits but fail to appreciate the impact of these deficits on daily functioning. Prigatano et al. found that patients with TBI frequently underestimated their behavioral limitations, abnormalities in social interaction, and emotional dyscontrol when compared to a family member's rating of the patient's abilities, while more objective criterion-based competencies, such as instrumental activities of daily living (IADLs), may be areas where the patient's insight is more accurate. Critically, a syndrome of impaired self-awareness will significantly complicate or impede the rehabilitation process or treatment adherence, since patients may not perceive the need for such treatments. Damage to the anterior medial prefrontal regions (behind the forehead) has been associated with impaired self-awareness for social interaction, judgment, and planning. These are common sites of injury with TBI as described above.

NEUROPSYCHIATRIC OUTCOME

One recent study compared 120 adults with TBI between the ages of 18 and 65 to a group of 45 adults older than 65 years. Psychiatric symptoms were assessed 1 year later. The study found that the younger group had double the proportion with psychiatric disorders (32%) compared to the older group (16%). Further, the younger group was more likely to experience irritability and sleep difficulty, while the older group was more likely to experience poor memory, dependence, and slowness of thinking. While the data suggest a greater incidence of psychiatric symptoms in younger adults following a TBI, prior research indicates that older patients may still be at risk of psychiatric symptoms. Prevalence of major depression is higher (18% prevalence), as is memory difficulty (75%), concentration (53%), personality changes (65%), and increased social isolation (68%) when compared to age-matched non-TBI peers.

TBI, SUBSEQUENT BRAIN ATROPHY, AND COGNITIVE AGING

Previous neuroimaging research has demonstrated that TBI results in diffuse cerebral atrophy and that these changes can be observed within months of injury. However, the brain continues to undergo changes over the next year or longer, which are faster than the rate of normal age-associated atrophy (**Figure 69-6**). However, limited research has been conducted on patients postinjury. Furthermore, the effect of TBI on cerebral integrity during the aging process is not well understood. Studies in normal aging have demonstrated that gray-matter volume peaks in late adolescence and then decreases over time. In contrast, it has been suggested that white-matter volume peaks much later, between the ages of 30 and 50. Since diffuse axonal injury affects white matter, one might expect TBI prior to accumulation of maximal white matter to alter its normal trajectory as the brain ages.

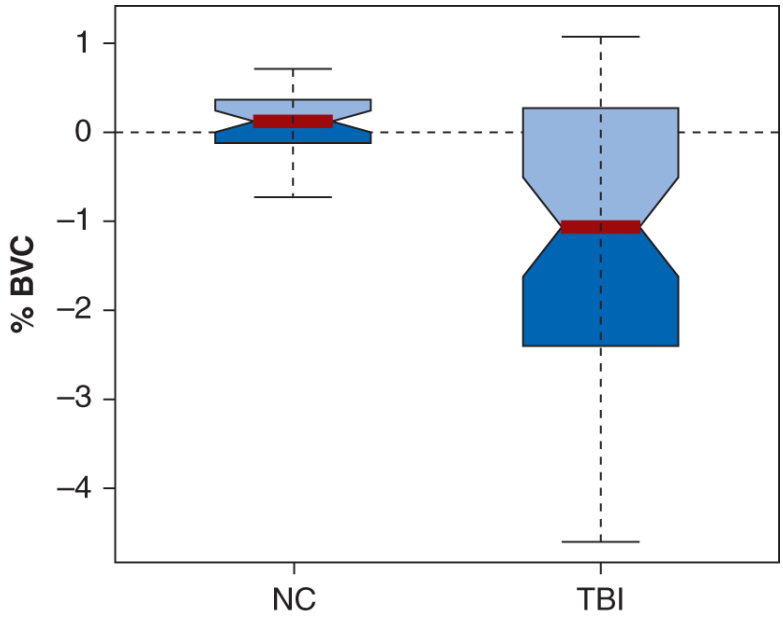


FIGURE 69-6. Patients with TBI show significant decline in global brain volume, here termed percent brain volume change or %BVC, more than a 1-year interval, while matched normal controls (NC) do not. The notches in the box plot are the 95% confidence interval. The mean, 5th, 25th, 75th, and 95th percentiles are also shown.

It is well accepted that aging results in gradual cognitive decline in many domains. One of the questions that needs to be addressed is whether TBI accelerates normal age-related cognitive decline (a rate of aging by TBI interaction). No studies have directly addressed this, but some studies have begun to approximate an answer. A 2006 study examined cognitive outcome after 30 years in 61 patients with TBI. The study found that older subjects showed significantly greater cognitive decline over the follow-up period. Whether the rate of change exceeded the rate of change associated with normal aging was not directly assessed. The cognitive areas that exhibited the greatest declines were mental arithmetic, visuospatial reasoning, and immediate memory.

DEMENTIA AND TRAUMA

Dementia (and/or "major neurocognitive disorder" as referred to in the DSM-5) is defined as loss of cognitive functions in multiple domains, which are severe enough to impair occupational or social functioning. Dementia onset (eg, immediate vs slowly progressive) and course (eg, static vs fluctuating or progressing) varies depending on the etiology. TBI is an etiology of dementia and is designated as such in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. After a single injury, dementia attributable solely to the injury, if present, is expected to be nonprogressive. Conversely, recent retrospective studies comparing TBI and non-TBI trauma hospital visits with a 5- to 7-year follow-up period found a 26% increased risk of incipient dementia following a mild TBI in adults 65 years or older and 44% increased risk of developing Parkinson disease (PD) after a TBI in adults 55 or older. Thus, in the late middle-aged and older population, neural injury because of TBI may serve as a "stressor" sufficient to instigate or exacerbate an existing neurodegenerative process such as AD or PD.

Does Trauma Increase the Risk of AD?

The single greatest risk factor for dementia is age. The apolipoprotein (*APOE*) gene and other genes increase the risk of dementia as does neurologic history such as trauma. The *APOE* gene may play a role in multiple age-related diseases. *APOE* is lipid transporter, and the gene coding for *APOE* has three alleles: e2, e3, and e4. By far, the most common allele is e3. Persons with the e4 allele (~ 15% of the general population) are at higher risk of dementia and cerebral vascular diseases, while e2 may be somewhat protective. The risk of dementia in TBI survivors has not always been clear-cut, but when studies include *APOE* status, the risk becomes somewhat clearer. For example, one large study of 236 community-dwelling older adults found that TBI by itself was not associated with risk of AD, while APOE4 was associated with a twofold increase. However, patients with APOE4-positive TBI had a 10-fold increased risk for AD. Older adults with APOE4 may also have a longer length of coma and earlier age of onset of dementia than non-APOE4 carriers. Another study examined patients with TBI at 6 months postinjury and found that patients

with the APOE4 allele were twice as likely (57% vs 27%) to have outcomes of 1 to 3 on the GOS (death, vegetative state, or severe disability).

Two related concepts of brain vulnerability are of interest here in explaining individual differences in decline to subsequent dementia. *Brain reserve* and *cognitive reserve* address the lack of measurable cognitive decline in the presence of brain disease or age. *Brain reserve* posits that, in the presence of tissue compromise, some brains have greater capacity to rely on spared heteromodal neurons and pathways to compensate in several possible ways, including activation of latent pathways and formation of new synapses. *Cognitive reserve* posits that age- and disease-related cognitive declines may be protected against by higher premorbid cognitive ability and resources; those that are higher functioning premorbidly may have a greater repertoire of cognitive compensatory strategies to draw upon postinjury or may simply have farther to decline before testing in the impaired range.

Chronic Traumatic Encephalopathy

Dementia symptoms associated with a history of TBI may result from chronic traumatic encephalopathy (CTE), a neurodegenerative disease with an insidious onset, which was once historically connected with head trauma from boxing (eg, "dementia pugilistica" or "punch-drunk syndrome"). With increased public and media attention, burgeoning clinical research has shown CTE may be caused by a history of repetitive head injury endemic but not limited to a variety of contact sports (American football, ice hockey, wrestling, rugby, soccer) and combat-related blast exposure during military deployment. Population-based epidemiologic evidence of CTE is unknown, with estimates limited to a few current studies of professional athletes, and indicating a lifetime prevalence of less than 20% in boxers and a conservative estimate of 3.7% in American professional football players. Possible factors contributing to limited epidemiologic data include the difficulty in obtaining an accurate retrospective history of repetitive TBI/concussive/subconcussive events, lack of prognostic longitudinal epidemiologic studies (though some are currently underway), and lack of in vivo biomarkers of CTE. Postmortem neuropathology analysis is currently the only method for which a definitive diagnosis can be made.

CTE is characterized by a constellation of microscopic neuropathologic features that includes the presence of phosphorylated tau pathology in the form of tau-immunoreactive neurofibrillary tangles (NFTs), astrocytic tangles (ATs), and neurites throughout the neocortex. An upregulation of 43 kDa TAR DNA binding protein (TDP-43) involved in regulating RNA metabolism and axonal pathology is also commonly found. While the mechanisms underlying the accumulation and distribution of these neuropathologic features are not well understood, deposits of tauopathies are initially observed in the neocortex and eventually distribute to more superficial layers of the cortex, medial temporal lobe, diencephalon, and brain stem. A recent four-stage (I–IV) system has been proposed and is based on progressive accumulation of tau, TDP-43, and axonal pathology leading to significant atrophy and loss of brain weight.

Symptoms of CTE typically take years to develop and involve a wide range of cognitive, behavioral, mood, and motor clinical symptoms. The symptom presentation has been categorized into three possible subtypes: behavioral and/or mood symptoms, cognitive symptoms, or mixed. A recent study observed that individuals with predominantly behavioral and/or mood symptoms were typically younger (mean age 35) than individuals with predominantly cognitive symptoms (means age of onset 59). Individuals with initial behavioral and/or mood symptoms were also more likely to develop cognitive symptoms before death whereas individuals with initial cognitive symptoms were less likely to develop behavioral and/or mood symptoms before death. CTE is considered a distinct neurodegenerative disease, however, it may be associated with the development of other common neurodegenerative diseases such AD, Lewy bodies, frontotemporal dementia, and motor neuron disease.

Clinical diagnostic criteria have been proposed and are currently being validated. In the late middle-aged or older patient, a diagnosis of CTE, or traumatic encephalopathy syndrome (TES) as some have suggested, will include the insidious onset of multiple cognitive and behavioral symptoms associated with a reliable remote history of repetitive head trauma (mTBI/concussion) and will be distinguished from other medical diagnoses or illnesses. The use of positron emission tomography (PET) imaging and cerebral spinal fluid biomarkers of tauopathy and amyloid are promising in vivo measures that have the potential to assist with the differential diagnosis of CTE in the future.

POSTACUTE MANAGEMENT OF GERIATRIC PATIENTS WITH TBI

The geriatric patient post-TBI presenting in the clinic may have difficulty with mobility and pain and have several less obvious problems including cognitive impairment, mood, anxiety and comportment-related issues, and decreased

social and physical inactivity. A careful comprehensive assessment is warranted.

Neuropsychological Assessment

Cognition decline and affective dysfunction are not specific to TBI and may, in fact, co-occur in several neurologic diseases and medical conditions. Neuropsychological evaluation may be helpful in making the differential diagnosis. Such an evaluation will identify cognitive profiles that are indicative of specific diagnoses and will identify patterns of strengths and weaknesses in order to inform and help maximize the effectiveness of treatments. Such an evaluation may also help prevent a misdiagnosis of dementia due to AD.

Neuropsychiatric Disturbances

Behavioral disturbances can have a negative impact on cognitive functioning, relationships with family and significant others, treatment compliance and motivation, and reintegration into the patient's social community. Common neuropsychiatric sequelae are provided in **Table 69-6**. A thorough clinical interview with the patient and with one or more other sources such as a spouse and adult child is important, in order to identify neuropsychiatric issues. Collateral sources are important because the patient may give an unreliable history and may have inaccurate insight into the extent of deficits and their effects on others in the patient's life.

TABLE 69-6 NEUROPSYCHIATRIC SEQUELAE

Dementia as a result of trauma; risk for Alzheimer disease
Posttraumatic confusion
Isolated cognitive disorders: Aphasia, apraxia, amnesia, anosognosia, and executive function
Comportment disorders: Apathy, disinhibition, paranoia, irritability, and lability
Affective disorders: Depression or mania
Anxiety disorders: PTSD, panic, generalized anxiety, obsessions, and/or compulsions
Psychotic disorders: Hallucinations and/or delusions
Sleep disorders: Insomnia and/or hypersomnia
Fatigue

PTSD, posttraumatic stress disorder.

When treatable neuropsychiatric disorders are present, it is important to try alternatives to medication when possible. Patients with TBI may be particularly prone to side effects and exaggerated and paradoxical responses to medications. Geriatric patients with TBI are even more vulnerable to adverse responses. Environmental changes may be helpful in some cases, such as increasing social engagement for depressed patients or reducing stressors in the environment that may be adding to agitated behavior. Supportive counseling may be tried for treatment of depression and anxiety. When psychotropic medication is warranted, the drug should be started with the lowest possible dose and titrated up. It has been shown that benzodiazepines and traditional antipsychotic medications hamper recovery in the geriatric patient, so alternatives with less sedating properties are preferred.

Depression in the older patient with TBI has a 30% to 77% prevalence rate. Studies have suggested that demographic (such as marital status and socioeconomic status) or injury characteristics (such as time since injury) are unrelated to postinjury depression. Both a more severe injury and a preinjury psychiatric history do predict postinjury depressive symptoms. Suicide risk is much higher in older adults with TBI, and suicidal ideation should be assessed. Anxiety disorders postinjury are also common. Posttraumatic stress disorder (PTSD) is the most frequent, with

prevalence rates of 20% to 30%; generalized anxiety disorder and panic disorder are also common. Identification and treatment of these neuropsychiatric sequelae of TBI may contribute greatly to rehabilitation outcome, interpersonal dynamics with family and care providers, and community integration.

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Chapter 70

Epilepsy

Daniel Winkel, Ioannis Karakis

Learning Objectives

- Understand the epidemiology, classification, and common clinical presentations of epilepsy in older adults.
- Learn the principles that guide treatment of epilepsy and how age-associated changes in body composition and drug metabolism affect therapy with antiepileptic drugs in older adults.
- Acquire knowledge about the mechanism of action, indications, efficacy, and adverse effects of commonly used medications to treat epilepsy in older adults.
- Learn about nonpharmacologic management of refractory epilepsy in older adults, including the role of resective surgery and neurostimulation.
- Understand how common comorbidities can confound the clinical presentation and treatment of epilepsy in older adults.

Key Clinical Points

1. **The incidence of epilepsy increases significantly with aging and is more likely to be associated with secondary causes, such as stroke, Alzheimer disease, trauma, and tumor. However, it is not uncommon to fail to identify a discernible cause for epilepsy in older adults.**
2. **Diagnosis of epilepsy in older adults requires a careful history. Brain imaging and electroencephalogram (EEG) are useful tools to make the diagnosis. A magnetic resonance imaging (MRI) brain scan can evaluate for culprits like infarction, tumor, or hemorrhage, while an EEG can be abnormal in about 50% of older patients.**
3. **Choice of drug therapy is driven by the overall efficacy, adverse effect profile, and age-associated changes in the body composition and organ function that can alter drug absorption, plasma levels, and excretion.**
4. **Treatment of a seizure in an acute medical setting generally requires short-term therapy or watchful waiting, while that related to conditions, such as stroke, brain tumor, trauma, or Alzheimer disease may need long-term drug therapy.**
5. **Management of refractory epilepsy may need additional nonpharmacologic therapies, such as resective surgery and neurostimulation.**

INTRODUCTION

Older adults, often defined as those 65 years and older, currently number 40 million in the United States alone. Demographic trends predict that this number is expected to double by 2030, and will at that point comprise nearly one in five Americans. Coupled with the fact that the incidence of epilepsy is highest in this cohort, this lays the foundation for a rapidly growing patient population in need of treatment for this complex disorder. Epilepsy, especially in older adults, tends to become a chronic condition. It is therefore imperative for a geriatrician to develop a working knowledge and level of familiarity with its evaluation and management.

DEFINITION

A poorly defined medical condition may lead to confusion about when and how to definitely diagnose and treat it. To that end, the International League Against Epilepsy (ILEA) revised its definition of epilepsy to be "*a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring greater than 24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome.*" This clarification seeks to help clinicians identify and distinguish those who need treatment from those who do not. The 60% general recurrence risk is a remaining challenge. It directs the clinician to attempt to predict a paroxysmal incident in the future, which is akin, for instance, to asking one to predict the risk of recurrent myocardial infarction in a patient with a history of prior cardiac event. In common practice, having either an abnormal EEG or brain MRI that suggests a potential epileptogenic focus, connotes approximately that degree of risk, and therefore can be used presumptively. This is of particular relevance for the geriatrician, as many older patients will have identifiable cerebral pathology that corresponds with a known risk of further seizures.

EPIDEMIOLOGY

Older adults are the fastest growing segment of the general population. In addition to the cumulative burden of patients with epilepsy who survive to older age, there is a substantial risk for epilepsy associated with medical conditions that affect older adults. This may be due to a combination of long-standing structural abnormalities along with accumulating damage from neurodegenerative and cardiovascular disease. By the seventh and eighth decades of life, there is a dramatic increase in the incidence (new cases per 100,000) of epilepsy (**Figure 70-1**). Similarly, studies of community-dwelling veterans suggested an increased prevalence (active cases in a population) of 1.8% compared to the general population. That rate may increase three to four times more in nursing home older adults, based on studies investigating antiepileptic drugs' (AED) use for the indication of epilepsy. Moreover, subdividing older adults into the "young old" (65–74 years), the "middle old" (75–84 years), and "old" (85 years) reveals discrepancies not only in their probability of developing epilepsy that increases with age, but also in their probability of being placed on AED, with age being surprisingly inversely related to AED use, at least in the nursing home setting.

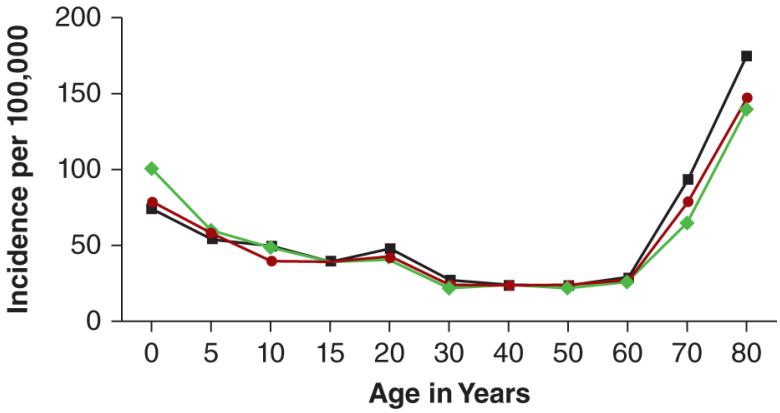


FIGURE 70-1. Age-specific incidence of epilepsy in Rochester, Minnesota, from 1934 to 1984. By age 60, there is a dramatic increase in new cases of epilepsy. The red circles depict totals, while the black squares and green diamonds depict men and women, respectively. All follow a nearly-identical trajectory. (Adapted from Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia*. 1993;34(3):453–468.)

PATHOPHYSIOLOGY

Epilepsy is broadly dichotomized into generalized and partial (focal). Generalized epilepsies are characterized by seizures that involve both hemispheres at onset. They are typically genetically predisposed and tend to manifest in childhood and adolescence in the form of discrete epilepsy syndromes (eg, childhood absence epilepsy, juvenile

myoclonic epilepsy). In contrast, partial or focal epilepsies, are characterized by focal-onset seizures that may or may not secondarily generalize (ie, propagate throughout the brain). These are often termed “localization-related” or symptomatic due to the known local pathology that serves as an epileptogenic focus. If the pathology is suspected but not visualized, the term cryptogenic is used.

Classification of Seizure Types

Seizure classification is based on their functional distribution and on the structural neuroanatomy of the brain. The location and extent of a seizure’s involvement are reflected in its clinical manifestation, termed its *semiology*. In partial seizures, involvement of only a small, discrete portion of the brain leads to simple partial seizures. By definition, these do not involve impairment of consciousness. Simple partial seizures can be motor, sensory, olfactory, auditory, visual, visceral (epigastric sensation), or psychic (déjà vu, depersonalization, or panic). When these seizures do not cause an overt motoric change (such as unilateral clonic activity in a simple focal motor seizure), they may be referred to as *auras.* It is important to note, however, that these auras are not merely a “warning sign” for seizures but in fact simple partial seizure themselves and should be treated accordingly. This history can be of great localizing value to aid the clinician in determining the area of seizure onset. Complex partial seizures are focal in onset, like simple partial seizures, but they propagate further and eventually alter consciousness to some extent and may therefore also be termed “focal onset seizures with dyscognitive features”. These should be distinguished from “absence” or “petit mal” seizures, a clinical manifestation of genetic generalized epilepsies in childhood, where the loss of consciousness is momentary, the frequency is increased, and the return to baseline is instantaneous. In contrast, complex partial seizures emanate typically from the temporal lobes and tend to be more prolonged events characterized by a bland semiology of behavioral arrest (ie, a “staring spell”) coupled by repetitive semi-purposeful behaviors (automatisms) such as lip smacking, chewing, or finger movements. Less commonly they arise from other parts of the brain, such as the frontal lobes, where they tend to be hypermotoric, characterized by dystonic posturing, bicycling, vocalizations, and more rapid return to baseline. If the extent of the seizure propagation reaches a certain critical threshold, it may progress to whole-body convulsions (a tonic-clonic, or “grand mal” seizure). Generalization implies that abnormal paroxysmal activity occurs in both cerebral hemispheres, either at onset, as with the primary generalized epilepsies, or secondarily, via the propagation of a focal-onset seizure. In older adults, generalized seizures tend to be of focal onset, as the portion of the population with primary generalized epilepsy (almost exclusively genetic) tends to decrease and the risk factors for focal-onset, localization-related epilepsy tend to accumulate with age.

Causes of Epilepsy in Older Adults

Cerebrovascular causes underlie approximately two-thirds of these partial epilepsies in older adults (**Figure 70-2**). Stroke in particular accounts for 30% to 40% of new cases of epilepsy in this group. In fact, approximately 10% of patients with a stroke will have a seizure within the first few months, and the overall incidence rises to approximately 20% by 2 years, with hemorrhagic stroke portending a higher risk than ischemic stroke. Also frequently implicated are degenerative (eg, Alzheimer or other dementia types), traumatic, and neoplastic etiologies. Still, a large number of older adults have epilepsy without an overt cause (aka cryptogenic).

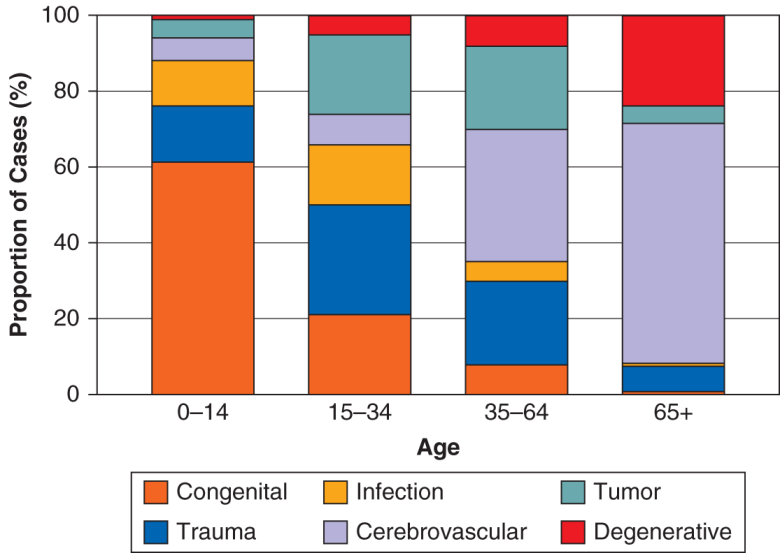


FIGURE 70-2. Proportion of cases of newly diagnosed epilepsy due to particular etiologies. By age 65, cerebrovascular injury is the leading cause of new-onset epilepsy. (Adapted from Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia*. 1993;34(3):453–468.)

DIAGNOSIS

History

History is the most important tool both to accurately make a diagnosis of a seizure, as well as that of epilepsy. Information about the events prior, during, and after the spell(s) should be sought both from the patient and bystanders. The type of onset, mode of progression, duration, and resolution should be clearly defined. Distinction should be made between "positive" phenomena, such as tingling, twitching, and visual hallucinations that are characteristic of an irritative focus (such as in seizures) versus "negative" phenomena, such as numbness, weakness, and scotomas that are characteristic of a destructive or disruptive lesion (such as in transient ischemic attacks/strokes), with a few notable overlapping exceptions (eg, aphasia present in both). This distinction between hyper- and hypoactive foci can be extremely beneficial. Patients and caregivers should be questioned about symptoms commonly seen with seizures, such as auras and staring spells, which may not be immediately identified as seizures. Risk factors for epilepsy as well as triggers for seizures should be explicitly investigated. Review of prescription drugs and over-the-counter agents used for weight loss or memory improvement should be performed. In addition to intoxication with proconvulsant agents, withdrawal from certain substances such as benzodiazepines, barbiturates, or alcohol can provoke seizures.

First and foremost, it is necessary to distinguish between seizures and their numerous mimics. These may be other neurologic paroxysmal events (eg, transient ischemic attacks, transient global amnesia, migraines), cardiovascular events (eg, vasovagal syncope, arrhythmias, hypoxia), sleep disorders (eg, rapid eye movement [REM] and non-REM parasomnias, narcolepsy, sleep apnea), movement disorders (eg, acute dystonic reaction, hemifacial spasm, tremor, asterixis), psychiatric conditions (eg, psychogenic nonepileptic spells, panic attacks, acute psychosis), and metabolic derangements (eg, hypoglycemia, electrolyte disturbances). Various common mimics are outlined in **Table 70-1**.

TABLE 70-1 DIFFERENTIAL DIAGNOSIS OF SEIZURES IN OLDER ADULTS

Transient ischemic attack
Transient global amnesia
Migraines
Cardiovascular (arrhythmias, vasovagal syncope)
Sleep disorders (REM and non-REM parasomnias, cataplexy)
Movement disorders (tremors, hemifacial spasm, acute dystonic reaction)
Metabolic derangements (hypoglycemia, hyperammonemia, electrolyte abnormalities)

Intoxication
Psychiatric disorders (psychogenic nonepileptic spells, panic attacks, acute psychosis)

REM, rapid eye movement.

The second important distinction is that between an epileptic and a provoked seizure. The latter typically occurs in a normal brain in the setting of an acute or subacute disturbance of cerebral function and/or physiology. Approximately 10% of the general population will have such an event in appropriate clinical settings, without developing epilepsy. Examples include medications' intoxication or withdrawal, metabolic derangements, cerebral hypoperfusion, or hypoxia (eg, micturition or cough syncope). These seizures tend to be of generalized onset, unless their trigger affected certain portion of the brain as can be seen in acute symptomatic seizures from a stroke or traumatic brain injury.

Imaging

In any patient with new-onset seizures, head imaging is imperative. In an emergent setting, a noncontrast head computed tomography (CT) is acceptable, as it is rapidly available and will readily detect intracranial blood and encephalomalacia, two common causes of seizures. An MRI, however, is much more sensitive for cortical ischemic injury, small structural lesions (including tumors), and hippocampal pathology. When the cause for the seizure is not readily apparent, MRI imaging is indicated. Specific epilepsy protocols have been designed to better reveal these types of pathology and should be therefore explicitly requested.

Electroencephalogram

To supplement the clinical history and imaging findings, an EEG is often performed. However, it is important to consider that an EEG can only reflect the electrophysiologic activity that occurs during the recording. It will be misleadingly normal in 50% of patients with epilepsy and thus does not exclude the diagnosis. Conversely, EEG abnormalities are not equivalent with the diagnosis of epilepsy, particularly when normal variants or artifacts may be misinterpreted as epileptiform activity by inexperienced readers. If clinically indicated, obtaining up to three studies may increase the yield to up to 85%. Alternatively, a prolonged ambulatory or inpatient video-EEG study to record longer periods of interictal activity or capture the events of interest may be necessary. A video-EEG may also provide useful information when an epilepsy mimic is in question (eg, sleep or movement disorder, cardiac arrhythmia, or psychogenic nonepileptic attacks). The diagnosis of epilepsy is ultimately a clinical one.

MANAGEMENT

When to Start and Stop Treatment

It is well established that a patient who has accurately been diagnosed with recurrent unprovoked seizures fulfills the traditional definition of epilepsy and should be treated for the condition. More challenging are the cases in which a single seizure has occurred. In such instances, a distinction should be made between provoked or acute symptomatic (ie, within the first week of brain insult) seizures versus remote symptomatic seizures. Typically, patients with provoked or acute symptomatic seizures do not require long-term treatment, although coverage with antiepileptic medications may be warranted in the acute setting, particularly if they have recurrent events. Conversely, patients with a prior brain insult who sustain their first seizure remotely to that insult are usually placed on long-term antiepileptic management if their risk of recurrence is deemed to be substantial based on clinical, electroencephalographic, or radiologic grounds. That is often the case with older adults. If doubt exists and direct supervision is available, watchful waiting can be attempted, provided that seizure precautions are maintained.

If an antiepileptic treatment was initiated for acute symptomatic seizures, a trial to taper off these drugs once the acute symptomatic phase lapses is reasonable, particularly if no permanent brain damage has occurred. In general, once a diagnosis of epilepsy is made in an older patient, most specialists will maintain the patient on lifelong antiepileptic treatment given the high risk of recurrence in this age group.

Selecting an Antiepileptic Drug for Older Adults

General principles There are certain principles common to epilepsy treatment that also apply to older adults to

varying degrees. As noted earlier, first it is important to ensure that the patient suffers from seizures and that he/she qualifies for the diagnosis of epilepsy and merits treatment. Second, the epilepsy should be classified as either generalized or focal (with or without secondary generalization), a distinction that will determine the best drug to manage the condition. This is less of a concern in older adults where epilepsy is almost exclusively localization-related and hence amenable to a broader selection of AEDs. When choosing an AED, one should consider the patient's comorbidities, both to potentially treat some (eg, headache, neuropathic pain, depression) with the same medication, and to avoid aggravating others (eg, cardiovascular risk, cognition, gait, mood, sleep, weight, bone health, etc). In older adults, renal and hepatic clearance and protein binding/drug interactions are critical for drug selection. Other factors such as mechanism of action (especially when "rational polytherapy" is required), compliance (especially in patients with cognitive or visual difficulties), and cost may need to be considered. Starting low and going slow on the dose is of paramount importance. Typically a medication is titrated to either the minimum effective dose or the maximum tolerated (or recommended) dose, whichever comes first. AED serum levels may be used to ensure compliance and broadly guide titration, although they are more stringently established for the older generation of AEDs and less so for the new medications. If a medication is insufficient to control seizures, a second agent, ideally with a synergistic mechanism of action, is attempted. If that is successful, the first AED is often tapered off gradually after an overlapping period of clinical stability. For most patients, generic medications work equally well as brand names, but for certain patients in whom small fluctuations in the medication bioavailability may precipitate recurrent seizures, generic substitution should be avoided. The goal is to maintain patients on a minimum number of medication(s) that control their epilepsy without causing intolerable or harmful side effects. In refractory cases, the diagnosis of epilepsy should be confirmed again, and nonpharmacologic treatment options (neurostimulation or surgery, see below) should be considered on an individual basis. Last but not least, epilepsy treatment should not just be confined to management of seizures and medication-related side effects, but should also address coexisting comorbidities (eg, mood disorders, bone health) and social/quality-of-life issues related to the patient and their caregivers (eg, seizure precautions, disability, etc). An overview of these general principles is provided in **Table 70-2.**

TABLE 70-2 GENERAL PRINCIPLES OF EPILEPSY TREATMENT IN OLDER ADULTS

1.	Ensure that the spell(s) of the patient are seizure(s)
2.	Ensure that the patient qualifies for the diagnosis of epilepsy
3.	Classify the patient's epilepsy as generalized or focal (with or without secondary generalization)
4.	Factor in comorbidities that may benefit from the selected antiepileptic drug (AED)
5.	Factor in comorbidities that may be aggravated by the selected AED
6.	Factor in other parameters such as mechanism of action, compliance, and cost
7.	Take into account AED metabolism (hepatic/renal clearance)
8.	Take into account protein binding and potential drug-drug interactions
9.	Start a low dose and titrate up slowly
10.	Titrate up to the minimum effective dose or the maximum tolerated or recommended dose, whichever comes first
11.	Check levels to ensure compliance and facilitate uptitration (particularly for older-generation AEDs)
12.	If the first AED is unsuccessful or not tolerated, add a second one, ideally with a synergistic mechanism and taper off the first after an overlapping period
13.	Maintain the patient on the minimal effective dose that provides seizure protection without causing adverse effects
14.	In refractory cases, confirm again the correctness of the diagnosis and explore nonpharmacologic options (neurostimulation, surgery) on an individual basis
15.	Always address epilepsy-related comorbidities (mood, bone health, seizure precautions, disability)

Clinical trials The data on specific AEDs for older adults are sparse, particularly beyond community-dwelling older adults. There are no AEDs that are contraindicated or expressly prohibited in older adults. Furthermore, most AEDs have a Food and Drug administration (FDA) indication for use for the seizure types most likely to be encountered in older adults (eg, partial onset). Two seminal studies on the pharmacologic treatment of epilepsy in older adults are worth highlighting. One, a multicenter, double-blind, randomized comparison between lamotrigine and carbamazepine

in older patients in the United Kingdom with newly diagnosed epilepsy (both partial onset and primary generalized) showed no differences in efficacy. The principal difference was in the drop-out rates between the treatment groups, with lamotrigine being better tolerated. The other significant study exploring the relative efficacy of AEDs in older adults was the VA Cooperative Study #428, an 18-center, parallel, double-blind trial in the United States comparing lamotrigine, carbamazepine, and gabapentin. Again, efficacy of the three drugs did not differ; however, the carbamazepine group had significantly higher drop-out rates, while lamotrigine and gabapentin were better tolerated. These findings have since been replicated in several studies and, to date, no compelling differences in the efficacy of various AEDs have been reported in older adults. Therefore, it is most reasonable to individualize AED selection, and tailor it to each patient using the aforementioned principles as a guide.

Pharmacokinetics Numerous well-established pharmaco-kinetic changes reportedly affect drug dosing in older adults. Considerable increases in total body fat and water increase volumes of distribution, and reduced liver mass and metabolic function lead to impaired breakdown of hepatically metabolized drugs. Impaired hepatic protein synthesis lowers serum albumin levels and subsequently raises free (active) drug levels. The increases noted in α-acid glycoprotein (AAG), an acute-phase reactant, during any incidence of pathophysiologic stress for an acute or chronic illness, may further complicate matters. After the age of 40, renal function begins to fall by approximately 10% each decade. Also, the age-associated changes in the gastrointestinal tract structure and function leads to reduced absorption of drugs. Collectively, these factors may yield significant fluctuations in AED levels over time. Furthermore, they may differentially affect various AEDs to varying degrees. For patients with very low serum albumin levels, or those taking multiple highly protein-bound AEDs that would be expected to compete for albumin-binding sites, it may be prudent to monitor not only the total AED levels (the standard laboratory order), but also free levels.

Currently a large number of antiepileptic drugs are approved by the FDA for use in the United States and several others are under review. In this chapter, we have focused largely on medications commonly used in older adults. A summary of these medications, along with commonly encountered problems, is provided in **Table 70-3**.

TABLE 70-3 GENERAL ISSUES FOR ANTIEPILEPTIC DRUG SELECTION

	PHENYTOIN	CARBAMAZEPINE	OXCARBAZEPINE	PHENOBARBITAL	VALPROIC ACID	GABAPENTIN	PREGABALIN	LAMOTRIGINE	TOPIRAMATE	ZONISAMIDE	LEVETIRACETAM	LACOSAMIDE
FDA-approved dose[a]	100 mg q6–8h	800–1200 mg/d divided BID–QID; start 200 mg BID	600–1200 mg BID; start 150 mg BID	60 mg BID–TID	30–60 mg/kg/d divided QD–TID	300–1200 mg TID; start 100 mg TID	150–600 mg TID; start 150 mg/d divided BID–TID	Depends on whether there is concomitant valproate use; see package insert for titration schedule	200 mg BID; start 25 mg QD–BID	100–600 mg/d divided QD–BID; start 100 mg QD	500–1500 mg BID; start 500 mg BID	150–200 BID; start 50 mg BID
Mechanism of action	Sodium channel blocking	Sodium channel blocking	Sodium channel blocking	Sodium channel blocking	Sodium channel blocking, enhanced GABAergic inhibition, decreased NMDA excitation	Modulation of GABA synthesis/release through calcium channel binding	Modulation of GABA synthesis/release through calcium channel binding	Sodium channel blocking	Sodium channel blocking, enhanced GABAergic inhibition, decreased AMPA excitation	Sodium and calcium channel blocking	SV2A binding	Sodium channel blocking and modulation of CRMP2
Pharmacokinetic impact on other AEDs	Common	Common	Minor	Common	Common	None	None	None	Minor (phenytoin only)	Minor	None	None
Pharmacokinetic impact on non-AEDs	Common	Common	Rare	Common	Common	None	None	None	Rare	Rare	None	None
Impact on cognitive function	Some	Some	Less	More	Some	Some	Some	Less	More	More	Less	Less
Potential for idiosyncratic life-threatening side effects	Hepatic failure, agranulocytosis	Aplastic anemia and hepatic failure	Low (profound hyponatremia possible)	Low	Hepatic failure	Low	Low	Stevens-Johnson syndrome	Low	Stevens-Johnson syndrome	Negligible	Negligible
Other common indications	None	Trigeminal neuralgia, bipolar disorder	Trigeminal neuralgia, bipolar disorder, motor tics	None	Bipolar disorder, migraine prophylaxis	Neuropathic pain, anxiety	Neuropathic pain, anxiety	Bipolar disorder	Migraine prophylaxis	None	None	None
Changes in weight	None	Gain	None	None	Gain (may be considerable)	Gain	Gain	None	Loss	Loss	None	None
Use in patients with hepatic impairment	Variable effect	Variable effect	Mild effect	Variable effect	Caution advised	No effect	No effect	Mild effect	No effect	Mild effect	No effect	No effect
Use in patients with renal impairment	No effect	No effect	May require mild dose adjustment	May require mild dose adjustment	No effect	Requires dose adjustment	Requires dose adjustment	May require mild dose adjustment	Requires dose adjustment	May require mild dose adjustment	Requires dose adjustment	Requires dose adjustment
Rapid titration possible	Yes	No	No	Typically only in intubated patient (respiratory depression)	Yes	Yes (monitor for excessive sedation)	Yes (monitor for excessive sedation)	No	Not recommended (tolerability)	Not recommender (tolerability)	Yes	Yes
IV formulation	Yes	No	No	Yes	Yes	No	No	No	No	No	Yes	Yes

AEDs, antiepileptic drugs; BID, twice a day; FDA, Food and Drug Administration; GABA, γ-aminobutyric acid; NMDA, N-methyl-D-aspartate; QD, every day; QID, four times daily; SE, side effects; TID, three times a day.

[a]Lower starting and total doses may be appropriate in older adults, especially in nonemergent situations in which attaining therapeutic levels quickly may be less critical. Different recommendations exist for use in status epilepticus.

Modified from French J. Treatment with antiepileptic drugs, new and old. Continuum Lifelong Learning Neurol. 2007;13(4, Epilepsy):71–90, Table 3–2.

First-Generation AEDs

Phenytoin A first-generation antiepileptic drug, phenytoin (Dilantin, Phenytek) has been FDA approved for treatment

of seizures since 1953, and has a well-established efficacy and adverse effect profile. It acts through blockade of sodium channels and is primarily indicated for management of tonic-clonic and partial seizures associated with partial epilepsy. It is also a standard treatment, second only to benzodiazepines, for status epilepticus. Phenytoin is highly protein bound (~ 90%), and undergoes mixed-order, saturation-dependent hepatic metabolism. This produces a J-shaped dose-concentration curve, whereby relatively small increases in dose can lead to significant increases in serum concentration and subsequent toxicity. This in turn leads to a narrow therapeutic window, with nystagmus, ataxia, dysarthria, and cognitive changes occurring acutely at doses exceeding 20 μg/dL. Chronic use may lead to gingival hyperplasia, cerebellar atrophy hirsutism, hypertrophy of subcutaneous facial tissue, and osteoporosis. All patients receiving phenytoin should be placed on vitamin D and calcium. As a class 1b antiarrhythmic, it should be used cautiously in patients with known concomitant cardiac conduction abnormalities.

Phenytoin has multiple well-established drug-drug interactions as a potent hepatic inducer. Warfarin is a particularly well-established culprit, and its use should prompt careful consideration about initiating phenytoin. Phenytoin may also increase the clearance of hormone replacement therapy, quinidine, chloramphenicol, dicumarol, calcium channel blockers, tricyclic antidepressants, chemotherapeutic agents, or other AEDs. Conversely, many medications may alter phenytoin levels. For example, chloramphenicol, sulfonamides, isoniazid, disulfiram, dicumarol, and cimetidine may increase serum phenytoin levels, while antacids or rifampicin may decrease them. Depending on the circumstances, its half-life may vary anywhere between 7 and 42 hours; hence, it can be given twice or even once a day.

Despite its limitations, phenytoin remains an affordable, well-studied, broad-spectrum, and consistently efficacious AED, and is used extensively. Its availability in various preparations, including extended-release, intravenous, and intramuscular, renders it favorable for use in emergent and intensive care settings.

Carbamazepine Another first-generation antiepileptic drug, carbamazepine (Tegretol, Carbatrol), also works via sodium channel blockage. It is effective for both partial (simple or complex) and secondarily generalized tonic-clonic seizures. It should be avoided though in primarily generalized seizures, such as absence and myoclonic seizures, as it can aggravate them. This is less of a concern in older adults, unless a history of childhood epilepsy is present. Like phenytoin, carbamazepine toxicity may elicit dose-dependent drowsiness, ataxia, diplopia, and nystagmus. Hyponatremia is another adverse effect, and if it proves refractory to fluid restriction, may require discontinuation. The most concerning side effect is idiosyncratic bone marrow suppression and aplastic anemia. This is extremely rare but may be life threatening, and regular monitoring of blood counts with differential are recommended during initiation and uptitration. It is not uncommon to see mild neutropenia with carbamazepine, but no evidence associates this with a risk of infection, and discontinuation is generally unnecessary with counts above 2.5×10^9/L. The incidence of rash with carbamazepine use is approximately 10%. There is often cross-reactivity with other aromatic AEDs such as phenytoin, phenobarbital, primidone, and lamotrigine.

Carbamazepine is a strong hepatic inducer, and with long-term use its half-life is approximately 15 hours. Extended-release formulations twice daily minimize dose fluctuations. Its use is complicated by various drug-drug interactions, principally those affecting the cytochrome P450 enzyme, CYP 3A4, including dose-dependent autoinduction. Carbamazepine decreases levels of certain medications such as warfarin, calcium channel blockers, and tricyclic antidepressants. On the other hand, its levels are increased by concomitant use of erythromycin, propoxyphene, and grapefruit juice and are decreased by herbal remedies such as St. John’s wort.

Despite tolerability that tends to rank at the lower end of the AEDs, carbamazepine is an affordable and efficacious AED that continues to be frequently prescribed.

Phenobarbital Phenobarbital, a barbiturate, was the first approved AED and by virtue of its affordability and very long half-life, it remains the most widely used AED in the developing world. It is a sodium channel blocker used primarily to control partial onset and tonic-clonic seizures, as well as occasionally in status epilepticus. However, because of its side effects of sedation, cognitive slowing, depression, and memory loss, it is infrequently used in the older population. Rarely, one may encounter a patient who has been taking it for decades and because of good seizure control is disinclined to switch to another agent. Therefore, familiarity with its side effects is relevant. In addition to the aforementioned side effects, hepatic failure and aplastic anemia are rare idiosyncratic effects, while its long-term use may lead to osteoporosis and connective tissue abnormalities (eg, frozen shoulders, contractures, and myofascial pain). Patients who develop these complications should be urged to switch to an alternative medication. Given the tolerance that develops with long-term use, phenobarbital withdrawal should be performed gradually over the course of months to avoid potentially life-threatening withdrawal seizures.

Primidone Primidone (Mysoline) is metabolized among others into phenobarbital and bears the same concerns with its use. Occasionally it is prescribed in patients with concomitant essential tremor, but its administration is limited with the advent of newer antiepileptic agents with a much more favorable side effect profile.

Valproic acid Valproate (Depakote, Depakene, Depacon) is a broad-spectrum agent. It has multiple mechanisms of action, including but not limited to sodium channel and γ-aminobutyric acid (GABA) receptor blockade. It is approved for partial-onset and primary generalized epilepsies, including childhood absence and juvenile myoclonic epilepsies. In fact, it is effective for essentially all seizures classes making it an often-chosen agent. Furthermore, it also has mood-stabilizing properties, and therefore is attractive for patients with both epilepsy and behavioral concerns. Like phenytoin, it is available in various formulations, including an intravenous one, facilitating its use in the emergent and intensive care settings. Side effects can be common and range from the more innocuous (eg, mild transaminitis, gastrointestinal distress, postural tremor, asymptomatic mild hyperammonemia, weight gain, hair loss) to more precarious (eg, hepatic failure, pancreatitis, parkinsonism, encephalopathy, and thrombocytopenia). Monitoring liver function tests and complete blood count intermittently is recommended. The incidence of a rash and osteoporosis is lower than with the rest of older AEDs.

Valproate is a strong hepatic inhibitor, and its concomitant use with other hepatically metabolized drugs must be monitored. It also has high affinity for serum proteins and competes with other agents for them. Phenytoin and carbamazepine lower valproate levels by 30% to 50%. Conversely, valproate may double the active metabolite of carbamazepine and markedly inhibit elimination of lamotrigine, prolonging its half-life by two to three times. Valproate half-life in adults is 13 to 16 hours and extensive-release formulations exist for once-per-day or twice-per-day use.

Benzodiazepines Benzodiazepines act through GABA-mediated inhibition and are effective for all classes of epilepsies. Given their substantial risk of sedation, tolerance, and dependence, they should not be used as first-line maintenance antiepileptic agents in the current era, nor should they be used as long-term adjuncts. However, they do comprise the first-line treatment in emergent situations and for that reason they have lately become available in multiple parenteral forms (rectal, sublingual, nasal, and intramuscular, in addition to intravenous).

Ethosuximide This drug acts by reducing low-threshold T-type calcium currents in thalamic neurons. Its use is limited to the treatment of childhood absence epilepsy, and hence, it is almost never administered in older adults.

Second-Generation AEDs

Levetiracetam Levetiracetam (Keppra) is a broad-spectrum antiepileptic efficacious for partial-onset and primary generalized epilepsies. While not entirely confirmed, it is thought to exert its action by binding to a synaptic protein in the brain known as SV2A. It has a very favorable safety profile. Potential side effects of levetiracetam include irritability, somnolence, and dizziness. More significant and lasting mood disturbances, including severe depression, suicidality, and psychosis, have been documented as well. To date, there is no evidence for levetiracetam causing idiosyncratic hepatic failure or aplastic anemia. It is extremely water soluble, is absorbed quickly and fully, binds minimally to proteins, does not interact with other medications, and is largely excreted unchanged in the urine. It can be administered in effective doses quickly and exists in IV formulations, making it useful for emergencies and for patients unable to take medications orally.

Levetiracetam is one of the most popular AEDs in older adults, given its broad-spectrum activity, favorable pharmacokinetics (particularly lack of drug-drug interactions), efficacy, and tolerability (particularly lack of significant impact on cognition).

Lamotrigine Lamotrigine (Lamictal) is a broad-spectrum antiepileptic, effective for essentially every type of seizure, with the possible exception of myoclonic seizures in some patients, making it a popular option. It is a sodium channel blocker, hepatically metabolized through the glucuronidation pathway, which is less affected by age than the P450 pathways that the majority of the other hepatically metabolized AEDs utilize.

It is generally one of the best tolerated AEDs, but occasional dose-related side effects include headache, insomnia, and tremor. An uncommon but well-documented and potentially lethal adverse effect is Stevens-Johnson syndrome (SJS), and therefore any report of a new rash should prompt a physical examination and possible discontinuation of the drug. The incidence of SJS increases significantly with concurrent use of valproate and with rapid uptitration of lamotrigine; it is rare with gradual titration of lamotrigine monotherapy. While lamotrigine does not affect the metabolism of other drugs, use of other drugs may alter lamotrigine metabolism. For example, phenytoin,

carbamazepine, and phenobarbital would nearly halve its half-life, while valproate would nearly double it.

Overall, lamotrigine is an attractive option for older adults, given it is broad spectrum and has equal efficacy but better tolerability than the first-generation AEDs. Additionally, it has insignificant impact on cognition and is potentially beneficial for concomitant mood disorders.

Oxcarbazepine Like carbamazepine, oxcarbazepine (Trileptal) is a sodium channel blocker with a narrow therapeutic spectrum for partial-onset seizures, having also the potential to exacerbate primary generalized epilepsies. It has more favorable pharmacokinetics (eg, rapidly and almost completely absorbed, lower plasma protein binding, weaker P450 isoenzymes inducer without enzyme autoinduction, minimal drug interactions) compared to carbamazepine. It is considered to be of equivalent efficacy, but better tolerability. The most common side effects are gastrointestinal (GI) and central nervous system (CNS) related. Certain side effects of carbamazepine such as aplastic anemia and agranulocytosis are less commonly encountered with oxcarbazepine. That is not the case with hyponatremia, however, which commonly occurs in older adults in greater than 7%, particularly those on diuretics.

Gabapentin and pregabalin Gabapentin (Neurontin) is a narrow-spectrum AED approved for partial-onset epilepsies; it should be avoided in primary generalized epilepsy as it may exacerbate it. Its mechanism of action is poorly understood, but may at least in part be the result of modulation of voltage-sensitive calcium channels affecting release and perhaps synthesis of GABA. In contrast to the majority of AEDs, it is not hepatically metabolized but rather renally excreted; this makes it advantageous for older adults with liver failure as well as for those with polypharmacy, given there will be fewer drug-drug interactions. Another attractive quality of gabapentin is its efficacy for neuropathic pain, thus it is a good option for patients with painful diabetic neuropathy, postherpetic neuralgia, radicular pain, headaches, or other neuropathic pain syndromes. Its principal side effect is sedation, which can be seen at much lower doses in older adults. Weight gain also appears dose related. A low risk of depression and suicidality has also been reported.

Pregabalin (Lyrica) is a refined version of gabapentin with a similar mechanism of action but more favorable pharmacokinetics. It is considered more potent due to higher affinity with its site of action and better absorption leading to higher bioavailability, allowing twice as opposed to three times dosing schedule.

In summary, the gabapentinoids have several advantages, including lack of organ toxicity, significant drug-drug interactions, lack of protein binding, renal clearance, and potential beneficial effects to neuropathic pain and anxiety.

Tiagabine Tiagabine (Gabitril) acts by blocking the reuptake of GABA following its release from postsynaptic GABA receptors. Similar to carbamazepine, oxcarbazepine, gabapentin, and pregabalin, it has a narrow therapeutic spectrum for partial-onset epilepsies, with the potential to aggravate primary generalized epilepsies. It has been approved as adjunctive treatment for partial seizures, is highly protein bound, and has a short half-life and predominantly CNS-related side effects, limiting its overall popularity, despite its lack of significant drug interactions.

Felbamate Felbamate (Felbatol) is a broad-spectrum AED efficacious both for focal and generalized epilepsies and has been approved for partial-onset seizures as well as seizures associated with Lennox-Gastaut syndrome. It has multiple mechanisms of action including sodium channel and glutamate receptors blockade. It has lost popularity due to the rare risk (cumulatively about 1 in 8000) of idiosyncratic fatal reactions such as aplastic anemia and hepatic failure. It is mainly reserved nowadays for the treatment of refractory idiopathic or symptomatic generalized epilepsies, a rare occurrence in older adults. Side effects include decreased weight and appetite, insomnia, headache, and GI distress.

Topiramate Topiramate (Topamax) is another broad-spectrum AED, efficacious for both partial-onset and primary generalized epilepsies. It has multiple mechanisms of action including sodium channel blocking, enhanced GABAergic inhibition, and decreased glutamatergic (AMPA) excitation. It is also commonly used for migraine headache prophylaxis, making it a good option for patients with migraines. It is primarily renally cleared (70%), with the remaining being hepatically metabolized through the P450 pathway. It has minimal protein binding. At high doses, it may function as a hepatic inducer but otherwise has few drug-drug interactions.

Side effects may be common and include impaired verbal fluency (reportedly as trouble finding words or naming objects), somnolence, psychomotor slowing, fatigue, weight loss, paresthesias, nephrolithiasis, and open-angle glaucoma.

Zonisamide Zonisamide (Zonegran) is a broad-spectrum AED, efficacious both for partial-onset and generalized seizures. It acts both on sodium and calcium channels. It is approximately 40% protein bound and is primarily eliminated through the hepatic pathway. It has a long half-life allowing once-per-day dosing. Its major side effects are

somnolence and dizziness. Similar to topiramate, it is associated with weight loss and renal calculi.

Newer ("Third") Generation AEDs

Lacosamide Lacosamide (Vimpat) is a newer antiepileptic approved for partial seizures. Its mechanism of action is at least twofold, with inactivation of sodium channels as well as modulation of collapsin response mediator protein 2 (CRMP-2), which is thought to prevent the generation of abnormal neuronal connections, thereby preventing secondary epileptogenesis. It is renally excreted, and therefore has significantly fewer drug-drug interactions than most AEDs. Other benefits include an intravenous formulation, near 100% bioavailability following oral dosing, and the ability to safely uptitrate. Side effects most commonly include headache, somnolence, dizziness, and diplopia.

Rufinamide Rufinamide (Banzel) acts by modulating sodium channels and is approved for seizures in Lennox-Gastaut syndrome. Hence, it is unlikely to be considered in older population.

Vigabatrin Vigabatrin (Sabril) acts by stimulating GABA release and is approved for infantile spasms and refractory partial epilepsy. Due to concerns of visual field changes, it has not gained popularity so far in the adult population.

Clobazam Clobazam (Onfi and Frisium) is a benzodiazepine with lower potential for dependence, tolerance, and sedation and is approved for seizures of the Lennox-Gastaut type.

Perampanel Perampanel (Fycompa) acts by decreasing glutamatergic excitation and is approved for partial seizures and recently also as an adjunctive treatment of primary generalized tonic-clonic seizures. Its major side effects are CNS related.

Ezogabine Ezogabine (Potiga) acts by blocking potassium channels and is approved for partial seizures. It has been associated among others with urinary retention, a potential concern for the older population, as well as potentially irreversible skin discoloration.

Eslicarbazepine acetate Eslicarbazepine acetate (Aptiom) is a refined form of oxcarbazepine with better pharmacokinetics allowing once-per-day dosing, lower incidence of a rash, and perhaps hyponatremia, but no significant difference in efficacy.

Nonpharmacologic Management

There are a variety of nonmedical options available for medically refractory epilepsy, which is generally defined as occurring when a person has failed to become and remain seizure-free with two concurrent or sequential, adequate dose trials of appropriate AEDs. Up to 30% of patients will fall into this category, at significant cost to their personal and professional lives. As appropriate, these patients may be offered a nonpharmacologic intervention. Although there is a different and frequently greater set of risks for older adults undergoing surgical consideration, but none of the surgical options for epilepsy are excluded solely on the basis of age.

Resective surgery The optimal candidate is a low risk for surgery, motivated patient with refractory and disabling epilepsy, who bears a single, lesion, epileptogenic focus, distant from eloquent parts of the brain. Thorough presurgical evaluation is required to establish surgical candidacy and includes prolonged video-EEG recordings (scalp vs intracranial), advanced neuroimaging modalities (eg, MRI, positron emission tomography [PET], single-photon emission computed tomography [SPECT], etc) and functional testing (eg, neuropsychological evaluation, intracarotid amytal test, etc). In carefully selected individuals, seizure-free ("cure") rates may be as high as 70%. Evolving technologies such as laser ablation, offer the opportunity of less invasive surgical avenues, potentially more appropriate to older adults than traditional open resections.

Neurostimulation So far, two neurostimulation devices have been approved by the FDA for the treatment of refractory epilepsy: the vagus nerve stimulation (VNS) and the responsive neurostimulation (RNS). A third type of deep brain stimulation (DBS) of the thalamus has been recently tested and is currently awaiting FDA approval.

VNS is a low risk procedure that is effective for both partial-onset and primary generalized epilepsies. It is therefore useful for refractory epilepsy patients with generalized, poorly localizable or multiple epileptogenic foci or those who do not wish or are considered high risk to undergo resective surgery. VNS acts by indirectly modulating brain activity via intermittent and per request stimulation to the vagus nerve. An implantable pulse generator (approximately the size of a cardiac pacemaker) is implanted in the left chest wall, with its leads wrapped around the

left vagus nerve. The stimulator then delivers short electrical pulses at programmed intervals, which may be modified in the office setting and optimized over time. Holding a special magnet over the stimulator can deliver additional impulses, which may be particularly useful for patients with auras or other premonitory signs during their seizures prior to loss of consciousness. Recently a refined version of VNS has been released using ictal tachycardia as surrogate indicator for timely stimulation. While not universally effective, it has consistently shown a greater than 50% seizure reduction in roughly 60% of patients. In older adults, there was a greater than 50% seizure reduction in 68% of patients, with striking increases in quality-of-life scores. The latter is largely attributable to—in addition to its clinical efficacy—the obvious lack of drug-drug interactions and the bland side effect profile. The most common adverse effects are hoarseness or voice alterations and coughing, both of which may be intensity related and may be ameliorated with decreasing settings. An additional benefit of VNS is that it appears to concurrently relieve depression, and in fact has a separate indication for that purpose, rendering an even more attractive option in this subset of patients.

Unlike VNS, RNS can record and stimulate directly the brain regions of interest. It involves a stimulator implanted within the skull connected to one or two leads placed into focal epileptogenic regions within the brain. Like resective surgery, RNS requires an extensive presurgical evaluation to ensure that implantation occurs at the precise site(s) of seizure onset. It is analogous to the function of defibrillator for cardiac arrhythmias in the sense that it can detect a focal seizure and immediately deliver an impulse, with the goal of aborting it before it propagates to other areas of the brain. Further advantages include the ability to individualize the parameters to best detect and abort the patient's seizures. In the initial clinical trials, the efficacy data were not dramatically different from VNS but with the anticipated improvement of detection and stimulation algorithms as more experience is accumulated, it is expected to become an attractive option for refractory focal epilepsy patients who do not wish or are not appropriate for resective surgery.

SPECIAL ISSUES IN EPILEPSY IN OLDER ADULTS

Epilepsy and Cardiovascular Disease

This is a complex and multifaceted topic, as there are causal effects in both directions. As stated earlier, cerebrovascular pathology underlies roughly two-thirds of new cases of epilepsy in this age group. A significant portion of the mechanisms contributing to this cerebrovascular pathology may be at play in the cardiovascular system as well, such as atherosclerotic risk factors or atrial fibrillation. These may independently lead to cardiac pathology. Furthermore, temporal lobe seizures often involve a brain network that is responsible for autonomic function. During a seizure, the excessive paroxysmal activity from these regions may lead to ictal tachycardia and other signs of catecholamine surge. This is suspected to contribute to the objective pathology seen in patients with chronic epilepsy, including cardiomegaly, QT dispersion (reflecting regional heterogeneity of cardiac repolarization), and late ventricular potentials. This cardiac pathology, along with neurogenic pulmonary edema and central and obstructive apnea are thought to be the driving forces behind the infrequent, albeit extant, phenomenon of sudden unexpected death in epilepsy (SUDEP).

Several of the AEDs used in epilepsy may in turn compound preexisting cardiovascular disease. For instance, phenytoin is an old class 1b antiarrhythmic, and may cause bradycardia and first-degree heart block. Carbamazepine and lacosamide have been known to have similar effects as well. Cautious review of patients' comorbid medical conditions and knowledge of common and rare but theoretically life-threatening adverse effects will aid in avoiding selecting a potentially harmful medication.

Epilepsy and Bone Health

Older adults are particularly susceptible to poor bone health and its sequelae. At baseline, there are much higher rates of osteoporosis in this population related to sedentary lifestyles, lack of exposure to sunlight, inadequate nutrition, and decreased sex hormones in women. Musculoskeletal and neurologic deficits along with poor balance from decreased agility and visual input render older adults at high risk for falls. Adding epilepsy to these preexisting handicaps increases the risk for falls and fractures by two- to sixfold. AEDs can significantly compound this, especially the hepatically metabolized, enzyme-inducing ones (phenytoin, phenobarbital, carbamazepine). In fact, long-term AED use in women over 65 years has been shown to increase the risk of hip fracture by 29% over 5 years. The data on newer antiepileptic drugs needs more investigation but at first glance is less concerning, aside perhaps for those with

mild enzyme-inducing capacity such as oxcarbazepine and topiramate. That should be taken into account during AED selection. Similarly, avoiding AEDs with high risk for sedation and imbalance as a potential side effect is prudent. It is recommended to monitor older adults with periodic dual-energy x-ray absorptiometry (DEXA) scans and serum vitamin D levels, preemptively supplement their nutrition with vitamin D and calcium, replete low levels with higher doses of those agents when identified, and add additional medications against osteoporosis (eg, bisphosphonates) when required.

Epilepsy and Mood Disorders

Depression and anxiety are quite common in epilepsy, and their incidence has been estimated to be as high as 23%. This should come as no surprise, as epilepsy is a chronic condition with significant morbidity and mortality, often associated with substantive changes to patients' lifestyles. The diagnosis may bring about the loss of driving privileges and therefore of independence and, if the episodes are frequent or disabling enough, may in certain cases warrant placement in a personal care home. These, along with concomitant changes in social standing, often lead to the onset of depression or to the relapse or aggravation of preexisting mood disorders. Comorbid depression in patients with epilepsy may be quite severe; the risk of suicide in people with epilepsy is three times higher than that of the general population. Antiepileptic drugs themselves have been implicated in that risk. Thus, close monitoring is especially recommended in older adults, and referrals for counseling and initiation of antidepressants may be indicated. Certain AEDs, such as lamotrigine and valproate, have potential antidepressant effects, while others such as gabapentin and pregabalin have potential anxiolytic effects, and these effects may play a role during AED selection.

Epilepsy in Older Adults With Renal Dysfunction

The extent of renal dysfunction affects the pharmacokinetics, particularly of AEDs dependent on the kidneys as the primary elimination pathway (eg, mostly levetiracetam, lacosamide, gabapentin, pregabalin, topiramate, vigabatrin, felbamate, and to a lesser extent oxcarbazepine, zonisamide, rufinamide, and lamotrigine). Older-generation AEDs are mostly metabolized through the liver and therefore less severely affected. Similarly, AED removal from hemodialysis is dependent on several factors, including its molecular weight, plasma concentration, protein binding, blood flow, hematocrit, and characteristics of the dialyzer. Predominantly renally excreted, low-protein–bound AEDs as above are significantly removed from hemodialysis and may require an additional supplemental dose following each session to restore therapeutic levels. Conversely, older-generation AED removal is negligible (aside for phenobarbital).

Epilepsy in Older Adults With Hepatic Dysfunction

Hepatic insufficiency can significantly alter the metabolism of many AEDs through changes in hepatic blood flow as well as protein binding alterations. This can result in intoxication, more considerable with heavy protein bound, predominantly liver metabolized AEDs, such as the first-generation AEDs (phenytoin, phenobarbital, carbamazepine, valproate, and benzodiazepines).

CONCLUSION

The incidence of epilepsy is highest in older adults, and as they comprise an increasingly large subset of the population, the prevalence of this condition will continue to rise. Their situation is fraught with complexities above and beyond those typically seen in other demographic groups, from diagnostic uncertainty to complications of therapy. It is a general dictum that all medications have side effects, and this is particularly true for AEDs, which—by design—are active within the central nervous system. Older adults are particularly susceptible to such adverse effects, and it is important to "start low and go slow" whenever feasible. No "one size fits all" solution is available. It is best to avoid agents with significant drug-drug interactions, and to monitor closely for the development of adverse effects, both acute and those resulting from long-term therapy. Fortunately, the range of both pharmacologic and nonpharmacologic interventions available for older adults with epilepsy is rapidly expanding.

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Chapter 71

Evidence-Based Treatment and Prevention of Major Depressive Episodes in Later Life

Charles F. Reynolds, III

Learning Objectives

- To understand the relationship between depression in older adults and comorbid medical and neurologic conditions, especially disability and health-related quality of life.
- To specify the downstream consequences of depression in later life, including increased risk for disability, poor treatment adherence, dementia, and shortened life expectancy.
- To review the evidence-based information for both short- and long-term treatment (pharmacologic and psychosocial) of depression in older adults.
- To address the importance and feasibility of depression prevention in at-risk older adults.
- To discuss a palliative care approach to depression assessment and treatment at end of life.

Key Clinical Points

1. **Depression is a highly prevalent, frequently undiagnosed disease in older adults and associated with significant disability, dementia, mortality, and a higher suicide rate.**
2. **Common symptoms of depression in older adults include cognitive deficits, functional deficits, sleep disorders, psychomotor retardation, and failure to thrive.**
3. **The treatment goal for depression is complete symptomatic remission, followed by long-term treatment that reportedly promotes brain health, prevents relapses, and reduces risk for dementia, disability, and suicide.**
4. **Effective treatments for depression include antidepressants, both selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), psychosocial interventions, evidence-based depression care management programs, and collaborative care interventions in primary care settings.**
5. **Depression can be potentially prevented through several reportedly effective strategies, including short-term depression-specific psychotherapies, problem-solving therapy (PST), coaching in healthy dietary practices, and cognitive behavioral therapy (CBT)–based bibliotherapy.**

DEFINITION

Depression is a mood disorder in which feelings of sadness, loss, anger, or frustration interfere with daily life for weeks or longer. Depression in older adults is a widespread problem, but it is not a normal part of aging. It can be prevented in some cases, and is often not recognized or treated.

EPIDEMIOLOGY

The Global Public Health Burden of Clinical Depression in Older Adults

Present in 6% to 10% of older primary care patients at any one point in time, clinical depression (or "major depression") in later life is associated with increased health care utilization and costs, in no small measure because it often goes undiagnosed and either untreated or undertreated. As such it undermines health-related quality of life, both physical and mental, amplifying the disability born of associated medical and neurologic conditions. The World Health Organization now estimates that depression is the second leading contributing factor, after cardiovascular disease, to the global burden of illness-related disability. Depression also shortens life expectancy by undermining treatment adherence to coprescribed medical regimens and interfering with the patient's ability to make healthy lifestyle choices. It also appears to accelerate cellular aging, possibly increasing the risk for cancer-related mortality. Depression is the major risk factor for completed suicide in older adults, particularly among white men over the age of 75 who, when they make a decision to end their lives, often do so by firearms. Finally, depression has emerged as an important risk factor for the onset of dementia in older adults, whether vascular dementia or Alzheimer dementia. For all of these reasons, the public health burden of depression and older adults is great, both in high-income and low- and middle-income countries. At the same time, it is both treatable and preventable and hence its diagnosis and management are key components of clinical practice in geriatric medicine. This chapter will summarize current evidence-informed treatment and prevention strategies for clinical depression in older adults. We will highlight results of key systematic reviews and meta-analyses, as well as those of randomized clinical trials published in high-impact journals. Readers may refer to the bibliography for major literature resources used in the preparation of this chapter.

An important, yet still underappreciated part of the public health burden of clinical depression in older adults stems from its often chronic, relapsing course. Psychosocial factors contribute to the chronic course of depression in old age. These factors include major role transitions in social roles (such as retirement), bereavement, prolonged or "complicated" grief, and increasing dependency and often personal conflicts with caregivers. Complicating the psychosocial context of depression in old age is a progressive depletion of economic resources. Clinically, chronic sleep disturbances, particularly insomnia, excessive daytime sleepiness, and breathing-related sleep disorder, as well as chronic pain and loss of mobility, increase the vulnerability to depression and worsen its severity and course. Changes in the aging brain, including both subclinical and clinical cerebrovascular disease and early changes of neurodegenerative disorders, also increase the risk of a chronic, relapsing course. There is limited access to adequate treatment, thus increasing the vulnerability of seniors to incomplete treatment and early relapse. Increasing functional dependency and impairment born of disabilities create a downward spiral—with both depression and disability each making the other worse. Finally, newly emerging evidence suggests that depression is associated with accelerated cellular aging; acceleration of aging processes at the cellular and subcelluar level may contribute to depression's often chronic course, although exactly how remains to be elucidated. In summary, depression in old age rarely occurs in "pure culture," but rather coexists with impairments of cognition and mobility. The co-occurrence of depression, cognitive impairment, and loss of mobility contribute to the loss of independence in older adults.

PRESENTATION

Symptoms may include persistent depressed mood, decreased interest or pleasure in nearly all activities, marked loss or gain of weight or increased/decreased appetite, sleep disorders and fatigue, observable agitation, feelings of guilt or worthlessness, poor concentration or indecisiveness, and thoughts of death or suicide.

EVALUATION

Measurement-Based Assessment and Care

For the assessment of major depression in older adults, it is clinically useful and valid to use brief self-report rating scales such as the Patient Health Questionnaire-9 (PHQ-9) (**Figure 71-1**). The PHQ-9 is based on the *Diagnostic and Statistical Manual* (DSM) of the American Psychiatric Association criteria for major depression. Scores of 0 to 4 indicate either no depression or clinically insignificant depressive symptoms. Scores of 5 to 9 indicate mild depression, generally subsyndromal, while scores of 10 or higher typically correlate with a diagnosis of clinical ("major") depression and warrant further evaluation and clinical intervention. The PHQ-9 is a good tool for measurement-based care to document the presence of symptoms and their change during treatment. Such instruments are also useful for

educating patients and pinpointing which symptoms represent targets of intervention. Item 9 on the PHQ-9 asks the patient about death wishes or more intensive suicidal ideation; this is clearly an important part of the assessment. There is a broad range of risk and protective actors for suicide in older adults (**Figure 71-2**).

Patient Health Questionnaire-9 (PHQ-9)

ID #: | | | | | | | Date: | | / | | / | | | | |

Timepoint: | |

Instructions For Use

Scoring of PHQ-9 Depression Assessment

Calculate the Total Number of Symptoms: Add the total number of symptoms in Questions 1-8 indicated by the patients as having experienced "more than half the days" or "nearly every day." Add an additional point if the patient answered question 9 [Suicidality Question] "several days, "more than half the days" or "nearly every day."

Total Number of Symptoms:

Calculate the Total (Severity) Score: Multiply the assigned point values by the number of responses given by the patient in each frequency column. Add these together to calculate the Total Score, which represents the severity of the symptoms:

"Several days" ____ × 1 = ____ a
"More than half the days" ____ × 2 = ____ b
"Nearly every day" ____ × 3 = ____ c

Total Score (a + b + c): _____

Using the PHQ-9 for Diagnostic Assessment

Symptoms	Provisional Diagnosis	Treatment Recommendation*
1 to 4 symptoms (from gray areas on questions 1-9) plus functional impairment (#10)	Other	-Reassurance and/or supportive counseling -Education to call if deteriorates
2 to 4 symptoms (from gray areas on question 1-9), plus question 1 or 2, plus functional impairment (#10)	Minor depression	-Watchful waiting -Supportive counseling -If no improvement after one or more months use antidepressant or brief psychotherapy
3 to 4 symptoms (from gray areas on questions 1-9). plus question #2 (mood) with symptoms of 2 years, plus functional impairment (#10)	Chronic depression (probably) dysthymia	-Antidepressant and/or psychocherapy
5 symptoms (from gray areas on questions 1-9), plus questions 1 or 2, plus functional impairment (#10)	Major depression (severity score) **Moderate** (PHQ-9 score of 15 to 19) **Severe** (PHQ-9 score of 20)	**For moderate** -Patient preference for antidepressant and/or psychotherapy **For severe** -Antidepressants alone or in combination with psychotherapy

*Additional treatment considerations: Referral or comanagement with mental health specialty provider for patients with:

- ⊗ High suicide risk
- ⊗ Bipolar disorder
- ⊗ Inadequate treatment response
- ⊗ Complex psychosocial needs and/or
- ⊗ Other active mental disorders

Patient Health Questionnaire-9 (PHQ-9)

ID #: | | | | | | | Date: | | / | | | / | | | | |

Timepoint: | | |

Over the *last* 2 *weeks*, how often have you been bothered by any of the following problems? (use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
	add columns:	+	+	+
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring.)	**TOTAL:**			

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all (0) _____ Somewhat difficult (1) _____ Very difficult (2) _____ Extremely difficult (3) _____

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs. Robert L. Spitzer. Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information. contact Dr Spitzer at ris8@columbia edu. Use of the PHQ-9 may only be mace in accordance with the Terms of Use available at *http://www.pfizer.com*. Copyright @1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.

FIGURE 71-1. Patient Health Questionnaire-9 (PHQ-9).

SUICIDE/SAFETY RISK FACTOR CHECKLIST

PHQ, Q9 ≥ 1
MADRS, Q10 ≥ 3
QIDS-SR Q12 ≥ 1

MR#: _____

Subject Initials : _____

Date: _____

Suicidal Items

- Thoughts _____
- Intent _____
- Plan _____
- Behavior _____

Fill in all that apply:

Risk Factors

- ○ Hopelessness
- ○ Demographics, eg, male, Caucasian
- ○ Impulsivity/agitation/anxiety
- ○ Perceived burden to others
- ○ Chronic pain
- ○ Acute medical problems
- ○ NP status _____
- ○ History of homicidal behavior
- ○ Aggressive behavior toward others
- ○ Available method(s) _____
- ○ Refusal or inability to contract for safety
- ○ Significant recent loss
- ○ EtOH or substance use
- ○ Family Hx of attempts/completed suicide
- ○ Sexual orientation
- ○ Isolated
- ○ Hx of abuse _____
- ○ Acute/chronic stressors, eg, caregiving, finances, grief

Risk Factors (cont.)

- ○ Insomnia, eg, hypnotics _____
- ○ Suspicion of SI minimization
- ○ Unemployment
- ○ Previous suicide attempt
- ○ Discharge from psychiatric hospitalization
- ○ Homicidal ideation
- ○ Wish to join deceased
- ○ History of molestation

Protective Factors

- ○ Reasons for living _____
- ○ Responsibility to others
- ○ Lives with others
- ○ Supports _____
- ○ Fear of death or dying
- ○ Suicide is immoral
- ○ Cultural/spiritual beliefs
- ○ Engaged in work/school
- ○ Motivated to overreport SI
- ○ Ability to solve problem/make decisions

Firearm Form Status _____

Action Plan _____

Driving Precaution Documentation: Participant informed of possible risks associated with driving when starting a new medication. These include sedation and impaired decision making. He/she was advised to use extra caution when driving until any negative effects of the medication that MAY affect driving are known. Yes ☐ N/A ☐

AUDIT C completed: Yes ☐ No ☐ Reason why not _____

_____ _____

Clinician Signature, No., & Date **Supervisor Signature, No., & Date**

FIGURE 71-2. Suicide risk checklist. MADRS, Montgomery-Asberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self Scale.

The DSM-5 diagnostic criteria for major depression differ little from those of the DSM-IV, with one important

exception, that is, the dropping of the bereavement exclusion criterion in DSM-5. DSM-IV had stipulated that a diagnosis of major depression could not be made within 2 months of the loss of a loved one. However, the DSM-5 Task Force, on revisiting the evidence, concluded that bereavement does not "immunize" one from major depression. The distinction between grief and major depression underscores the importance of suicidal ideation and psychomotor disturbance in major depression, in contrast to normal grief. However, as discussed later in this chapter, about 10% of persons get "stuck" in prolonged or complicated grief (a provisional diagnosis now in section III of the DSM-5). Prolonged grief often coexists with major depression and post-traumatic stress disorder (PTSD)—patterns of comorbidity that make it "complicated" both diagnostically and therapeutically.

Another important aspect of measurement-based assessment of depression in old age is evaluation of cognitive impairment. Cognitive impairment, especially slowing of information processing speed and impairment in executive functions, is substantial and highly prevalent among older adults with major depression. Impairment improves but often persists after remission of symptoms. Thus, even when clinical depression can be adequately treated to remission, it is common for cognitive impairment to persist. There is substantial risk of progressive cognitive decline and dementia even among individuals without initial impairment. Indeed, depression is a risk factor for the development of future dementia, whether of the vascular type or the Alzheimer type. The Montreal Cognitive Assessment (MoCA) is a useful cognitive screener in older adults, with scores of less than 21 indicating clinically significant impairment. For the assessment of depression in dementia, the Cornell Rating Scale for Depression in Dementia is the most specific and best tool available.

MANAGEMENT

Goals of Treating Clinical Depression in Older Adults: Better Life, Longer Life

Within this context, the goal of treatment for depression in later life is both better life and longer life (**Table 71-1**). The clinician should seek to achieve symptomatic remission in order to promote functional recovery and to reduce the risks of a relapsing, recurrent illness course. Treatment should aim to attenuate, to delay, or even to prevent the downstream consequences of depression in older adults (eg, worsening of coexisting medical conditions, complicated grief, dementia, and death). A good treatment plan can also reduce the considerable caregiver burden that attends depression in older family members. Depression is indeed a "contagious" illness, often associated with demoralization, stress, and depression in family caregivers. Finally, the goals of treating depression in old age include facilitating the appropriate use of general medical and social casework services.

TABLE 71-1 GOALS OF TREATMENT: BETTER LIFE, LONGER LIFE

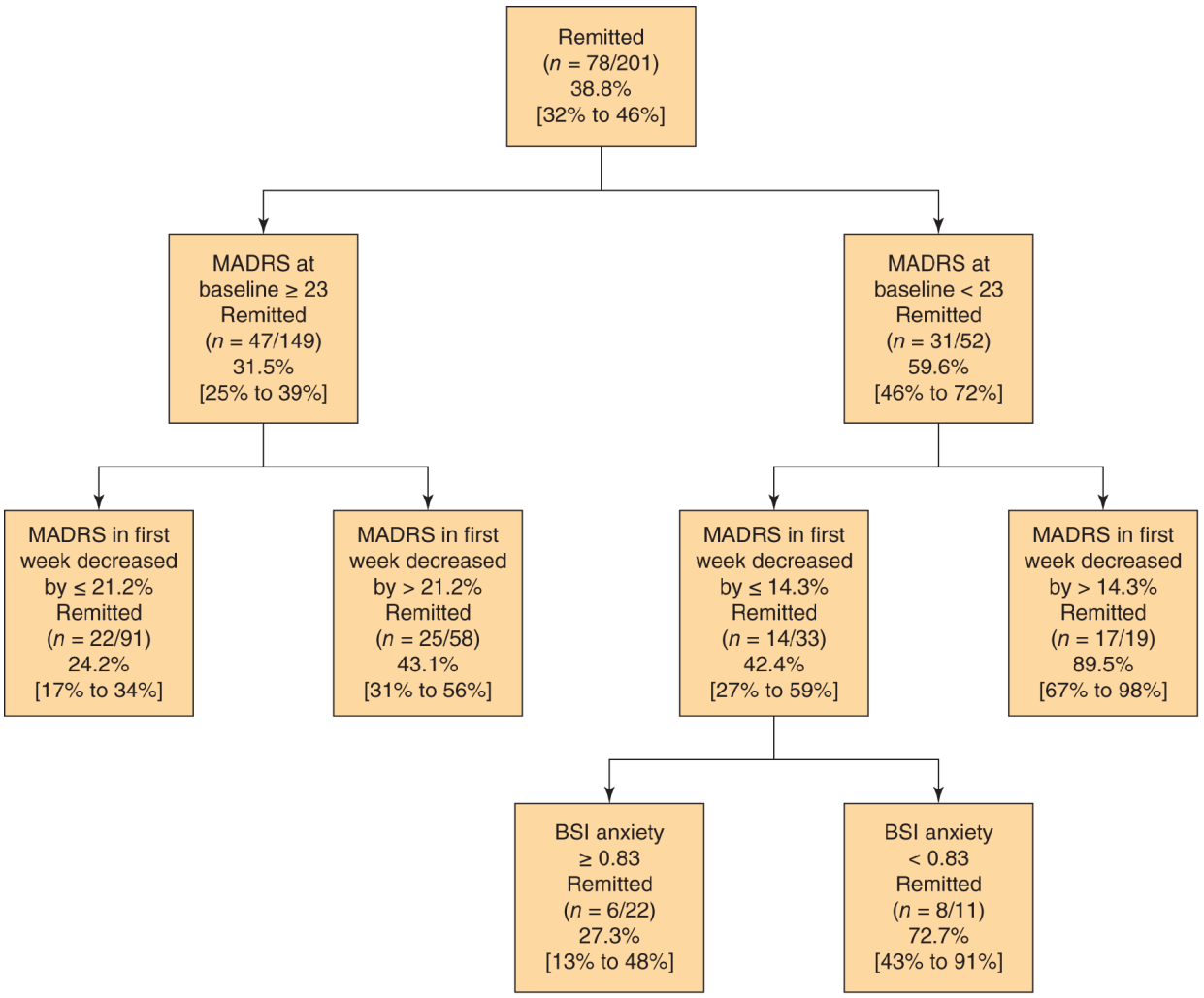
Achieve symptomatic remission
Promote functional recovery
Prevent relapse and recurrence
Attenuate, delay, prevent downstream consequences
Reduce caregiver burden
Facilitate appropriate use of general medical and social casework services

Remission of symptoms is the first goal of treating major depression in older adults because response without full symptomatic remission continues to be associated with disabling symptoms, higher rates of relapse and recurrence, impaired psychosocial functioning, and higher rates of often inappropriate health care utilization. Getting well, however, is not enough; it is staying well that counts. There is a strong rationale for long-term or maintenance treatment of major depressive disorder in older adults. Longer-term treatment to prevent relapse and recurrence may attenuate or prevent at least some, if not many, of the negative health outcomes of major depression in old age, including cognitive and functional impairment. Treatment may promote brain health and may reduce the risk for dementia. Finally appropriate treatment of depression in older adults may prolong life and also reduce the risk for completed suicide.

Drugs

Pharmacotherapy A recent meta-analysis of response rates to antidepressant pharmacotherapy versus placebo in 10 randomized clinical trials showed an overall drug response rate of 44.4% among drug-randomized patients versus 34.7% among placebo-randomized patients. The odds ratio for response to medication was 1.4 with a 95% confidence interval of 1.24 to 1.57. Thus drug treatment was significantly better than pill placebo but only modestly so, with a number needed to treat (NNT) of 13.

There are clinically actionable predictors of remission to antidepressant pharmacotherapy in depressed older adults. These predictors can be modeled in decision trees and then used to guide clinical decision making, such as how long to persist with a given medication versus switching to another course of action (**Figure 71-3**). It is useful clinically to measure pretreatment illness severity and change in symptoms during the first 2 weeks of treatment, in order to predict the likelihood of remission of late life major depression treated with medication. Higher baseline depression symptom severity and smaller symptom improvement during the first 2 weeks of treatment are useful predictors of likely nonresponse and nonremission, thereby enabling the clinician to discuss alternative treatment approaches sooner in the course of intervention.



Proportion of subjects who remitted during 12 weeks of open treatment with venlafaxine XR = 38.8% (adjusted Wald 95% confidence interval = 32% to 46%). A sensitivity threshold of 30% was used, corresponding to a clinical situation in which an aggressive approach would be needed because falsely concluding that the patient would eventually remit to treatment could be harmful (eg, a disabling depression or a high suicide risk). Baseline MADRS score is the main predictor of remission in this model. A baseline MADRS < 23 predicts 59.6% chance of responding at week 12 vs 31.5% if MADRS is greater than 23. Subjects whose symptoms did not change much in the first week had the lowest chance of remitting. Subjects with low baseline severity combined with large decrease in symptoms during the first week or smaller decrease in symptoms during the first week with low baseline anxiety had the greatest chance of attaining remissions (89.5% and 72.7%, respectively).

FIGURE 71-3. Hierarchy of predictors of treatment remission with an aggressive treatment approach (ie, a threshold of 30% for sensitivity). BSI, Brief Symptom Inventory; MADRS, Montgomery-Asberg Depression Rating Scale.

There is, however, still a paucity of evidence to guide clinical decision making in patients who are not responding well to first-line antidepressant pharmacotherapy. Incomplete or nonresponse is an issue in approximately 50% of older adults with clinical depression. While decision trees can inform the decision to stay the course or to switch to something else, the evidence base supporting second-line treatment is still sparse. Clinical practice typically involves

adding a second antidepressant in patients who are responding partially to the first antidepressant. The Food and Drug Administration (FDA) has approved the use of the atypical antipsychotic agent aripiprazole as an augmentation strategy in patients with difficult-to-treat depression. In patients who are showing little evidence of response to the first agent, clinical practice typically involves switching to another class of antidepressant medication, for example, from an SSRI (eg, sertraline) to an SNRI (eg, venlafaxine or duloxetine). Cumulative response rates to stepped-care algorithms of this sort usually approach 80% if patients are willing to remain in treatment. Family support is extremely important in this regard, to support patients in staying the course long enough to derive benefit. The most common error in general medical practice involves inadequate exposure to antidepressant medication—either too low a dose or too little time at maximal dose to achieve full benefit. For the 10% to 20% of patients whose illness is resistant to pharmacotherapy or to the combination of pharmacotherapy and depression-specific psychotherapy, electroconvulsive therapy (ECT) remains a viable option and one that is typically very helpful.

It is also important for the clinician to be mindful of the hazards, as well as the benefits, of acute or short-term antidepressant pharmacotherapy in older adults. This is particularly the case with respect to the sedative and anticholinergic properties of the older tricyclic antidepressants (TCAs), such as amitriptyline, imipramine, and nortriptyline. The use of these agents should probably be reserved to mental health specialists, and they should generally be considered third-line treatment. One advantage of these agents is the possibility to monitor blood levels for both adherence and for estimating the likelihood of efficacy. Thus there is a predictable relationship between TCA blood levels and likelihood of treatment response—a relationship that has not been documented in the case of newer SSRI and SNRI agents. The latter are, however, far safer in overdose than the TCAs. The use of antidepressants of any class is associated with falls and fractures in older adults, though it is difficult to know whether this is a direct consequence of the medication per se or, as seems more likely, the result of depressive illness itself. A small percentage of frail older adults, especially after the age of 75, are vulnerable to hyponatremia as a result of syndrome of inappropriate antidiuretic hormone secretion (SIADH), especially those with pretreatment serum sodium levels of 135 or lower. Also, bradycardia is a risk in patients with pretreatment heart rates of less than 60 and in the presence of β-blockers. Finally, per an FDA Medwatch published in August, 2010, there is a dose-dependent increased risk of arrhythmia associated with the use of citalopram in adults aged 60 and older, including risk for torsade de pointes.

Drug-drug interactions also need to be considered, especially with monoamine oxidase inhibitors and with medications metabolized by the cytochrome P450 (CYP450) family of isozymes. SSRIs and SNRIs are metabolized by the CYP450 complex in the liver (especially 2D6, 2C19, and 2C9). The patient's metabolizer status (eg, poor or ultrarapid) and the coadministration of other drugs that are metabolized by this complex may influence antidepressant response and the emergence of adverse side effects. CYP polymorphism testing may be helpful in patients who do not show antidepressant response with the usual doses, those with severe side effects at low doses, and those under polypharmacy. The emergence of suicidal thoughts and attempts, usually in the first 2 months of treatment, is an important concern in adolescents and young adults, while in older adults antidepressants are deemed by the FDA to protect against suicide. The coprescription of blood center anticoagulants and antiplatelet agents may pose some risk for patients who were taking SSRI medications. **Table 71-2** lists antidepressants recommended for use in older patients, with starting and maximal doses. Usually, short-term or acute treatment lasts on the order of 12 to 16 weeks, but may last 24 to 28 weeks if second- or third-line agents are needed to achieve wellness. The important principles of acute pharmacotherapy in older adults encompass the following "clinical pearls": (1) start low (with respect to dose), go slow, but go all the way; (2) educate both patients and family caregivers about the rationale for treatment and importance of adherence to achieve full symptomatic remission; (3) if a second augmentation agent is required for the achievement of remission, it is also very likely to be necessary to sustain remission; and (4) the dose that brings about remission is the dose that sustain remission ("the dose that gets you well is the dose that keeps you well"; in other words, dosage should *not* be decreased once remission is obtained; doing so puts the patient at risk for early relapse.)

TABLE 71-2 COMMONLY USED ANTIDEPRESSANT MEDICATIONS FOR LATE-LIFE DEPRESSION

MEDICATION	STARTING DOSE	COMMON THERAPEUTIC DOSES	HALF-LIFE (hour)	COMMON SIDE EFFECTS	COMMENTS
SSRI (selective serotonin reuptake inhibitors)				Nausea, dyspepsia, anorexia, tremors, anxiety, insomnia, sexual dysfunction, jitteriness, hyponatremia	Risk of serotonin syndrome if combined with certain drugs.
Fluoxetine	10 mg	10–40 mg once daily	70–80		Very long acting.
Sertraline	25 mg	50–200 mg once daily	25–30	Loose stools, diarrhea	
Citalopram	10 mg	20–40 mg once daily	40–50		Note: FDA Medwatch regarding arrhythmias.
Escitalopram	10 mg	10–30 mg once daily	40–50		
Paroxetine	10 mg	20–40 mg once daily	10–20	Dry mouth, drowsiness, fatigue, weight gain	More anticholinergic side effects. High risk of discontinuation syndrome if drug stopped abruptly.
SNRIs (serotonin-norepinephrine reuptake inhibitors)				Nausea, drowsiness, fatigue, weight gain, hyponatremia, diastolic hypertension at higher doses	Risk of serotonin syndrome if combined with certain drugs. High risk of discontinuation syndrome if medication stopped abruptly.
Venlafaxine XR	37.5 mg	75–300 g once daily	5–9		
Duloxetine	20 mg	20–120 mg once daily	8–17		
Other newer antidepressants					
Mirtazapine	15 mg	15–45 mg at bedtime	20–40	Sedation, increased appetite/ weight gain	No sexual side effects.
Bupropion SR	100 mg	100–150 mg twice daily	15		No sexual side effects. Contraindicated in patients with seizures. Not recommended for patients with comorbid anxiety.
TCAs (tricyclic antidepressants)				Sedation, weight gain, dry mouth, urinary retention, constipation, blurry vision, orthostatic hypotension, impairment of cardiac conduction	**High risk in overdose:** 10 days of typical daily dose may result in a fatal cardiac arrhythmia. Get baseline ECG and follow-up ECG at steady state or if new cardiac symptoms occur.
Nortriptyline	10 mg	50–125 mg every night	18–56	Fatigue	Therapeutic blood levels range from 50 to 150 ng/mL.
Desipramine	25 mg	100–200 mg once daily	12–28	Insomnia, agitation	

Adverse Effects

The adverse effects of long-term antidepressant pharmacotherapy in older adults are relatively few but should be reviewed with patients and family caregivers as part of shared decision making. Some epidemiologic studies suggest higher risk for osteoporosis, especially in women, but it is not clear whether this is the product of antidepressant medication or is related to the underlying depressive illness and inactivity. The use of venlafaxine over 12 weeks has been associated with increased markers of bone resorption and reduced bone formation in older adults. With tricyclic antidepressants, patients must be monitored for orthostatic hypotension and cardiac arrhythmia as well as worsening of cognitive performance, typically due to anticholinergicity. Finally there is an increased risk for falls with patients on

antidepressant medication. Tolerability is an important issue for the long-term use of nortriptyline because of side effects such as daytime somnolence, dry mouth, constipation, urinary retention, and all anticholinergic side effects. Given that SSRIs are safer in overdose than the older TCAs, the use of TCAs should be reserved for difficult-to-treat cases and is probably best conducted by a mental health specialist experienced in their use. It is appropriate to monitor blood levels of TCAs as a gauge of adherence and of adequate exposure, given that there are threshold blood levels required to maximize the probability of satisfactory response (eg, 80–120 ng/mL in nortriptyline-treated patients).

Most of the available studies have not included the oldest old, that is, those 85 and older. This is the most rapidly growing segment of the population and there is no evidence-based information to inform maintenance treatment in this group. Many of these patients have coexisting depression and dementia; the weight of the evidence suggests that antidepressant pharmacotherapy is no more effective than pill placebo in alleviating the suffering of such patients, but that supportive care can be effective in alleviating their distress. Finally, we lack data on biomarkers and pharmacogenetic information that can help to individualize treatment with respect to the best drug, dose regimen, or treatment length of antidepressant pharmacotherapy in individual patients.

Because of the complexity of medical decision making required to manage older adults with bipolar depression and those with psychotic major depression, and because of the substantial risk for suicide, the treatment of such patients is left most appropriately to psychiatrists, especially those with added qualifications in the care of older adults with complex medical, neurologic, and psychosocial comorbidities.

Continuing and maintenance treatment of depression Continuing and maintenance treatment of depression in older adults is important for the purpose of preventing relapse and recurrence, as well as other "downstream" consequences of depression. A systematic review and meta-analysis of double-blind, randomized controlled trials with antidepressant medication showed a NNT of 3.4 for active pharmacotherapy versus placebo (a considerably more favorable NNT than the 13 documented for acute, short-term, placebo-controlled trials). Placebo-controlled studies conducted by the author's group have shown the benefits of long-term (3-year) nortriptyline and monthly interpersonal psychotherapy in older adults with long-standing histories of recurrent major depression (**Figure 71-4**). In a second trial involving the use of the antidepressant paroxetine, the relative risk of recurrence among patients receiving placebo was 2.4 times greater than among patients randomly assigned to paroxetine (**Figure 71-5**). In this study patients with a greater number and more severe concomitant medical illnesses (as indicated by a score of 10 or more on the Cumulative Illness Rating Scale for Geriatrics) had higher rates of recurrent depression and did not fare as well during 2-year maintenance treatment with paroxetine, as compared with patients having fewer and less severe concomitant medical illnesses (**Figure 71-6**). A third study from the author's group addressed maintenance treatment of depression in old age with a specific focus on coexisting cognitive impairment. While cognitive impairment is a core feature of major depression in older adults, there has been relatively little information concerning the value of adding cholinesterase inhibitors (ChEIs) such as donepezil to maintenance antidepressant pharmacotherapy. Since depression is a risk factor for both mild cognitive impairment (MCI) and for progression of MCI to dementia, it is clinically important to assess the place of ChEI pharmacotherapy in depression's long-term (maintenance) management. The study found that relative to placebo plus antidepressant, the combination of donepezil (5–10 mg/day) plus antidepressant temporarily improved global cognition at 1 year, but effect sizes were small. Of 57 participants with MCI, 10% on donepezil and 33% on placebo converted from MCI to dementia (primarily of the Alzheimer type) over the course of 2 years of maintenance pharmacotherapy, suggesting a protective effect for the cholinesterase inhibitor when added to antidepressant medication. By contrast, of 73 cognitively normal subjects, 16% on donepezil experienced cognitive decline and 22% on placebo showed cognitive decline, suggesting no protective effect for patients initially with normal cognition. Although donepezil showed some benefit in enhancing performance on cognitive instrumental activities of daily living (IADLs), its use was also associated with a greater incidence of recurrent depressive episodes (which were managed relatively easily by dosage adjustment of antidepressant medications such as escitalopram, venlafaxine, or duloxetine, usually to higher doses).

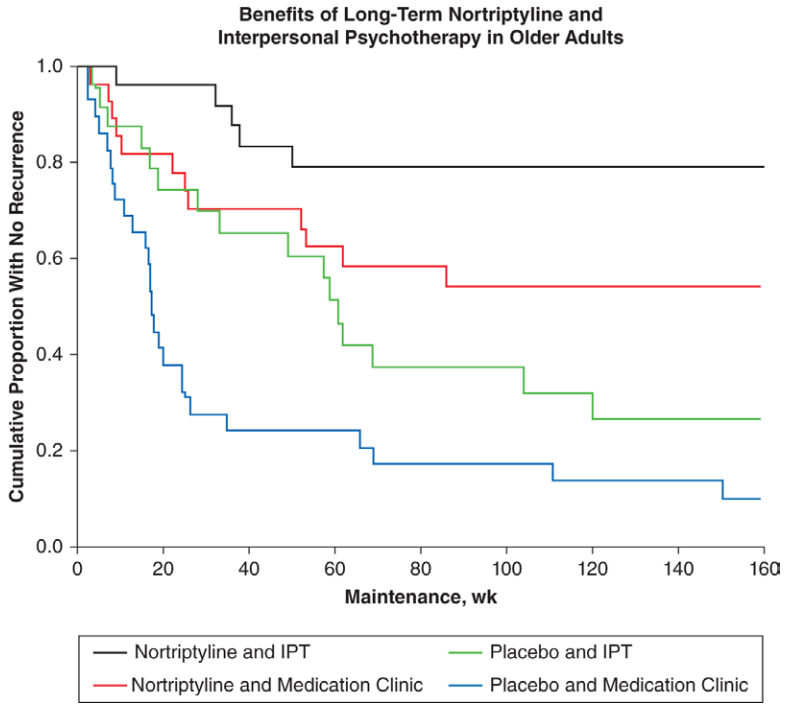


FIGURE 71-4. Recurrence Rates of Major Depressive Episodes. Survival function of 4 treatment groups (log-rank statistic = 34.31; df = 3; P=.001). On pairwise analysis, each of the 3 active treatment groups was significantly better than placebo. IPT indicates interpersonal psychotherapy. (Reproduced with permission from Reynolds CF 3rd, Frank E, Perel JM, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression: a randomized controlled trial in patients older than 59 years. *JAMA*. 1999;281(1):39–45. Copyright © 1999 American Medical Association. All rights reserved.)

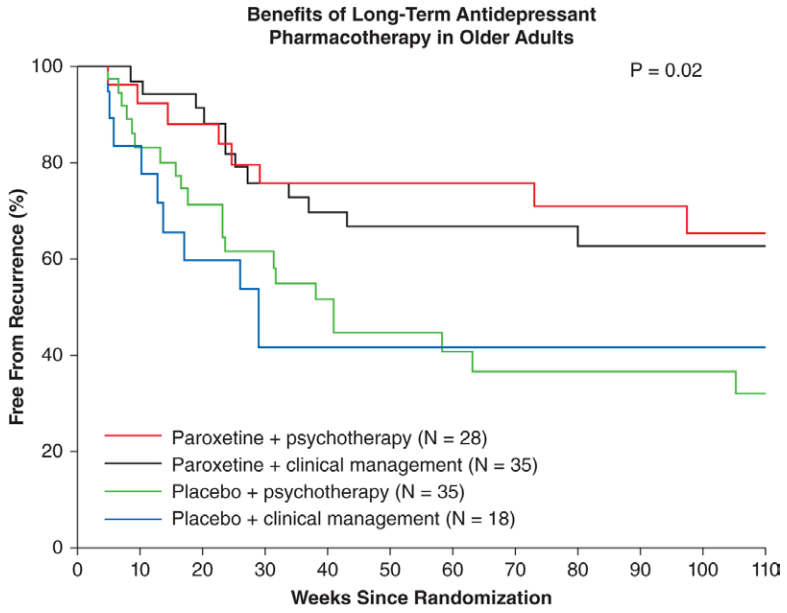


FIGURE 71-5. Time from Randomization to Recurrence. The relative risk of recurrence among patients receiving placebo was 2.4 times that among patients receiving paroxetine (p = 0.02; chi-square statistic = 9.77 with 2 df). No effect of maintenance psychotherapy on recurrence was detected. Kaplan–Meier survival analysis with log-rank chi-square statistics was used to test for overall differences in recurrence rates among the groups. P values were based on the log-rank chi-square test. (reprinted with permission of the Massachusetts Medical Society). (Reynolds CF 3rd, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med*. 2006;354(11):1130–1138.)

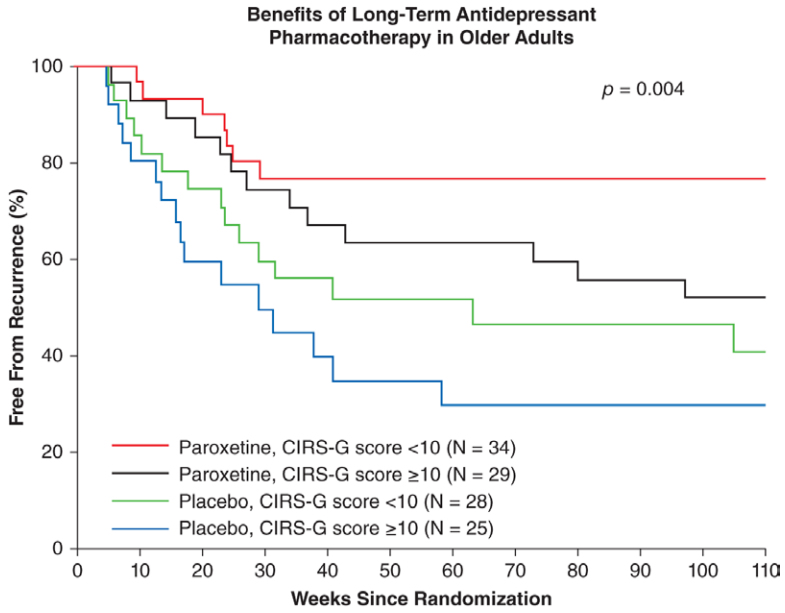


FIGURE 71-6. Effect of the Number and Severity of Concomitant Medical Illnesses on the Efficacy of Maintenance Therapy with Paroxetine. Patients with a greater number of and more severe concomitant medical illnesses, as indicated by scores of 10 or more on the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), had higher rates of recurrent depression and did not fare as well during treatment with paroxetine as those with fewer and less severe concomitant medical illnesses. Although both paroxetine use and the score on the CIRS-G affected risk (main or direct effect, $p = 0.004$), paroxetine was more effective in preventing recurrence in patients with fewer and less severe concomitant medical illnesses (interaction effect, $p = 0.03$). Kaplan–Meier survival analysis with log-rank chi-square statistics was used to test for overall differences in recurrence rates among the groups. P values were based on the log-rank chi-square test. (reprinted with permission of the Massachusetts Medical Society). (Reynolds CF 3rd, Dew MA, Pollock BG, et al. Maintenance treatment of major depression in old age. *N Engl J Med*. 2006;354(11):1130–1138.)

Long-Term Effect of Evidence-Based Depression Care Management on Mortality in Older Adults

The primary question here is whether an evidence-based depression care management program reduces mortality for depressed older adults (nonbipolar, nonpsychotic) in primary care. The summary answer is that a depression care manager working with primary care physicians to provide evidence- and algorithm-based care for depression can indeed save lives. Prospective studies have consistently shown a relation between depression and increased mortality in older adults, but until recently no randomized trials have reported whether treatment can actually prolong life. Using data from Prevention of Suicide in Primary Care Elderly Collaborative Trial (PROSPECT), investigators recently observed that after 8 years of follow-up, relative mortality risk was reduced by 24% among participants who had received evidence-based care, as compared with patients who had received usual care. PROSPECT involved 20 primary care practices in New York City, Philadelphia, and Pittsburgh, enrolled in a cluster randomized trial. Practices were randomly assigned to either the intervention arm of PROSPECT or to enhanced usual care. PROSPECT's intervention consisted of guideline-based treatment involving both antidepressants and, in about one-third of participants, the use of interpersonal psychotherapy (**Figure 71-7**). A depression care manager, typically a social worker or mental health nurse, was placed in primary care practices to monitor symptoms, side effects, and treatment adherence. The depression care manager also educated family caregivers and assisted in medication management by the primary care physician through a process of consultation with primary care and with attending geriatric psychiatrists. Participants were followed for up to 2 years through acute, continuation, and maintenance phases of treatment. After 1 year patients with major depression in the intervention condition were more likely to have experienced remission of major depression as measured by at least a 50% improvement in symptoms and reductions in suicidal ideation. The benefits on depression persisted for at least 24 months. On 8-year follow-up, the hazard ratio for mortality relative to nondepressed control patients in the same practices was 1.9 in usual care practices, but only 1.09 in intervention practices as compared with nondepressed controls in those practices (**Figure 71-8**). Examination of specific causes of death indicated that reductions in mortality on the order of 24% at 8-year follow-up reflected reduced number of deaths due to cancer among patients in PROSPECT's intervention practices (**Figure 71-9**).

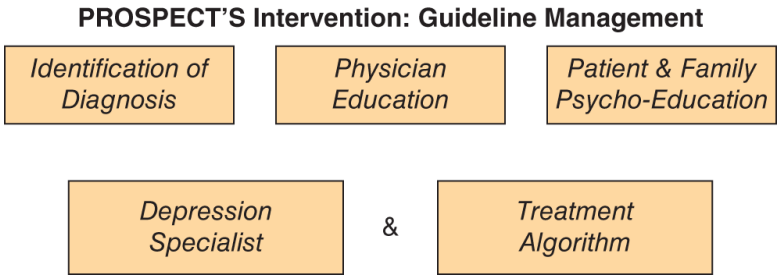


FIGURE 71-7. PROSPECT's intervention.

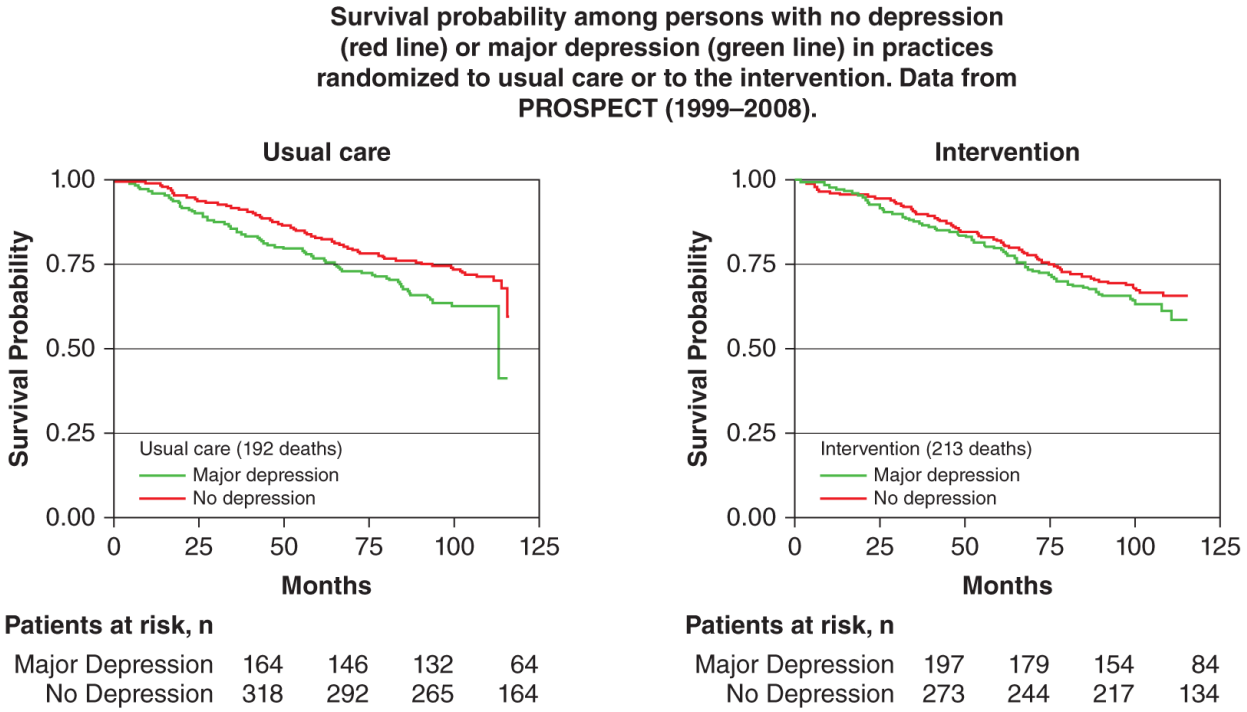


FIGURE 71-8. Survival probability among person with no depression (*red line*) or major depression (*green line*) in practices randomized to usual care or to the intervention. (Gallo JJ, Morales KH, Bogner HR, et al. Long-term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care. *BMJ*. 2013;346:f2570.)

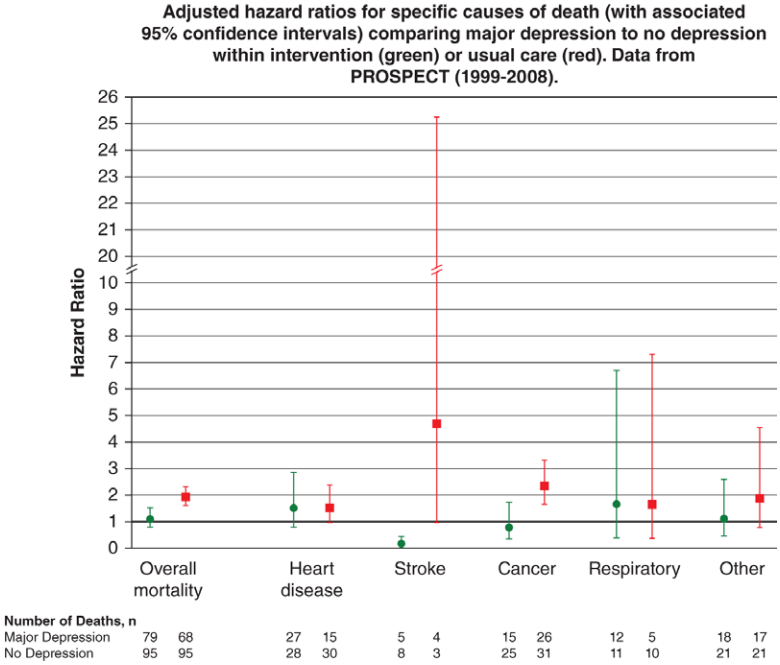


FIGURE 71-9. Adjusted hazard ratios for specific causes of death comparing major depression to no depression within intervention (*green*) or usual care (*red*). (Gallo JJ, Morales KH, Bogner HR, et al. Long-term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care. *BMJ*. 2013;346:f2570.)

Nonpharmacologic

Collaborative care, algorithm-based models Over the past 15 years, the most public health–relevant advance in the treatment of depression in older adults has been the development of evidence-based, collaborative care interventions in the setting of primary care. The development of these models was stimulated by the fact that more than half of mental health treatment for depression in later life is delivered in primary care settings. Depression like other chronic diseases with a relapsing and recurring course responds favorably to collaborative care treatment models. Such models include a structured management plan, together with a multiprofessional approach to patient care including case managers such as nurses, social workers, or psychologists. One study, conducted in Goa, India, found the use of lay health counselors, working under the supervision of primary care physicians and mental health specialists, to be effective for the treatment of common mental disorders, such as depression and anxiety, in mixed-aged adults, including older adults. Some of the most influential models of collaborative care in the primary care management of late-life depression include Improving Mood-Promoting Access to Collaborative Treatment (IMPACT), PROSPECT, and MANAS (from the Konkani language meaning "promoting mental health"), a trial that utilized lay health counselors in the implementation of a simple, behaviorally oriented, stepped care algorithm. Collaborative care interventions such as IMPACT and PROSPECT have been shown to be effective at treating depression and bringing about response and remission. Of these studies, PROSPECT has also been shown to reduce mortality over 8-year follow-up among those who had been in the intervention arm of the study, who were 24% less likely to have died than were participants in practices that had been randomly assigned to usual care. Collaborative care models have been successfully implemented into nonresearch practice settings. A meta-analysis reviewing 37 trials of depression collaborative care found that antidepressant adherence rates were twice those of usual care and favorable treatment outcomes persisted for up to 5 years. Other studies have applied collaborative care approaches to the treatment of depression in the context of chronic medical diseases such as diabetes, cancer, stroke, and postcoronary artery bypass grafting surgery.

Collaborative care interventions for depression in old age have better response rates than usual care, even when usual care has been enhanced by regular feedback to primary care physicians. The advantages of collaborative care interventions over usual care generally have modest but clinically meaningful effect sizes of around 0.3 or 0.4. This finding underscores the need for consultation with or referral to mental health specialists for patients who have not responded satisfactorily to first-line treatment.

Psychosocial interventions Managing depression in older age is also strongly supported by the evidence of efficacy for psychological interventions. A recent meta-analysis of psychotherapy of depression in old age identified 44 studies comparing psychotherapies to control groups to other therapies or to pharmacotherapy. The overall effect size indicating the difference between psychotherapy and control groups was 0.64, corresponding to a NNT of 3. These effects were maintained at 6 months or longer after randomization. Certain types of psychotherapy were found to be particularly effective. These included cognitive behavioral therapy (CBT), life review therapy, and problem-solving therapy (PST). Comparison between different types of psychotherapy suggested that learning-based approaches such as CBT and PST may be more effective than nondirective counseling. Learning-based approaches encourage the development of active coping and self-management skills, the use of behavioral techniques to improve sleep, and engagement in pleasant activities. Another systematic review of studies that used medication, psychotherapy, or both found that older adults with clinical depression derive significantly greater benefit from combined therapy compared to pharmacotherapy alone or psychotherapy alone. **Table 71-3** shows the component steps for PST in primary care (PS-PC).

TABLE 71-3 SEVEN STEPS OF PROBLEM-SOLVING THERAPY (PST)

1. Clarify and define the problem.
2. Establish an objective, achievable goal.
3. Brainstorming—develop solution alternatives.
4. Follow decision guidelines—pros and cons.
5. Choose the preferred solution.

6. Action plan: implement the solution.
7. Evaluate the outcome.
8. Restart if needed.

Psychosocial interventions in older adults with major depression should involve interdisciplinary collaboration beyond mental health. These may include primary care, specialty care, rehabilitation, and homecare. Also, psychosocial interventions should involve family members and caregivers whenever possible, to increase retention and adherence and to lower family caregiving burden. The clinician should plan for at least 6 weekly sessions in order to ensure adequate exposure to an evidence-based treatment such as PST for depression. Effective first-line treatments include behavioral activation, particularly encouraging patients and family caregivers to engage in pleasurable activities. Behavioral activation is a core part of both PST and CBT with or without antidepressant medications. For older adults with anxiety disorders, current evidence indicates first-line treatment is the use of a SSRI. For those who resist taking medications, first-line behavioral interventions include relaxation training together with motivational interviewing to encourage a medication trial. In older adults with co-occurring depression and anxiety, the depression should be treated first.

PREVENTION

Depression Prevention in Older Adults

Preventing depression across the life cycle has become increasingly recognized as a global public health priority. According to the World Health Organization, clinical depression has now become the second leading contributor to the global burden of illness-related disability, following cardiovascular disorders (with which it frequently coexists). Preventing depression is important also because the ability of currently available treatments to avert years lived with disability is limited. In addition, issues of stigma preclude treatment seeking, especially in racial and ethnic minorities. Workforce limitations in the specialty mental health sector, together with financial barriers to the provision of mental health services, also reinforce the need for effective, acceptable, and feasible depression prevention strategies. A recent systematic review and meta-analysis showed that there is strong evidence to support the feasibility and efficacy of depression prevention generally through the use of short-term depression-specific psychotherapies. In this meta-analysis the authors identified 32 studies which qualified for inclusion. The incident rate ratio, or IRR, was 0.79, with a 95% confidence interval of 0.62 to 0.91. This ratio indicates a 21% decrease in the incidence of depression in the prevention arms as compared with control groups (typically, usual care). Relevant to older adults specifically, other studies have found that prevention of depression in poststroke patients is possible through the use either of PST or low doses of escitalopram (5 mg/day). In older adults living with age-dependent macular degeneration, prevention of depression is possible with the use of a structured short-term learning-based psychotherapy such as PST. In a recent study of “indicated” prevention via early interventions to preempt major depressive episodes in 247 older black and white adults living with subsyndromal depressive symptoms, the authors found that both of two interventions, PST for primary care (PST-PC) and coaching in healthy dietary practices (DIET), were effective in reducing the expected incidence of major depressive episodes from about 20% to 25% to 8% to 9%. Participants in both arms of the trial experienced a low incidence of such episodes. Among black participants the incidence rate was 9% and among whites 8%. Despite the greater burden of depression risk factors among black participants, no differences with white participants were found in either the time to episode of major depression or scores of overall symptom burden measured over 2 years of participation in the trial.

A second noteworthy study of depression prevention in older primary care patients was conducted in the Netherlands. This study exemplified what the Institute of Medicine has termed “indicated” prevention of depression because of its focus on older patients already mildly symptomatic. The study involved 170 patients above the age of 75 in primary care practices reporting subthreshold symptoms of depression and anxiety but who did not yet meet diagnostic criteria for threshold or syndromal mental disorders, such as major depression or generalized anxiety disorder. Participants were randomized to receive either usual care or a preventive stepped-care intervention. The intervention consisted of four steps each lasting 3 months: watchful waiting, CBT-based bibliotherapy, PST, and referrals to a primary care physician if symptoms continued to be present. The incidence of episodes of major depression and of anxiety disorders were reduced by 50% at 1 year in patients randomly assigned to receive the stepped-care intervention. Thus 24% of patients in the usual care arm experienced the onset of common mental

disorders such as major depression or generalized anxiety, compared with 11% of patients randomly assigned to the stepped-care intervention. These effects were found to be cost-effective and were maintained over 2 years. From the perspective of public health, depression prevention is needed to preempt episodes of major depression in those with either known risk factors such as stroke, cardiac disease, or macular degeneration (so called "selective" prevention per the Institute of Medicine's lexicon) and those who are already mildly symptomatic ("indicated" prevention). Evidence suggests that prevention strategies are effective and inexpensive and may serve to mitigate the burden of depression-related disability. Current research in depression prevention is investigating the use of internet-based strategies to reach persons who otherwise have no access to mental health services.

SPECIAL ISSUES

"Complicated" or Prolonged Grief

With the publication of the American Psychiatric Association's *Diagnostic and Statistical Manual-5* in 2013, there has been great interest concerning the diagnosis of "complicated" or prolonged grief. Criteria for the diagnosis of "prolonged, complex bereavement disorder" (also termed "complicated grief") have been placed in section 3 of the DSM-5, indicating that they require further study before they can be deemed as reliable, valid, and clinically useful. An estimated 10% of persons who are bereaved will develop persistent complex bereavement disorder, characterized by symptoms that have lasted for at least 12 months (and usually for years) after the death of a loved one. These symptoms include primarily persistent yearning and longing for the deceased, as well as intense sorrow and preoccupation with the deceased and circumstances of the death, and avoidance of reminders of the death. Clinically, it is as if loss occurred only yesterday because the grief is so intense even 12 months later. Those at highest risk for persistent complex bereavement disorder are women, people with low educational and socioeconomic status, those with poor social support, and older persons with preexisting mood or anxiety disorders. Complicated grief is seen more often after the death of a child than after an "on-time" death, or following suicide. Depression and complicated grief often coexist in the same person. Antidepressant pharmacotherapy may relieve some of the suffering of complicated grief, allowing the grief work to resume and to get back on track. A specific type of psychotherapy, termed "complicated grief therapy" (CGT) has been shown to be effective in reducing the suffering of people living with complicated or prolonged grief. CGT aims at both loss-focused and restoration-focused coping, employing strategies of both cognitive-behavioral and exposure-based psychotherapy. The Inventory of Complicated Grief (ICG) is a useful tool for screening and for measuring the intensity of symptoms of complicated grief (**Table 71-4**). Typically a score of 30 or higher on the ICG indicates the presence of syndromal complicated grief warranting clinical intervention. In the absence of appropriate intervention, symptoms and disability persist and are strongly associated with suicidal ideation.

TABLE 71-4 ■ IDENTIFYING COMPLICATED GRIEF (CG): THE INVENTORY OF COMPLICATED GRIEF

The Inventory of Complicated Grief (ICG) is a self-report instrument that allows for the dimensional assessment of the severity of complicated grief symptoms. Scores of 30 or higher (over a range of 0–76) indicate a high likelihood that the syndrome is present. Each of the 19 items is rated 0 (not at all) to 4 (severe).

1. Preoccupation with the person who died
2. Memories of the person who died are upsetting
3. The death is unacceptable
4. Longing for the person who died
5. Drawn to places and things associated with the person who died
6. Anger about the death
7. Disbelief
8. Feeling stunned or dazed
9. Difficulty trusting others
10. Difficulty caring about others
11. Avoidance of reminders of the person
12. Pain in the same area of the body
13. Feeling that life is empty
14. Hearing the voice of the person who died

15. Seeing the person who died
16. Feeling it is unfair to live when the other person has died
17. Bitter about the death
18. Envious of others
19. Lonely

Depression in Palliative and Supportive Care Medicine

Palliative and supportive care medicine is uniquely well-positioned to confront depression in terminally ill patients. When screening for depression in such patients, clinicians must differentiate depression from other commonly co-occurring conditions including delirium, hypercalcemia, hypothyroidism, and brain metastases. Changes in mood may also occur as a side effect of medical treatments such as steroids. Physical symptoms found in depression such as lack of appetite and poor sleep may also be due to illness burden or disease-related treatments. For these reasons cognitive symptoms of depression are particularly important to consider in the setting of terminal illness. Patients can be asked if they have felt depressed or hopeless most of the time in the past 2 weeks and whether they have found that little brings them pleasure or joy over the same period of time. The presence of low mood and sadness to the point of despair and the presence of anhedonia represent core symptoms of depression that are useful for palliative medicine screening for depression.

The goal of palliative and supportive care medicine is to relieve suffering and to improve the quality of the patient's remaining life. In the setting of terminal illness, depression can be worsened by physical symptoms such as pain, fear of dying, family distress, and grief. Depression has been shown to affect survival in cancer patients, as well as to prolong hospital stays and to decrease compliance with treatment.

Palliative care patients often experience distressing physical symptoms that contribute to depression. One of the most common such symptom is uncontrolled pain, which is also a major risk factor for depression and completed suicide among cancer patients. The first step in depression treatment, therefore, in palliative medicine is to control physical symptoms. Antidepressant medications have benefit in treating symptoms commonly encountered in palliative care patients such as insomnia, decreased appetite, nausea, and pain. Mirtazapine and trazodone can be used for insomnia, while mirtazapine also has beneficial effects on appetite. Neuropathic pain is best treated with combined therapy using opioids and antidepressants. The antidepressants used to treat neuropathic pain have mainly been the tricyclic antidepressants, but SNRIs such as venlafaxine and duloxetine and SSRIs may also be helpful. The time needed for therapeutic effect may be greater than the expected survival time. For this reason, psychostimulants such as methylphenidate and dextroamphetamine may be useful because they have a shorter time to therapeutic effect, often within 24 to 48 hours. The use of ketamine to treat depression is also gaining interest among palliative care physicians because of its ease of administration, low cost, and rapid onset of action.

CONCLUSION

As recognized by the US Preventive Services Taskforce, it is important in geriatric medicine to screen for depression in older adults because of the high prevalence of depression and the risk that it imposes for increased morbidity, disability, dementia, mortality (including suicide), and poor adherence with coprescribed medical therapies (**Table 71-5**). Above all, however, it is important to screen because depression is a treatable source of suffering, family caregiver burden, and excess disability in older adults. Many factors both biological and psychosocial, influence variability in the clinical presentation of depression in old age and in the response to treatment. Collaborative care interventions for depression in old age have a better response rate than usual care. The advantages of collaborative care interventions are important but still somewhat modest in effect size. This underscores the need for consultation or referral to mental health specialists for patients who have not responded to treatment fully or for those with suicidal ideation. Colocation of such specialists within primary care settings removes or lessens the barrier of stigma, since most older adults with depression prefer treatment within their primary care practices. Because of factors including modest treatment effects in primary care, stigma, and the moderating role of excessive medical burden on long-term treatment response, efforts to prevent depression in older adults at risk are also critical and have been shown to be effective. There is now substantial evidence that efforts to prevent depression can be effectively implemented using brief structured counseling approaches such as PST or interventions to promote healthy lifestyle choices such as coaching in healthy dietary practices and sleep practices.

TABLE 71-5 SUMMARIES OF KEY OBSERVATIONS ON ILLNESS COURSE OF DEPRESSION IN LATER LIFE

- Maintenance antidepressant pharmacotherapy protected older adults from recurrence of depressive illness (NNT = 4) over 2 y, including those in the first lifetime episode (Reynolds CF 3rd, *JAMA*, 1999; Reynolds CF 3rd, *N Engl J Med*, 2006).
- Older adults with major depression are liable to develop mild cognitive impairment and dementia (Diniz BS, *BJP*, 2013). However, the addition of a cholinesterase inhibitor reduced the incidence of conversion to dementia but heightened the risk of recurrent depression (Reynolds CF 3rd, *Arch Gen Psychiatry*, 2011).
- Evidence-based treatment of depression in primary care reduced the incidence of mortality by 24% over 8 y, secondary to reduced deaths from cancer (Gallo JJ, *BMJ*, 2013).
- The use of either problem-solving therapy for primary care or coaching in healthy dietary practices reduced the incidence of major depressive episodes to 8.5% from an expected incidence of 20%–25% and improved health-related quality of life, with blacks doing as well as whites despite a greater burden of risk factors for depression (Reynolds CF 3rd, *Psychiatr Serv*, 2014).

NNT, number needed to treat.

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Chapter 72

Schizophrenia

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Learning Objectives

- Understand the epidemiology, etiopathogenesis, definition, and clinical presentations of schizophrenia in older adults.
- Learn about the differential diagnosis, atypical presentations, and nonpsychotic conditions commonly confused with schizophrenia in the older population.
- Acquire new knowledge about drugs and psychosocial strategies used to treat scizophrenia.

Key Clinical Points

1. ***Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition (DSM-5) defines schizophrenia as continued presence from a minimum of 1 to 6 months of the classic positive or negative symptoms of the disease.**
2. **Presence of psychotic symptoms in older adults does not directly imply a diagnosis of schizophrenia. Patients should undergo full evaluation to exclude other diagnoses such as dementia, medication side effects, schizoaffective disorders, and delirium before a diagnosis of schizophrenia is made.**
3. **Antipsychotics are the mainstay of therapy; however, psychosocial interventions are effective and should be considered along with the drug therapy.**

DEFINITION

Schizophrenia is a chronic, debilitating disease characterized by positive symptoms of hallucinations, delusions, and thought disorder (also referred to as psychosis), and negative symptoms of chronic social dilapidation. Emil Kraepelin first distinguished schizophrenia (then termed dementia praecox) from bipolar psychosis more than 100 years ago, by contrasting the long-term deteriorating course of delusions and hallucinations characteristic of schizophrenia to the intermittent course and lack of permanent social and occupational deterioration in bipolar illness. Schizophrenia remains a clinical diagnosis made on the basis of the individual's psychiatric history and mental status examination, as no laboratory or imaging studies can validly diagnose it.

Inclusion Criteria

Schizophrenia is described in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* as two or more of the following symptoms active for a minimum of 1 month's duration (unless adequately treated) as well as the continuing presence of a symptom for 6 months: delusions, hallucinations, disorganized speech, disorganized behavior, and negative symptoms along with a significant disturbance of the individual's functioning that results in disturbances in occupation, social interaction, or the management of one's self-care. These symptoms of schizophrenia can be characterized as either positive or negative.

Positive symptoms The positive symptoms of schizophrenia consist of abnormalities of sensory experience and cognitive processing. These manifest as hallucinations, delusions, bizarre behavior, or formal thought disorder.

Hallucinations are perceptions in the absence of physical stimuli. In schizophrenia, auditory hallucinations usually predominate, but, in patients with late-onset schizophrenia, olfactory, visual, tactile, or gustatory hallucinations may be present. In schizophrenia, the hallucinated voices are described as coming from outside the person's head and providing a running commentary on the patient's behavior. At times, these speak directly to the individual or converse with each other. Voices that tell the individual what to do are referred to as command hallucinations.

Delusions are fixed, false, idiosyncratic beliefs and consist of ideas and beliefs that are persecutory, bizarre, or grandiose. The idea that the person is being controlled by outside forces is common.

Bizarre behavior may be observed in the person's appearance (odd/inappropriate layering of clothing) or in their aggressive, agitated, or repetitive/stereotyped behavior (eg, flipping the light switch multiple times or repeated closing and opening the door). *Formal thought disorder* includes illogical or incoherent speech in the absence of aphasia. It manifests as tangentiality, loose associations (a lack of logical connection between sentences), or derailment (the sudden loss of train of thought).

Negative symptoms The negative symptoms of schizophrenia result in a decline in the person's baseline social, interpersonal, and volitional activity. People with schizophrenia often have a diminished range of facial expression, a phenomenon termed affective flattening, poor eye contact, and decreased expressive gesturing. Spontaneous speech decreases and speech latency increases. Individuals with schizophrenia become less social and form few close relationships with others. As the disease progresses, avolition and apathy become common and impair work and school performance, grooming, and hygiene.

Clinical course Schizophrenia often has a prodromal period during which individuals become socially awkward and isolated. Negative symptoms emerge, and work or school performance gradually declines. Positive symptoms and bizarre, disorganized behavior then manifest more overtly. For example, people with schizophrenia frequently speak and laugh when they are by themselves, symptoms that are thought to represent patients' responses to internal stimuli such as hallucinations. The negative symptoms can result in a lowered socioeconomic status manifested by unemployment, estrangement from family members, and even homelessness.

Exclusion Criteria

Schizophrenia is not the only cause of hallucinations and delusions. For this reason, patients presenting with psychotic symptoms need to be fully evaluated and all other potential causes of these ruled out before a diagnosis of schizophrenia is made. The presence of hallucinations or delusions with subacute onset of fluctuating disturbance of consciousness and attention suggests a delirium. In older adults, psychotic symptoms often occur in the setting of dementia; the presence of memory loss and either aphasia, apraxia, agnosia, or dysexecutive function should raise the possibility of dementia, since individuals with schizophrenia generally remain oriented to their surroundings. The presence of prominent mood symptoms during the psychotic episode raises the possibility of a mood disorder or schizoaffective disorder. Hallucinations and delusions can also be induced by exogenous substances (eg, medications, illicit drugs, and toxins) or general medical conditions such as seizure disorder, stroke, brain tumor, and encephalitis.

Associated Symptoms

Abnormal psychomotor activities such as rocking, pacing, immobility, or repetitive stereotyped behaviors can impair social functioning. Hallucinations can impair concentration owing to the distraction produced by aberrant experiences. Demoralization and anhedonia, a loss of interest and enjoyment in activities, may also be found. Mortality is increased in schizophrenia; 28% of the increase in early death is attributed to suicide and 12% to accidents. The prognosis is worse in patients with impaired insight into their illness.

Age of Onset

Early onset The lifetime prevalence of schizophrenia is 1%. Although schizophrenia occurs with equal frequency in men and women, the age of onset is earlier in males, with a peak age of onset between 10 and 25 years. Women have a bimodal age distribution with a first peak between 25 and 35 years and another peak in late middle age (**Table 72-1**). The disease tends to have a more severe course in males with greater predominance of negative symptoms, and females tend to retain their social and premorbid function. However, patients with early-onset schizophrenia who live into late life usually have a many-year history of illness with prominent negative symptoms and an inability to live independently.

TABLE 72-1 DIFFERENCES BETWEEN EARLY- AND LATE-ONSET SCHIZOPHRENIA

	EARLY ONSET	LATE ONSET
Age of onset	Teens to early adult	Fifth decade or later
Family history of schizophrenia	Frequently a positive family psychiatric history	Rare
Gender	Equal prevalence between men and women	Predominantly women
Symptom type	Negative and positive	Mostly positive symptoms; thought disorder rare
Prognosis	Poor	Moderate

Late onset A consensus of international experts has identified two diagnostic forms of late-age disease: late-onset schizophrenia, with onset after the age of 40, and very-late-onset-schizophrenia-like psychosis, with onset after the age of 60.

Schizophrenia beginning after the age of 40 is characterized by prominent positive symptoms, but fewer negative symptoms than early-onset schizophrenia. However, thought disorder is rare in the late-onset condition. In addition, individuals with late-onset schizophrenia are less likely to have a family history of schizophrenia than those with early onset and are more likely to be female. Compared to the cognitive deficits seen in early-onset patients, late-onset illness is characterized by relatively intact learning, abstraction, and cognitive flexibility. Very-late-onset schizophrenia frequently occurs in the setting of sensory impairment (decreased auditory acuity and low vision states) and social isolation. It is important to note that late-onset schizophrenia is responsive to lower does of antipsychotics than early-onset schizophrenia.

DIFFERENTIAL DIAGNOSES

Mood Disorders

Mood disorders include both major depressive disorder and bipolar affective disorder. In both, depressive episodes characterized by a loss of vital sense (a sense of physical discomfort, sleep disorder, appetite loss, poor self-attitude (lack of self-confidence, self-blame, and guilt), and sad mood. Bipolar affective disorder differs from major depressive disorder in that those affected also experience manic episodes. Although psychosis is not required for diagnosis, it can occur during either severe depressive or manic episodes.

One important distinction between psychosis in mood disorders and schizophrenia is that in the psychosis of mood disorders, symptoms are present only during severe mood episodes and resolve when the mood disturbance resolves. Although those with schizophrenia may experience mood symptoms during the course of their illness, psychosis is the dominant feature that persists regardless of mood disturbance. Another clinically useful distinction is that the delusions of mood disorder are congruent with the patient's mood state. For example, in mania, grandiose delusions accompany euphoric or elevated mood, while, in depression, self-blaming, self-deprecating, and guilty delusions parallel a sad mood.

Schizoaffective Disorder

Schizoaffective disorder is similar to schizophrenia in that psychotic symptomatology is prominent and may persist between episodes, but there is also a prominent disturbance in mood. Thus, the diagnosis of schizoaffective disorder requires a period of psychosis, lasting at least 2 weeks in the absence of any mood disturbance. However, criteria for a mood disorder must also be met for a predominant portion of the active and residual periods of the disease.

Dementia

Twenty percent to 30% of individuals with dementia experience hallucinations, and 30% to 40% develop delusions during the course of their illness. Delusions and hallucinations are less elaborate and complex in dementia than in schizophrenia. In the case of Alzheimer dementia, the most common form of dementia, the onset is gradual, typically beginning with memory deficits, and progresses to death over the course of 10 years. Visual hallucinations are very common in dementia with Lewy bodies and may be the presenting symptom. Although schizophrenia may include

cognitive deficits, these are less severe than in dementia, do not have the characteristics of aphasia or apraxia, and progress more slowly.

Delirium

Delirium is characterized by an acute or subacute onset of cognitive impairment and a disturbance of attention and cognition. Fluctuation over the course of the day is common, as is disturbance in the sleep-wake cycle. Misperceptions of environmental stimuli, referred to as illusions, and visual hallucinations are also common. Delirium is usually caused by a toxic, metabolic, or infectious disorder that requires immediate identification and treatment. Delirium's acute onset and fluctuating cognitive deficits distinguish it from schizophrenia.

Delusional Disorder

Delusional disorder is characterized by a single, prominent delusion, which is described as "nonbizarre," that is, plausible, and has been present for at least a month. The individual with delusional disorder usually remains fully functional apart from the dysfunction that results directly from the delusion. The negative symptoms found in schizophrenia are absent in delusional disorder, and the individual with delusional disorder behaves normally when the delusion is not being acted upon or discussed.

Substance-Induced Psychotic Disorder

Hallucinations and delusions may be a result of intoxication or withdrawal of substance use. Sedatives (barbiturates and benzodiazepines), alcohol, and stimulants (amphetamines and cocaine) are common causes. These are not seen in withdrawal from opiates.

Schizophreniform Disorder and Brief Psychotic Disorder

The criteria to fulfill schizophreniform and brief psychotic disorder are the same as in schizophrenia, except for shorter illness durations than schizophrenia. Schizophreniform disorder lasts between 1 and 6 months, while brief psychotic disorder lasts anywhere from 1 day to 1 month. Social and occupational impairment is not required in these disorders.

Ictal Psychosis

Schizophrenia-like psychosis occurs in complex partial seizures, particularly those of the temporal lobe. A nonconvulsive status epilepticus can rarely mimic schizophrenia, but the symptoms are present only hours to days. Automatisms of the mouth and lips and eye fluttering can be seen. In these cases, an encephalogram (EEG) will show active seizure activity. Psychosis also occurs postictally and following a flurry of seizures lasting an average of 70 hours. A seizure disorder is often present at least 10 years before the manifestation of interictal psychosis. Postictal suppression may be seen on EEG.

ETIOLOGY

Genetic

First-degree relatives of individuals with schizophrenia have a 10 times greater risk of developing schizophrenia than the general population, and twin studies show higher concordance rates among monozygotic twins than dizygotic twins. Nonetheless, monozygotic twins are 50% discordant, suggesting that environmental factors contribute as well. Whole genome sequencing of early-life onset schizophrenia has identified multiple genetic loci that contribute a vulnerability to schizophrenia.

Developmental

Risk factors for early-life onset schizophrenia are being born in the winter and early spring. While no clear explanation for this has emerged, potential hypotheses include seasonal variability in diet or higher rates of prenatal virus exposure at different times of the year. Observational studies suggest that a complicated fetal history may predispose to the development of schizophrenia. This suggests a potential etiologic role for maternal exposure to influenza virus during pregnancy, perinatal hypoxia from obstetric complication, nutritional deprivation in utero, and autoimmune processes

in the pregnant mother.

Risk factors for late-onset and very-late-onset schizophreniform psychoses include female gender, schizotypal premorbid personality, having never married, and hearing impairment.

Brain structural abnormalities found in schizophrenia include a larger right temporal horn and third ventricle as well as decreased amygdala, hippocampus, and parahippocampal gyrus volumes. These changes are felt to represent a reduced synaptic density. Since synaptic density is maximal at the age of 1 and decreases until adolescence, one etiologic theory postulates that synaptic pruning is excessive in schizophrenia and leads to the emergence of symptoms during late adolescence and early adulthood. Neuronal disorganization within the hippocampus has also been found and has been suggested to represent that disorganization may be the result of impaired neuronal migration during development.

TREATMENT

Antipsychotics

Antipsychotic neuroleptic drugs are divided into typical and atypical or second-generation agents, although this distinction is somewhat controversial. Second-generation agents are the agents of choice because of a lower risk of tardive dyskinesia. These drugs all block the D2 dopamine receptor, while the atypicals are generally more potent at blocking serotonin receptors. D2 blockade is thought to cause many of the observed side effects of these drugs. Dopamine blockade of the nigrostriatal dopamine pathway projecting from the substantia nigra to the basal ganglia, a part of the extrapyramidal nervous system that modulates motor movement, causes symptoms similar to those found in Parkinson disease (increased muscle tone with cogwheel rigidity, shuffling gait, masked facies, and resting tremor). These are referred to as extrapyramidal symptoms and are especially impairing in older adults, since the resultant shuffling gait may lead to falls in an already susceptible population. A decrease of dopamine in the basal ganglia is thought to cause *akathisia*, an intense subjective feeling of restlessness, particularly in the thighs, accompanied by pacing, shifting weight from foot to foot when asked to stand still, and difficulty remaining seated, and *dystonia*, persistent (tonic) involuntary contractions of muscles, most commonly of the neck and tongue. Dystonia is less common in older adults but may present as lateral flexion at the waist (“Pisa syndrome”). Another side effect of neuroleptics that can become persistent and disabling is *tardive dyskinesia*, thought to result from the upregulation of dopamine postsynaptic receptors in the nigrostriatial pathway leading to persistent, repetitive, abnormal movements of the tongue, face, and lips. Choreoathetoid movements of the limbs, head, or trunk can also develop. Older adults, females, and individuals with brain injury are more susceptible to tardive dyskinesia. Tardive dyskinesia may resolve weeks or months after discontinuation of the medication, but often persists.

The final dopamine pathway can also be affected. These dopaminergic neurons that project from the hypothalamus project to the pituitary gland in the tuberoinfundibular pathway inhibit the secretion of prolactin. As a result, neuroleptics can elevate prolactin levels and cause galactorrhea. In postmenopausal women, neuroleptics can cause an increased rate of bone demineralization.

Antipsychotics also affect muscarinic-cholinergic, α_1-adrenergic, and histaminergic receptors. Histaminergic blockade causes weight gain and sedation. Sedation, blurred vision, dry mouth, and constipation result from blockade of the muscarinic-cholinergic receptors. α_1-adrenergic inhibition causes light-headedness, drowsiness, and orthostatic hypotension. Since all of these increase susceptibility to falls and hip fractures, frequent monitoring in older patients is crucially important.

Impaired glucose metabolism and the metabolic syndrome are potential side effects of antipsychotics. The mechanism is unclear. Weight should be monitored.

Rarely, blockade in the hypothalamus can caused temperature dysregulation and the neuroleptic malignant syndrome characterized by hyperthermia, rigidity, and delirium. Elevated white blood cell count, incontinence, and dysphagia may also be seen. Creatinine phosphokinase levels are raised when muscle rigidity is present. Management of this syndrome includes stopping the neuroleptic drug, protecting the kidneys from muscle breakdown products with intravenous fluids, supportive medical measures, and, occasionally, administration of the dopamine agonists bromocriptine or dantrolene.

Currently, there are six atypical antipsychotics available for clinical use. Although these are all considered atypical, these vary in their side effect profiles and receptor affinities (**Table 72-2**). There is increasing concern over metabolic syndrome as a potential side effect of antipsychotics. Therefore, patients taking atypical antipsychotic drugs should be

monitored for high blood pressure, obesity, high cholesterol, and insulin resistance. Patients taking olanzapine may be at higher risk than those taking other atypicals.

TABLE 72-2 COMMONLY USED PHARMACOTHERAPEUTIC AGENTS FOR SCHIZOPHRENIA

ANTIPSYCHOTIC	STARTING DOSE (MG)	USUAL DOSE RANGE (MG/D)	PREDOMINANT SIDE EFFECTS	RECOMMENDED MONITORING
Haloperidol	0.25	0.5–4	EPS, TD, dystonia	Monitor for EPS
Clozapine	6.25–12.5 BID	25–150	Agranulocytosis (1%–2%), sedation, tachycardia, decreased seizure threshold at doses > 600 mg, sialorrhea	Weekly granulocyte counts, enforced by manufacturer
Risperidone	0.25–0.5 qd	0.25–3	Hypotension, sedation, EPS	Monitor for EPS
Olanzapine	2.5 qd	2.5–10	Sedation, weight gain, metabolic syndrome	Cholesterol and fasting blood sugar level every 6 mo
Quetiapine	12.5–25 qd	25–200	Sedation, postural hypotension	Orthostatic blood pressures with dose increases
Ziprasidone	20 qd	40–80	QTc prolongation, cataracts	ECG at baseline and after dose increase, yearly ophthalmologic examination
Aripiprazole	5	5–15	Hypotension	

ECG, electrocardiogram; EPS, extrapyramidal symptoms; TD, tardive dyskinesia.

Note: Monitoring for all antipsychotics should include monitoring for EPS, weight, and cholesterol and fasting blood sugar levels every 6 months for metabolic syndrome.

Psychosocial Treatments

Individuals with schizophrenia obtain benefit from psychosocial intervention in addition to drug therapy. To combat noncompliance, education and support should be given to individuals with schizophrenia as well as their family members. Supportive and behavioral therapy can be offered. Vocational and social skill training may be used to promote independence and quality of life.

DISORDERS THAT CAN BE CONFUSED WITH SCHIZOPHRENIA

Charles Bonnet Syndrome

Charles Bonnet syndrome is a condition in which vivid visual hallucinations and generally good insight into the false nature of these hallucinations occur in the setting of poor vision. There is an absence of delusions. The poor vision, usually central, results from conditions such as macular degeneration or cataracts. If vision improves, the hallucinations often remit. Often the visions seen are figures or objects that are diminutive in size, termed Lilliputian hallucinations. Patients with this condition often do not report their hallucinations to health care providers for fear of being labeled crazy.

Delusional Parasitosis (Ekbom Syndrome)

Delusional parasitosis is a condition in which the affected individual has a delusion of infestation by parasites. The individual visits multiple physicians with this complaint, is unshaken by negative test results, and often brings in skin scrapings and nail clippings as proof. Patients may try to kill the parasites by pouring kerosene, rubbing alcohol, insecticide, or other irritants over their skin. Some may physically pick or scrape at themselves. This condition will sometimes respond to antipsychotics.

Diogenes Syndrome

Diogenes syndrome is a condition of self-neglect. The affected individual tends to live in domestic squalor and be socially withdrawn. A tendency to hoard items (syllogomania) with no clear purpose may also be present. These individuals are reluctant to seek treatment, resist help when it is offered, and may remain undetected for years.

Hallucinations in Grief

Hallucinations commonly occur during the grief reactions of deceased loved ones. Patients report that they hear the voice of a loved one or see them pass by. This is more appropriately termed an illusion, as it usually consists of misinterpretation of stimuli. However, true hallucinations may occur and are normative.

Organic Delusional Disorder

Organic delusional disorder is characterized by a delusion that is the result of a metabolic, toxic, or neurologic abnormality. This disorder has a wide range of delusional content as well as potential causes (eg, HIV, seizure disorder, brain damage, drug use, Alzheimer, and Huntington). Sudden onset, association with physical symptoms characteristic of the disorder, lack of a typical course, and lack of personal or familial psychiatric history suggest a nonpsychiatric etiology and should prompt further evaluation.

FURTHER READING

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Chapter 73

General Topics in Geriatric Psychiatry

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Learning Objectives

- Understand the prevalence of mental health and psychosocial problems associated with aging, and their adverse consequences on longevity and quality of life.
- Learn about the epidemiology, common clinical presentations, evaluation tools, and management of psychiatric conditions commonly seen in older adults.
- Acquire information necessary to recognize suicidal behavior in older adults, best ways to assess suicide risk, and effective strategies to manage suicidal patients.
- Understand the principles underlying use of antipsychotic medications in older adults, assessment of their risk-benefit ratio, clinical indications, side effect profile, and monitoring of clinical response.
- Learn about the prevalence, diagnosis, and treatment of substance use and personality disorders in older adults.
- Gain new knowledge about how “successful aging” can enhance emotional and psychological health in older adults, and promote longevity through salutary effects on cognition, physical function, and social interaction.

Key Clinical Points

1. **The prevalence of psychiatric diseases increases with aging and exerts adverse effects on longevity, cognition, physical health, social interactions, and comorbid illnesses.**
2. **Mood disorders are common in older adults and associated with a high risk of suicide. It is important to recognize suicidal behavior and learn how to assess suicide risk and best ways to manage suicidal patients.**
3. **Use of antipsychotic medications in older adults is associated with serious adverse effects, including higher death rates in patients with dementia. None of these medications are Food and Drug Administration (FDA) approved for management of behavioral or psychological symptoms of dementia (BPSD), and there is no evidence from randomized trials that they are effective in managing psychotic symptoms.**
4. **Anxiety disorders are common in older adults and can present in many forms, including as generalized anxiety disorder (GAD), posttraumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), or panic disorder (PD). Additionally, anxiety symptoms are often associated with depression, dementia, medical comorbidities, and substance abuse. Psychotherapy and selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) are the cornerstone of therapy for most anxiety disorders.**
5. **Promoting the principles of “successful aging” and positive psychological traits, such as optimism, resilience, and social engagement, enhances neuroplasticity and improves cognition, physical function, and overall quality of life.**

MENTAL HEALTH ISSUES IN AGING

Relevant Population Demographic Information

The fact that the population in the United States will grow older in the coming decades is now widely understood. Health care professionals continue to devote increasing time to the management of geriatric patients reflecting the dramatic growth in the old and very old adult populations. The overall structure of the population will also change. Projections by the US Census Bureau estimate that by 2050, the number of individuals older than 65 years will be more than double from the current 40 million to 88.5 million people. **Figure 73-1** depicts the rapid growth in individuals 65 years or older between 1900 and 2060. Those in the oldest age group, 85 years and older, will increase from 5.8 to 8.7 million individuals. Changes are also projected in racial and ethnic diversity with increases in both the older and the oldest old cohorts over the next four decades. By 2050, the racial distribution of those 65 and older will be 77% white (of which 20% will be Hispanic), 12% black, 9% Asian, and 2% other. While female life expectancy is projected to continue to exceed that of men, there will be a decrease in the gap between this sex-driven disparity in life expectancy, which could lead to secondary social and economic changes. Among the 65-years-old and older age group, the percentage of women will decrease from 57% to 55%. This shift in the percentages of women versus men will be even greater in the oldest old population subgroup, 85 years and older, with 61% women down from the current 67% currently owing to the increase in life expectancy for men. As health care providers, it is essential to prepare for these dramatic shifts in population demographics in order to ensure that a proportional growth in geriatric-specific health care occurs.

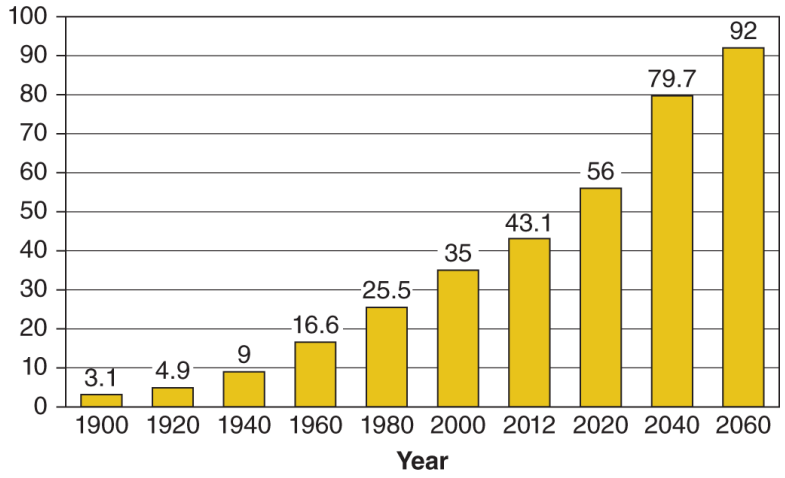


FIGURE 73-1. Number of persons 65 years and older between 1900 and 2060 (numbers in millions.) This chart shows the large increases in the older population from 3.1 million people in 1900 to 43.1 million in 2012 and projected to 92 million in 2060. Note: Increments in years are uneven. (US Census Bureau, Population Estimates and Projections.)

The federal Administration on Aging data reveal the current living arrangements and incomes for older adults. In 2013, 57% of older noninstitutionalized individuals lived with their spouse, which represented 71% of men and 45% of older women. For noninstitutionalized older persons, 28% were living alone (19% of men and 35% of women). Of the 65 years old and older demographic, 3.5% lived in institutional settings, including nursing homes. This number, however, increases substantially with increasing age and rises to 10% for those 85 years and older. **Figures 73-2A** and **B** display this information separately for men and women, respectively. Data from 2010 showed the median income of older persons was about $26,000 for men and $15,000 for women. In 2010, households, whose head of the family was over 65 years, the median income was about $46,000. **Figure 73-3** presents additional information about income for individuals 65 years and older. This data varied by race with non-Hispanic whites making more than Hispanics, African Americans, and Asians.

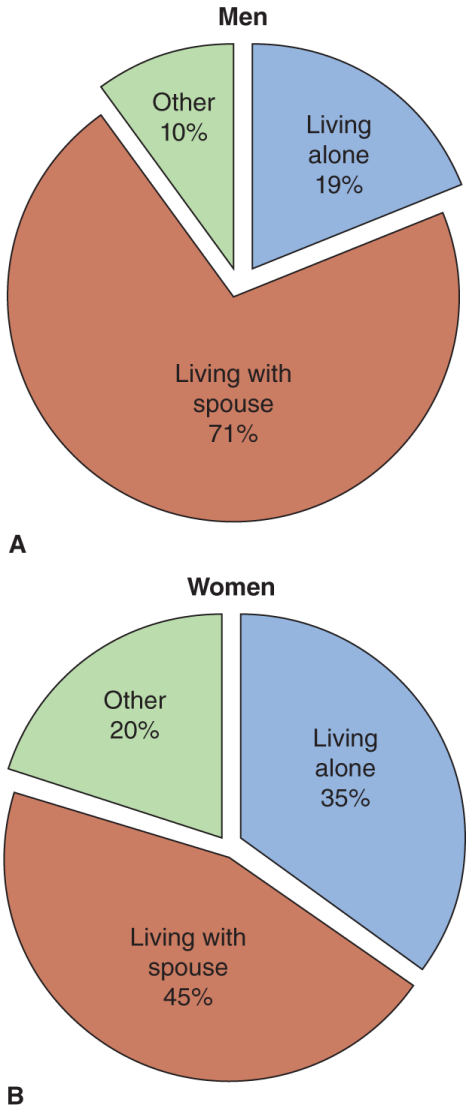


FIGURE 73-2 **A.** Living arrangements of men 65 years or older, 2012. This figure shows that 71% of older men live with a spouse and 19% live alone while 10% live in other arrangements. (US Census Bureau, Current Population Survey, Annual Social and Economic Supplement.) **B.** Living arrangements of women 65 years or older, 2013. This figure shows that 45% of older women live with a spouse and 35% live alone while 20% live in other arrangements. (US Census Bureau, Current Population Survey, Annual Social and Economic Supplement.)

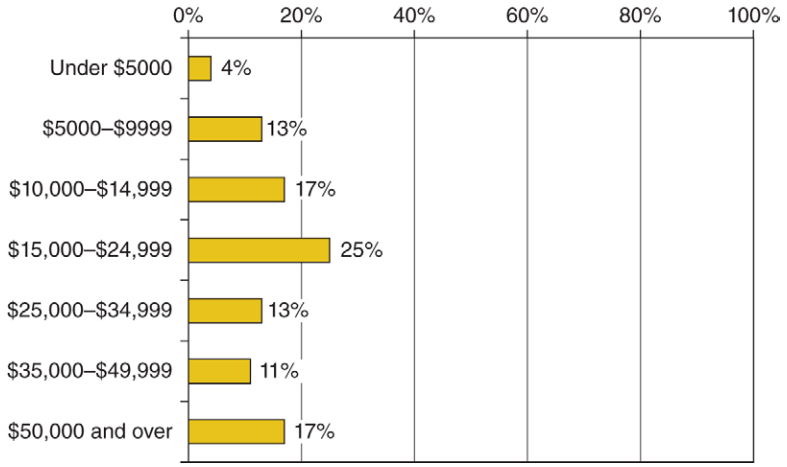


FIGURE 73-3. Percent distribution by income of persons 65+ reporting income, 2012. This figure is a chart showing personal income of older persons. Seventeen percent report under $10,000. About half are in the middle categories ($10,000–$35,000) and the median income for nearly 42 million persons over the age of 65 is $20, 380. Almost 28% have personal incomes of $35,000 or more. (US Census Bureau, Current Population Survey, Annual Social and Economic Supplement.)

Psychosocial Development Across the Lifespan

Health-defining, expected psychosocial developmental tasks or goals, sometimes referred to as psychological developmental milestones, vary according to age range. Psychologist Erik Erikson conceived of one of the most widely used and best-known models for human psychosocial development from infancy through old age and the end of life. Just like Sigmund Freud, Erikson believed that personality develops in a series of stages, however, Erikson's theory represented a marked shift from Freud's psychosexual theory. While Freud's theory of psychosexual development essentially ended at early adulthood, Erikson's theory described development through the entire lifespan from birth until death and took into account the impact of social experience across the entire lifespan. The importance of Erikson's contribution to our modern understanding of psychosocial development cannot be overstated. For example, his efforts have inspired modern contemporaries such as George Valiant, author of a number of books in this area including the book *Aging Well*. In large part, because of the concepts and theories that Erikson espoused, it is now widely understood that adults of all ages, including the oldest old, may benefit from various forms of psychotherapy as long as these individuals have intact short-term memory and are motivated to make changes in their thoughts, beliefs, and behaviors.

In Erikson's model, the eighth and final stage of psychosocial development is characterized by the core conflict of integrity versus despair. This late adult stage includes those in the oldest age group aged 65 and older. During this time, individuals grapple with answering deeper, existential questions such as, "Did I have a meaningful life?" and they reflect back on the life that they had. Wisdom is the "basic virtue" or resolution for this stage. Those who feel proud and satisfied with their accomplishments will master a sense of integrity. They have a sense of wisdom and acceptance when facing death and other end-of-life challenges. In contrast, someone who fails to master the developmental milestones of this stage may feel that his or her life has been wasted or lacked meaning and may experience feelings of regret, bitterness, and despair.

Ageism

In spite of the steadily growing interest among scientists, clinicians, and members of the general public in the field of successful aging, a topic discussed in a later section of this chapter, it unfortunately remains true that aging and later-life stages are often characterized by negative generalizations, myths, and stereotypes. These toxic attitudes and misconceptions remain ubiquitous, are often propagated by various forms of media, and may even be perpetuated by health care professionals whose opinions are inaccurately biased by sampling error because of daily professional exposure to only those older individuals who are ill and in distress. In addition, the older individual may also adopt inaccurate understandings or expectations, when a pejorative view of later life obtained through media or some other type of exposure is internalized and enacted. In addition to stigmas associated with aging in general, an even greater stigma exits for people living with a diagnosis of neurocognitive impairment. Perceptions of the relationship between sexuality, aging, and dementia illustrate some of these misconceptions and stereotypes. While some studies have found sexual activity decreases in frequency with increasing age, there is no limit to sexual responsiveness, and many older people, including those with cognitive impairment, remain sexually active. Furthermore, sexuality has become increasingly important in successive groups of older cohorts. In professional training programs and in clinical care venues there is a pressing need to challenge these biases and to correct these inaccurate views because of their potential to impact negatively the health and well-being of older adults. For example, because of the ageistic belief that older individuals do not engage in sexually intimate experiences, a clinician may omit questions about the older individual's recent and ongoing sexual experiences resulting in a missed opportunity to discuss how condom use is not only a form of contraception but also a good method to reduce the risk of sexually transmitted diseases. In addition, ageistic beliefs may be one reason that some clinicians are surprised to learn that many older adults living with dementia illness are leading meaningful, productive, and satisfying lives and may contribute to missed opportunities to help these older adults achieve the highest quality of life possible in spite of their dementia illness.

Common Emotional and Psychosocial Challenges Associated With Aging

With aging, certain mental health and psychosocial issues begin to emerge. Most notably, the later years of life may be characterized by various losses that for many may not have been present in earlier life stages. Some of these losses are specific to the individual such as loss of function, physical limitations, and decline in physical health and cognition. Medical comorbidities, injuries, or pain may limit mobility while cognitive decline may jeopardize instrumental activities of daily living or other aspects of independence. As these new issues arise, aging adults may draw upon

previous patterns of coping or discover opportunities for positive change and growth. Retirement is a common change and a potential challenge that arises later in life. Many look forward to retirement as the golden years of their life. Although retirement may offer opportunities for traveling, spending time with family, nurturing old hobbies, and exploring new ones, it also marks a dramatic role transition and change in identity that may not measure up to idealized expectations and may contribute to social isolation. Many individuals also experience notable losses to their social support system including family members, friends, and peers during these years. In these settings, bereavement and grieving are normal responses to loss, but monitoring for an adjustment disorder, complicated grief, depression, or substance misuse may be warranted. Complex grief affects up to 7% of geriatric patients. It may present symptomatically like a major depressive disorder (MDD) triggered by a loss. An individual with complicated grief may meet criteria for MDD and may require treatment of the depression with pharmacotherapy, individual therapy, supportive counseling groups, referral to a specialist, or some combination of these options. Feelings of self-worth are often preserved in normal grief reactions. Symptoms such as pervasive hopelessness, helplessness, guilt, diminished ability to experience pleasure, and suicidal ideation should raise concern for a major depressive episode. While a longing to be reunited with a deceased loved one or family member is often normal, careful screening and aggressive treatment may be indicated for more well-defined or active thoughts of suicide.

As physical and functional challenges arise in older patients, the need for a caregiver increases. The primary caregiver is often a spouse or adult child of the older patient. The role of a caregiver is wrought with physical, psychological, and emotional challenges when caring for someone with or without dementia. The caregiver may often suffer from significant morbidity and mortality and new-onset mental health issues may arise in caregivers during this time. Screening for stressors, coping, and social support helps the clinician direct caregivers to helpful resources and information, which indirectly also helps support the patient and family or caregiving unit. Resources and support groups are often underutilized but effectively offer an opportunity for education, stress management, community, and solidarity. When resources are available, a hired caregiver may help ease the caregiving burden or may be necessary when support from family or close friends is not available.

COMMON EVALUATION TOOLS

Cognitive Tests

Cognitive tests are effective tools for screening and diagnosis in ambulatory clinic and inpatient settings when patients are suspected to have cognitive impairment or a neurocognitive disorder. Several different tests are widely used, each with different strengths and weaknesses. Short questionnaires such as the Mental Test Score (MTS) or Six Item Cognitive Impairment Test (6 CIT) are quick to administer but provide limited information. These are used most effectively as screening tools in a population with a high prevalence of cognitive impairment or deficits. The Clock Drawing Test, General Practitioner Assessment of Cognition (GPCOG), Mini-Cog, and Memory Impairment Screen have higher selectivity for neurodegenerative disease and are also quick to administer but similarly provide a limited amount of information. Multidomain evaluation tools include the Mini Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), St. Louis University Mental Status Examination (SLUMS), Addenbrooke's Cognitive Examination (ACE), and Test Your Memory (TYM). These tests provide broader and somewhat more comprehensive picture of the patient's cognitive abilities and may be best used to detect mild cognitive problems. Disadvantages of these tools include a longer time to administer with the exception of the TYM, which is a self-administered report. These tools are most helpful when assessing patients who are presenting with known memory problems. They help characterize the type and quantify the severity of cognitive deficits when they exist. While these tests are effective in identifying cognitive deficits, they are limited in their ability to diagnose or determine the etiology and type of a dementia.

The gold standard for diagnosing dementia and assessing neurodegenerative diseases and other cognitive deficits is a neuropsychological battery also called neuropsychiatric testing. This extensive and comprehensive assessment is performed by a specialist and may require at least 3 to 5 hours depending on the case. In addition to a full history and clinical interview, a complete neuropsychiatric battery often includes, but is not limited to, the following: California Verbal Learning Test (CVLT-2), Wechsler Adult Intelligence Scale (WAIS-4), subtests of the Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-2), the Mattis Dementia Rating Scale (DRS), subtests of the Wechsler Memory Scale such as Visual Reproduction and Logical Memory, Test of Memory Malingering (TOMM); the Boston Naming Test (BNT), the Halstead-Reitan Battery, the Wide Range Achievement Test (WRAT-4), the Clock Drawing

Test, the Trail Making Tests Part A and Part B, the Verbal Fluency tests from the Delis-Kaplan Executive Function Scale (D-KEFS), and the Wisconsin Card Sorting Test-64 (WCST-64). This type of testing also often includes screens for depression and anxiety symptoms which could be influencing cognitive performance such as the Geriatric Depression Scale (GDS) and Geriatric Anxiety Inventory (GAI), respectively. Other psychiatric screening tools which may be used in conjunction with, or in addition to, neuropsychiatric testing for clinical suspicion of other diagnoses or comorbidities include the PHQ-9 for depression, the Young Mania Rating Scale, GAD-7 for anxiety, PC-PTSD for PTSD, and Y-BOCS for OCD.

Other Evaluation Modalities

Other evaluation modalities, in addition to cognitive testing and screening, help determine the etiology of cognitive deficits or other psychiatric problems. For example, brain imaging, whether obtained from a computed tomography (CT) or magnetic resonance imaging (MRI), may help exclude a neurologic or general medical condition in the differential diagnosis. A brain CT or MRI may also help establish the etiology of dementia. Specifically, a brain CT or MRI assesses cerebral gray matter volume, cortical thickness, and vascular changes such as those that result from chronic untreated hypertension or atherosclerosis. Referrals to specialists in geriatric psychiatry and neurology may be warranted when considering or interpreting results of these tests. Other diagnostic tests and emerging methods specifically for making a diagnosis of Alzheimer dementia include cerebrospinal fluid (CSF) amyloid and tau, computer-assisted volumetric brain imaging, fluorodeoxyglucose positron emission tomography (FDG-PET), which measures cerebral glucose metabolism, and single-photon emission computed tomography (SPECT), a measure of cerebral perfusion. At present, Medicare will pay for an FDG-PET in cases when the clinician is not certain whether the patient has Alzheimer dementia or frontotemporal dementia. Future studies seek to identify reliable biomarkers or the combined use of several biomarkers for diagnosing dementia and its subtypes and engaging in prevention and treatment measures early in the course of the disease.

Evaluation for Delirium

Including delirium in the differential diagnosis is appropriate when assessing changes in mentation, confusion, notable behavioral changes from a previous baseline, and new or sudden onset of psychiatric symptoms. An evaluation for delirium involves a clinical interview and diagnostic evaluation of possible medical causes including medical conditions, medication side effects, or substance intoxication and withdrawal among others. The clinical hallmark of delirium is fluctuations in mental status, especially attention and alertness, and the symptoms are potentially reversible. Tools used in cognitive screening such as the MoCA or SLUMS and other cognitive exercises requiring sustained attention are especially helpful in making the diagnosis of delirium.

PSYCHOSIS IN OLDER PATIENTS

Introduction

Psychosis is a general term referring to a mental condition affecting thinking, perceptual experiences and behaviors in a way that almost always impairs functioning. “Positive” psychotic symptoms include delusions, hallucinations, disorganized speech, and disorganized behavior. “Negative” psychotic symptoms may include reduced social interaction, reduced facial expressivity, reduced physical activity, reduced thought content, and reduced speech. Psychotic symptoms are common in older adults where they may be related to chronic psychotic disorders, mood disorders, neurocognitive disorders, or a symptom of delirium (ie, related to an underlying medical condition). Psychosis is almost always distressing for both patients and their families, and is associated with decreased quality of life and functioning, more caregiver distress, increased health care costs, and increased risk for placement in long-term care facilities. The most common primary psychotic disorders found in older adults are discussed here; mood disorders and delirium are discussed in detail elsewhere in the text.

Schizophrenia

Schizophrenia is a chronic psychotic disorder that causes significant social and occupational dysfunction. Symptoms of schizophrenia may include delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and negative symptoms. A diagnosis of schizophrenia requires at least two of these symptoms, one of which must be

delusions, hallucinations, or disorganized speech. The symptoms must persist over at least a 6-month period of time and other conditions explaining the symptoms must be ruled out (eg, delirium, mood disorders). The prevalence of schizophrenia is estimated to be 0.6% among adults ages 45 to 64 and 0.1% to 0.5% in older populations. A minority of patients, approximately 20%, have onset of schizophrenia after age 40. Therefore, a majority of older adults with schizophrenia have had an earlier onset followed by a chronic course over many years. Studies suggest that schizophrenia with onset between the ages of 40 and 60, which is described as late-onset schizophrenia (LOS), differs from early-onset schizophrenia (EOS) in several important ways. Specifically, LOS is generally associated with a lower average severity of positive symptoms (ie, delusions, hallucinations, disorganized speech or behavior), and lower average antipsychotic dose requirement. Further, the vast majority of patient with LOS are women. Accordingly, some have proposed that LOS is a distinct subtype of schizophrenia. At this time, it is not clear if LOS incidence in aging men will increase due to their gradually increasing life expectancy. However, the term LOS has not been incorporated into the *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5) which states "late-onset cases can meet the diagnostic criteria for schizophrenia, but it is not yet clear whether this is the same condition as schizophrenia diagnosed prior to midlife." **Table 73-1** summarizes some of the key differences between early-onset and late-onset schizophrenia.

TABLE 73-1 KEY DIFFERENCES BETWEEN EARLY-ONSET AND LATE-ONSET SCHIZOPHRENIA

FEATURE OR CHARACTERISTIC	EARLY-ONSET SCHIZOPHRENIA	LATE-ONSET SCHIZOPHRENIA
Age of onset	Most common in late adolescence or early adulthood	Most often between ages 40 and 60
Proportion of older individuals with schizophrenia	75%	25%
Male-to-female ratio	Slightly more common in males	1:2 to 1:10
Levels of childhood maladjustment, measured retrospectively	Higher than those in healthy subjects	Higher than those in healthy subjects
Adult developmental milestones (marriage, job, children)	Not often met	Somewhat more likely than in early-onset schizophrenia
Proportion with self-reported family history of schizophrenia compared to the general population	10%–15%	10%–15%
Rates of minor physical anomalies compared to health subjects	Increased	Increased
Nonspecific structural abnormalities such as enlarged ventricles and increased white matter hyperintensities	Less common	More common
Affect	Flat, blunted, inappropriate	Nearly normal
Thought and behavior disorganization	Prominent	Less prominent
Nature of delusions	Various types, often complex and persecutory; paranoid delusions (50%)	Usually paranoid (75%)
Cognition	Impairment in abstraction, learning, flexibility in thinking and psychomotor function but retention *ok* and no evidence of progressive deterioration—consistent with a neurodevelopmental rather than a neurodegenerative process	Same pattern but deficits tend to be less severe and long-term follow-up revealed no evidence of cognitive decline—consistent with a neurodevelopmental rather than a neurodegenerative process
Average required daily doses of antipsychotic medications in later life	Higher	Lower

Modified from Jeste DV, Harris MJ, Krull A, et al. Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. Am J Psychiatry. 1995;152(5):722–730; with permission.

Delusional Disorder

Delusional disorder is characterized by the presence of delusions without other primary symptoms of schizophrenia (eg, hallucinations, disorganized speech or behavior, restricted effect). The disorder typically first appears in middle-to-late adulthood, with an average age at onset of 40 to 49 for men and 60 to 69 for women and is, therefore, more common in older adults than their younger counterparts. A diagnosis of delusional disorder can only be made when all other possible explanations for delusions have been ruled out (eg, delirium, neurocognitive disorders, mood disorders, and schizophrenia). According to DSM-5, the lifetime prevalence of delusional disorder is estimated to be 0.2%.

Psychosis in Neurocognitive Disorders

Psychotic symptoms are common in neurocognitive disorders. For example, it is estimated that 41% of patients with Alzheimer disease (AD) will experience psychotic symptoms at some point in the course of their illness. Some common psychotic symptoms in AD include misidentification of caregivers, suspiciousness, and delusions of theft. Hallucinations in AD are less common but may occur. Visual hallucinations are common in Lewy body disease and psychotic symptoms may also be associated with other neurocognitive disorders. **Table 73-2** compares the psychosis commonly seen in a patient living with AD and the psychosis characteristic of schizophrenia.

TABLE 73-2 CHARACTERISTICS OF SCHIZOPHRENIA VERSUS ALZHEIMER DISEASE ACCOMPANIED BY PSYCHOSIS

FEATURE OR CHARACTERISTIC	SCHIZOPHRENIA	ALZHEIMER DISEASE
Age of onset	Bimodal with most common in late adolescence or early adulthood and a second smaller peak of onset between 40 and 60 years	Progressively more common with age after 60
Male-to-female ratio	Overall, no significant gender difference	Somewhat more common in women. The prevalence in those over age 71 was found to be 16% in women and 11% in men
Affect	Flat, blunted, inappropriate	Nearly normal
Thought and behavior disorganization	Prominent early but often less prominent in later life	Less prominent until the later stages of the illness
Social skills	Often deficits are apparent in social skills and communication, although recent research is documenting partial remediation of these deficits in some treated patients	Often surprisingly well-preserved until fairly late in the illness, which contributes to delays in diagnosis
Time of onset of psychosis relative to stage of illness	Early and usually within the first 6 mo	More common in mid-to-late stages, 4–5 y after initial symptoms appear
Nature of delusions	Various types, often complex and bizarre; commonly persecutory; paranoid delusions (50%), eg, extraterrestrial forces have invaded the planet and are controlling people using subliminal messages sent through the TV	Simple, rarely bizarre, concrete, and usually paranoid, eg, delusions of theft when the patient has misplaced something
Hallucinations	Most commonly auditory but can also include visual, tactile, and olfactory	Visual hallucinations (eg, seeing an intruder) are relatively more common than other forms including auditory (eg, voice of a deceased relative)
Cognition	Impairment in abstraction, learning, flexibility in thinking, and psychomotor function but retention *ok*, and no evidence of progressive deterioration—consistent with a neurodevelopmental rather than a neurodegenerative process	Rapid forgetting/profound short-term memory problems are usually the first complaint, and subsequently patients experience progressive deterioration in multiple cognitive domains including anomia and expressive aphasia
Average required daily doses of	Higher	Lower

Evaluation

The evaluation of psychotic symptoms in older adults begins with a careful history, ideally by interview with both the patient and a reliable informant such as a family member. The time-course of symptoms can be particularly helpful as patients with chronic psychotic disorders (such as schizophrenia) and mood disorders, which are generally episodic, have a history of symptoms consistent with their diagnosis. Because psychosis is a common symptom of delirium, a medical evaluation should be performed to assess for any possible underlying medical condition. This evaluation may include a physical and neurologic examination, laboratory tests, and brain imaging. A careful review of medications that could be contributing to the symptoms should also be done and substance use should be ruled out. The importance of a thorough medical evaluation cannot be overemphasized. Studies suggest that undetected medical conditions may be etiologically responsible for as many as 34% of hospital admissions for behavioral symptoms in older individuals. The possible explanations for this phenomenon have ranged from the influence of ageism (eg, the myth that paranoia is expected in older individuals), the extra time and effort required to obtain immediately useful historical information from older individuals due to normal age-associated changes in communication (eg, increasingly circumstantial speech, delayed retrieval of information stored in memory and slower speech production), discomfort associated with performing certain aspects of the physical examination in an older individual such as pelvic and rectal examinations, or the extra steps and staff needed to perform certain components of the physical examination in an older individual with a neurodegenerative illness which has taken away the patient's ability to understand and cooperate with the examiner. In spite of these and other potential barriers to an optimal medical evaluation, accurately diagnosing and optimally treating medical conditions lead to more rapid restoration of the patient's health and avoid wasting increasingly precious resources. After assessment for contributing medical conditions and medication side effects, referral to a geriatric psychiatrist may be helpful.

Management and Treatment

Antipsychotic and other medications Antipsychotic medications are commonly used to treat psychotic symptoms in older adults. Antipsychotic medications have been approved by the FDA primarily for treatment of schizophrenia. In addition, some are FDA approved for use in the treatment of bipolar disorder and for use in combination with antidepressants in the treatment of MDD. Antipsychotics are also widely used "off-label" in the treatment of psychosis related to neurocognitive disorders despite limited data to support the long-term safety and effectiveness of these medications in this population. This widespread "off-label" use of antipsychotics reflects the lack of FDA-approved pharmacologic alternatives for psychosis associated with neurocognitive disorders and the stress and suffering these symptoms cause for patients, their families, and others such as individuals living in the same residential care environment. In spite of what is known about the risks of prescribing antipsychotic medications to older individuals, it bears remembering that there are no FDA-approved medications from any class or category for the treatment of BPSD including psychosis nor have there been an adequate number and quality of head-to-head comparison studies of various antipsychotic medications versus medications from other classes or categories to determine if any of the other possibly helpful medications are better at reducing symptoms and/or less likely to cause serious side effects. The American Psychiatric Association Council on Geriatric Psychiatry recently published on line a "Resource Document on the Use of Antipsychotic Medications to Treat Behavioral Disturbances in Persons with Dementia." This document is, perhaps, the most thoughtful, balanced, and helpful summary currently available to help guide clinicians and references recent longitudinal findings indicating that it may actually be the symptoms of psychosis and agitation that lead to increased rates of mortality and institutionalization rather than the antipsychotic medications themselves. In addition, this document emphasizes that nonpharmacologic behavioral treatment strategies should be attempted as first-line approaches unless the behaviors are so severe that the patient or others are in imminent danger. Lastly, this document notes that the currently available evidence demonstrating that nonpharmacologic approaches are safer or more effective than antipsychotics in the treatment of dementia-related psychosis or behavioral disturbance is limited.

Despite their widespread use, caution is warranted and the potential benefits and risks of antipsychotic use in each older individual patient must be carefully weighed. Pharmacokinetic and pharmacodynamic changes that occur with age lead to an increased sensitivity to antipsychotics in older individuals. Specifically, decreases in total body water and muscle mass combined with a relative increase in the proportion of adipose tissue result in an increased volume of distribution and slower elimination of antipsychotic medications while decreased hepatic protein synthesis results in

more “free” drug in the circulation. Further, increased permeability of the blood-brain barrier occurring with age can lead to higher concentrations of antipsychotic medications in the central nervous system (CNS). Ageing is also associated with decreased synthesis and increased metabolism of dopamine, a decreased number of dopaminergic neurons, and decreased density of dopamine receptor subtype 2 (D2) in the brain. This age-related increase in sensitivity to antipsychotics often translates to lower antipsychotic dose requirements for treatment of psychotic symptoms in older adults and places older adults at greater risk for antipsychotic-induced side effects such as extrapyramidal symptoms (EPS; eg, parkinsonism). Also of concern in older adults is an increased risk of falls in those taking antipsychotics, likely due to a combination of the autonomic effects, EPS, and sedative properties of the medications.

Because second-generation or “atypical” antipsychotics (eg, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, iloperidone, asenapine, lurasidone) are generally associated with a lower risk for parkinsonism and tardive dyskinesia than first-generation antipsychotics, they have become popular for treatment of psychosis. Numerous studies, however, have now documented other liabilities associated with atypical antipsychotics including elevated risk of metabolic side effects and the FDA has issued a warning regarding increased risk for cerebrovascular adverse events and mortality in older patients with neurocognitive disorders treated with both atypical antipsychotics and, subsequently, for typical antipsychotics. One study evaluating the long-term safety and effectiveness of atypical antipsychotics in older adults compared four commonly prescribed atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) in 332 outpatients over the age of 40 with psychotic symptoms related to a variety of psychiatric diagnoses over 2 years of treatment. Concerning findings included a high 1-year cumulative incidence of metabolic syndrome (36% in 1 year), high rates of both serious and nonserious (50.8%) adverse events, and no significant improvement in symptoms. Further, over half of the study participants discontinued their assigned medication within 6 months, most often due to side effects (51.6%) or lack of efficacy (26%). These findings suggest that the commonly used atypical antipsychotic medications may be helpful short term but neither safe nor effective over longer periods of treatment in middle-aged and older adults.

The use of antipsychotic medications to treat schizophrenia in older adults is largely based on studies conducted on younger adults. Risperidone and olanzapine have been shown to be effective for treatment of psychotic symptoms in middle-aged and older adults with schizophrenia in short-term studies. Single short-term trials suggest that aripiprazole and paliperidone could also be beneficial. It is noteworthy that, many older adults with early-onset schizophrenia have fewer and less severe delusions and hallucinations compared to their younger counterparts and small minority of patients may experience a sustained remission of illness. A reduction in dose or discontinuation of antipsychotic medication, therefore, may be possible in later years in some aging patients with schizophrenia. Their use for treatment of LOS has not been adequately studied. LOS is generally associated with a better prognosis and lower daily antipsychotic dose requirement than early-onset illness. Data regarding the pharmacologic treatment of delusional disorder in older adults are limited in part because patients with delusional disorder tend to lack insight and are difficult to enroll in randomized placebo-controlled trials. A survey of 48 experts in geriatric care in 2004 found antipsychotics to be the only recommended treatment for delusional disorder in older adults. Case studies and retrospective studies published since that time continue to support that view.

As noted earlier, there are currently no FDA-approved pharmacologic treatments for psychosis related to neurocognitive disorders. However, given the lack of safe and effective evidence-supported alternatives, atypical antipsychotics continue to play a role in the treatment of some patients with memory illness, particularly when the symptoms are severe (with potential for harm to self or others) requiring aggressive treatment. The risk-to-benefit analysis in these situations is often complex. Potential benefits may include mitigation of agitation-associated injuries to patients (including falls), staff, and family members. Most dementia illnesses are progressive and the need for antipsychotic may recede as the patient’s illness advances and associated additional brain injury has occurred. The only way to determine if antipsychotic medication is still required is to reduce the dose incrementally and observe whether problem symptoms reemerge on the lowered dose. Standardized measures of behavioral symptoms in neurocognitive disorders, such as the Pittsburgh Agitation Scale or the Cohen-Mansfield Agitation Inventory, can be useful to monitor the effects of treatment. Finally, it should be noted that patients with Lewy body disease are commonly sensitive to antipsychotic medications and particularly at risk for severe adverse reactions including parkinsonism and anticholinergic and hypotensive effects. This sensitivity is most commonly associated with the antipsychotic medications which are known to be potent D2 blockers, but it has also been observed and reported even with the very-low-potency antipsychotics such as quetiapine.

Educating patients and their caregivers about possible risks and benefits associated with antipsychotic use in older adults and sharing the decision-making process is critical. Whatever treatment plan is implemented the prescribing

clinician should carefully document in the patient's record the fact that informed consent was obtained from the patient or, when the patient lacks capacity for the decision, the appropriate proxy decision maker for the patient. If antipsychotic medications are used in older adults for any condition, we recommend starting with a low initial dose (25%–50% of that used in a younger patient) and titrating slowly. In patients who have been stably maintained on antipsychotic medications consideration should be given to incremental dose decreases in order to determine the lowest effective dose. Patients should be vigilantly monitored for side effects and to determine whether the prescribed medication is effectively treating their symptoms.

Non-Antipsychotic Medications In clinical practice, mood stabilizers, antidepressants, and sedative hypnotics are frequently used to treat psychosis and associated symptoms such as agitation and aggression, especially in persons with neurocognitive disorders. Yet, none of these medications have received FDA approval for those conditions. Moreover, they carry a clear risk of several major side effects. Therefore, considerable caution is warranted in using these medications in older patients.

Nonpharmacologic interventions There are several nonpharmacologic interventions which are beneficial for older adults with psychotic disorders. Cognitive Behavioral Social Skills Training (CBSST), a 36-session weekly group therapy program combining cognitive behavioral therapy, social skills training, and problem-solving training resulted in improved functioning of middle-aged and older patients with schizophrenia or schizoaffective disorder compared with a supportive therapy control. Helping Older People Experience Success (HOPES), a year-long program combining social skills training and preventive health care was associated with improved community-living skills and functioning, greater self-efficacy, and lower levels of negative symptoms in older adults with serious chronic mental illness, more than half of whom had schizophrenia or schizoaffective disorder. Functional Adaptation and Skills Training (FAST), a 24-week functional skills course, was also associated with improvement in functioning and decrease in utilization of emergency medical services in older adults with schizophrenia.

As noted above, data regarding psychosocial interventions for psychosis related to neurocognitive disorders are more limited. Small studies have reported benefit with interventions such as one-to-one social interaction, support groups, music therapy, dance therapy, aromatherapy, bed baths, person-centered bathing, and muscle relaxation therapy. Thus far, studies testing these approaches have been limited by small sample sizes, lack of appropriate control groups, and suboptimal outcome measures. More research is therefore needed in this area including better-powered, well-designed randomized controlled trials. Many studies of psychosocial interventions for behavioral symptoms in patients with neurocognitive disorders report a high placebo response rate suggesting that increased attention they receive as part of a research study is beneficial.

MOOD DISORDERS

Introduction and Suicidal Behavior

Given the preference of many older patients to seek mental health care from their primary care provider coupled with their reluctance to seek care from a mental health specialist, including psychiatrists, the primary care physician often is presented with the very challenging task of assessing and caring for older patients at risk for suicide. Although the emerging trend of "embedding" mental health providers within the primary care clinic environment seems to be an effective method of overcoming the resistance of older individuals to receive care from psychiatrists and other mental health clinicians, for the time being most older individuals, including those at risk for suicide, will be evaluated and treated by primary care providers.

Chapter 71 in this textbook provides a summary of mood disorders in older individuals. This section of the current chapter provides additional information about three topics related to mood disorders: suicide, suicide risk assessment, and the treatment of suicidal ideation.

Older individuals account for a significant proportion of death by suicide in the United States. Fortunately, statistics from the Centers for Disease Control and Prevention (CDC) indicate that the rate of suicide in the 65 and older age group has been decreasing since 1991, a year in which nearly 20 out of every 100,000 people over the age of 65 died from suicide. In 2009, the most recent year for which data are available, the rate had decreased to about 15 per 100,000. White males have the highest risk at any adult age; white males over age 85 complete suicide at a rate of 50 per 100,000, which is four times higher than the nation's overall rate. With increasing age, the use of firearms as the method for completed suicide becomes ever more common. About 75% of suicide deaths by whites and blacks and

50% of deaths by Hispanics are caused by firearms.

Suicide Risk Assessment

Establishing rapport is essential when caring for older patients. This is especially true when evaluating and assessing suicide risk. No matter how skilled the interviewers are, older patients are frequently unwilling to disclose thoughts about suicide and self-harm and yet the evaluation is an integral part of the treatment process because it opens up discussion between the patient and clinician, thereby allowing prevention through decreasing access to available means of suicide, building trust, facilitating a supportive therapeutic relationship, and tailoring treatment interventions.

Common barriers to open, effective communication about suicide with older patients include (1) the belief that people should be able to deal with emotional problems without medical help; (2) the fear of being labeled “mentally ill” and referred to a psychiatrist; (3) the fear of being negatively judged by the clinician; and (4) the belief that primary care physicians do not understand and cannot help people suffering from depression. Using an empathic approach, the clinician should correct any misinformation. Educating patients and members of their social support system is essential. Tremendous benefits are usually obtained by sharing with older patients that depressive illness is relatively common, that scientific research has begun to illuminate the underlying physiologic basis for the illness and, therefore, views that depression is invariably a sign of character weakness or moral corruption are antiquated, and that scientifically proven, highly effective treatments are now available for depression and associated suicidal symptoms.

All patients with mood, substance use, and psychotic disorders should be assessed for suicide risk. This assessment need not be time consuming, especially when occurring in the context of an established therapeutic relationship. Simply asking questions pertaining to suicide can yield very helpful information. A suicide risk assessment requires the identification of suicidal ideation and intent, risk factors, and protective factors. The most important questions to ask concern present suicidal ideation. Contrary to what some may believe, asking about suicidal ideation does not increase the likelihood of a patient subsequently developing suicidal ideation. Often using a “normalizing” statement as preface to questions about suicide is helpful. For example, “Sometimes individuals suffering from depression contemplate taking their lives. Have you had similar thoughts?” If a patient responds that he or she is having thoughts of suicide, the clinician should ask if any plans have been made. The lethality of a plan should be weighed. For example, a plan to shoot oneself represents high lethality whereas a plan to drink oneself to death represents lower lethality. If a plan has been made, the clinician should inquire if steps have already been made to carry out the plan such as buying ammunition for a firearm, purchasing rope, or stockpiling medications. Asking about a plan helps the clinician get a better sense of the patient’s actual intent to act on the suicidal thoughts.

Another important part of the interview of a patient with depression is the identification of risk factors. A history of suicide attempts represents the most important risk factor for future attempts; however, it should be remembered that most completed suicides are not preceded by unsuccessful attempts. Additional risk factors include hopelessness, including having no reason for living or no sense of purpose in life; feelings of helplessness; high levels of pessimism, rage or anger; a desire for revenge; impulsiveness; increasing use of drugs or alcohol; withdrawal from friends and family; anxiety; agitation; insomnia; diminished “social connectedness” (eg, being single or living alone or living in a rural area); uncontrolled or chronic pain; male sex; and firearm access. Recent social losses also represent important risk factors, such as the death of a friend or family member, divorce, loss of employment, financial loss, and loss of housing. Worrisome activities include carrying out preparations for death, such as reassigning the responsibility of caring for dependents (children, pets, or a spouse), creating or updating wills, and giving away personal belongings.

Among psychiatric diagnoses, mood disorders carry the greatest risk. The majority of suicide occurs within the context of an active mood episode. The presence of an active substance use disorder along with a mood disorder leads to even greater risk. Physical illness, such as stroke, and disability are also important risk factors for suicide. Generally, the greater the number of physical illnesses from which an individual suffers, the greater is their risk of suicide. Risk is also elevated in the week following admission to, or discharge from, a psychiatric inpatient unit. The impact of neurocognitive disorder on suicide risk is difficult to establish, however, impairment in executive function has been found to be more prevalent in depressed older patients with a history of suicide attempts compared to those without a history of attempts.

Protective factors are also important to identify. High perceived social support, close interpersonal relationships, feelings of usefulness, perceived ability to achieve goals, a realistic and positive future outlook, and a successful adjustment to aging are examples of protective factors. The presence of these protective factors generally indicates a positive future orientation, meaning that the patient expects life to continue. Additional protective factors include religiousness and spirituality, being married, having children, and having a sense of responsibility to family. Using the

above information, a general assessment of risk, such as low, moderate, or high should be determined and documented in the patient's medical record. Determining the overall risk for suicide subsequently helps to determine the nature of the treatment that is required.

To increase the reliability of the interview, structured suicidal assessment scales can be used. A commonly used suicide risk assessment tool is the Scale for Suicide Ideation which is a 19-item clinician-rated measure that assess suicidal thoughts and behaviors during the preceding 7 days as well as for the worst moments in the patient's life as determined by the patient. The Scale for Suicide Ideation thoroughly measures many components of suicide, including suicidal plan, behavior, preparation for an attempt, and anticipation of an attempt. The Geriatric Suicide Ideation Scale is a recently developed, relatively easy to administer scale specifically developed for use with older individuals which has standardized administration and scoring procedures and is sensitive to suicide detection. This scale consists of 66 items and assesses four factors including suicidal ideation, death ideation, loss of personal and social worth, and perceived meaning of life. The SAFE-T is yet another recently developed structured suicide assessment. The SAFE-T reflects the American Psychiatric Association's (APA) practice guidelines for the assessment and treatment of patients with suicidal behaviors and consists of the following five steps: (1) eliciting any modifiable risk factors; (2) discovering protective factors that may help reduce suicide risk; (3) inquiring about current suicidal thoughts, behaviors, plans, and intent; (4) weighing factors 1 to 3 to calculate a level of risk and then identifying potential interventions to reduce risk; and (5) documenting risk, risk mitigation efforts and their respective rationales, and plans for follow-up. The well-written guidelines for use of the SAFE-T are available on the internet. In addition, a free pocket card of the SAFE-T is available on the Suicide Prevention Resource Center website (www.sprc.org).

Management and Treatment of Suicidal Patients

Any patient assessed to be at high, acute risk of suicide should receive an emergent mental health evaluation. If such services are not immediately available, most states have laws permitting emergency hospitalization for psychiatric evaluation of patients who, due to a mental illness, present an imminent risk of harming themselves. In general, various types of law enforcement officers are prepared to assist in securing and transporting patients for such an evaluation.

Managing and treating geriatric patients with suicidal tendencies initially involves three steps. The first is to diagnose and treat the current psychiatric disorder. The second step is to assess the suicidal intent and lethality with an emphasis on prevention. The third is to construct a specific treatment plan tailored to the patient. Guidelines for managing suicide in adults are provided by the APA's practice guidelines for the assessment and treatment of patients with suicidal behavior.

Major goals of treatment are to help the patient reduce modifiable risk factors while reinforcing protective factors. For example, the clinician could prescribe no more than a 1-week supply of medication to reduce the risk of death by overdose. Enlisting the help of family members to remove firearms from the home is another valuable intervention especially given that removing the means of suicide is one of the most effective interventions in suicide prevention. Improving social support through increased supervision from family members and friends, as well as referrals as appropriate to home care and other supportive services can also markedly diminish suicide risk. In any instance in which a clinician has significant concerns about suicide risk, a referral to a psychiatrist is highly recommended.

For older adults, specific guidelines for treating and managing suicide were provided from the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT). **Table 73-3** shows the PROSPECT general recommendations for working with patients at risk of suicide as well as management techniques for patients at high risk. In addition, guidelines for managing suicidal ideation in adults are provided by the APA.

TABLE 73-3 PROSPECT[a] RECOMMENDED GUIDELINES AND MANAGEMENT TECHNIQUES FOR WORKING WITH PATIENTS WITH SUICIDAL IDEATION

Guidelines while working with patients with suicidal ideation

- Be attentive
- Stay calm and nonthreatening
- Provide the patient with space and time to vent
- Be collaborative, use a team approach
- Be willing to say the word "suicide"

Management techniques for patients with high risk

- Directly assess the frequency and content of suicidal ideation and risk factors
- Explore the initial problem
- Have the patient describe reasons for and against suicide
- Assess the patient's access to means
- Provide the patient with education regarding depression including its etiology, prognosis, and treatment
- Decide how to manage an increase in suicidal ideation through either a formal contract or some other formality
- Provide education regarding alcohol and illicit substances and encourage their discontinuation
- Meet with the patient weekly at minimum if suicidal ideation is present
- Write prescriptions for no more than 1 wk until suicidal risk has decreased
- Provide family education regarding suicide, including how to appropriately respond to the patient and assuring the living environment is safe (ie, remove firearms)
- Provide supportive and collaborative interaction with the patient

At each treatment assess hopelessness, suicidal ideation, and substance abuse

[a]PROSPECT, Prevention of Suicide in Primary Care Elderly: Collaborative Trial.

Data from Brown GK, Bruce ML, Pearson JL. High-risk management guidelines for elderly suicidal patients in primary care settings. Int J Geriatr Psychiatry. 2001;16:593–601.

ANXIETY DISORDERS

Introduction

Anxiety disorders are the most common psychiatric disorders from which people suffer, and this remains true for individuals in later life. In fact, twice as many older individuals suffer from anxiety disorders as suffer from major neurocognitive disorders and anxiety disorders affect about five times more older individuals than do mood disorders. The nature of anxiety in older adults, however, does tend to differ in characteristic ways from that of their younger counterparts. For example, in older individuals somatic preoccupation is more common and more intense, and, due to a weakened autonomic response, the intensity of the physical symptoms associated with panic attacks is diminished. Fewer older patients meet full criteria for an anxiety diagnosis, though subthreshold anxiety affects a greater proportion of this population. Prevalence rates for full-criteria anxiety disorders among older adults have been estimated to range from about 5% to 15%, with a 2:1 female predominance.

GAD represents approximately 50% of all anxiety disorders diagnosed in later life, and about half of all cases of GAD develop after an individual reaches 65 years of age. Specific phobia represents approximately 40% of anxiety disorders in older patients. The most common phobia in older adults is fear of falling. Approximately 60% of older adults with a history of falling and 30% of older individuals with no such history report this fear. PTSD, OCD, and PD represent almost all of the remaining 10% of anxiety diagnoses in older individuals.

Anxiety disorders often present atypically in older individuals including the reported frequency of certain symptoms of anxiety and the manner in which the anxiety symptoms are described. For example, shortness of breath or stomach discomfort may be the only way an older individual may be able to describe feelings of anxiety. In addition to differences in reporting, the diagnostic differential is far broader. A methodical approach to evaluation is recommended with the first step being to assess whether medical conditions and medications/substances might be mimicking, precipitating, or exacerbating the patient's anxiety symptoms. Medical conditions known to precipitate anxiety include delirium, chronic obstructive pulmonary disease (COPD), pulmonary embolism, anemia, hypoglycemia, hyponatremia, hyperkalemia, angina, and arrhythmias. If the symptoms of anxiety are determined to indeed be the physiologic consequence of a medical condition (such as panic attacks caused by a COPD exacerbation, or anxiety due to a seizure disorder), anxiety disorder due to another medical condition should be diagnosed.

Substance-induced anxiety disorder should be diagnosed if the anxiety symptoms are due to substance intoxication or withdrawal. The substance may or may not be a medication (eg, both cocaine and albuterol are "substances"). To accurately make this diagnosis (and, ie, to exclude a primary psychiatric or medical etiology of the anxiety), establishing timing of symptoms in relation to use of the substance(s) in question is crucial. Importantly, the anxiety symptoms should not have been experienced prior to use of the substance and the symptoms should not continue in the absence of continued use of the substance. Anxiogenic medications include anesthetics and analgesics,

sympathomimetics and other bronchodilators, anticholinergics, insulin, thyroid preparations, oral contraceptives, antihistamines, antiparkinsonian medications, corticosteroids, antihypertensive and cardiovascular medications, anticonvulsants, lithium, antipsychotics, and antidepressants. In addition, alcohol and benzodiazepine withdrawal are commonly accompanied by intense anxiety, as is caffeine, cocaine, and amphetamine intoxication.

Primary psychiatric diagnoses should be considered after a medical etiology has been ruled out. The clinician should seek to ensure as much parsimony in diagnosis as possible. For example, might the pathology of an individual with three specific phobias be better explained by a diagnosis of generalized anxiety disorder? The DSM-5 made few major changes to the diagnostic criteria for most anxiety disorders; perhaps the most substantial change was eliminating the requirement that a patient have insight that their anxiety is "excessive." Instead, the focus is placed on the frequency of the worry and degree of impairment it causes.

Specific Diagnoses

Neurocognitive disorder with features of anxiety Anxiety is common in the setting of neurocognitive disorder. In this clinical context, preexisting anxiety disorders may be altered in character or sometimes exacerbated and new-on set anxiety symptoms may arise. Degeneration in various brain regions has been implicated, including the dorsolateral prefrontal cortex, which is involved in modulating the anxious response. A bidirectional effect has been well established in this clinical setting: cognitive impairment tends to worsen anxiety symptoms and anxiety tends to worsen cognition. Just as neurocognitive disorder in the setting of a depressive episode is known to often portend the development of a neurocognitive disorder, so too can new-onset late-life anxiety be a prodrome of neurocognitive disorder. Parkinson disease, with its subcortical pattern of neurodegeneration and characteristic autonomic dysfunction, has been of particular interest because of its high association with not only anxiety but also depressive symptoms. Interestingly, PTSD has been shown to be a risk factor for neurocognitive disorder. Unfortunately, as a person's neurocognitive disorder progresses, the benefits of previous successful psychotherapeutic treatment may be lost and problematic symptoms may reemerge. Cognitive declines may result in loss of previously mastered coping strategies. For example, loss of inhibitory control in an individual suffering from PTSD can result in a return of anxious rumination about past traumas.

Depressive disorder with features of anxiety Approximately 25% of all older individuals with an anxiety disorder also suffer from MDD, while nearly 50% of older individuals with MDD also suffer from an anxiety disorder. In some individuals, anxiety may be of clinical significance only during depressive episodes, but in others the anxiety is chronic and seems to be an independent risk factor for developing late-life MDD. Those who suffer with both GAD and MDD may be more difficult to treat successfully. Fortunately, in many cases, when depression is properly treated, patients will experience an improvement or even remission of anxiety.

Generalized anxiety disorder GAD represents the extreme on the continuum of human anxiety. The core feature is excessive, uncontrollable, an often irrational worry about a broad range of life circumstances. In older individuals the focus of anxiety is often related to their own health, including fears of memory loss and death. Worries also commonly include the health of loved ones, finances, falls, and loss of independence. The worries are also accompanied by physical symptoms such as muscle tension, insomnia, irritability, restlessness, being easily fatigued, and difficulty concentrating. The worries severely interfere with the patient's ability to function and, as a result, many people become more isolative and limit social and other activities.

When evaluating for GAD, it is important to ask about a broad array of age-appropriate topics that might be a source of anxiety, such as health and finances. With the patient's permission, interviewing friends and family may help to determine if the worry is substantially adversely affecting life quality and to obtain confirmation regarding the frequency and severity of symptoms. If new-onset GAD is suspected, it is recommended that the clinician also check closely for signs of a depressive disorder, as GAD-like anxiety can be a prominent feature of a major depressive episode. GAD is particularly important to diagnose and treat, as it is one of the least likely mental illnesses to spontaneously remit.

Panic disorder A panic attack is a brief, time-limited, well-circumscribed period of autonomic hyperarousal accompanied by physical symptoms (chest pain or palpitations, sweating, tremor) and cognitive symptoms (fear of imminent death or "losing control"). An individual who suffers repeat panic attacks and who develops a fear of future events as well as avoid situations which they associate with panic is said to suffer from PD. Fortunately, PD rarely develops after the age of 65, and, as previously noted panic attacks tend to be less severe. If an individual does develop

panic attacks after the age of 65 there is a substantial chance the panic symptoms are related to a medical condition, such as Parkinson disease, exacerbations of asthma, COPD, or angina.

Agoraphobia Agoraphobia literally means "fear of the marketplace" and an individual suffering from this disorder tends to avoid public places because of fear they will be unable to escape should they develop a panic attack or other embarrassing symptoms (such as incontinence). The condition often develops after an event which the sufferer interprets as being traumatic, such as a myocardial infarction or fall-related injury. Stroke has been associated with late-life onset of agoraphobia. In DSM editions prior to the DSM-5, agoraphobia was linked with panic disorder, but this is no longer the case. In DSM-5 the two are now recognized as distinct, but often overlapping, entities.

Posttraumatic stress disorder Following exposure to a traumatic (generally life-threatening) stressor, the development of specific, characteristic symptoms defines PTSD. Briefly, the affected individual involuntarily reexperiences the event (via thoughts, flashbacks, or dreams), avoids situations that induce memories of the event (but may also experience generalized detachment from life), and develops abnormal symptoms of arousal/reactivity, such as an exaggerated startle response or irritability.

Compared to the general population, older adults are less likely to meet the full criteria for PTSD; in particular, fewer symptoms of hyperarousal and avoidance have been noted. Life events associated with aging, such as the death of a spouse, financial and physical decline, and chronic pain may cause reemergence of quiescent symptoms of PTSD (called "delayed PTSD").

Obsessive-compulsive disorder Unwanted, persistent obsessions and their repetitive, often ritualized compulsive responses form the core of OCD. Most cases of geriatric OCD represent a continuation of an illness that most commonly has an onset in the teen years; in other words, new-onset of OCD is quite rare in the geriatric population. Interestingly, brain lesions, especially in the basal ganglia, have been detected in those rare individuals who develop late-onset OCD, suggesting neurodegeneration and other brain injury as possible mechanisms.

Social anxiety disorder and illness anxiety disorder A fear of negative evaluation and the anxiety, avoidance, and other responses to social situations that follow characterize social anxiety disorder (SAD). SAD appears to decrease slightly in prevalence with age, as do the precipitating circumstances. Common concerns include incontinence, anxiety related to poor hearing or because of problems remembering people's names, and embarrassment about personal appearance. Illness anxiety disorder, previously referred to as hypochondriasis, is characterized by worry about having a serious illness. One study has shown it to affect about 3% of the visitors to primary care settings. Individuals are often unconvinced by their physician's reassurances that, in fact, they do not have such an illness.

Specific phobias and other specified anxiety disorder The essence of a specific phobia is fear or anxiety about circumscribed objects or situations that is out of proportion to the actual risk posed, coupled with avoidance behavior. Other specified anxiety disorder is diagnosed when the anxiety features do not meet full criteria for a specific anxiety disorder, such as panic attacks with fewer than four (of the possible 13) associated symptoms. Unspecified anxiety disorder (previously "anxiety disorder NOS") is most commonly given when an anxiety disorder is suspected, but further information and work-up would be needed to arrive at a more conclusive diagnosis (such as in emergency room settings). Adjustment disorder, with anxiety, should be diagnosed when the reaction to a stressor is out of proportion to the reaction that would normally be expected.

Overview of Treatment

Psychotherapy is mentioned here first because, while it requires more time to administer and may present additional difficulties in the geriatric population, it is largely free of adverse side effects. The most rigorously studied modality is cognitive behavioral therapy (CBT). However, while the CBT literature consistently documents a positive response relative to no treatment, response rates in the older population, generally, are lower than for younger adults. Further, there is no consistent evidence that CBT provides greater benefit than other therapy modalities (eg, supportive therapy). Psychotherapy represents the prominent mode of treatment of agoraphobia, social anxiety disorder, and illness anxiety disorder, and is used in conjunction with pharmacotherapy in the treatment of other anxiety disorders. Complementary therapy is also useful and largely without adverse side effect; examples include biofeedback, progressive relaxation, acupuncture, yoga, massage therapy, art, music, dance therapy, meditation, prayer, and spiritual counseling. A phobia of falling is first treated by accurately assessing the risk of falls and instituting fall-risk precautions, as well as vision optimization, weight-bearing exercise, and balance training such as Tai Chi.

In terms of pharmacologic management, the treating clinician should first consider which of the patient's

medications might be removed. Older patients are particularly at risk for various forms of suboptimal prescribing, including unnecessary polypharmacy which, even in the absence of agents well-known to cause anxiety, may provoke subclinical delirium and associated anxiety symptoms. For example, a patient with overactive bladder suffering from anxiety might first be treated by testing the efficacy of a decreased dose of oxybutynin before prescribing an anxiolytic medication.

The cornerstone of pharmacologic treatment is similar across anxiety disorders. Current evidence most strongly supports the use of an SSRI or SNRI at a dose higher than would be usually used to treat a depressive disorder. The recommended starting dose in geriatric individuals is generally half that recommended for a younger adult. The maximal antianxiety effect of an SSRI generally is achieved after 6 to 12 months of treatment with a therapeutic dose. In treating GAD, there is some evidence that buspirone is effective, but generally requires 2 to 4 weeks to reach maximal efficacy. Gabapentin, and to a lesser extent pregabalin, have also been studied and appear to be helpful. These medications can be given on a PRN basis, have little habit-forming potential, and also possess analgesic properties. Panic disorder is typically treated with a high-dose SSRI combined with psychotherapy (typically CBT and exposure therapy). Surprisingly few rigorous studies of pharmacologic treatment of PTSD have been conducted in older adults. Evidence of efficacy has been shown in individual studies of citalopram, mirtazapine, and, for sleep-related PTSD problems only, prazosin. Caution is advised with the use of tricyclic antidepressants (TCAs), given their known cardiotoxicity and anticholinergic side effects (confusion, sedation). Benzodiazepines are also to be used with great caution in older patients, given their negative impact on cognition, tendency to cause physiologic dependence, increased risk of falls, and risk of driving impairment. Prescribing benzodiazepines as a knee-jerk reaction to a complaint of anxiety also can reinforce a message to patients that anxiety must be immediately relieved. If benzodiazepines are used, there is only infrequently an indication to continue for more than 6 weeks. In addition to drug-drug interactions, SSRIs carry risks of hyponatremia, bleeding (particularly gastrointestinal [GI] bleeding, and especially when used in conjunction with an nonsteroidal anti-inflammatory drug [NSAID]), and may rarely cause parkinsonism and akathisia.

SUBSTANCE USE DISORDERS

Introduction

As the younger population cohorts age, prevalence of substance use will increase. Some estimates indicate about 60% use of alcohol, 2.6% use of marijuana, and 0.41% use of cocaine in those above the age of 50. Additionally, while marijuana use accounted for about 0.7% of those above the age of 65, those between 50 and 64 had about 4% use. Even more concerning is the prediction that by 2020 there will be 2.7 million prescription drug abusers among those who are older. While stimulants and other substances have not been examined closely in the older population, some estimates place cocaine use at 0.41%, inhalants at 0.11%, hallucinogens at 0.10%, and methamphetamine at 0.11%. These studies suggest a gradual increase in prevalence rates of drug misuse as younger cohorts age. The overall impact on the health care system includes that by 2020 an estimated 4.4 million older individuals will need treatment of substance abuse. Unfortunately, this rise in need has not led to increasing emphasis on substance treatment for older adults. Among the many suggested reasons for this are ageism and the associated inaccurate beliefs that the prevalence of substance use among the aging population is low and that the exploration of possible alcohol and substance misuse is not routinely indicated in older adults.

Alcohol Misuse

This section focuses mostly on alcohol misuse because alcohol is the most misused substance, the most well-studied substance, and the substance most associated with an increased rate of other substance use in the older population. The National Institute on Alcohol Abuse and Alcoholism recommends no more than two drinks in one sitting for older adults. This means that those who use eight or more drinks per week would be considered at-risk for alcohol misuse. Approximately 10% to 15% of men and 5% to 7% of women above the age of 65 drink more than one drink per day in a given week. Research also indicates that these individuals also may suffer from associated mental health issues such as depression and anxiety. The impact of alcohol on the aging body cannot be underestimated. Older adults experience significantly higher blood alcohol concentrations from a given quantity of alcohol as compared to younger adults and so what is considered an appropriate or safe amount of alcohol use significantly decreases as we age. In addition to the normal age-associated physical and physiologic changes, the higher rate of comorbid medical issues

and the greater use of various medications in older adults, also significantly increase the risk for serious adverse consequences from alcohol consumption.

Screening for alcohol use must begin with low index of suspicion by clinicians in the context of a thorough medical and psychiatric history and physical. Special attention should be paid to the onset of use, the current and past use pattern, the frequency of use, the indications for tolerance, and any evidence of withdrawal symptoms. Collateral information from family members or significant others is extremely important as older adults may not report accurate alcohol use patterns due to impairment from use itself or from cognitive deficits. Physical signs of excessive alcohol such as an enlarged or tender liver, bilateral symmetric tremor of the hands especially when the arms are extended, or changes in the skin such as red palms or acne rosacea, the latter of which is not caused by alcohol use but may be significantly worsened by alcohol. Helpful laboratory tests include elevated mean corpuscular volume, γ-glutamyl transpeptidase level, and aspartate aminotransferase levels. For chronic use, elevated carbohydrate-deficient transferase, serum uric acid, and decreased albumin levels are often seen. The CAGE questionnaire for alcohol use has some variable sensitivity and specificity in older adults. Better questionnaire tools include the Short Michigan Alcohol Screening Test—Geriatric Version (SMAST-G) and the Alcohol Use Disorders Identification Test (AUDIT). Both are 10-item screening tools that have been validated in older adults.

Isolated, often binge, alcohol use can lead to increased falls, confusion, poor executive functioning, and other traumatic events. Long-term, chronic use can lead to multiple organ system damage. It is important to note that alcohol use in older adults often accompanies depression and anxiety. In fact, often alcohol use treatment must take into account concurrent mental health disorder treatment. Notably, alcohol use is the second most common category of psychiatric risk for suicide attempts and completions. Additional consequences of alcohol use are sleep pattern changes and both short-term (blackouts) and long-term (dementia) cognitive deficits.

The best treatments for alcohol misuse are prevention, early screening, and early intervention. If formal treatment is indicated, a combination of nonpharmacologic and pharmacologic treatment routes should be considered. Unfortunately, older age–specific studies of nonpharmacologic interventions for alcohol misuse have been characterized by small sample sizes and have yielded unclear outcomes. Even long-tested 12-step programs may have variable outcomes for older adults. Pharmacologic options for alcohol abuse are designed to either decrease craving or negatively reinforce use so that individuals can reduce or abstain from use. Naltrexone is an opioid-receptor antagonist that decreases craving by attenuating pleasure derived from alcohol use. Acamprosate is thought to function by affecting the reward pathway in the brain. Disulfiram inhibits aldehyde dehydrogenase leading to uncomfortable accumulation of acetaldehyde and is often used in younger adults to discourage alcohol consumptions (ie, establish an association between use and significant physical discomfort). Disulfiram, however, is seldom used in older adults due to potential side effects such as significant changes in blood pressure and heart rhythm that can complicate heart disease and a number of significant drug-drug interactions due to inhibition of the metabolism of a number of medications including warfarin, phenytoin, isoniazid, and some benzodiazepines (eg, diazepam).

Perhaps the most important aspect of alcohol misuse management in older adults is the accurate recognition and appropriate treatment of withdrawal. Alcohol withdrawal is especially dangerous in older patients due to the increased likelihood of seizures, irreversible damage to the brain, delirium, and other potential clinical consequences of alcohol withdrawal. In the context of possible alcohol withdrawal, clinical assessment must be detailed and special attention must be paid to comorbid medical conditions and associated medication use. Supportive therapy to replace volume loss, correct electrolyte abnormalities, prevent falls, and correct vitamin deficiencies must be initiated immediately. The standard of care regarding medication to mitigate withdrawal symptoms and to prevent delirium tremens is a benzodiazepine. Unlike in younger adults, chlordiazepoxide is not the preferred or common choice among benzodiazepines. Lorazepam, oxazepam, or temazepam are preferred for older patients due to their intermediate half-life, relatively low lipid solubility which minimizes undesirable accumulation in the lipid compartment and their major biotransformation pathway of conjugation with glucuronic acid resulting in 70% to 75% of the administered dose being excreted as the glucuronide conjugate in the urine. This last characteristic allows for their use even in patients with severe hepatic dysfunction. Even with these advantages for the older patient, the use of one of these benzodiazepines must proceed with great care in order to avoid compounding the problems of withdrawal by increasing risks associated with oversedation and delirium including falls and respiratory sedation. The combined effect of the benzodiazepine with other medications being used by the older patient must be continuously assessed.

Benzodiazepine Misuse

While benzodiazepines are integral in treatment for alcohol withdrawal, they are also highly abused and misused in the

older population. Commonly they are overprescribed and dosed above amount required for the indication for use. Even when initially started at low doses, often they are continued without a definitive end point of use and this leads to tolerance. The most common reason for benzodiazepine prescription is insomnia which accounts for up to 59% of all prescriptions. The causes of and potential contributors to insomnia in older adults are legion and include gender (higher risk for women), social status (single relationship status, widowed or divorced), medical (multiple medical conditions or dementia), polypharmacy, poor sleep hygiene, and mood disturbances. Despite these multiple possible etiology of insomnia, benzodiazepines are often used as the first-line agent for sleep complaints. The second most common reason for benzodiazepine prescription is for the treatment of anxiety.

As with insomnia, causes of anxiety are often multifactorial and benzodiazepines are not the ideal treatment in most instances. Furthermore, despite antidepressants being the long-term medication treatment of choice for anxiety disorders, more than 50% of prescriptions for anxiety disorders are benzodiazepines. Over time many patients require ever increasing doses to achieve anxiety symptom abatement which leads to complications, adverse events, and ultimately the potential for dependence. Just like in the case of alcohol misuse, older adults have increased sensitivity to benzodiazepines. Generally, benzodiazepine metabolism is significantly slower in older adults. The risk for cognitive impairment, delirium, falls, sedation, and other unwanted effects are elevated. With physiologic dependence setting in, benzodiazepine withdrawal mimics that of alcohol withdrawal and puts the older adult at similar risk as that of alcohol misuse. The evaluation and treatment of benzodiazepine withdrawal is virtually identical to that of alcohol withdrawal. To prevent benzodiazepine overuse, misuse, and complications, it is highly recommended that the clinician carefully elicits the etiology of the sleep or anxiety complaints as there are much safer treatment alternatives than benzodiazepine.

Opiate Misuse

A disturbing trend in the United States is opiate pain medication misuse. It is estimated that over 11% of older adults use opiates on regular basis and opiate use accounts for 22% of inpatient admissions that are related to substance misuse. By far the most common rationale for opiate use is the treatment of chronic pain. Although undertreatment of pain continues to be problem for older adults, there is no evidence that sustained, long-term use of opiate family pain medications lead to better outcomes. Furthermore, as older adults are very sensitive to medications, opiate misuse often causes sedation, constipation, cognitive impairment, and respiratory suppression, especially in context of polypharmacy and concurrent alcohol use.

The best treatment for opiate misuse is prevention by utilizing alternative treatments for pain in older adults. These alternative treatments can be tailored to each patient by examining the causes for the pain complaints and by not treating pain as a single entity unto itself. Even the medication alternatives to opiates for pain control also have potential serious adverse reactions and side effects. For example, overuse of NSAIDs can lead to gastropathies and tricyclic antidepressants and are not well-tolerated in the older population. Considering acetaminophen as the first-line agent for pain control is recommended. Additionally, consideration should be given to SNRIs, gabapentin, and pregabalin as treatments for chronic pain. In context of opiate dependence, the clinician is advised to consider community substance abuse programs that include peer support and educational groups. The use of methadone, naltrexone, and buprenorphine as treatment for opiate dependence has not been well studied in the older population.

Misuse of Other Substances

Some important other substances which are misused in older patients include nicotine and marijuana. Despite widespread cigarette smoking prevention and cessation efforts, among older adults, misconceptions about nicotine use persist. For example, some continue to believe that in older adults, smoking cessation does not yield any benefit, and that smoking can help with pain, mood, and cognition. None of these are validated nor should be reasons to omit screening for smoke cessation when caring for an older adult. Another aspect to keep in mind is that smoking is commonly related to comorbid anxiety and other substance misuse. Behavioral modifications can be very helpful for smoking cessation. Pharmacologic methods for cessation include nicotine replacement therapy and medications designed to impact the reward pathway for smoking. Bupropion and varenicline have good evidence for smoking cessation in adults but evidence for their effectiveness in older adults is lacking. If bupropion is prescribed as a smoking cessation aid, it is important to keep in mind this medication's potential mood elevating and activating properties which can lead to increased anxiety symptoms in some patients. For varenicline, there is a widely publicized negative effect on mood and potential to increase suicidal behavior. With a high prevalence rate of co-occurring anxiety and depression in older adults with substance use issues, it is important that varenicline's potential negative

effects on mood and suicidal behavior are closely monitored by the clinician.

Marijuana use is expected to increase in older adults. A prevalence rate of up to 23% in those aged 50 to 64 has been reported and was found to be related to higher mental health distress. There does not seem to be sharp drop-off in use pattern as this group ages and so it is likely that prevalence of marijuana use will increase in older adults and will likely be compounded by the increasing movement toward marijuana legalization in the United States. In the older adult population, the full, overall health impact of casual or chronic marijuana use has yet to be determined but recent studies indicate that marijuana ultimately negatively impacts cognitive functioning and, despite speculation, there is no strong evidence to support the belief that it can serve as effective treatment for dementia. There are also some studies that indicate increased respiratory issues with chronic marijuana use and possible increased risk for myocardial infarction in the older population. At this time, ultimately, the clinician is recommended to screen for and provide support for possible marijuana use in the older adult.

PERSONALITY DISORDERS

Research in personality and personality pathology in older cohorts is an emerging field primarily driven by the increasing number of older individuals, but already some patterns and key findings have emerged. Personality traits are enduring, consistent behaviors forming a unique profile that distinguishes individuals from each other and predicts an individual's response to experiences or stressors. These traits are apparent as older adults respond to normal milestones and pathology associated with aging. Because personalities are defined by long-standing patterns of behavior, global personality and personality structure tend to remain stable with aging, however, neurologic or degenerative disease and brain injury in addition to positive changes associated with aging can lead to observed personality changes and shifts. For example, traits such as neuroticism, extraversion, and openness tend to decrease with age while altruism and conscientiousness increase with age.

Personality disorders are organized into three groups or clusters in the DSM-5. Cluster A disorders include paranoid, schizoid, and schizotypal personality disorders. They are characterized by bizarre, eccentric behavior, and magical or delusional-type thinking. Cluster B disorders are characterized by impulsive behaviors, interpersonal instability, and unstable or labile effect. The cluster B disorders include antisocial, borderline, histrionic, and narcissistic personality disorders. The cluster C disorders are avoidant, dependent, and obsessive-compulsive personality disorders. Disorders in this cluster are driven by an anxious diathesis that leads to worry, fear, rigidity, and isolation.

The prevalence of personality disorders in the general adult population ranges from 3% to 13%, and prevalence rates in older adults is, overall, slightly lower than that in younger adults. In certain geriatric subpopulations, however, the prevalence may be higher. For example, in geriatric patients with major depressive disorders and dysthymia, up to a third also have a personality disorder, most commonly avoidant, dependent, or other cluster C disorders and traits. In older adults, the odd traits associated with cluster A personality disorder and the anxious behaviors of cluster C personality disorders are more common than the impulsive behaviors seen in cluster B personality disorders, which are more common in younger adults. Of those older adults in the psychiatric outpatient population, anywhere from 5% to 30% meet criteria for personality disorder. Rates increase in geriatric patients receiving inpatient mental health treatment with prevalence rates ranging from 7% to 80%. In some cases, the impact and severity of symptoms in those with a known diagnosis of a personality disorder may worsen later in life. For example, an exacerbation of symptoms and behaviors may occur in the setting of significant social stressors such as the loss of a supporting person or other stabilizing environmental factors such as a job. Currently, prevalence data in older age groups is limited by the current methods and assessment tools used in epidemiologic studies directed at personality and personality disorders, which may inadequately correlate to the specific behaviors in older individuals. Further research in and attention to this emerging field is needed to better understand the manifestation of traits and diagnosis of personality disorder in older adults. Additional disorders outside of this classification system include personality change due to another medical condition, other specified personality disorder, and unspecified personality disorder.

In the DSM-5, personality disorders are defined as "an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture." This definition suggests a chronic course of long-standing, maladaptive coping behaviors with typical onset in adolescence or early adulthood that may persist into later life stages. The diagnosis of a personality disorder in an older adult requires integrating multiple sources of information such as patient information and medical history, self-reported autobiographical history, self-description, collateral from peers, family, supports or other informants, clinical observation of exhibited behaviors and patterns of

coping. Structured interviews or personality questionnaires may also aid in the diagnosis and synthesizing a formulation of personality and behavior patterns.

The diagnosis of a personality disorder can be challenging in presence of an exacerbation of acute psychiatric symptoms especially in the setting of limited history or collateral. For example, maladaptive coping behaviors and traits observed in an individual with a mood or anxiety disorder may be symptoms of the mental illness. In this case, further history or resolution of the behaviors or traits with treatment of the underlying mental illness may help clarify the diagnosis. Making a distinction between functional impairments due to psychological or environmental factors associated with aging and impairments resulting from personality pathology may further complicate assessment and diagnosis of a personality disorder.

Borderline personality disorder (BPD) is a commonly encountered challenge in primary care and mental health settings with high comorbidity associated with other psychiatric disorders, chronic pain, fibromyalgia, and migraines. In addition, it is associated with worse outcomes in the treatment of other comorbid psychiatric illnesses. The disorder is characterized by interpersonal instability that is not only present in their personal life and support systems but may also play out in the doctor-patient relationship through what is commonly referred to as transference and countertransference. Other traits include affective instability, emotional lability, impulsive behavior, identify disturbance, fear of abandonment, and feelings of emptiness or other dissociative symptoms. The etiology is often multifactorial including genetic vulnerability, brain abnormalities, developmental arrests, and experiences early in life especially with respect to trauma, abuse, abandonment, and absence of secure attachments. Remission rates are relatively high compared to other personality disorders, however, relapses can occur. In addition, remission of diagnostic criteria does not necessarily correlate with functional improvement. Up to 80% of patients with BPD exhibit suicidal behavior, and 60% to 70% make suicide attempts. Although this suicidal behavior does not necessarily lead to completed suicide, it remains a significant cause of death in this population. In addition, the severity or potential lethality of suicide attempts may increase or escalate with subsequent attempts or suicidal behaviors. Manualized, structured therapy such as dialectical behavior therapy (DBT), transference-focused psychotherapy and mentalization-based therapy (MBT) are the mainstays of treatment. While symptom focused psychopharmacology can be a helpful adjunctive treatment, polypharmacy should be avoided when possible.

Geriatric patients with personality disorders are at greater risk of depression, suicide, cognitive impairment, and social isolation. Developing a treatment plan that addresses the symptoms, behaviors, and associated functional impairments is an essential part of recovery and wellness in this population. There are several approaches to the treatment of personality disorder and depending on the case, a multifactorial strategy may be warranted especially in complicated or treatment-resistant cases.

In the evaluation and diagnostic period, the first step is to identify and treat any comorbid primary psychiatric illnesses. This will help clarify the target symptoms and clarify the nature of more long-standing maladaptive behaviors in contrast to symptoms of a mental illness. Common diagnoses or comorbidities to consider in the differential diagnosis include mood or depressive disorders, anxiety disorders, late-onset schizophrenia, delusional disorder, and delirium. Medical comorbidities should also be considered and ruled out. Somatization is a common symptom encountered in personality disorders where physical symptoms and perceptions may be psychologically driven. If somatic symptoms persist even after medical conditions have been ruled out, consideration of an underlying personality disorder, somatization disorder, or other commonly comorbid condition such as fibromyalgia and their respective treatments may be warranted.

Given the chronic and pervasive nature of personality disorders, full remission may be unrealistic, but evidence-based treatments have been characterized that improve the severity of symptoms, decrease impairment, and provide insight. Research in older adults with personality disorders demonstrates that DBT and schema therapy are effective treatment options. Other possible therapies include CBT, interpersonal therapy (ITP), and problem-solving therapy (PST). The efficacy of therapy may be more limited in the setting of significant neurocognitive disorders with associated memory and executive functioning impairments.

Other effective behavioral interventions include the implementation of structure and clear boundaries. Clinicians can use aspects of the therapeutic treatment frame to set appropriate boundaries and limitations, schedule regular appointments to check in and prevent escalating crisis, and communicate with all providers to unify the treatment strategy and avoid common defenses such as splitting between members of the treatment team. Clear communication, minimizing polypharmacy, and learning how to respond to commonly encountered behaviors further enhances therapeutic rapport and positive treatment outcomes. The use of a behavior contract or treatment agreement is helpful especially when problem behaviors persist despite the aforementioned measures. This is a document drafted in conjunction with the patient where boundaries, expectations, treatment goals, and consequences to nonadherence are

agreed upon by the patient and the treatment team. Therapeutic power of a treatment agreement is increased if members of the patient's support system are allowed to read and then subsequently support its content. Signing such a document adds an additional level of clarity to boundary setting and commitment to the treatment.

Some studies also suggest improved outcomes with a combination of therapy and medications, which also speaks to the high rate of comorbidities between personality disorders and other psychiatric illness or diagnoses. When considering pharmacotherapy, strategies should consider targeting specific symptoms or the predominant presenting problems. Classes of medication to consider when targeting individual symptoms include second-generation antipsychotics, mood stabilizers, and serotonergic medications. Naltrexone and clonidine are used in the setting of self-mutilation and the associated impulsivity of this harmful, maladaptive behavior. Similar to treatment of any medical or psychiatric condition a geriatric patient, safe and effective pharmacotherapy accounts for compliance and risk for noncompliance, abuse potential, pharmacokinetics, pharmacodynamics, interactions with other medications, and effect on other age-specific comorbidities.

SUCCESSFUL AGING AND PSYCHIATRIC DISORDERS

As part of the trend toward ever increasing life expectancy and the unprecedented increase in the proportion of the population which is older, a new focus has been placed on what is now called "successful aging." The concept of "successful aging" stands in stark contrast to the deep rooted cultural and societal ageistic beliefs, which were discussed earlier and which affect our patients and how they may be perceived. The definition of "successful aging" and its determinants remain variable. The original model by Rowe and Kahn included three domains: absence of disease and disability, high cognitive and physical functioning, and active engagement with life. This model, however, has been criticized for its overemphasis on health and because it fails to account for many individuals who do not meet the Rowe and Kahn criteria for physical health and yet subjectively rate themselves as aging successfully and report a high degree of satisfaction in later life stages. Newer definitions of "successful aging" have been modified so that they apply to older individuals with and without medical and psychiatric morbidities. Qualitative studies of successful aging indicate that older adults consider the ability to adapt to circumstances and positive attitude toward the future as being more important than an absence of physical disease and disability. Investigations have revealed a paradox of aging: even as the physical health declines, self-rated successful aging and other indicators of psychosocial functioning improve in later life.

Neuroscience research during the past 15 years has demonstrated neuroplasticity of aging—that is, if there is optimal physical, cognitive, and social activity, development of new synapses, dendrites, blood vessels, and even neurons in specific regions such as dentate gyrus of the hippocampus can happen, in older animals and probably in humans. Clinical research supports a model in which positive psychological traits such as resilience, optimism, and social engagement interact with and feed into each individual's evaluation of the degree of well-being, and are a stronger predictor of outcomes such as self-rated successful aging than physical health. Moreover, several of these traits have been shown to have a positive effect on survival that rivals or exceeds that of well-established health risk factors such as smoking, hypertension, obesity, and sedentary lifestyle. One quality that has been reported to increase with age in some, but not all, studies, is wisdom, conceptualized as a complex trait associated with advanced cognitive and emotional development, which is experience-driven. Research on wisdom has only recently gained some interest among scientists, although the concept of wisdom dates back to ancient times. Despite variability among the different published definitions of wisdom, there are several common elements, including prosocial attitudes and behaviors (eg, compassion, empathy), social decision making, insight, decisiveness, acknowledgement of uncertainty, emotional regulation, openness to new experience, spirituality, and sense of humor. What unites these components is their utility for the self (eg, greater well-being) and for others (serving common good).

Successful aging is also seen in some people with serious mental illness. Studies have found that relative to their younger counterparts, middle-aged and older adults with schizophrenia tend to have better psychosocial functioning, including better adherence to medications and self-rated mental health, and lower prevalence of substance abuse and psychotic relapse. Survivor bias is not the primary explanation for this finding. A minority of older persons with schizophrenia experience sustained remission. Reported predictors of sustained remission include psychosocial support, early initiation of treatment, better premorbid functioning, and having been married.

Mental health and primary care providers have a unique opportunity to help promote "successful aging" by teaching patients and their family members principles of health, nutrition, and wellness and by facilitating improved quality of life by treating symptoms, improving function, and developing psychosocial interventions. Ongoing studies

of “successful aging” are continuing to clarify the definition and are focusing on findings that have clinical utility. Strategies to enhance successful aging include calorie restriction, physical exercise, stopping smoking and substance use, eating the so-called “super foods” (eg, broccoli, cabbage, cauliflower, spinach, vitamin E, curcumin) rich in antioxidants, and ensuring appropriate health care. Equally important are cognitive and psychological strategies such as developing positive attitudes and resilience, learning new skills, engaging in stimulating activities, and optimizing stress. An important principle to remember is that it is never too early or too late to start on the path to successful cognitive and emotional aging.

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Chapter 74

Management of Agitation in Dementia

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Learning Objectives

- Learn the epidemiology, pathophysiology, and common behavioral problems seen in patients with dementia.
- Understand the best approach to evaluate neuropsychiatric symptoms in patients with dementia, and effective strategies to manage such symptoms.
- Learn about the significance and efficacy of nonpharmacologic interventions and appropriate indications, limitations, and adverse effects of antipsychotic medications.
- Acquire a clear understanding of the important role that supportive care plays in reducing caregiver stress and improving behavioral symptoms in patients with dementia.

Key Clinical Points

1. **Behavioral symptoms are seen in up to 98% of patients with dementia and are the result of high-order loss of behavioral control and involvement of major neurobiological networks and neurotransmitters.**
2. **Patients with neuropsychiatric symptoms have higher mortality and progress more rapidly from mild to severe stages of dementia.**
3. **Careful history-taking is essential and exclusion of delirium is paramount for proper diagnosis and management of behavioral symptoms associated with dementia.**
4. **Onset of new behavioral symptoms in patients with dementia, especially systematized delusions should suggest onset of another psychiatric disorder, such as a major depressive disorder with psychotic features or schizophrenia.**
5. **Nonpharmacologic interventions should be the first-line treatment and antipsychotics should be avoided as much as possible, given their lack of efficacy in randomized trials and higher incidence of side effects.**
6. **Appropriate indications for antipsychotic medications include failure of nonpharmacologic therapies and presence of neuropsychiatric symptoms severe enough to interfere with the patient's overall quality of life and function.**

EPIDEMIOLOGY

Dementia is epidemic. It is a leading cause of disability in developed countries. Alzheimer Disease International estimates there were approximately 35.6 million individuals living with dementia worldwide in 2010. The number of people living with dementia worldwide is expected to approximately double every 20 years to 65.7 million in 2030 and 115.4 million in 2050. Seventy percent of dementia is due to Alzheimer disease (AD) and the Alzheimer's Association estimates there are 5.2 million Americans currently living with AD. Dementia can have grim effects on those afflicted with the syndrome, their families, and society.

Neuropsychiatric symptoms (NPS) are nearly universal in dementia, affecting up to 98% of individuals across

dementia stages and etiologies. NPS tend to persist over time. Around 80% of individuals with dementia at baseline demonstrate at least one symptom across an 18-month interval. Over time, the number of NPS increase with the most common symptoms being depression, apathy, agitation, and restlessness (75% of individuals with dementia will manifest at least one of these symptoms), followed by sundowning and verbal outbursts (50% of individuals will manifest one of these).

NPS are associated with increased morbidity and mortality, decline in cognition and function, increased rate of disease progression, earlier nursing home placement, and increased health care utilization. NPS are also associated with greater caregiver burden and negative caregiver outcomes such as depression, anxiety, increased stress, sleep disruption, medical illnesses, decreased employment, and increased mortality. Caregiver burden, in turn, significantly influences rate of institutionalization. Thirty percent of the cost of caring for community-dwelling individuals with dementia can be directly attributed to NPS management.

At least 20% of outpatients and 40% of long-term care residents exhibit disruptive symptoms such as agitation and aggression. These are commonly referred to as "dysexecutive" symptoms because of the higher-order (executive) loss of behavioral control. Manifestations include cursing, combativeness, irritability, disinhibition, restlessness, wandering, hyperactivity, and repetitive calling out. Agitation and aggression tend to co-occur with other NPS such as hallucinations, delusions, sleep disorders, anxiety, and depression.

PATHOPHYSIOLOGY OF NEUROPSYCHIATRIC SYMPTOMS

The Neuropsychiatric Syndromes of AD Professional Interest Group of the International Society to Advance Alzheimer's Research and Treatment recently described three major sets of neurobiological networks relevant to NPS in AD: frontal-subcortical networks (eg, dorsolateral prefrontal circuit, orbitofrontal prefrontal circuit, and a circuit involved in motivated behavior) mediating human behavior, corticocortical networks mediating emotional and cognitive processes, and the extensive ascending monoaminergic system. NPS have been associated with lesions involving the brain's white matter tracks (which act as relay stations between the structures) in these networks. For instance, disinhibition and apathy are observed with frontal-subcortical circuit lesions, even when the lesion is distant from the frontal cortex. Dysfunction in the projections of excitatory and inhibitory interneurons from the brain stem to cortical regions modulating monoamines (dopamine, serotonin, and norepinephrine), glutamate, and acetylcholine, can contribute to NPS. For instance, agitation and aggression in AD has been associated with cortical dysfunction in the insula, amygdala, anterior cingulate gyrus, hippocampus, middle frontal gyrus, lateral frontal gyrus, and lateral temporal gyrus; these behaviors may be related to deficits in acetylcholine neurotransmission. Similarly, prominent aggressive behavior in patients with AD has been associated with loss of serotonin in the inferior frontal cortex. This may explain the moderate benefits seen with citalopram, a selective serotonin reuptake inhibitor (SSRI) (see later). Striatal dopamine (D2/D3) receptor binding availability has been associated with severity of delusions and disinhibition in patients with AD to an extent comparable to what is observed in patients with schizophrenia who are drug-naïve. Aggressive behavior has also been associated with upregulation of α_1-adrenoceptors in the prefrontal cortex. Prazosin, a norepinephrine antagonist at postsynaptic α_1-adrenoreceptors, improved behavioral symptoms in one clinical trial of patients with AD with agitation and aggression. Lesions do not tend to occur in isolation. It is likely that dysfunctions resulting from multiple lesions synergize to produce NPS.

Neuropsychiatric symptoms tend to cluster into distinct groups and various studies have explored the possibility of subsyndromes of NPS in AD. The Neuropsychiatric Inventory (NPI) and more recent Neuropsychiatric Inventory–Clinician Rating (NPI-C), the most commonly used measures of NPS, have helped elucidate these clusters. Relevant domains on the NPI-C for agitation and aggression include disinhibition, aggression, aberrant vocalizations, and aberrant motor behavior. In the Cache County Memory Study which identified individuals with AD within a cohort of elders, three groups of symptom constellations were identified using the NPI: primarily affective syndrome (28%), monosymptomatic disturbance (19%; mostly delusions), and primarily psychotic syndrome (13%). Forty percent of the individuals had no symptoms at the cross-section studied. These groups may represent distinct phenotypes of AD with their own genetic basis, as seems to be the case with psychosis. The practical implications of this body of research include an improved understanding of the neurobiology of NPS with eventual tailoring of treatment to specific subsyndromes of distinct neurobiology.

NEUROPSYCHIATRIC SYMPTOMS AND DISEASE PROGRESSION

Neuropsychiatric symptoms have been correlated with disease progression in AD. Among individuals with incident AD in the Cache County Memory Study, agitation/aggression, psychosis, affective symptoms, mild symptomatic neuropsychiatric symptoms, and clinically significant neuropsychiatric symptoms were associated with more rapid progression from mild AD to severe dementia and death. Similarly in the Predictors Study, individuals in early AD with agitation and restlessness had faster cognitive and/or functional decline compared to those without these symptoms. Some studies have found an association between genetic factors (most notably the APOE ε4 allele) and an increased risk of NPS (aggression, psychosis, and depression) in AD. However, the majority of studies have not demonstrated such a relationship. Whether there is an association between NPS and mortality remains debatable, although recent work from the Cache County Study suggests that agitation, affective symptoms, and psychosis in early dementia accelerate mortality. Additionally, it is unclear whether there is a causal relationship between NPS and disease severity, between interventions for NPS and disease severity, or whether symptoms and interventions interact to influence severity. Finally, whether pharmacologic or nonpharmacologic intervention targeting NPS influences the rate of progression of AD remains unknown.

DIAGNOSTIC APPROACH TO PATIENTS WITH NEW ONSET OF AGITATION

This section focuses on crucial aspects of the evaluation of a patient with dementia and agitation, such as taking a history, conducting a cognitive assessment, and using diagnostic tests. For a thorough discussion on evaluating a patient with dementia and agitation, including reasons for performing the evaluation, appropriate settings for an evaluation, and ways to communicate your recommendations to the patient and caregiver, please see *Practical Dementia Care* by Rabins, Lyketsos, and Steele (2006).

History-Taking

A thorough medical history is essential. A patient with dementia may have difficulty providing history due to language problems, memory impairment, nosognosia (lack of insight), agitation, and delusions. Thus it is essential to involve a reliable informant who knows the patient well during history-taking. Because informants can be influenced by personal factors such as depression or denial of the situation, it is often useful to speak with more than one informant to explain discrepancies between the history and the patient's evaluation. The clinician should try to date the onset of symptoms, elucidate whether the onset was insidious versus abrupt, clarify the frequency of the episodes and how long they last, and determine if they are precipitated or aggravated by any situations. For example:

- Do symptoms predominantly occur with care (bathing, grooming, toileting, feeding, or administering medications), in the evening and overnight, when a patient is left alone, or in unfamiliar situations?
- Was there a recent medication change or change in the patient's diet?
- Has the patient recently suffered a comorbid acute medical illness?

The clinician should also determine whether the agitated behavior is in fact an appropriate response to the situation. For example, the result of abuse or neglect. In these cases, it may be necessary to involve a local or state social services agency that serves adult populations to investigate the situation. Conversely, it is important to inquire if the caregivers feel they are at risk of being harmed by the patient. An important part of the history-taking is asking caregivers how behaviors are currently being managed and how patients respond to these interventions. As common causes of agitation include interpersonal or environmental triggers, the patient may present differently (for instance, appear more or less agitated or delusional) in the structured clinical setting compared to what has been described in the home environment. A differential diagnosis of common etiologies of agitation in patients with dementia is shown in **Table 74-1**.

TABLE 74-1 COMMON CAUSES OF AGITATION IN DEMENTIA

A change in behavior or delirium that results from a recurrent or new medical condition	• Constipation • Urinary infections • Upper respiratory infections and/or hypoxia • Decubitus ulcers

	• Full bladder • Uncontrolled or inadequate pain management • Fatigue • Excessive caffeine use • Poor dentition • Headaches • Recent stroke • Recent head trauma • Sleep disruption from poor sleep hygiene, sleep apnea, incontinence, or inadequately treated pain • Inadequate sleep • Immobility • Vision or hearing loss • Alcohol/substance withdrawal
Medication related	• Medication side effects (anticholinergics, benzodiazepines, opioids) • Drug-drug interactions • Accidental misuse, whether from new medications or previously prescribed medications • Medication-related electrolyte imbalances
Environmental stressor(s)	• Excessive noise or stimulation • Lack of structure or stimulation • Excessive heat or cold • New or unfamiliar surroundings • Disruption in the patient's daily routine
Unmet needs	• Hunger • Dehydration/thirst • Poor nutrition • Being left alone or feeling lonely
Inexperienced or intrusive caregiving	• Inadequate communication • Excessive hands-on care • Rushing the patient • Approaching from behind • Caregiver stress or burnout manifesting emotionally or physically
Aspects of the cognitive disturbance itself	• Inability to express oneself verbally due to aphasia • Fear due to agnosia—misinterpreting stimuli such as a shower for a torrential rain pour • Catastrophic reaction to minor provocation/stressor
An identifiable psychiatric syndrome that is either recurrent or associated with the dementia	• Disturbance of mood with irritability, anxiety, and/or dysphoria • Sleep deprivation/disorder • Reaction to delusions or hallucinations • Loss of executive control of behavior

Diagnostic Testing

Work-up using laboratory studies is needed in many cases of new-onset agitation in dementia, particularly to evaluate

for delirium and/or an underlying general medical cause. Work-up typically includes a metabolic panel, liver function tests, complete blood count, and urinalysis/culture. The clinician may consider additional tests such as thyroid function studies, folate and vitamin B_{12} levels, toxicology, and electrocardiogram. Chest radiography is indicated if respiratory symptoms are present. Brain imaging, such as computed tomography or magnetic resonance imaging, may be indicated in some cases, particularly if focal neurologic findings are present. Electroencephalogram and cerebrospinal fluid analysis are rarely needed but indicated if seizures or meningitis, respectively, are suspected.

Agitation and Delirium

Delirium is commonly seen in patients with dementia on account of their advanced age and decreased cognitive reserve. It is a frequent cause of acute onset or exacerbation of agitation. The hallmarks of delirium are a fluctuating disturbance in attention (eg, reduced ability to focus or sustain one's attention) and orientation that develops over a short period of time. The etiology of delirium is usually multifactorial with common causes including recurrent or new medical illnesses, electrolyte disturbances, and medication effects (eg, drug-drug interactions or side effects). Clinicians should maintain a high index of suspicion for delirium when assessing the patient with dementia who is agitated, and aggressively evaluate and treat underlying causes, particularly as delirium is associated with high mortality.

It can be especially challenging to diagnose delirium in the context of dementia because both syndromes can present with memory deficits, fluctuating attention and concentration, disorientation, language impairment, perceptual disturbances, or agitation. The rate of onset of the disturbances can differentiate between the two syndromes. An abrupt onset (hours to weeks) typically points to delirium while a more insidious decline (weeks to months) points to progression of dementia. In patients with AD, Mini Mental State Examination (MMSE) scores decline anywhere from one to three points per year. If a patient exhibits a sudden drop or fluctuation in score, the clinician should consider delirium in the differential diagnosis.

In the inpatient or nursing home setting, examining the hospital chart in detail can help determine whether delirium is present along with its underlying cause(s). Notes from the primary team, consults, and ancillary staff may describe fluctuating disturbances in attention, orientation, or agitation; acute on chronic medical problems; and laboratory abnormalities. The clinician should review current and recent medication lists, scrutinizing for recent changes, whether medications and dosages are appropriate for older adults and/or individuals with dementia, and investigating the possibility of drug-drug interactions. Of particular concern are medications with anticholinergic properties (**Table 74-2**), such as benzodiazepines/sedatives and narcotics, as these are commonly prescribed in to inpatients and can cause or exacerbate delirium. Assessment of delirium should include a physical and neurologic examination, and often includes laboratory studies and imaging as outlined in the earlier section, Diagnostic Testing.

TABLE 74-2 MEDICATIONS WITH ANTICHOLINERGIC ACTIVITY[a]

Amantadine (Symadine)
Benztropine (Cogentin)
Cyproheptadine (Periactin)
Digoxin (Lanoxin)
Diphenhydramine (Benadryl)
Dipyridamole (Persantine)
Doxylamine (Aldex, Doxytex, Nitetime Sleep-Aid, Sleep Aid, Unisom)
Furosemide (Lasix)
Hydroxyzine (Vistaril, Atarax)
Low-potency antipsychotics
Meclizine (Dramamine)
Metoclopramide (Reglan)
Oxybutynin (Ditropan)
Prochlorperazine (Compazine)
Promethazine (Phenergan)

Ranitidine (Zantac)
Scopolamine (Transderm-V)
Theophylline (Aerolate)
Tricyclic antidepressants

[a]Not an exhaustive list.

Once the underlying cause is corrected, a patient's mental status and behavior should improve, albeit some patients take a "cognitive hit" and do not return fully to their prior baseline. Delirium commonly persists well beyond (in some cases weeks to months) correction of the underlying cause. Short-term, low-dose use of oral or intravenous haloperidol or atypical antipsychotics can be considered for management of significant agitation in the context of delirium. Commonly used medications and starting doses include the following:

- Haloperidol (0.25–0.5 mg oral or intravenous every 6 hours as needed for agitation)
- Quetiapine (12.5–25 mg oral every 6 hours as needed for agitation)
- Olanzapine (2.5 mg oral or 1.25–2.5 mg intramuscular every 6 hours as needed for agitation)
- Risperidone (0.25–0.5 mg oral or intravenous every 6 hours as needed for agitation)

Agitation and Primary Psychiatric Disorders (Depression, Anxiety, and Psychotic Disorders)

Individuals with primary psychiatric disorders such as major depressive disorder, bipolar disorder, anxiety disorders, and schizophrenia can develop dementia superimposed on their psychiatric illnesses in later years. There are also late-onset forms of these disorders. Late-onset depression and anxiety are common among older adults (and among individuals with dementia) while late-onset bipolar disorder and schizophrenia are rare. In the latter cases, alternative diagnoses (eg, delirium and progression of dementia) should be sought. Psychiatric disorders can be associated with agitation, irritability, anxiety, and psychosis.

Depression

Up to 50% of individuals with dementia will suffer from depression over the course of their illness. It is probably the most common psychiatric symptom early in the course of dementia, affecting 29% of individuals, and tends to be underrecognized. Depression is associated with health care utilization, greater severity and acceleration of cognitive impairment, decreased quality of life for the affected individual and caregiver, and increased risk of suicide. Among individuals with AD, risk factors for depression include older age, female gender, and less education. Depression in individuals with dementia may go undetected because the symptoms they experience as part of a major depressive disorder can differ considerably from older individuals with normal cognition. Compared to cognitively normal older depressed individuals, those with AD and major depression have diminished ability to concentrate and/or indecisiveness, fewer sleep disturbances, a reduction in reported feelings of worthlessness or excessive guilt, while experiencing higher rates of delusions and hallucinations. Depression in dementia is more likely to present with agitation, irritability, and anxiety. Self-assessment screening tools such as the Geriatric Depression Scale or Patient Health Questionnaire 9 (PHQ-9) are less reliable in capturing depressive episodes in dementia because patients underreport due to inability to recall or lack of awareness of their depressive symptoms. Patients may have language impairment which further limits their ability to respond. Apathy, which affects up to 70% of individuals with mild-to-moderate AD and up to 90% individuals with late-stage AD, is often mistaken for depression. Screening tools that incorporate responses from other informants (eg, Cornell Scale for Depression in Dementia) may be more reliable. Cornell Scale scores above 12 typically require treatment while scores above 8 require close follow-up and possibly treatment. Clinicians should maintain a low index of suspicion for depression and initiating treatment. Nonpharmacologic interventions should be considered first line for treating most cases of depression in individuals with dementia. These interventions should target the patient and caregiver. Examples of interventions include encouraging patients to participate in activities and enrolling them in adult day care. Pharmacologic interventions should be considered if a patient does not improve with nonpharmacologic interventions or if a depressive episode is severe.

Anxiety Disorders

Anxiety disorders are relatively common in older adults and may be accompanied by agitation. They are often

associated with comorbid depression and tend to go unrecognized. The most common anxiety disorders include generalized anxiety disorder, panic disorder, and phobias. Patients with posttraumatic stress disorder may become agitated when reexperiencing traumatic and painful memories ("flashbacks"). These episodes may become difficult for patients with dementia to distinguish from reality due to cognitive impairment (eg short-term memory loss and disorientation) and because remote memory tends to be preserved until late in the course of many dementias. Clinicians should routinely inquire about a history of trauma when evaluating patients with dementia who are agitated.

Psychotic Symptoms

Psychotic symptoms, such as delusions and hallucinations, occur in 20% to 30% of patients with AD and in over 50% of patients with dementia with Lewy bodies (DLB) or Parkinson disease dementia. They may cause distress for the patient (and caregiver), and often contribute to the development of agitation. Delusions tend to be more common than hallucinations in AD and are often cognitively based. For instance, memory deficits may lead to the fixed and false belief that a misplaced object was stolen. A patient with agnosia (failure to recognize the identity of an object or person despite intact perceptual abilities) may misidentify individuals or objects such as their homes. Less commonly, patients may develop delusions that they are being poisoned or that their partners have been unfaithful. Grandiose, nihilistic, bizarre, or systematized delusions are uncommon in AD. They should cue the clinician to the development or recurrence of another psychiatric disorder, such as schizophrenia or major depressive disorder with psychotic features. Unlike in schizophrenia, in AD, hallucinations are more likely to be visual than auditory. They tend to occur in the moderate-to-severe stages of dementia. In many circumstances, auditory hallucinations do not cause distress to the patient and as such, do not need to be treated pharmacologically. Visual hallucinations are more common in DLB than AD and may be the most clinically useful feature to distinguish DLB from AD. Hallucinations tend to be well-formed images of people, animal, or objects, but can be as simple as shapes in the corner of one's eye. While they can occur at any time, they are more common at night. Typically, hallucinations in DLB are not distressing unless they are accompanied by delusions or occur in severely demented individuals. Of note, many medications used to treat Parkinson disease, such as anticholinergic agents, amantadine, dopaminergic agents, and catechol-*O*-methyl transferase (COMT) inhibitors, can exacerbate visual hallucinations and delusions.

DEMENTIA CARE MODELS

Effective, systematic care models exist for patients with dementia and often revolve around a team approach. An optimal dementia care team often includes a clinician, occupational and physical therapists, nurse, psychologist, social worker, and case manager, working closely with the primary care physician and caregivers. Evidence from randomized trials indicate that "packages" of dementia care provide benefits to patients and caregivers in terms of improving quality of care and life, reduction of NPS, and reduction of caregiver burden, unmet needs, and depression. These improvements are in part a result of more appropriate use of medications and interventions targeting both caregivers and patients. Caregiver-targeted interventions (eg, counseling and support programs) can prolong the time patients spend in the community.

Management of Agitation in Dementia

A useful approach, developed by Kales, Gitlin, and Lyketsos, for the management of agitation and other NPS in patients with dementia is "DICE" (Describe, Investigate, Create, and Evaluate).

Describe During this evaluation phase, informants (eg, the patient and caregivers) characterize in detail what is happening behaviorally. This helps identify underlying patterns that may be contributing to the behavior. Another important goal of this phase is to determine what behaviors are most disturbing for the patient and caregiver as well as the goals of treatment.

Investigate Here, the clinician examines the patient, orders laboratory tests and other diagnostic studies, and identifies underlying and modifiable factors. Such factors can include undiagnosed medical conditions (eg, pain, dehydration, constipation, infection, or sensory impairment), functional impairment (bathing, dressing, and toileting), medication side effects and drug-drug interactions, underlying psychiatric comorbidity (eg, depressive or psychotic disorders), functional limitations, poor sleep hygiene, psychological factors (inadequacy, boredom, helplessness, or fear), and environmental factors (over- or understimulating environment, diminished pleasurable activities, or lack of predictable

routine). Generally speaking, most disturbances are multifactorial and it is best to address several contributing factors simultaneously.

Create The patient, caregiver, and care team collaborate to develop and implement a treatment plan. The plan consists of behavioral strategies, environmental modifications, educating caregivers, and pharmacologic interventions targeting the identified causes of agitation and other NPS. For instance, a clinician may treat an underlying urinary tract infection while concomitantly teaching the caregiver not to rush a patient while urinating, and to use a combination of scheduled and prompted toileting for incontinence. The dementia care team may educate a caregiver about pureeing foods for patients with swallowing difficulties while simultaneously tapering daytime sedating medications that may increase the risk of aspiration. The treatment plan should target physical problems, functional deficits, underlying psychiatric conditions, safety concerns, and other environmental factors. Common physical problems that often need addressing include pain, constipation, dehydration, sedation and sleep disturbances, sensory impairment (visual, hearing, and gustatory impairments are commonly seen), and infections. A recent randomized controlled study found that a stepped pain management significantly reduced agitation in nursing home patients with dementia with an effect size similar to risperidone trials. The clinician may consider prescribing medications and/or discontinuing medications contributing to agitation and other NPS. Patients with functional deficits in bathing, dressing, and toileting frequently become agitated when others try to help them. Interventions may include person-centered showering (focusing on patient comfort and preferences) or in-bed sponge baths (particularly for individuals who cannot tolerate showers and their caregivers cannot assist them in and out of a bathtub). Patients with difficulty dressing do better with Velcro fasteners over buttons, zippers, or laces. The care team should address safety concerns such as removing weapons, placing safety devices on stove knobs, eliminating throw rugs, providing sufficient lighting, color coding doors and rooms, using safety alarms, encouraging identification bracelets or necklaces such as those offered by the Alzheimer's Association, and bolting doors with difficult-to-open key latches when necessary. Ultimately, continuous supervision is the best preventive measure. Caregivers should be educated about the importance of establishing structured routines and meaningful (and cognitively appropriate) activities for the patient. In instituting pharmacologic and nonpharmacologic management, it is useful to discuss with caregivers what has worked for the patient in the past and what has not. Taking into account the patient's and caregiver(s)' interests, the dementia care team can effectively tailor a patient-specific treatment plan. Team members assist caregivers by modeling problem solving, providing constructive feedback, offering emotional support, validating that what the caregiver is doing is important, and ensuring the caregiver is engaging in self-care.

Evaluate In this phase, the team assesses whether or not a caregiver attempted an intervention and whether it was effective. The team evaluates whether the intervention helped to decrease the behavior as well as the patient's and caregiver's distress, and whether there were any unintended side effects or consequences. In cases where the caregiver did not implement an intervention, the team should attempt to understand why not and think of alternative solutions with the caregiver. If the intervention included a psychotropic medication, the provider and caregiver should monitor behaviors and potential side effects over time, and consider tapering the dose or a discontinuation trial to ensure that the medication remains necessary.

The primary reason to treat disruptive agitation is to improve the quality of life for both the patient and caregiver. However, it is important that the dementia care team and caregiver discuss and set realistic expectations, particularly regarding the likelihood of target behaviors responding to an intervention. Total eradication of disruptive behaviors is achieved infrequently and often at the cost of adverse side effects. Certain behaviors respond better to pharmacologic interventions than others. In general, physically aggressive behaviors, irritability, auditory hallucinations, and delusions tend to respond better to pharmacologic intervention. Psychotropic medications are unlikely to improve aimless wandering, shadowing, inattention, repetitive vocalizations or questions, hoarding, poor self-care or refusal of care, memory problems, or behaviors attributable to apraxia or agnosia (eg, urinating in a flower pot because it resembles a toilet bowl).

Nonpharmacologic Interventions

The dementia care team should consider using nonpharmacologic interventions to treat agitation in patients with dementia as first-line therapy to avoid the risks and side effects associated with medications. An exception is emergency situations when agitation can compromise the safety of the patient or others in which case psychotropic use is part of the standard of care. Multiple small studies have shown modest improvement with music therapy, bright light therapy, aromatherapy, pet therapy, physical therapy, occupational therapy, exercise training, speech therapy, and

multisensory stimulation (snoezelen). These therapies are often useful during the treatment session but have not demonstrated longer-term benefits. Psychotherapy can be useful, particularly in patients with early dementia who are demoralized, depressed, or anxious. Behavioral monitoring log can provide sustained improvements in behavior in individuals with dementia by identifying triggers to avoid or manage. A key aspect is for caregivers to provide the patient with a stable environment with a stable, structured routine. The environment should avoid over- or understimulation. Behaviors such as distracting or redirecting the patient, removing physical objects that cue behaviors (eg, removing car keys if the caregiver wants to discourage driving), offering simple choices, or modifying the caretaker's interactions with the patient can be useful in decreasing agitation. For instance, caregivers should provide patients who tend to wander safe environment in which to do so. Educating caregivers and professional staff about how to deal with agitation and other NPS can reduce behavioral outbursts and restraint use. Interventions with the best evidence to support their use are outlined in **Table 74-3**.

TABLE 74-3 GENERAL NONPHARMACOLOGIC STRATEGIES FOR MANAGING AGITATION

DOMAIN	KEY STRATEGIES
Disorientation or confusion with object recognition	• Identify individuals if patient does not remember names or has aphasia • Use environmental cues (calendar showing current date, blinds raised during the day, lights off at night) • Use simple visual reminders (eg, arrows pointing to bathroom, paint doors to identify or disguise them) • Keep all objects for individual tasks in separate, labeled containers
Confusion/overwhelmed with tasks and environment	• Eliminate noise and distractions while patient is engaged in an activity • Break each task into very simple steps and provide one to two step simple verbal commands • Offer simple choices (no more than two at a time) • Remove unnecessary items from the room while patient is engaged in a task • Learn how to relax the rules (eg, a patient can wear the same clothes several days in a row). There is no right or wrong way to perform tasks as long as the patient and caregiver are safe • Provide daily, structured, and predictable routines • Inform patient of events as they occur
Wandering or inability to respond properly to an emergency	• Provide 24-hour supervision for the patient • Place locks on all exits • Develop an emergency plan. Inform neighbors, fire department, and police of patient's condition • Outfit with medical alert and safe return ID bracelets
Nighttime awakening, feeling insecure at night	• Evaluate environment for modifiable elements such as temperature, noise level, light, shadows, and bed comfort • Implement good sleep hygiene • Reduce caffeinated and alcoholic beverages that may affect sleep • Use a nightlight • Play calm music and engage in a calm activity prior to bedtime • Limit daytime napping • Hire nighttime assistance to allow caregiver to sleep
Repetitive questioning and following	• Use a relaxed and reassuring voice and light touch to calm or redirect • Avoid negative words and tone • Help patient with aphasia find the words to express him/herself • Allow patient sufficient time to respond to questions

	• Distract the patient as necessary • Understand that behaviors are not always intentional • Go along with patient's point of view of what is true. Avoid arguing or trying to reason
Boredom and restlessness	• Create a structured, daily schedule that includes entertainment and exercise and addresses loneliness and boredom • Provide meaningful activities that draw on preserved capabilities and interests • Engage patient in activities involving repetitive motion (eg, folding towels, putting buttons in containers)

Note: Strategies listed are potential approaches that have been used in randomized clinical trials but are not exhaustive. Some strategies will work more effectively for some patients than others. Only consider implementing the above strategies after conducting a thorough assessment and diagnostic work-up.
Adapted from Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA. 2012;308(19):2020–2029. Used with permission.

Regrettably, there are few controlled data to suggest that nonpharmacologic approaches work. Furthermore, these are often difficult to implement in real-world settings, especially in primary or institutional care. In a study of newly admitted nursing home residents, only 12% of residents received nonpharmacologic interventions within the first 3 months of admission, while 71% received at least one psychotropic medication. Moreover, more than 15% were taking four or more psychotropics. Sixty-four percent and 71% of residents treated with psychotropics had not received psychopharmacologic treatment or a psychiatric diagnosis, respectively, for the 6 months preceding admission.

Pharmacologic Interventions

Over time, medications often become a necessary and integral part of symptom management. Appropriate instances of use are when nonpharmacologic approaches have failed and/or when NPS rise to the level of severity that they affect the patient's quality of life or functioning, the caregiver's ability to care for the patient, or are dangerous. Clinicians should obtain informed consent of the patient or their legal representative, after discussing potential risks (including black box warnings of mortality in case of antipsychotics) and benefits. A useful and well-known maxim for managing medications in older patients is "start low and go slow." Medications should be slowly titrated using starting doses appropriate for older individuals and increasing to the minimum dose necessary to produce improvement in target symptoms. A good rule of thumb is to time the dose(s) to target difficult behaviors (eg, half an hour prior to bathing, dressing, or getting into a car). Clinicians should pay close attention to developing side effects (and educate the caregiver about what to look for) and potential worsening of cognition. We recommend reviewing the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. The clinician should be mindful of the following when initiating or changing medications:

1. Older patients have decreased renal clearance and slowed hepatic metabolism.
2. Older patients often have multiple medical illnesses and are on many medications. The clinician must evaluate for potential drug-drug interactions.
3. Due in part to decreased vascular tone, older patients are at increased risk of orthostasis and falls. Medications contributing to orthostasis should be used cautiously.
4. Deliriogenic medications (eg, anticholinergics and benzodiazepines) should be used sparingly.

There are no Food and Drug Administration (FDA)-approved medications for dementia-related agitation or other NPS. Clinicians continue to use psychotropics in treating agitation as the primary option despite their well-known safety and efficacy concerns. Furthermore, clinicians routinely prescribe psychotropics without systematically identifying potential underlying causes of behaviors. They may imprecisely pair a medication with a symptom that resembles a symptom of an illness. For instance, a clinician may decide to use an SSRI to treat a patient's reluctance to leave the house because the behavior resembles agoraphobia. Most dementias are progressive and NPS can fluctuate over time. Clinicians and caregivers may find themselves attempting to hit a moving target with medications. Clinicians and caregivers often try to manage several behaviors simultaneously, frequently with multiple medications, leading to unpredictable results. Various psychotropics cause side effects such as extrapyramidal symptoms that persist

for months following discontinuation of the medication. If medications are indicated, it is important to follow several guidelines as listed in **Table 74-4**. Sink et al. (2005) published a widely used algorithm for using medications to treat NPS in dementia.

TABLE 74-4 GUIDELINES FOR USE OF MEDICATIONS TO TREAT AGITATION

- Explore potential contributing factors to agitation. Consider the need for medical work-up.
- Define targets for intervention.
- Implement nonpharmacologic interventions concomitantly.
- Avoid knee-jerk prescribing of psychotropic medication in response to symptoms.
- Be mindful that isolated neuropsychiatric disturbances are unlikely to respond to medications.
- Use medications gingerly and sparingly, closely monitoring for adverse effects, particularly delirium, sedation, orthostasis, and falls.
- Change one medicine at a time to have a clearer picture of how it affects target symptom and to minimize adverse effects and drug-drug interactions.
- Start low and go slow. Use the minimum necessary dose to improve target symptoms.
- Time dose(s) to target difficult behaviors (eg, administer a dose half an hour prior to morning care).
- Psychotropic use should always be time limited, as symptoms may resolve spontaneously over time with or without pharmacologic treatment.
- Obtain informed consent prior to starting medications. Routinely review the risk-benefit ratio of treatment with patients and caregivers.
- Educate caregivers to inform the dementia team immediately should the patient experience an adverse drug reaction.
- Have a plan in place to deal with after-hours crisis.

Adapted from Gitlin LN, Kales HC, Lyketsos CG. Nonpharmacologic management of behavioral symptoms in dementia. JAMA. 2012;308(19):2020–2029. Used with permission.

Antipsychotics The use of conventional and atypical antipsychotics in patients with dementia remain controversial because their efficacy is modest and they have been associated with adverse effects (including rapid cognitive decline), a higher risk of cerebrovascular or cardiovascular events, and mortality. Several large retrospective cohort studies evaluating all-cause mortality of older individuals in outpatient settings or nursing homes have found higher mortality risk with haloperidol than with risperidone, olanzapine, aripiprazole, ziprasidone, or quetiapine. The highest risk of mortality appears to occur soon after therapy is initiated. Furthermore, there appears to be a dose-dependent relationship of mortality for haloperidol and atypical antipsychotics except quetiapine. The DART-AD trial demonstrated that there is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medication. As a result, the FDA issued a black box warning for the use of atypical (issued in 2005) and conventional (issued in 2008) antipsychotics in treating patients with dementia-related psychosis. Of note, the increased rate of all-cause mortality observed with antipsychotics has not been observed with various classes of antidepressants or with anticonvulsants. Centers for Medicare and Medicaid Services launched an initiative in 2012 aimed at enhancing person-centered care for nursing home residents, particularly those with dementia-related behaviors, by improving behavioral health and safeguarding residents from unnecessary antipsychotic drug use. Despite the above concerns, antipsychotic medications remain the core treatments of agitation and psychosis in dementia.

The Clinical Antipsychotic Trial of International Effectiveness—Alzheimer Disease (CATIE-AD) was designed to compare the efficacy of antipsychotics versus placebo in reducing psychotic symptoms or agitated/aggressive behavior in outpatients with AD. Risperidone and olanzapine showed the most, albeit modest, benefit of symptom reduction. There was no difference in time to discontinuation for any reason. Also, use of atypical antipsychotics over 36 weeks was associated with worsening cognitive function at a magnitude consistent with 1 year's deterioration compared with placebo. There were no apparent beneficial effects on measures of functional abilities, quality of life, or caregiving time needed. In the European Union, risperidone is approved for the short-term treatment of persistent aggression in patients with moderate-to-severe AD when there is risk of harm to self or others and the patient has not responded to nonpharmacologic approaches. Although antipsychotics are not contraindicated in dementia, the risk-to-benefit ratio is

high, and they should be used with caution.

Several randomized controlled trials have demonstrated that antipsychotics can be discontinued in individuals with dementia without a worsening of behavior. However, the antipsychotic discontinuation in AD trial found that after patients with AD and psychosis or agitation achieved and maintained treatment response with approximately 1 mg of risperidone for 4 to 8 months, patients rapidly relapsed compared to those who continued to take risperidone. Factors that predict successful discontinuation of antipsychotics include lower baseline severity of NPS and lower dosages of antipsychotics necessary to receive symptom control.

It is particularly challenging to prescribe antipsychotics for individuals with DLB as they are extremely sensitive to extrapyramidal side effects, with the exception of clozapine. Adverse events range from parkinsonian symptoms to acute dystonia to neuroleptic malignant syndrome. Clinicians should avoid conventional antipsychotics in patients with DLB. Similarly, while antipsychotics are often used to treat visual hallucinations and delusions associated with dementia in individuals with Parkinson disease, they need to be used cautiously due to the inherent risk of exacerbating extrapyramidal symptoms. Clozapine, especially, and quetiapine are the least likely to worsen parkinsonian symptoms.

Selective serotonin reuptake inhibitors There is growing evidence to suggest that SSRIs, such as sertraline, citalopram, and escitalopram are effective at treating depression, anxiety, agitation, and apathy in patients with Alzheimer dementia. Recent randomized controlled trials demonstrated that citalopram may be as effective as risperidone or perphenazine and more effective than placebo in hospitalized patients with dementia and NPS. In a recent 9-week, randomized, placebo-controlled trial, the Citalopram for Agitation in Alzheimer Disease (CitAD) Study evaluating 186 patients with probable AD and clinically significant agitation, patients treated with 30 mg of citalopram showed a clinically relevant, significant reduction of agitation compared to placebo on several rating scales. This improvement is comparable with that of antipsychotic drugs in various trials. Patients in the treatment arm demonstrated a one point greater decline in MMSE score compared to placebo. This drop was less than what is considered to be a clinically significant change. Adverse effects were modest and consistent with known side effects of SSRIs, such as gastrointestinal complaints, respiratory tract infections, and falls. One limitation factor in using citalopram (and escitalopram, the active *S*-isomer of citalopram), is a dose-dependent risk of QT prolongation, which can potentially lead to torsade de pointes. In 2011, the FDA generated an advisory warning stating citalopram should no longer be used at daily doses greater than 20 mg in individuals older than 60 years because of potential cardiac electrical abnormalities. There are insufficient data on the efficacy of doses of citalopram lower than 30 mg for agitation in dementia. Several placebo-controlled trials have looked at the efficacy of fluoxetine, sertraline, and trazodone in treating agitation in dementia. These trials have not shown benefit of the individual SSRIs compared to placebo.

While rates of adverse events with antidepressants may be lower than with antipsychotics, antidepressants are by no means harmless. Serotonergic agents have been associated with injurious falls even at low doses but increasing as much as threefold at higher doses, fractures, bleeding, and hyponatremia. SSRIs can also induce an amotivational or apathy syndrome which tends to be reversible when the medication is stopped or the dose decreased. Some observational studies have demonstrated an increased risk of stroke and death. SSRIs have a better side effect profile compared to older classes of antidepressants (eg, tricyclic antidepressants and monoamine oxidase inhibitors) and remain first line for treating depression and anxiety pharmacologically.

Anticonvulsants Large, well-controlled randomized controlled trials have not supported using anticonvulsants to treat agitation in dementia. Initial case studies involving valproic acid suggested possible efficacy regarding treatment of agitation in dementia. However, recent trials involving outpatients or nursing home residents with dementia failed to show benefit with respect to agitation, regardless of short- or long-acting preparation of the medication. Furthermore, valproic acid is poorly tolerated with numerous adverse effects such as sedation, diarrhea, ataxia, and thrombocytopenia. Laboratory monitoring is typically necessary to monitor for adverse effects and toxicity. A 2009 Cochrane Review stated valproic acid “could not be recommended for management of agitation in dementia.”

Multiple studies involving carbamazepine to treat agitation in outpatients or nursing home residents with dementia did show improvement in agitation compared to placebo. However, carbamazepine was significantly associated with side effects compared to placebo and its use was limited by drowsiness, disorientation, confusion, and ataxia. It is also associated with bone marrow toxicity and hyponatremia, is an autoinducer (making its titration somewhat difficult challenging), and is a potent hepatic enzyme inducer with potential for drug-drug interactions. Laboratory monitoring is also necessary to monitor for adverse effects such as hepatotoxicity, hyponatremia, and aplastic anemia.

There has only been one controlled study looking at oxcarbazepine as a treatment for agitation and aggression in

dementia. In the study, there were no significant differences in primary or secondary outcomes between the treatment and the placebo groups. Furthermore, adverse events (sedation, fainting, and ataxia) occurred more frequently in the treatment group. Oxcarbazepine has also been associated with hyponatremia, particularly in older individuals.

In one randomized study evaluating the treatment of behavioral disturbances in AD with topiramate or risperidone, topiramate demonstrated better efficacy. However, there have been no placebo-controlled trials involving topiramate for the same population and primary outcome. There have been no controlled studies involving lamotrigine or gabapentin. However, observational studies and retrospective chart review suggest potential benefit as a treatment of agitation and aggression associated with dementia. However, as with other anticonvulsants, adverse effects such as gait instability and sedation with gabapentin and the need for a slow titration with lamotrigine may limit its use.

Cholinesterase inhibitors and memantine Evidence is limited regarding the efficacy of cholinesterase inhibitors and memantine in treating NPS, agitation specifically. They may help treat very mild symptoms or delay the emergence of symptoms over 12 to 18 months. Cholinesterase inhibitors (donepezil, galantamine, rivastigmine, and tacrine) inhibit the enzymes acetylcholinesterase and/or butyrylcholinesterase, which degrade acetylcholine and effectively increase the concentration of acetylcholine at synaptic clefts in the brain. Acetylcholine is a neurotransmitter hypothesized to be important in cognition. Donepezil, rivastigmine, and galantamine are all approved for the treatment of mild-to-moderate AD. Donepezil and the patch preparation of rivastigmine are also approved for the treatment of severe AD. Tacrine, the first agent approved for use in AD, is no longer available in the United States because it can cause a transient and reversible transaminitis. Several randomized controlled trials and meta-analyses of cholinesterase inhibitors showed modest but statistically significant benefits in the acute treatment of NPS in dementia. However, in one 12-week trial, donepezil was no more effective than placebo in treating agitation. It is unclear whether the modest improvement seen is secondary to cognitive improvement. Common symptoms among cholinesterase inhibitors include nausea, vomiting, diarrhea, dyspepsia, anorexia, weight loss, dyspepsia, headache, dizziness, insomnia, and vagotonic effects leading to bradycardia and heart block.

Memantine, an N-methyl-aspartate receptor antagonist, at best has very modest “anti-agitation” properties. The medication, thought to work by preventing the excitotoxic effects of glutamate in the brain, is approved for the treatment of moderate-to-severe AD. A 2009 Cochrane Review found that patients with moderate-to-severe AD taking memantine were slightly less likely to develop agitation compared to placebo. Furthermore, memantine was well tolerated. There was no evidence to support whether it had an effect either way on agitation already present. In two randomized controlled trials, however, memantine was no more effective than placebo for agitation. Common side effects include dizziness, headache, confusion, constipation, and fatigue.

In general, cholinesterase inhibitors and memantine should not be considered first-line agents in managing acute NPS of moderate or greater severity until better evidence of their efficacy emerges. However, given their potential benefit in delaying cognitive symptom progression and their modest improvement of NPS, they remain reasonable options for treating long-term agitation in dementia.

Antiadrenergic compounds In a small randomized, placebo-controlled trial, prazosin, an α_1-adrenergic antagonist, improved behavioral symptoms in patients with agitation and aggression in AD. There was no significant difference in adverse effects including hypotension between the two groups. However, patients with orthostatic hypotension or with systolic blood pressures less than 110 mm Hg were excluded from the study. The results have yet to be replicated in other placebo-controlled trials. In one randomized, placebo-controlled trial, propranolol, a β-adrenergic antagonist, was significantly more effective than placebo in improving agitation, aggression, and anxiety in individuals with AD whose other psychotropics were maintained constant. Unfortunately, overall behavioral status appeared to deteriorate following 6 months of open-label continuation treatment.

Gonadal hormones In theory, increasing estrogen activity or decreasing androgen activity can reduce agitation and aggression. Several case reports have suggested that treating men with dementia with estrogen or gonadotropin-releasing hormone agonists such as leuprolide and goserelin may be beneficial. Depot medroxyprogesterone acetate, a long-acting, progestin-only medication delivered by injection, has been reported to control sexually inappropriate behavior in men with dementia. However, results of randomized, controlled trials have been mixed. One study that included both men and women favored treatment with estrogen. In another study evaluating the use of transdermal estrogen in men with advanced dementia, estrogen was not associated with improvement in aggressive behavior. Furthermore, in this latter study, discontinuation of estrogen patches at the end of the 8-week study was associated with a rebound increase in agitation.

Benzodiazepines Benzodiazepines should be used sparingly or avoided all together because they are deliriogenic and

increase the likelihood of falls and fractures. The exception is in emergency situations in which severely agitated patients are at risk of harming themselves or others and have not responded to alternative medications. In these situations, patients may benefit from brief treatment with a short-acting benzodiazepine such as oxazepam, temazepam, or lorazepam. Short-acting medications are preferable because they do not accumulate with repeated dosing as do longer-acting preparations. The three benzodiazepines mentioned above are particularly useful among older adults or with individuals with complex medical problems as they are metabolized by the liver through glucuronidation. They have no active metabolites and are rarely susceptible to drug-drug interactions. There are no placebo-controlled trials of benzodiazepines for agitation in dementia. If a benzodiazepine is necessary, it is probably best to start with lorazepam 0.25 mg oral daily.

SUPPORTIVE CARE FOR PATIENTS WITH DEMENTIA

The Alzheimer's Association estimates that 60% to 70% of older adults with AD and other dementias live in the community and are cared for by family members and friends. Nearly 100% of these individuals have unmet needs regarding care, services, and support. Recently the Maximizing Independence at Home (MIND at Home) Study set out to determine the prevalence of unmet needs of community-residing individuals with dementia and their caregivers. The majority of patients had unmet needs in the following domains: safety (personal and home), general health and medical care, meaningful activities, and legal issues and advanced care planning. Unmet needs among individuals with dementia may be higher in minority and low-income patients, caregivers with lower education, and individuals in the early stages of dementia. **Table 74-5** highlights areas that a dementia care team should address in every case. The care team should work with the patient and caregiver to maintain the patient's optimal physical and mental health, to provide a safe environment for the patient that maximizes the patient's physical and cognitive abilities, and to preserve the patient's dignity. Ideally, such an environment would allow patients to receive support for their activities of daily living (ADLs) and instrumental activities of daily living (IADLs), be well-nourished, maintain good sleep hygiene, and engage in activities and socialization. In-home activities tailored to the interests and capabilities of patients with dementia have been demonstrated to significantly increase the patient's engagement, reduce NPS, and reduce caregiver burden. In-home occupational therapy assessments, using a functional assessment method such as the Assessment of Motor and Process Skills (AMPS), can provide useful data about a patient's care needs as well as assess the safety of the home environment. For more information about providing supportive care for patients, we refer you to the book *The 36-Hour Day* by Mace and Rabins (2011) and the Alzheimer's Association website (www.alz.org).

TABLE 74-5 SUPPORTIVE CARE FOR THE PATIENT WITH DEMENTIA

- Carefully evaluate the patient's dementia-related needs. Educate patient (as appropriate) and caregivers about the diagnosis and trajectory of dementia.
- Aggressively manage medical comorbidities. Routine follow-up with primary care, and dental, vision, and hearing specialists. Assist with medical decision making.
- Address safety needs, particularly regarding falls, wandering, driving, ability to live alone, environmental hazards (eg, access to weapons, removing items patients can stumble upon), and medications. Consider obtaining a home safety and driving evaluation, and encouraging the use of monitoring devices.
- Maintain a predictable place to live with structured routine. Consider graded support (as little help as possible), role modeling, and cueing for activities of daily living. Simplify tasks (eg, Velcro fasteners instead of buttons) to maximize independence. Provide environmental cues for behaviors (eg, laying out a toothbrush to cue the importance of dental hygiene).
- Provide comfort and emotional support.
- Provide meaningful activities (adult day care, senior centers, and in-home activities), stimulation, and socialization.
- Maintain and document wishes for end-of-life care and distribution of finances after death. These should be addressed while individuals still have decision-making capacity.
- Provide quality nursing care in advanced stages.

SUPPORTIVE CARE FOR CAREGIVERS

Caregivers have the daunting tasks of assisting with ADLs, managing safety concerns and NPS, organizing activities, facilitating health care visits, making proxy health care and financial decisions, navigating through often-complicated networks of long-term care, and advocating for the patient. All this occurs while caregivers lose the person they used to know. Caregiver burden and stress can be severe and depression is common. Caregiver stress, financial hardship, and deteriorating mental and physical health can all have negative impacts on the patient. Caregiver stress is predictive of nursing home placement of patients with dementia while unmet caregiver needs are associated with worse patient quality of life. In MIND at Home, nearly 100% of caregivers had one or more unmet needs, the most common being referrals to community resources, caregiver education, and caregiver mental health care. Unmet needs among caregivers were higher among caregivers who were nonwhite, less educated, and reported more symptoms of depression. Caregivers who considered themselves to be less healthy, had a history of poor interaction with the patient, and described the patient as having a greater number of agitated behaviors perceived themselves as more burdened. It is imperative for the dementia team to consider interventions that will reduce caregiver burden. Teams should encourage caregivers to attend to their own medical and emotional needs. If necessary, teams should give caregivers "permission" to have some respite through using adult daycare centers and recruiting outside help to assist in the patient's care. Referring a caregiver to individual mental health services is often helpful. We recommend referring caregivers to a local chapter of the Alzheimer's Association for dementia-related education (eg, developing caregiver skills), to learn about available community resources, and to get involved in support groups. Caregiver interventions can have effect sizes as great as or greater than pharmacotherapy in delaying out-of-home placement for patients with dementia. **Table 74-6** provides an unexhausted list of potential areas of intervention. It is imperative that dementia teams educate caregivers about dementia and its trajectory, ensure caregivers are able to access community resources and use respite, and have a dementia expert available for crisis situations.

TABLE 74-6 SUPPORTIVE CARE FOR THE CAREGIVER

- Educate the caregiver about dementia and its trajectory.
- Discuss dementia-related needs and review problem-solving techniques.
- Provide an expert clinician around the clock for consultation, particularly in times of crisis.
- Urge caregivers to seek respite and to socialize.
- Ensure caregivers are able to navigate through and use community resources.
- Refer the caregiver to a local chapter of the Alzheimer's Association.
- Provide comfort and emotional support.
- Address caregiver's medical and mental health needs, including encouraging preventative healthcare visits.
- Teach caregivers caregiving skills in providing activities, helping with ADLs, or managing problematic/inappropriate behaviors.

ADLs, activities of daily living.

CONCLUSION

Disruptive symptoms such as agitation and aggression are common in patients with dementia syndromes and can be disabling to the patient and onerous to the caregiver. The differential diagnosis of agitation is wide and must be thoroughly evaluated with its underlying causes corrected, prior to considering treatment. In particular, clinicians should maintain a high index of suspicion for delirium, a frequent cause of agitation in individuals with dementia. Behaviors are often episodic and may change or disappear spontaneously with or without intervention. A dementia care team can be invaluable in delivering effective, personalized care to patients with dementia. Nonpharmacologic interventions should be considered first-line therapy, prior to implementing medications. Pharmacotherapy is appropriate when nonpharmacologic approaches are unsuccessful, when symptoms are distressing to the patient or caregiver, when symptoms disrupt the care environment, and in emergent situations. All psychotropic medications can be associated with adverse effects in dementia, particularly as older patients often have multiple medical illnesses and are on many medications. When starting a new medication, it is best to "start low and go slow," using the lowest possible doses for the shortest possible times, and frequently reassessing the risk/benefit ratio of the particular medication. A crucial role of the dementia care team is supporting the patient and caregivers, particularly as nearly all patients and caregivers have unmet care needs. Numerous community programs and support services are available and

should be encouraged.

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Chapter 75

Effects of Aging on Cardiovascular Structure and Function

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Learning Objectives

- Understand the effects of normal aging on cardiovascular structure and function.
- Describe the effects of normal aging on anatomy and physiology of the heart and vasculature.
- Understand the possible implications of the age-related changes in resting cardiovascular function.
- Understand the role of age-related changes on lowering the threshold for clinical disease.
- Describe the effect of age on the cardiovascular response during exercise.

Key Clinical Points

1. **Normal aging is accompanied by substantial alterations in anatomy and physiology of the heart and vasculature.**
2. **There are declines in most aspects of cardiovascular function, and these create significantly reduced reserve capacity, which becomes more apparent during exercise and stress.**
3. **Many of the age-related changes may lower the threshold for clinical disease and, thus, predispose to a variety of cardiovascular disorders in older people.**
4. **Awareness of the principles of aging biology, in general, will help clinicians tailor intelligent treatments to the older patient.**
5. **Age-related declines in cardiovascular and exercise performance have been shown to be partially preventable and reversible with exercise training. Thus, maintaining regularly scheduled physical activity is an important strategy to mitigate the adverse effects of aging on cardiovascular function.**

PRINCIPLES OF AGING BIOLOGY PERTINENT TO THE CARDIOVASCULAR SYSTEM

As the aging process begins after maturation, deteriorative, regenerative, and compensatory changes develop over time and result in diminished physiologic reserve capacity and an increased vulnerability to challenges, particular disease, and, as a result, a decrease in the ability to survive. Importantly, aging itself does not result in disease; however, it does lower the threshold for the development of disease and can intensify and accelerate the effects of disease once initiated. The increased vulnerability with age to external or internal challenges is one of the tenets of geriatrics and

gerontology and is called homeostenosis.

These concepts are particularly relevant to aging of the human cardiovascular system, especially older persons living in developed countries. When studying normal aging in these populations, it is important to consider screening for clinical and subclinical disease, particularly atherosclerosis, as well as to consider other cultural and environmental factors that are distinct from aging yet can mimic aging effects. These can manifest in human population studies as cohort and period effects, can be subtle or overt, and are easily confused with aging. It has been proposed that a true age-related change should be absent in young persons, increase with age, be universally present in very old persons, and not be related to any known, definable disease.

In some early human aging studies, subjects with clinical and subclinical disease were not excluded, leading to an overestimation of the effects of aging on the cardiovascular system. Coronary atherosclerosis is highly prevalent in western societies and is one of the important disorders that can be occult and can significantly affect cardiac function. Systemic arterial hypertension is even more common. Therefore, reasonable screening for these two most common disorders is prudent to separate aging from disease.

In addition to the effects of subclinical disease, there are additional effects of physical inactivity. Humans and many animals become increasingly sedentary as they age. For example, rats given free access to a running wheel will run 20 km/week when they are young, but this decreases to less than 7 km/week when approaching the age of 23 months. Many older people are even less active. Another increasingly important lifestyle-related factor relatively new to civilization is obesity. Adipose tissue owing to excess caloric intake has numerous effects involving nearly all physiologic systems, including cardiovascular, and obesity increases substantially with age. Thus, the changes that are seen in an older population reflect the combination of all these factors, period, cohort, lifestyle, and disease-related changes, as well as the biological effect of age itself. It is often challenging to precisely separate and discern, both qualitatively and quantitatively, the latter from the former. However, awareness of the important nuances of normal aging can help avoid most errors.

AGING OF THE VASCULATURE

Age Changes in Arterial Structure

With age a number of ultrastructural changes occur in the aorta, and all appear to contribute to increased stiffness. Elastin becomes fragmented in the internal elastic lamina and media perhaps because of inappropriate activation of matrix metalloproteinases. Calcification of the media is also seen. Collagen increasingly becomes cross-linked, making a stiff matrix, especially in the subendothelium.

Irregularities in size and shape of endothelial cells are seen at areas of turbulence, and high cellular turnover occurring at those sites suggest that replicative or cellular senescence may be occurring at those sites. Further evidence of this “in situ” replicative senescence may be provided by manipulations that inhibit telomere shortening. In endothelial cells with persistently long telomeres, age-associated abnormalities may be significantly reduced.

The aortic lumen diameter increases with age, as do vessel length and wall thickness. Because the aorta is fixed proximally and distally, the increase in length results in the tortuous, ectatic, and rightward-shifted aorta seen often on chest X-rays of older persons.

Angiogenesis is impaired in the old vascular tree in response to ischemia or chemical signals. Explants of arteries from old animals have decreased spouting of microvessels and decreased vascular invasion of implants. There is no deficit of smooth muscle cell proliferation, but endothelial cell proliferation is impaired. The impact of this is uncertain because neovascularization of myocardial infarcts or dermal wounds, which may be a bit slower in old rats, is ultimately quantitatively similar for young and old rats.

Functional Changes of Aging Arteries

The older conduit artery may be less responsive to vasoactive substances. For example, nitric oxide (NO) is a vasorelaxant and (at least in the rodent) contributes to the balance that dictates resting arterial tone. Aortic strips isolated from older animals have higher NO synthase activity but produce less NO. Old aortas will relax appropriately when exposed to direct NO donors (nitroprusside) but are less responsive to agents whose effects are mediated by NO such as acetylcholine. Similarly, forearm arterial blood flow is increased less in older individuals in response to acetylcholine compared to younger and athletically active older individuals. As NO is produced from circulating arginine, with age a relative increase in arginase (a scavenging enzyme that competes for arginine) results in reduced

arginine availability for the endothelium, explaining the relatively poor efficacy of arginine supplementation. Isoform-specific arginase inhibitors are not yet available, but genetically induced decreases in arginase protein attenuate age-related changes in arterial function, making this a promising area for research. Again, the response to direct-acting agents is the same in old and young. While the reasons for this paradox remain unclear, the net result is that the old artery is contracted and, again, stiffer.

Old arteries are also tonically contracted by an age-related increase in receptors to endothelin-1 and circulating levels of this potent vasoconstrictor. This results in a decreased maximum response to added endothelin in older persons. Exercise training appears to decrease basal endothelin-1 levels and restore its responsiveness.

Arterial wall stiffness can be assessed noninvasively as pulse wave velocity (PWV), augmentation index, distensibility, and systolic and pulse blood pressure (BP). PWV increases twofold from age 20 to 80, independent of blood pressure. A stiffer arterial wall allows pressure to reflect from periphery to the heart while the aortic valve is still open, increasing the load on the heart, and thus PWV is a physiologically relevant parameter. Typically PWV is measured from start to start of the pressure or flow waves meaning the distending pressure is the diastolic (minimum) pressure. This tends to minimize the PWV change with age because older people have much steeper PWV as pressure increases. Augmentation index, another measure of the impact of aortic stiffness, increases fourfold over that same age range, contributing to the increase in systolic pressure that occurs with age. For men in the Framingham study, systolic BP increased 5 mm Hg per decade until the age of 60; then the slope shifted to 10 mm Hg per decade. For women, systolic BP started lower but shifted to the higher slope earlier. Over the same age range, diastolic BP increases a little and then decreases, so overall it remains unaltered (80 in men, 70–80 in women). Older athletes have lower systolic pressures and PWVs than sedentary old people, but higher than young people. In fact, PWV correlates inversely with maximum oxygen consumption (VO_{2max}) in healthy people of all ages. VO_{2max} is strongly associated with measures of vessel stiffness, particularly PWV, which may be a true contributor to the age-related decline in exercise capacity via a number of mechanisms, including increased load on the left ventricle as well as altered peripheral blood flow distribution. However, this has not been fully explored.

As noted above, at least one mechanism for the increase in arterial stiffness involves nonenzymatic glucose cross-links between vessel collagen molecules. ALT-711 (alagebrium) is a prototypical cross-link breaker and is effective in decreasing PWV and augmentation index as measures of vessel stiffness in older primates and people. Interestingly, plasma advanced glycosylation end products correlate with PWV in normals and hypertensives.

The net result of these changes is reduced compliance and increased impedance, leading to increased systolic blood pressure and little, if any, effect on diastolic blood pressure, such that pulse pressure increases.

Aging and Atherosclerosis

In addition to the changes in the matrix, old smooth muscle cells appear to be less differentiated and proliferate more readily. In studies of smooth muscle cells isolated from young and old rat aortas, the freshly isolated old cells grew more rapidly and migrated more rapidly in comparison to those isolated from the young rat. The smooth muscle cells appear to have polyploidy, which may be another marker of dedifferentiation. While atherosclerosis is not a normal age-related change, especially in species other than man and possibly pigs, the higher propensity to proliferate may increase the probability of developing atherosclerosis if the environment is right.

It is important to understand that age-related changes in large arteries are different from atherosclerosis. First, atherosclerosis is essentially unique to western populations. In animal models including genetically engineered mice it has been difficult to reproduce the complicated plaque characteristic of advanced disease in humans. Atherosclerosis is heterogeneous compared to the age-related changes that occur quite uniformly throughout the conduit arteries. Atherosclerosis leads to a compromise of the vessel lumen compared to the relative dilation of the large vessels with age. The severity of atherosclerosis is related to blood turbulence and shear stress, whereas age-related changes have no such localization. Atherosclerosis has an inflammatory component; none of the activation of white cells typical of atherosclerosis is seen in the age-related process. Cholesterol is a cofactor in atherosclerosis; it has no clear-cut role in age-related changes.

Nevertheless, it is clear that the functional and structural changes in the large arteries make the older person or animal at higher risk of atherosclerosis, given the proper setting. If older rabbits are switched to atherogenic diets, the resulting lesions are more severe after an interval than young rabbits exposed for a similar duration. Thus, the aged arterial wall provides a more fertile ground for atherosclerosis to occur. And because both atherosclerosis and diabetes mellitus also increase large artery stiffness, these disease processes are multiplicative with age in increasing PWV, systolic blood pressure, and pulse pressure and their ultimate effects on the heart.

The impact of aortic stiffening and its clinical manifestations, increased systolic blood pressure and widened pulse pressure, are well appreciated. In addition to the recognition that increased systolic blood pressure and widened pulse pressure are risk factors for stroke, renal failure, and heart disease, the more rapid propagation of pressure waves by the stiff aorta may induce left ventricular hypertrophy and early fibrosis within the myocardium via increased load, as well as altered ventricular-vascular coupling. Combined ventricular-vascular coupling elevates acute afterload, thus increasing cardiac metabolic demand and the energy cost for cardiac output.

If the PWV is high enough, early pressure wave reflections return while the aortic valve is still open, increase workload, and induce hypertrophy. Importantly when the pressure waves return later (as in the young), these may improve coronary artery perfusion by increasing the pressure in the proximal aorta.

AGING CHANGES IN THE HEART

Substantial changes occur with aging in myocardial composition, cardiac structure, and cardiovascular function at rest and during exercise. The changes in anatomy are summarized in **Table 75-1**.

TABLE 75-1 NORMAL AGE-RELATED CHANGES IN THE ANATOMY OF THE HEART

- Increased heart weight, LV mass, LV wall thickness; mild hypertrophy
- Fibrosis, collagen accumulation in the myocardium
- LV cavity size decreases, shortening of long axis, rightward shift and dilatation of the aorta, dilation of left atrium, senile septum
- Calcific and fatty degeneration of valve leaflets and annuli
- Coronary artery dilation and calcification
- Conduction system: fibrosis and loss of specialized cells and fibers: 75% of pacemaker cells in SA node lost; fibrosis of AV node and left anterior fascicle

AV, atrioventricular; LV, left ventricular; SA, sinoatrial.

Changes in Myocardial Composition

Myocyte hypertrophy and degeneration Cardiomyocyte hypertrophy has been recognized and seen as a part of the response to the pressure reflections and increased afterload described above. However, this should be interpreted in light of the evidence that the heart is renewing itself, continuously repopulated from stem cell population's resident and/or sequestered in the bone marrow. The cellular hypertrophy associated with age may mark depletion of the process, as the youngest cells, those most recently differentiated into cardiomyocytes, are thought to be the smallest and in the mouse heart the heterogeneity of myocyte size increases dramatically with age. Interestingly, the largest cells are also the most vulnerable to stress.

The loss of myocytes with age is greater than the ability to repopulate the heart. This loss is due to cardiac aging-induced oxidative stress and mitochondrial damage that are responsible for triggering cardiomyocyte death including necrosis, apoptosis, and autophagy. The total number of cardiomyocytes may be reduced across the lifespan by 50% in healthy human and animal hearts. As above, those cardiac myocytes that remain are increased in size and are much more variable in size. Nearly universal findings in hearts from older individuals are focal basophilic degeneration, a result of abnormal glycogenolysis, and lipofuscin, a "wear-and-tear" pigment, which results in a macroscopic darkened appearance to the aged myocardium, which has been termed brown atrophy. Lipofuscin occupies up to 10% of myocardial volume in very old hearts. While profound, these changes are not detectable by routine diagnostic techniques, such as cardiac ultrasound, and their functional significance is not currently known.

However, older cardiomyocytes are intrinsically stiffer. This may be the contribution of active stiffness in part because of an increased leak of calcium from the sarcoplasmic reticulum (SR) with age in the setting of decreased ability to resequester that calcium, as well as passive stiffness as a result of viscoelastic changes within the cell. Each mitochondrion has its own genome, with relatively sparse ability to correct mutations. A number of investigators report that mitochondrial DNA deletions may increase with age. The implications of this finding remain uncertain, since there are approximately 1000 mitochondria per myocyte, and there is evidence of active mitochondrial quality control mechanisms.

Nowhere is cellular dropout more impressive than in the sinoatrial node. The volume of the sinoatrial node

decreases with age. The number of pacemaker cells is reduced (90% by the age of 70), with most volume replaced by fat. More modest cellular losses occur at the atrioventricular (AV) node, and minimal changes are present in distal conduction system. The dropout of sinoatrial nodal cells is accompanied by a decrease in the slow, L-type calcium channel that is critical to initiation of depolarization. The sensitivity of the older sinoatrial node to calcium channel blockers appears to increase, as assessed in the older guinea pig pacemaker.

Connective tissue Diffuse foci of fibrosis are seen microscopically in the myocardium owing to an increase in interstitial collagen. The fibrous tissue appears in a delicate pattern, unlike the patches of fibrosis seen after acute injury, such as after myocardial infarction. The fibrosis does not appear to be related solely to either ischemia or hypertension, although both of these disorders accelerate the process. Quantitatively, collagen content approximately doubles in the old rat heart. The collagenous weave is not only thicker but increased cross-linking among the collagen filaments confers greater rigidity to the myocardium.

Aging may produce a shift in the balance between matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases that ultimately translates in increased matrix accumulation. These changes may partly underlie age-related alterations in Doppler diastolic filling, which are discussed later.

Senile cardiac amyloid Amyloid deposition is seen to varying degrees in the majority of hearts from persons older than 90 years but is uncommon before the age of 60. It is easily recognized at autopsy, particularly along the left atrial endocardium. Its significance is incompletely understood but might also contribute to left ventricular (LV) diastolic stiffness seen by Doppler.

Adiposity With aging, there is deposition of adipose, particularly in the right ventricular epicardium and the atrioventricular groove. This is most pronounced in women and in the obese. These observations from autopsy studies correlate with the well-known increase in the size of the epicardial and pericardial fat stripes that superficially mimics pericardial effusion on echocardiography. In the Framingham study, the incidence and size of the echocardiographic clear spaces in the area of the pericardium increased significantly with age and were seen in the posterior as well as anterior regions. The increase in adipocytes may reflect loss of the tight control of differentiation of resident stem cells. Emerging data suggest that this adipose infiltration may have consequences for cardiac function—the adipose cells are metabolically and hormonally active and can generate a range of factors including cytokines. Moreover, increased pericardial fat has been associated with atherosclerosis and coronary calcification and other changes.

Changes in Cardiac Structure

Mass In an autopsy study of 765 normal hearts evenly distributed by age and gender from age 20 to 99 from subjects without a history of hypertension or evidence of significant coronary atherosclerosis, Kitzman and colleagues found that mean heart weight indexed to body surface area in men was not age related and was consistently greater than in women. For women, however, the indexed mean heart weight increased significantly with age. This interaction of gender and age was confirmed in a study in 111 healthy subjects using 2D-guided M-mode echocardiographic measurements of LV mass. Furthermore, in seminal work by Gardin et al., when data from healthy men and women were combined, echocardiographic LV mass was found to increase 15% from age 30 to 70. These age and gender trends in echocardiographic LV mass were confirmed by Gardin et al. with an analysis of data from the Cardiovascular Health Study (CHS), an NHLBI-funded population-based, observational cohort study of more than 5000 persons aged greater than or equal to 65 years.

Not surprisingly, there is a substantial impact of body size, particularly weight and lean body mass, on LV mass. In a healthy subgroup of participants in CHS, when weight was adjusted for, there was an approximately 1 g/year increase in LV mass from age 65 to 80. In the healthy subgroup of the Framingham study, when obese persons were excluded, there was a minimal influence of age on LV mass. We conclude that the annual change in mass is modest, but the cumulative effect over half a century is a 10% to 15% increase in LV mass in healthy individuals.

Ventricular wall thickness In the large autopsy study described earlier, right and left ventricular free wall thicknesses remained relatively constant with age, while ventricular septal thickness increased with age for both men and women as shown in **Figure 75-1**. Wall thickness measurements at autopsy may not correlate well with those made in living subjects, when measurements can be made in systole and diastole. However, most echocardiographic studies of healthy subjects confirmed autopsy-based findings showing mild age-related increases in both ventricular septal and LV free wall thickness in women and men.

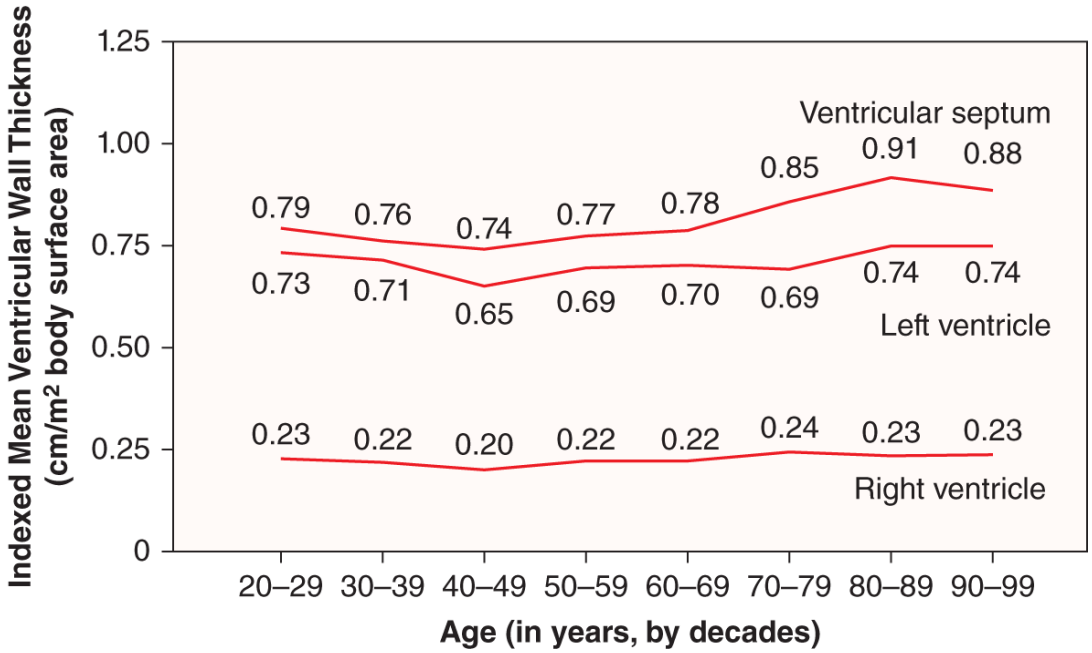


FIGURE 75-1. Ventricular wall thickness. Indexed mean ventricular wall thickness versus age in normal hearts from 765 adult subjects. (Modified from Kitzman DW, Edwards WD. Age-related changes in the anatomy of the normal human heart. *J Gerontol*. 1990;45:M33–39.)

A frequent finding at autopsy and on echocardiograms of persons without apparent heart disease is mild disproportionate thickness of the basal ventricular septum. This has also been called sigmoid ventricular septum and senile septum. This finding may be the result of hypertension rather than biological aging. It has potential clinical relevance in that it can confound to some degree the diagnosis of hypertrophic cardiomyopathy in older patients.

Chamber size There is disagreement in the literature of the effect of aging on chamber size. Some investigators have found a decrease in LV internal diastolic and systolic dimensions with age, by echocardiography in live subjects or direct measurement in autopsy studies. Others have shown no age-related change in LV size.

Most echocardiographic and autopsy studies have found a significant age-related increase in left atrial size in subjects without apparent cardiovascular disease, with an increase in left atrial dimension between ages 30 and 70. However, frankly increased LA volume before age 70 may reflect disease, whereas after age 70 increased LA volume can occur in the absence of disease, from aging alone. The mechanisms of this age-related increase in LA volume is unknown, but may be related to the age-related alterations in diastolic LV function. Serial echocardiographic measurements of LA size in humans have indicated that age and disease have additive effects on increases in LA size over time. Some have suggested assessment of LA size for the purpose of assessing the presence of heart failure with preserved ejection fraction. However, this is likely confounded by the effects of aging alone. While LA size appears to reflect chronic elevations in LV end diastolic pressures, it does not discriminate whether this is due to systolic or diastolic dysfunction or restriction from pericardial or infiltrative processes. Therefore LA volume may not be helpful in discriminating between the types of cardiac dysfunction that cause the elevations in pressure or volume. However, the age-related left atrial dilation likely has consequences for specific disorders that are common in older adults, such as atrial fibrillation. Further, in population-based cohorts, left atrial size is significantly associated with the age-adjusted risk for stroke and for death in both sexes.

Aorta A uniform finding in all studies, including large population-based studies such as the Framingham study, has been a substantial age-related increase in aortic diameter, particularly the aortic root. The degree of change, 22% between age 30 and 70, is sufficient that nomograms for aortic root diameter should probably be adjusted for age. The thickness of the aortic wall also increases significantly with age, probably independent of atherosclerosis, and the pulsatility (compliance) of the aorta decreases. These changes are most discernible by ultrasound with transesophageal and intravascular echocardiography.

Valves The cardiac valves undergo several significant age-related changes. When measured directly at autopsy, the thicknesses of normal aortic and mitral leaflets increase, particularly along the closure margins. This is associated microscopically with collagen deposition and degeneration, lipid accumulation, and focal dystrophic calcification in the leaflets and annuli.

In those subjects most affected, this is recognized clinically and echocardiographically as aortic valve sclerosis, valve thickening without significant hemodynamic dysfunction. In the CHS, this was found in 26% of participants and was related to male gender and hypertension. The relationship between these presumably age-related degenerative changes and the development of clinical aortic stenosis is incompletely defined. It was found in CHS that echocardiographically defined aortic sclerosis was independently associated with a 1.5-fold increased risk of cardiovascular mortality, calling into serious question whether this should be considered a normal age-related change.

Although not normal, age-related degenerative calcification of an otherwise normal-appearing tricuspid aortic valve may apparently result in progressive aortic stenosis and is currently the most common cause of aortic stenosis requiring valve replacement. The relationship between expected, near-universal age-related thickening and mild calcification of the aortic valve leaflets and the development of degenerative calcific aortic stenosis in a subset of older persons is unclear, but the lack of efficacy of statins in modifying this natural history suggests that typical atherosclerosis is unlikely to be the driver.

Microscopic deposits of calcium in the mitral annulus are expected with aging. However, gross mitral annular calcification should generally be considered a disease process. Relatively little is known about the true natural history of mitral annular calcification. It has been reported to be present in up to 40% of hearts from women older than 90 years, and there is a large (4 to 1) female predominance. Echocardiographically, it is often associated with modest degrees of mitral regurgitation but rarely with stenosis. A high incidence of atrioventricular block and bundle branch block has been described.

The circumferences of all four cardiac valves, measured at autopsy, increase with age in normal hearts from women **(Figure 75-2)** and men, and this appears to be associated with collagen degeneration and lipid accumulation in the valve annuli. This is most notable for the semilunar (aortic and pulmonary) valves than the atrioventricular (mitral and tricuspid) valves. In the case of the aortic annulus, this normal age-related dilatation has been confirmed in living subjects with echocardiography.

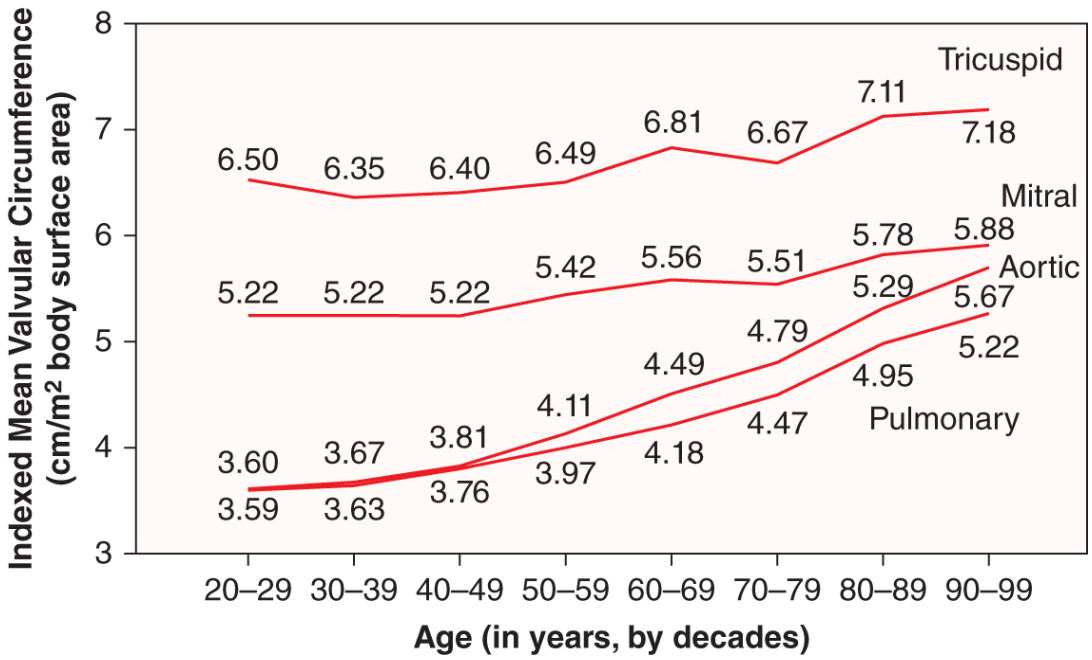


FIGURE 75-2. Normal indexed mean cardiac valve circumferences versus age. Results in 392 women. (Modified from Kitzman DW, Edwards WD. Age-related changes in the anatomy of the normal human heart. *J Gerontol.* 1990;45:M33–M39.)

It is likely that annular dilatation contributes to the age-related increase in valvular regurgitation documented by Doppler in healthy, normal, asymptomatic subjects. By the age of 80, 90% of apparently healthy subjects had multivalvular regurgitation, and the aortic valve was affected earliest and to the greatest extent. The degree of valvular regurgitation caused by normal aging is always trivial or mild, central, and associated with normal (for age)-appearing leaflets.

As in aortic stenosis, there is an association between this normal age-related change and an important cardiovascular disorder. Age alone is the strongest risk factor for isolated severe aortic regurgitation, and idiopathic dilatation of the aortic annulus is the most common cause of aortic regurgitation in patients undergoing aortic valve surgery. This disease may be an exaggeration of an expected age-related degenerative change exacerbated by systemic

hypertension, and there is most likely an additional, contributing factor as yet unidentified.

An interesting, although unanswered, question is whether these normal age-related changes in the cardiac valves, individually or collectively, increase the risk for infective endocarditis.

Pericardium Wavy bands of collagen bundles comprise the normal pericardium. The straightening of these wavy bands allows a degree of distensibility when pericardial pressure or volume increases acutely. With aging, these bands of collagen become straighter and the pericardium becomes thicker. This causes the pericardium of older subjects to be stiffer. The significance of this aging change is unknown, but it could impact diastolic compliance in older adults. As discussed earlier, the degree of epicardial and pericardial fat increases with age, particularly in women and obese persons, and the resultant echolucent spaces seen on echocardiography can superficially mimic a pericardial effusion.

Atrial septum The atrial septum thickens and becomes stiffer with advancing age, probably owing to fatty infiltration and fibrosis. This causes the atrial septum to become less mobile with phasic respiration. This phenomenon is helpful in echocardiographic diagnosis. The finding of a thinned, hypermobile atrial septum by echocardiography in an older person should raise the suspicion of an atrial septal aneurysm (which often is accompanied by fenestrations), patent foramen ovale, or atrial septal defect and prompt further evaluation with color Doppler and a peripheral venous injection of agitated saline contrast.

An exaggerated form of the age-related fatty infiltration is found essentially exclusively in older patients and is called lipomatous hypertrophy of the atrial septum. It can mimic the appearance of an intracardiac tumor but is recognizable by its characteristic dumbbell shape.

A probe-patent foramen ovale is seen in approximately 35% of normal hearts younger than 30 years and in 20% by age 80. This lower prevalence of patent foramen ovale is accompanied by an increase in the size of patent foramen ovale in older compared to younger persons. Therefore, while paradoxical embolism is usually considered in the context of an atypical stroke in a person younger than 55 years, it likely is a contributor, although of unknown proportion, to strokes among older adults. Because of this, injection of venous agitated saline contrast is often used as an adjunct to echocardiographic imaging even in older patients referred with atypical stroke.

Coronary arteries With aging, the coronary arteries tend to become more dilated and tortuous, possibly because of hemodynamic drag. Coronary collaterals may also increase in number and size with age, but it is not clear whether this is independent of atherosclerosis. While atherosclerosis is always considered a disease process, Mönckeberg medial calcification (arteriosclerosis) probably represents an age-related degenerative process. It is a nearly universal finding in the very old and is independent of gender. In the peripheral vasculature, it may contribute to the age-related elevation in systemic systolic blood pressure and arterial impedance. A syndrome often seen in older patients and those with end-stage renal failure is the triad of cardiac calcifications involving the aortic cusps, mitral annulus, and coronary arteries, called the senile calcification syndrome. In these older persons, no evidence of altered calcium metabolism has been found, and, although a relationship with elevated serum cholesterol levels has been described, the etiology is not known.

Overall Appearance

It has been stated that a characteristic geometric configuration is imparted to the older heart heart by these age-related changes, particularly those observed in the cardiac chambers: shortening of the long-axis dimension, a mild decrease in the internal systolic and diastolic LV cavity dimensions, dilatation and rightward shifting of the aortic root, and dilatation of the left atrium as shown in **Figure 75-3**. These changes, as well as the mild regional calcification seen in the aortic and mitral valve annuli, are so characteristic that these can be used as clues to help detect the age group of patients during blinded readings of echocardiograms.



A



B

FIGURE 75-3. Age-related changes in the cardiac chambers. **A.** Normal heart from an 18-year-old for comparison (left ventricular long-axis views). **B.** Normal heart from an 84-year-old man demonstrates shortening of the base-to-apex (long-axis) dimension, decreased internal left ventricular dimension, aortic root dilatation with rightward shift, sigmoid-shaped septum, and left atrial dilatation. (Modified from Kitzman DW, Edwards WD. Age-related changes in the anatomy of the normal human heart. *J Gerontol.* 1990;45:M33–M39.)

Changes in Cardiac Function With Age at Rest

Since there are significant changes in the anatomy of the cardiovascular system, discussed earlier, and since aging is accompanied by significant changes in function in most other organ systems, one would expect alterations in cardiac physiology as well. Several important age-related changes have already been discussed briefly earlier, including

changes in valvular function and the potential anatomic substrates for altered diastolic function. While the effect of age on cardiac function has long been a topic of research efforts, only recently have studies been able to be performed using adequately robust techniques combined with appropriately defined reference populations. However, it is still true that little information is available regarding how these changes in function impact on the epidemiology, presentation, diagnosis, prognosis, and therapy of cardiovascular disease. Changes with age in cardiovascular function are summarized in **Table 75-2**. Most studies of cardiovascular function at rest show either no substantial change in cardiac output, stroke volume, heart rate, and ejection fraction with aging or mild-to-moderate and significant increases in systemic and pulmonary arterial blood pressure, with resultant increases in left and right ventricular afterload.

TABLE 75-2 NORMAL AGE-RELATED CHANGES IN CARDIOVASCULAR PHYSIOLOGY

- Peak cardiac output declines
- Peak heart rate declines
- Peak ejection fraction declines
- LV stiffness increases, diastolic relaxation decreases
- Valvular regurgitation develops
- Prolongation of PR, QRS, QT; left axis deviation
- Arteries stiffen, aortic impedance increases
- Systolic blood pressure and pulse pressure increases

Heart rate and rhythm There is no change in resting heart rate with adult aging. However, as will be discussed further later in the section on exercise, there is a clear and marked decrease in maximum heart rate in response to exercise that is highly predictable and can easily be estimated by a simple equation. For men, (220 – age) predicts the target maximum predicted heart rate for exercise testing. Women have lower peak heart rate in youth and more gradual fall in maximum; thus, a correction factor of 0.85 is often used.

The age-related change in maximum heart rate is perhaps the most substantial change in cardiac function, both in magnitude and in consequence. Although its mechanism(s) are not fully understood, a number of studies have been performed. In the presence of the β-adrenergic antagonist, propranolol, and the parasympathetic antagonist, atropine, given to ablate both sympathetic and parasympathetic input to the heart, the intrinsic heart rate is seen. Intrinsic heart rate decreases by 5 to 6 beats/min each decade of age so that the resting heart rate in an 80-years-old is not much slower than the intrinsic heart rate. This means that, at rest, the parasympathetic nervous system is not actively slowing the heart, and, as would be expected, the increase in heart rate after atropine is less than half that in the young.

There is also decreased response to sympathetic agonists. Administration of isoproterenol to healthy young and old people demonstrated that the chronotropic effects of this sympathomimetic agent were markedly attenuated in the old. At doses that increased heart rate by 25 beats/min in young healthy males, heart rate increased by only 10 beats/min or less in older persons.

Further supporting the decline in maximal heart rate as a primary age-related biological change is that it cannot be significantly modified by even vigorous exercise training, suggesting that it is not a secondary consequence of an age-related decline in physical activity level. Also, it does not appear to be caused by inadequate sympathetic stimulation, as plasma norepinephrine levels are increased rather than decreased at rest in normal older adults. Further, with stress or exertion this catecholamine increases even more than in young persons under similar stress.

Perhaps as a direct reflection of the decreased parasympathetic nervous system input and decreased responsiveness to what autonomic input is present, there is a significant decrease in heart rate variability. Heart rate variability is a measure of the variations in instantaneous heart rate (or RR interval). This results in a decrease in complexity, which may not seem important in itself but correlates with the decrease in physiologic reserve. Any loss of complexity may then render the older person or animal less likely to tolerate challenges to their homeostasis. Furthermore, the loss of complexity with age occurs in a number of physiologic systems and is forestalled by interventions like exercise training, which improve robustness.

In highly screened older people to exclude potential confounding effects of disease, the prevalence of atrial premature beats reaches 88% on 24-hour ambulatory monitoring. Because there is no association with cardiac risk over the next decade with the presence of even frequent atrial premature beats (APBs), this is thought not to reflect subclinical coronary artery disease. At exercise testing, isolated ventricular ectopic beats occurred in more than half of

highly screened people older than 80 years. Therefore, this increase in ectopy of both atrial and ventricular origin is thought to be a normal aging process.

Diastolic function Increased LV stiffness associated with aging using invasive techniques was first described in young and old beagles. Ten years later, similar findings were identified by invasive techniques in humans. In between these two developments, there was the advent of spectral Doppler echocardiography, which greatly expanded our ability for noninvasively assessing LV diastolic filling. All studies, including the large population-based databases from the Framingham study and the CHS, have uniformly found that diastolic LV filling is substantially altered in older normal subjects. In addition, similar changes with aging are found in monkeys, rats, dogs, and mice.

The age-related changes in the pulsed Doppler diastolic transmitral flow pattern that have been observed in humans are reduced early (E) and increased late atrial (A) flow velocities and decreased E/A ratio. Klein et al. expanded these findings by documenting an age-related increase in early deceleration time and isovolumic relaxation time, important parameters that were not included in many previous papers or in the population-based studies. The finding of a normal age-related change in early deceleration time may be particularly relevant, since this parameter predicts intrinsic LV chamber stiffness. In addition, the report by Klein et al. showed that similar age-related changes take place in pulmonary venous flow, with increased peak systolic flow velocity, decreased diastolic flow velocity, increased peak atrial reversal flow velocity, and increased percentage of forward flow in systole.

These Doppler indexes of diastolic filling may be altered early in the course of a variety of disorders that are common and sometimes unrecognized in older adults. They are significantly influenced by a number of physiologic variables, including LV mass and chronotropic, inotropic, and loading states, which may also be altered by aging. Thus, it had been questioned whether the age-related alterations in Doppler diastolic filling indexes were simply secondary to these or whether they occurred independent of cardiovascular disease and other confounding physiologic variables. In a study of old and young healthy volunteers, rigorously screened for cardiovascular disease, comprehensive Doppler echocardiography, radionuclide ventriculography, and invasive measurements of right heart and left atrial pressures were performed. The old and young subject groups were closely matched for LV mass, volumes, ejection fraction, and end-systolic wall stress; left atrial size and heart rate; and right atrial, pulmonary arterial, pulmonary capillary wedge, and systemic arterial pressures. Despite this, there persisted the characteristic age-related alterations in Doppler LV filling. In univariate and multivariate regression analyses, peak early and atrial flow velocities were not related to any of the potentially confounding variables measured once age was taken into account. A complementary study showed that even though substantial changes in Doppler filling patterns were inducible by gravitationally induced alterations in LV load, filling patterns in older subjects were still distinguishable from those of young subjects. Taken together, these studies suggest that an altered Doppler diastolic LV filling is a primary, biologic effect of aging, intrinsic to the aged human heart, and not explicable by other physiologic and pathologic changes that frequently accompany the aging process and reflect a true alteration in LV diastolic function.

Since normal healthy older individuals are expected to have an altered pattern of Doppler LV filling, what then should be considered abnormal? First, the large population-based databases have yielded important data that have been underappreciated and are significantly underused in current practice. In the CHS, among subjects aged 65 to 100, with no indicators of cardiovascular disease, the upper and lower 95% confidence limits for the E/A ratio included 0.65 to 1.45 for women and 0.64 to 1.56 for men. Similar results were found in a smaller group of healthy older subjects in the Framingham study. Thus, Doppler diastolic filling patterns within this range should be considered normal in patients in this age range. Accordingly, it is preferable to use the term, “delayed relaxation” or “normal for age” in clinical descriptions of this finding, rather than the terms, “impaired relaxation” or “abnormal relaxation” which denote abnormality and is inconsistent with aging principles. In addition, findings obtained in older patients during basal conditions that fall outside these ranges should be considered abnormal, regardless of age. Second, the pattern of LV filling is helpful. Certain patterns, such as the pseudonormalized and restrictive patterns as shown in **Figure 75-4**, can be more easily discerned from normal and can be more specific for disease when found in older than in younger patients, because these differ more from the expected pattern. The more recent introduction of mitral annulus tissue Doppler has significantly boosted the ability to assess LV diastolic function noninvasively because the annular velocity measures are relatively load dependent. As would be expected, based on the above study, age alters the tissue Doppler velocities as well. Unfortunately, age-related normative reference data are relatively sparse.

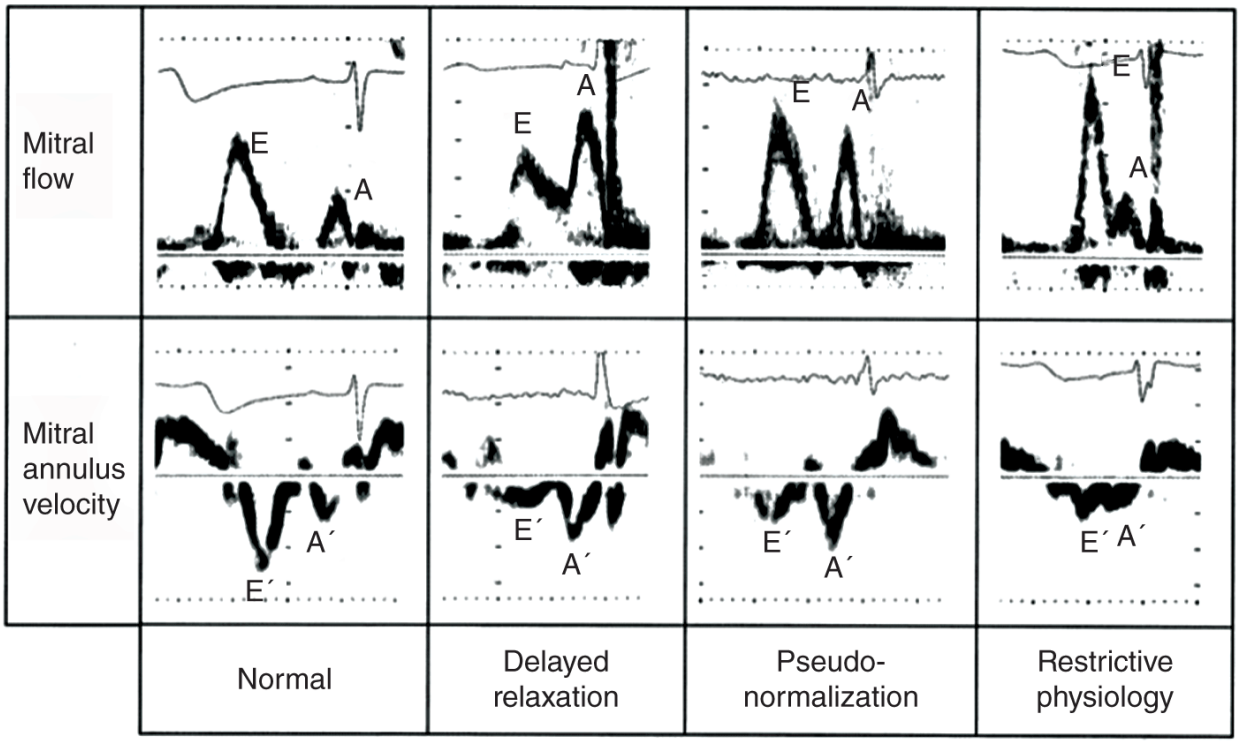


FIGURE 75-4. Patterns of mitral inflow and mitral annulus velocity from normal-to-restrictive physiology. (Modified from Sohn DW, Chai IH, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol*. 1997;30:476–480.)

In isolated papillary muscles from older rat hearts, the change in pattern of contraction and relaxation is clearly seen: slower force generation and relaxation with no change in peak force. In addition, the inotropic and lusitropic (facilitating relaxation) responses to sympathetic stimulation are also decreased with age. Cardiac contraction and relaxation are dictated by calcium fluxes. For contraction a small amount of calcium enters the cells via the slow L-type calcium channels and stimulates the release of 10- to 20-fold more calcium from the SR. Active relaxation includes the calcium reuptake by the cardiac SR after contraction and extrusion from the cell by the Na-Ca exchanger and the sarcolemmal Ca pump. Ninety percent of calcium cycles in and out of SR. Aging has been reported to reduce the capacity of SR to accumulate, retain Ca^{2+}, and inhibit excitation-contraction coupling in the cardiomyocytes by interfering with the calcium transient. Calcium reuptake into the SR is decreased by almost 50% in old hearts from rats and mice, and the content of the SR Ca-ATPase pump is decreased in old human hearts as well. Concurrently the old SR has enhanced calcium leak manifested by small spontaneous localized releases called calcium sparks. All these slow cardiac relaxation, perhaps increase diastolic calcium concentrations, and results in smaller Ca stores in the SR for release in the next contraction. To a small extent, compensation occurs in other calcium fluxes in that the SR Ca-ATPase activity is increased in old rat hearts.

The significance of these age-related alterations in diastolic filling has not been fully established. An atrial gallop (S4) is a normal finding on physical examination in those older than 75 years, a manifestation of the increased contribution of left atrial systole to ventricular filling. Brain natriuretic peptide (BNP) elaboration and release by the left ventricle also increases mildly with age, a possible reflection of altered diastolic function with age; however, it may also reflect known age-related reduction in renal clearance of the peptide. The 95% limit for serum BNP from normal was doubled for those over 75 years compared to a reference group aged 45 to 55. The decrease in rapid cardiac relaxation during early diastole results in increased dependence on LA systole in late diastole for adequate LV cardiac filling. However, as things worsen, LA pressures increase and early filling subsequently increases again. This pseudonormalization of LV filing is another marker that the aging process has tipped over to heart failure. Altered diastolic filling may play a role in reduced exercise capacity seen in normal older subjects, the lower threshold for expression of heart failure with preserved ejection fraction, and the poorer prognosis in older patients with heart failure.

Gene therapy, increasing the content of the SR Ca-ATPase has markedly improved the function of old rat hearts. The age-related changes in diastolic function can also be modified and improved by exercise training. In old rats trained on treadmill exercise for 1 to 2 months SR calcium uptake and cardiac relaxation improved to that seen in

young sedentary rats. Similarly, improvements in early filling, which is dependent on active relaxation, are also seen in humans after 6 months of endurance training. Humans who put themselves on a diet comparable to the caloric restriction diets have better diastolic function than age-matched controls, corroborating experiments in experimental animals. While this approach may not be highly practical, only 5 years of caloric restriction is needed to produce the change.

Systolic function In healthy humans, no age-related changes in measurable, overall LV contractility, assessed at rest by the ejection fraction, fractional shortening, or mean velocity of circumferential fiber shortening, have been reported in those studies in which it has been measured. Wall motion abnormalities should not be considered normal, even in the very old adults. In CHS, the prevalence of unexpected wall motion abnormalities, in the absence of history and symptoms of coronary heart disease, was 0.4% in women and 0.5% in men.

The contraction and relaxation of the older left ventricle are not uniform. In older people, segments of the heart have started to relax while others are still contracting. As LV pressure must be low before filling can start, this prolonged contraction shortens the time available for filling to occur.

Age-related alterations in several Doppler measures of aortic outflow have been demonstrated. Aortic peak flow velocity, time-velocity integral, and acceleration are reduced with advancing age. While these hemodynamic factors relate to LV systolic performance, these are also substantially affected by afterload, which increases with aging.

Possible Implications of the Age-Related Changes in Resting Cardiovascular Function

As noted in the introduction, aging decreases one's ability to tolerate challenges to homeostasis. This is most evident in the cardiovascular system. For example, the mortality and probability of developing heart failure after a myocardial infarction increase dramatically with age. While, clearly the pathogenesis of atherosclerosis and the myocardial infarction itself is not normal aging, the response to the systemic challenges produced by the infarction may well be impaired because of the aging process. Consistent with this, there is an age-related increase in mortality after experimental infarction in mice and rats. We suggest that homeostenosis, the depletion of reserves, may be the cost of invoking compensatory mechanisms just to maintain homeostasis.

Similarly, acute hypertension is poorly tolerated in the old. Old (18 months) and adult (9 months) rats had afterload increased by constriction of the aorta. Immediate early response gene signals were attenuated in the old rats. Decreased skeletal actin expression after pressure overload was present, and skeletal actin expression precedes cardiac actin expression in most models of hypertrophy. Atrial natriuretic peptide (ANP) stimulates excretion of water and sodium by the kidney. ANP is only expressed by the atria in normal young hearts, but ANP is a marker of stress and compensation when seen in the ventricles. In the old rat, ANP is elevated in the ventricles at baseline and could not be further stimulated after additional stress. This suggested that the hypertrophy response was already invoked as part of aging in the older rats and was therefore less available to respond to the acute stress.

While the normal heart is unlikely to ever be exposed to ischemia, ischemic preconditioning is an adaptation of the young heart that is not present in the old heart. Young hearts, if repeatedly exposed to brief episodes of ischemia, tolerate longer episodes well with less resultant damage, by possibly increasing levels of heat-shock proteins, opening ATP-gated potassium channels, stimulating the tumor necrosis factor alpha (TNF-α) cascade, and activating antioxidant enzymes. Old hearts cannot make this adaptation, perhaps contributing to the increased mortality after myocardial infarct in the old, but exercise training, caloric restriction, and certain growth factors may restore this adaptive capability.

The responsiveness is decreased to some cardioactive drugs, including atropine, dobutamine, and other β-adrenergic active agents. These agents may require higher doses to reach a desired effect in the old. Congestive heart failure becomes increasingly common, reaching a prevalence of more than 10% and being the most common reason for hospitalization of Medicare beneficiaries (see Chapter 79). The syndrome of heart failure with normal ejection fraction, the most common form among older persons, is likely facilitated by the above- and below-discussed age-related changes in diastolic function and myocardial composition additive to the arterial and myocardial changes caused by hypertension and other diseases. Age-related changes in vessels and the heart do not by themselves produce disease, but, because of the changes in compliance, systolic hypertension is incredibly common. Finally compensation for these changes makes the old cardiovascular system more prone to decompensation in response to other insults.

Effect of Age on the Cardiovascular Response During Exercise

If aging affects cardiovascular performance even at rest or with moderate stress, one would expect this to be magnified

and become even more apparent during exercise. This is indeed the case. Exercise capacity can be quantified objectively by measurement of maximal oxygen consumption (VO_{2max}) during exercise. It is solidly established that normal aging is inescapably accompanied by a reduction in VO_{2max}. While the age at which this decline begins is unclear, it is probably variable and begins early in adult life. The reduction in VO_{2max} is independent of gender and changes in body size. The magnitude of the decline is approximately 3% to 8% per decade and can be modified but not completely halted or reversed by exercise training.

A study from the Baltimore Longitudinal Study on Aging (BLSA) in 1988 showed results that the authors interpreted as showing a decline at the lowest part of this range (3%) and attributed a significant proportion of the age-related decline in VO_{2max} to loss of muscle mass. In addition, a study reported in 1984 using subjects from the BLSA and subsequent reviews and commentaries have implied that these cross-sectional estimates for the age-related decline in VO_{2max} were probably substantial overestimates of the true longitudinal decline and that declines in multiple measures of exercise cardiac function, including cardiac output, were relatively modest. However, such conclusions were at substantial variance with other studies. At the time, the difference compared with prior studies was attributed to rigorous screening. However, a subsequent report from the BLSA in 2005, which examined a large number of subjects, both sedentary and well condition by training, during a 7.9-year period of follow-up, thereby providing true longitudinal rather than cross-sectional data, showed that, in actuality, the decline in exercise capacity (VO_{2max}) among older persons was actually more accelerated and greater in magnitude than all previous estimates. In addition, another subsequent report from the BLSA in 1995 showed that, in contrast to the original study in 1984, both men and women do have substantial age-related declines in maximal exercise cardiac output, accompanying and contributing to a 40% decline in VO_{2max}. This is in accord with reports from all other studies. Thus, there is now uniform agreement that aging, even in the absence of any identifiable disease, is associated with substantial declines in overall cardiovascular performance and reserve capacity, including maximal cardiac output.

By the Fick principle for oxygen, only a limited number of factors could be responsible for a decline in VO_{2max}. The following equations are pertinent to this discussion:

VO_2 = cardiac output × arteriovenous oxygen (AVO) difference

Cardiac output = stroke volume × heart rate

Stroke volume = end-diastolic volume – end-systolic volume

The arteriovenous oxygen difference (AVO) is determined by a number of noncardiac factors, including peripheral vascular and skeletal muscle mass and metabolic function. Thus, if VO_{2max} declines with aging, there must be a decline in peak cardiac output or AVO or both during exercise as shown in **Figure 75-5**.

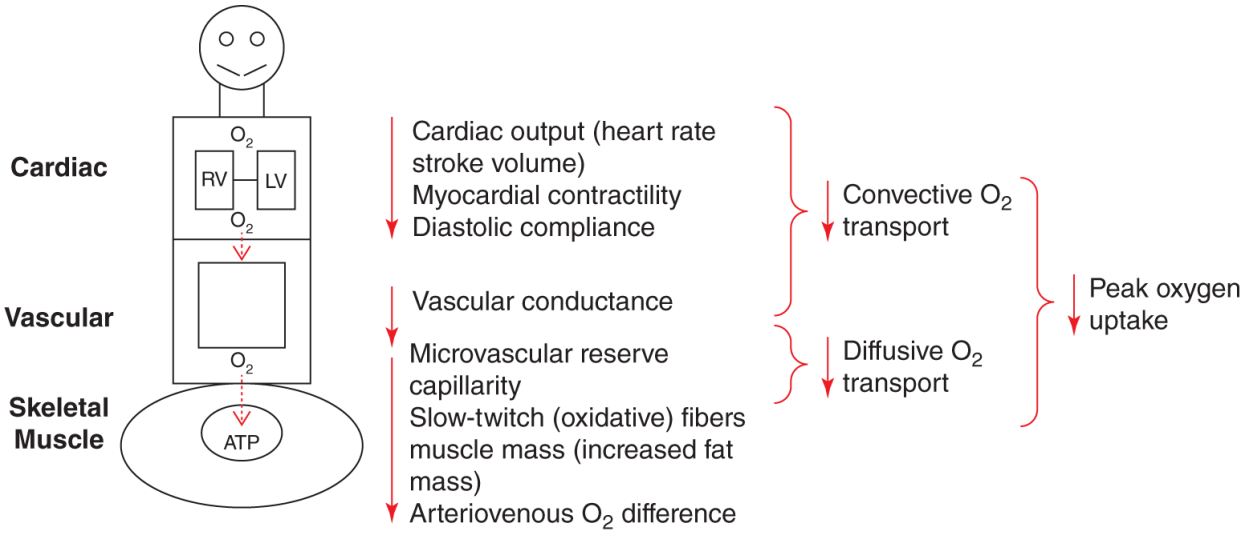
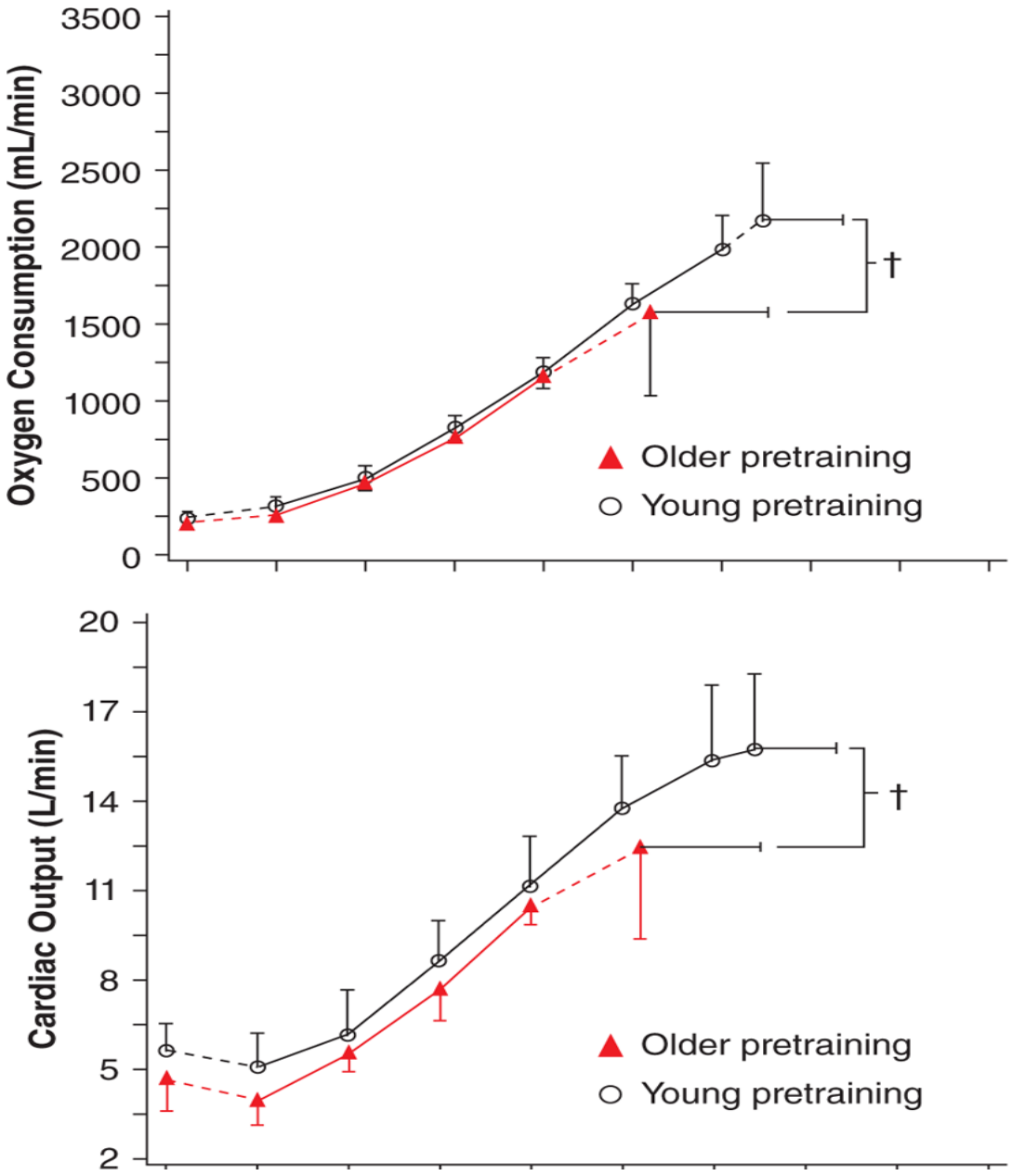


FIGURE 75-5. Determinants of exercise intolerance. ATP, adenosine triphosphate; LV, left ventricle; O_2, oxygen; RV, right ventricle. (Modified from Haykowsky MJ, Kitzman DW. Exercise physiology in heart failure and preserved ejection fraction. *Heart Fail Clin*. 2014;10:445–452.)

Measurement of cardiac output in healthy human subjects during exercise is challenging methodologically. Investigators have used a variety of techniques, including direct Fick (probably the most reliable), dye dilution,

equilibrium-gated radionuclide angiography, and gas rebreathing. Each of these methods uses a number of variables to derive the cardiac output measurement. Direct measurement of AVO by oximetry, however, is quite accurate and reliable. Most investigators who have measured AVO during maximal exercise have documented no difference or increased AVO in older compared with young subjects. By simple algebra, this suggests that the age-related decline in VO_{2max} must be because of reduced cardiac output. This has, indeed, been the finding reported by virtually all investigators. Accordingly, the inotropic (contractility) as well as lusitropic (diastolic function) responses to dobutamine decrease.

Higginbotham et al. reported results of a study using invasive techniques to directly measure all components of the Fick equation in healthy human subjects. The subjects had a very low probability of coronary disease as they were all aged less than or equal to 50, were asymptomatic volunteers, and had normal electrocardiograms and radionuclide angiograms during exercise. Yet even over the small age range, maximal cardiac output, declined significantly. These healthy subjects had the expected age-related decline in VO_{2max} and heart rate. They found that stroke volume, ejection fraction, and end-diastolic volume were unchanged with aging or showed a slight downward trend. Thus age-related decline in maximal heart rate was translated into reduced maximal cardiac output, since stroke volume was unchanged. Similar results have been obtained by others in groups of older men and women, and in beagles. Furthermore, an invasive study confirmed those results in a group of older (age 66) versus younger (age 28) healthy subjects, as shown in **Figure 75-6**. These data indicated that both cardiac output and systemic AVO were reduced in older versus young healthy subjects and contributed to their 28% age-related reduction in VO_{2max}.



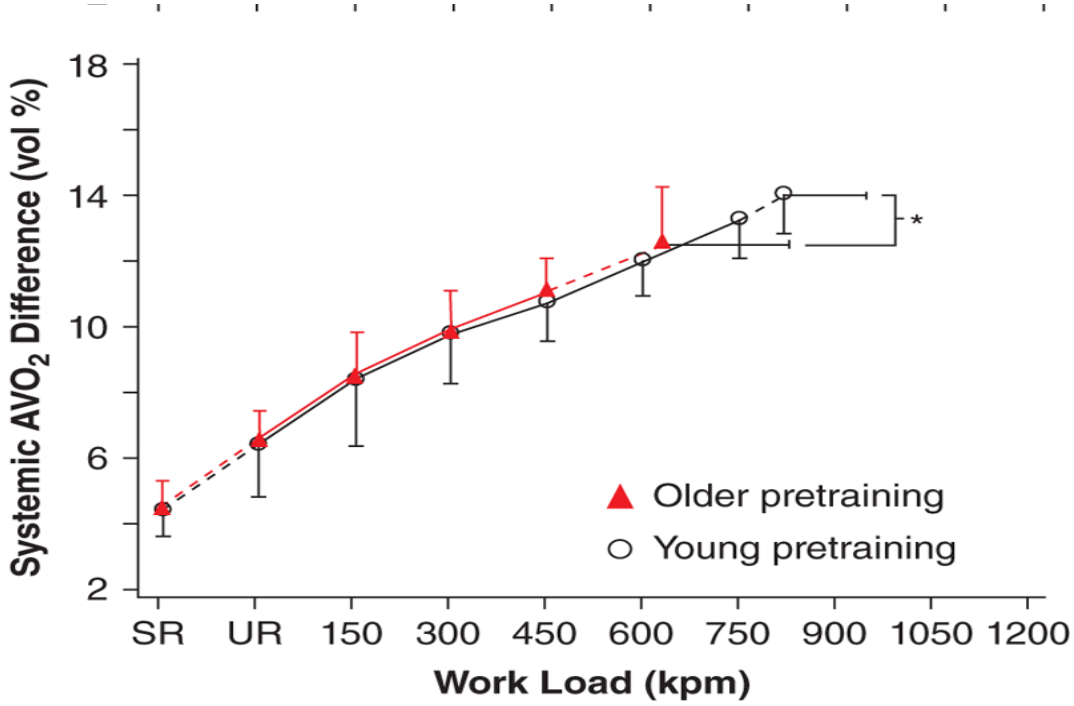


FIGURE 75-6. Oxygen consumption by expired gas analysis, cardiac output by the direct Fick technique, and systemic arteriovenous oxygen difference by direct oximetry at supine rest (SR), upright rest (UR), and during maximal exercise in younger and older healthy volunteers. Note that there are substantial and significant reductions in older compared to younger subjects in all measures, including maximal cardiac output. $^{\dagger}p < 0.01$; $^{*}p < 0.05$. (Modified from Beere PA, Russell SD, Morey MC, Kitzman DW, Higginbotham MB. Aerobic exercise training can reverse age-related peripheral circulatory changes in healthy older men. *Circulation*. 1999;100;1085–1094.)

Thus, the reduced VO_{2max} and exercise capacity seen with aging are caused predominantly by reduced exercise cardiac output. That the heart should be responsible for the age-related exercise limitation is not surprising, since it has been observed that the skeletal muscles have a greater capacity for work than can be supported by the cardiac output. The primary mechanism of the age-related decline in exercise cardiac output is primarily the age-related reduction in maximal heart rate. Reduced maximal exercise heart rate appears to be a universal observation and to meet the criteria for a basic biological aging phenomenon. Its mechanism is unclear but may be related, in part, to an age-related decline in β-adrenergic sensitivity.

Although reduced maximal heart rate is the primary mechanism for reduced maximal exercise cardiac output and oxygen consumption in older subjects, younger subjects in whom exercise heart rate is limited, either by congenital complete heart block or by β-adrenergic blockade, stroke volume is increased and partially compensates for the reduced heart rate via the Frank-Starling response (increased end-diastolic volume). The effect of aging on end-diastolic volume and the Frank-Starling mechanism during exercise is not clear, since repeated studies from one group using invasive techniques described above show no change with aging. Studies from another group suggest end-diastolic volume at peak exercise increases with aging. Older subjects have either no change or a modest decline in stroke volumes at maximal exercise with aging compared to younger subjects, including in women in the BLSA. An age-related decline in Frank-Starling reserve would be consistent with observations suggesting increased LV diastolic stiffness with aging.

A lower stroke volume in older adults could be because of higher end-systolic volume or lower end-diastolic volume. LV end-systolic volume was higher and ejection fraction was lower at peak exercise in the older subjects in most studies in which these were measured. Thus, systolic LV function reserve is reduced with aging as well. Reduced stroke volume could also result partially from increased afterload, since systolic blood pressure, aortic impedance, and systemic vascular resistance are higher during exercise in old than in young healthy subjects. When afterload is taken into account, maximal stroke work is fairly similar in young and old subjects.

In evaluating older patients for coronary heart disease, particularly with radionuclide angiography, it should be recognized that in healthy older people the LV ejection fraction does not increase as much from rest to peak exercise as it does in young healthy subjects. In fact, a flat response in older men and a mild decline in older women should be considered normal. However, the development of wall motion abnormalities should be considered abnormal, even in the presence of a mild nonspecific decline in ejection fraction.

There has been less information regarding peripheral cardiovascular function with aging, including systemic

arterial function, which is required to efficiently deliver oxygenated blood to working muscle, and working muscle itself. The study by Beere et al. extended prior work by using a pediatric thermodilution pulmonary artery catheter inserted into the femoral vein, in order to acquire the best available measures of leg blood flow, oxygen consumption, and AVO. Their findings indicated that, in addition to reduced peak exercise cardiac output, older men have reduced exercise leg blood flow. The study also repeated the detailed measurements of central and peripheral cardiovascular functions following exercise training. Their results confirmed the findings of a number of previous investigators that exercise training can improve VO_{2max} by 15% or more and thereby "reverse" some of the age-related decline in physical work capacity. Furthermore, they found that the primary mechanism of improvement in exercise capacity following training in older subjects was a large improvement in leg arterial blood flow **(Figure 75-7)**.

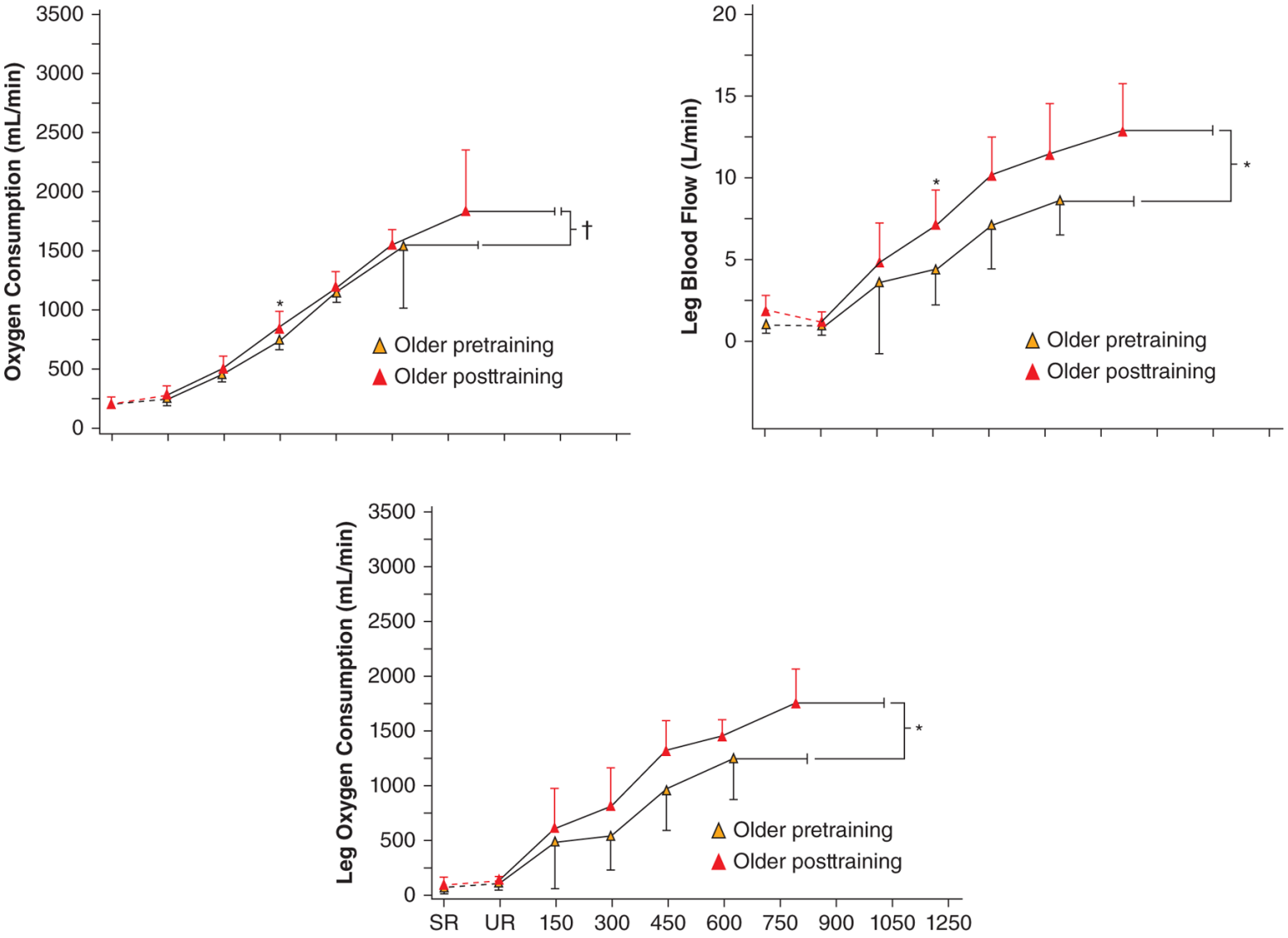


FIGURE 75-7. Leg blood flow measured by indwelling catheter, and leg oxygen consumption by expired gas analysis during supine rest (SR), upright rest (UR), and during exercise in older healthy volunteers before and after aerobic exercise training. After exercise training, there is a 28% improvement in maximal body oxygen consumption, and this is accompanied by a 50% improvement in leg arterial blood flow and leg oxygen consumption during exercise. $^{\dagger}p < 0.01$; $^{*}p < 0.05$. (Modified from Beere PA, Russell SD, Morey MC, Kitzman DW, Higginbotham MB. Aerobic exercise training can reverse age-related peripheral circulatory changes in healthy older men.. *Circulation.* 1999;100;1085–1094.)

Skeletal muscle function is another potential contributor to the age-related reduction in VO_{2max}. With aging, there is a decline in skeletal muscle mass and increase in the amount of fatty infiltration, a shift in fiber type, and variable alterations in mitochondrial density and function. Each of these could contribute to reduced exercise capacity in older persons.

SUMMARY

Normal aging is accompanied by substantial alterations in anatomy and physiology of the heart and vasculature. There are declines in most aspects of cardiovascular function, including both cardiac output and blood flow distribution, and these create significantly reduced reserve capacity, which becomes more apparent during exercise and stress.

The age-related alterations in the anatomy and physiology of the heart and vasculature likely have varying degrees of significance. Some may not have functional significance and are essentially epiphenomena of aging. Others, such as aortic sclerosis, ventricular septal thickening, and attenuated cardiac function response during exercise, may simulate disease. Some findings, which are associated with age and are prevalent in older hearts, such as senile amyloid and calcified mitral annulus, are likely part of poorly understood disease processes rather than aging. With currently available information, it is not always possible to distinguish the effects of aging from the effects of disease, particularly in very old hearts. However, it is reasonable to propose that many of the age-related changes discussed may lower the threshold for clinical disease and, thus, predispose to a variety of cardiovascular disorders in older adults, including congestive heart failure, hypertensive hypertrophic cardiomyopathy, valvular stenois and regurgitation, systolic hypertension, supraventricular arrhythmias, and conduction disturbances. Awareness of these age-related changes, as well as the principles of aging biology in general, will help investigators avoid potential errors in research study design or interpretation and help clinicians tailor intelligent treatments to the older patient.

Because these age-related declines in cardiovascular and exercise performance are modifiable and have been shown to be partially preventable and reversible with exercise training, maintaining regularly scheduled physical activity and conditioning is a potentially important strategy to mitigate the potential adverse effects of aging on cardiovascular function.

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Chapter 76

Vascular Aging and Atherosclerosis

George A. Heckman, Daniel E. Forman, Susan Cheng

Learning Objectives

- Understand the basic conceptual similarities and differences between vascular aging and vascular disease.
- Describe mechanisms by which vascular aging predisposes to atherosclerosis.
- Understand the clinical manifestations of vascular aging versus atherosclerosis, including cognitive impairment, and systemic and functional manifestations.
- Discuss the approach to managing vascular aging and age-related atherosclerosis.

Key Clinical Points

1. **Vascular aging is a distinct process that underlies the development of atherosclerosis and its clinical manifestations.**
2. **Increased vascular stiffness is a consequence of vascular aging that leads to the development of age-associated conditions such as hypertension and heart failure.**
3. **Emerging evidence points to potentially causal associations between vascular aging and geriatric syndromes such as cognitive impairment and frailty.**
4. **Lifelong promotion of a healthy lifestyle is essential to delay and attenuate vascular aging and its complications.**

INTRODUCTION

"A man is as old as his arteries."

Thomas Sydenham, Father of English Medicine, 1624–1689

The notion, so succinctly expressed by Sydenham, that aging and cardiovascular pathology are intrinsically linked was first articulated thousands of years ago. Cardiac disease figures prominently in the Ebers papyrus from 1550 BC that describes medicine as practiced in ancient Egypt. Many cardiovascular syndromes can be recognized. For example, the following clearly describes angina pectoris: *"If thou examinest a man for illness in his cardia and he has pains in his arms, and in his breast and in one side of his cardia … it is death threatening him."* Its accounts depict heart failure as a form of premature aging, and suggest apparent associations with cognitive impairment (in ancient Egypt, the heart was the center of knowledge and consciousness) and frailty: *"His heart is overflooded. This means that his heart is forgetful like one who thinks something else,"* and, *"Weakness of old age…"*

From the seventeenth to twentieth centuries, the work of Binswanger, Kraepelin, and Alzheimer established vascular disease as the major cause of senile dementia. Most recently, the contribution of vascular risk factors and disease to the development of the geriatric syndromes of frailty and dementia, including Alzheimer disease itself, has again come to the fore.

This chapter addresses vascular aging, and how changes in the structure and function of the arterial tree with age not only lead to atherosclerosis and its manifestations of coronary artery disease, peripheral vascular disease, and

cerebrovascular disease, but also to the development of the important geriatric syndromes of frailty and cognitive impairment.

GENETIC AND NONGENETIC FACTORS CONTRIBUTE TO AGE-RELATED ATHEROSCLEROSIS OVER THE LIFE COURSE

The development and progression of age-related atherosclerotic vascular disease results in most cases from a combination of genetic predisposition and cumulative chronic exposure to cardiovascular risk factors over the life course. With respect to genetic factors, it is important to note that a wide variety of genetic variants predispose to accelerated atherosclerosis with varying levels of severity. The specific genetic disorders associated with Werner or Hutchinson-Gilford syndrome—exceedingly rare and typically presenting in childhood or adolescence—both lead to accelerated aging phenotypes involving multiple organ systems, including the arterial vascular system. The more common types of clinical atherosclerotic disease presenting in late middle or older age are considered complex genetic disorders and, in large epidemiologic studies, have been associated with variants in multiple loci. While the function of most of these genetic loci remain unknown, those with the most validated associations have implicated loci coding for lipid traits and APOE. However, even specific cases of accelerated atherosclerosis in the general population appear predominantly due to nongenetic factors. Accordingly, investigations of genetic risk scores indicate that even the presence of multiple variants contributes a relatively small amount of increased risk for clinical atherosclerotic disease when accounting for the contribution of traditional cardiovascular risk factors.

The traditional cardiovascular risk factors that most commonly contribute to cumulative exposure and risk for atherosclerotic disease in older adults also, themselves, exhibit age-related patterns with respect to prevalence and severity. These risk factors most notably include easily identifiable clinical traits such as elevated blood pressure and cholesterol. Investigators continue to search for the common biological pathways that underlie the effects of these risk factors and that contribute to vascular aging and accelerated atherosclerosis.

VASCULAR AGING VERSUS VASCULAR DISEASE

Vascular senescence transforms vascular morphology and physiology, and increases susceptibility to atherosclerosis. However, the progression to atherosclerosis is not inexorable. More than 75% of individuals older than 60 years have clinically significant coronary stenoses on autopsy, but at least 25% of this age group will have only mild or no significant coronary plaque burden. Clearly, aging and atherosclerosis are associated but not inevitable, implying that strategies to delay or even halt age-related atherosclerosis may be feasible. The basic structure of the arterial blood vessel consists of three layers, each separated by a distinct elastic membrane (**Figure 76-1**). The intima is the innermost layer and consists of a monolayer of endothelial cells resting on a basement membrane made up of collagen and other extracellular matrix (ECM) molecules. The media consists primarily of smooth muscle cells (SMCs) on the background of an elastin-rich skeleton of ECM. Collagen, elastin, glycoproteins, and proteoglycans constitute the ECM. The outermost layer, the adventitia, contains a loose array of collagen fibrils as well as the vasa vasorum (blood vessels supplying the vasculature itself), nerve endings, fibroblasts, and mast cells.

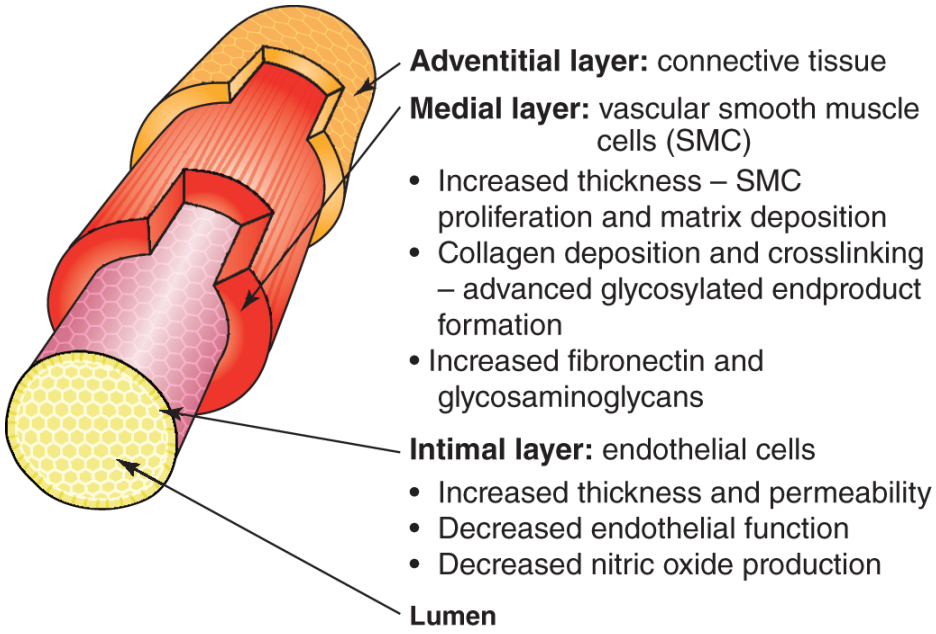


FIGURE 76-1. Arterial wall cross-section.

Because the heart generates pulsatile flow, a key attribute of the circulatory system is to translate pulsatility into laminar flow via a Windkessel effect. Aortic wall composition, particularly the ECM framework, helps to achieve this function: resultant downstream laminar flow is a key aspect of healthful physiology. Flow-related sheer stresses stimulate endothelial cells to produce nitric oxide (NO), which mediates appropriate vasodilation through a variety of signaling pathways and ultimately leads to physiologic vasomotor regulation.

Senescent vascular changes include multiple subclinical structural and physiologic modifications that disrupt this delicate physiologic balance. Structurally, vessel diameters increase, subintimal thickening evolves, smooth muscle cells and collagen hypertrophy, and fibrosis and calcification proliferate, all contributing to vascular stiffening, elevated sheer stresses, and greater afterload against which the heart must pump. The multifaceted impact of altered flow dynamics on senescent endothelial function leads to diminished capacity to synthesize nitric oxide, with impaired vasodilation, increased substrate for atherogenesis, and susceptibility to mounting clinical abnormalities (eg, increased demand stress, increased supply and demand ischemia, peripheral arterial disease, and more).

Atherosclerosis, by definition, entails the presence of an atheroma covered by a thin fibrous cap. An atheroma is a focal collection in the intima of foam cells (macrophages that have engulfed lipoproteins), proliferative SMCs (which have migrated from the media) and ECM. Remarkably, postmortem studies of young Korean War soldier casualties revealed that the initial stages of atheroma formation can occur early in life, suggesting that lifestyle may play a large role in predisposition to disease. Variations in flow mechanics and the biological milieu within the vasculature of each individual determine which segments of the arterial tree are more or less susceptible to atherosclerotic progression relative to differences in sheer stresses, oxidative stress, chronic inflammation, and the capacity of local homeostatic mechanisms to respond to such stresses. However, advanced age has been repeatedly demonstrated to be the dominating independent risk factor for atherosclerosis. With age, lifestyle patterns (especially as physical function declines), cumulative risk factor exposure, and additional comorbid diseases further contribute to age-associated risk.

BIOLOGICAL CHANGES WITH VASCULAR AGING AND VULNERABILITY TO ATHEROSCLEROSIS

Table 76-1 provides a partial list of molecular, cellular, structural, and physiologic dynamics that are associated with vascular aging and disease. Three major intertwining themes highlight how the biology of vascular aging predisposes to atherosclerotic disease (**Figure 76-2**). First, exposure to various physical and metabolic stresses over time can alter normal pathways and processes. Second, progressive accumulation of metabolic by-products can adversely affect arterial structure and function. Finally, time-dependent attrition of the basic arterial constituents and adaptive and reparative mechanisms of the arteries can lead to their dysfunction and, in turn, promote atherogenesis.

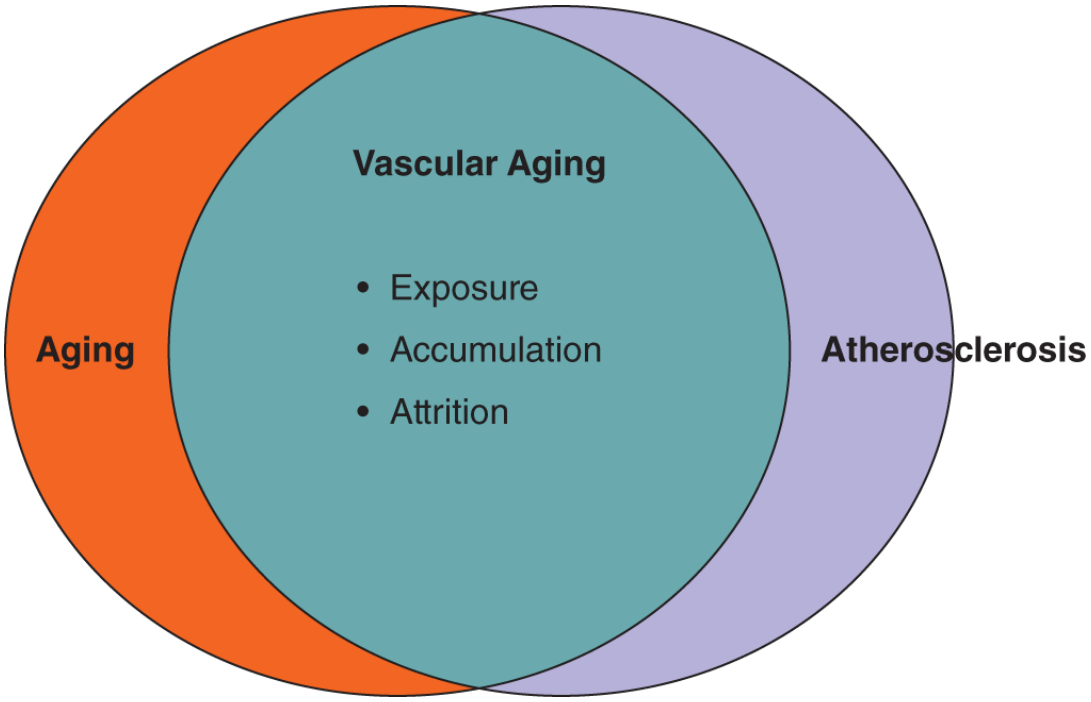


FIGURE 76-2. Schematic view of the intersection and overlap between aging and atherosclerosis.

TABLE 76-1 COMMON UNDERLYING PATHOLOGIES OF VASCULAR AGING AND ATHEROSCLEROSIS

LAYER	MOLECULAR	CELLULAR	STRUCTURAL	DYNAMIC
Endothelium	• ↑ROS • NOS uncoupling • ↓Total and free NO • ↓SOD, FOXO, sirtuins, AMPK, mTOR activity • ↑Adhesion molecule expression	• ↓Angiogenesis • Endothelial cell senescence • Progenitor cell senescence	• ↑Permeability	• ↓Vasoreactivity • ↑Sheer stress and susceptibility to sheer stress
Intima	• ↑ROS • ↑MMP levels and activity • ↑Adhesion molecule expression • ↑ACE activity • ↑AT-II activity • ↑TGF-β	• ↑SMC proliferation • SMC senescence	• ↑Thickness (from SMC proliferation and matrix deposition) • ↑Luminal diameter • Basement membrane permeability	• ↑Susceptibility to mechanical stress
Media	• ↑ Interleukins • ↑Advanced glycation end products • ↑Collagen • ↓Elastin (calcification and fragmentation) • ↑Fibronectin • ↑Glycosaminoglycans	• ↑SMC proliferation and migration • SMC hypertrophy • SMC senescence • Fibroblast senescence (resistance to apoptosis)	• ↑Thickness • ↑Luminal diameter • Collagen cross-linking • Elastin breakage • ↑Collagen fibrils • Fibrosis	• ↑Stiffness • ↓Elasticity and compliance

ACE, angiotensin-converting enzyme; AMPK, AMP-activated protein kinase; AT-II, angiotensin-II; FOXO, forkhead box O; MMP, matrix metalloproteinases; mTOR, mammalian target of rapamycin; NO, nitric oxide; NOS, nitric oxide synthase; ROS, reactive oxygen species; SMC, smooth muscle cell; SOD, superoxide dismutase; TGF-β, transcription growth factor beta.

Exposure

Elevated sheer stress over time provokes vascular injury, particularly at vessel bifurcations and curves, where atheromas tend to form. Endothelial cells play a key role in nearly every step of the atherosclerosis process, including plaque formation, platelet adhesion and aggregation, cellular migration, and proliferation. Endothelial cells subjected to chronic sheer stress can physically deform and display altered intracellular activity. Age-related endothelial dysfunction is characterized by the decreased ability of smaller arteries to dilate in response to increased blood flow. Similar to shear stress, chronic biomechanical stress can also affect endothelial function by activating mechanoreceptors, thereby converting physical stimuli to biochemical signals. Pulsatile stretch stimulates vascular smooth muscle cell hypertrophy and proliferation, and also activates matrix metalloproteinases (MMPs), some of which are proliferative while others are destructive. Imbalanced activation of MMP subtypes leads to adverse vascular remodeling, including fibrosis, which increases arterial stiffness, further exacerbating sheer and pulsatile stresses.

At the molecular level, augmented oxidative stress, measured by reactive oxidant species (ROS), underlies both vascular aging and atherogenesis. ROS are implicated in every step of atherogenesis, and this relationship is magnified in older vessels. Lipid oxidation is accelerated by ROS and, in turn, stimulates many atherogenic processes. ROS are especially potent contributors to vascular senescence as well as to atherogenic processes involving the intima and media. Mounting ROS effects may in part be attributable to dwindling antioxidant protection such that homeostatic balance depending on superoxide dismutase and other intrinsic antioxidants is no longer maintained. Changes in body composition and metabolism with age also likely increase ROS production. Effects of ROS include reduced endothelial cell synthesis of nitric oxide (due to the oxidation of NO into peroxynitrite as well as eNOS uncoupling). High ROS also leads to reduced telomere homeostasis, with telomere shortening further exacerbating the damaging effects of ROS on cellular function.

Accumulation

With aging and time, metabolic by-products can accumulate in the vascular wall, creating adverse structural and metabolic sequelae. The prototypical example is accumulation of oxidized lipids in the bloodstream and their subsequent incorporation into atheromas. The arterial wall also accrues increased amounts of normal and dysfunctional collagen, as well as broken and frayed elastin fibrils caused by elastase enzyme upregulation. Additionally, chronic and recurrent inflammatory processes result in vascular fibrosis, playing a particularly important role in vascular senescence and atherosclerosis. Activation of the proinflammatory nuclear transcription factor kappa B (NF-κB) leads to increased cytokines interleukin 1B (IL-1B), IL-6, tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein 1 (MCP-1) that further suppress endothelial cell function and increases vulnerability to atherosclerosis. Notably, early manifestations of inflammation are associated with intimal thickening that in turn exacerbate stiffening and injurious sheer stresses that trigger injury and progression of atherosclerotic pathophysiology. Accumulation of angiotensin-II has also been implicated as a key trigger of vascular remodeling. Both age-related increases in angiotensin-converting enzyme I (ACE-I) within the senescent vascular wall as well as chymase (an alternate angiotensin convertase) contribute to increased angiotensin-II. Downstream effects of renin-angiotensin-aldosterone system activation include vascular remodeling changes of thickening, fibrosis, and inflammation.

These alterations decrease arterial compliance to pulsatile flow, thicken the intima, and increase vascular permeability. Disruption in membrane permeability facilitates smooth muscle cell proliferation and migration from the media to the intima as well as transit of immune and inflammatory cells that stimulate atherogenesis. Progressive accumulation of advanced glycation end products (AGEs) also contribute to pathology over time. AGEs result from irreversible nonenzymatically formed bonds between glycated proteins, a reaction that progresses over time and with elevated glucose concentrations. Long-lived proteins (collagen) are most susceptible to glycation and, once cross-linked, are less susceptible to routine hydrolysis and thus accumulate. Structurally, AGE cross-linked arterial collagen is less compliant and contributes to age-associated central arterial vascular stiffness. Similarly, AGE cross-linked myocardial collagen fibrils in the heart result in ventricular stiffness. Through a variety of mechanisms, time- and age-dependent accrual of AGEs, especially in diabetics, likely contributes to age-associated increased endothelial dysfunction, vascular wall thickening, arterial stiffening, inflammation and fibrosis, restenosis, and atherogenesis.

Attrition The third age-related component predisposing to atherosclerosis is the reduced ability of reparative or compensatory biological processes to appropriately adapt to the age-associated structural, dynamic, and molecular alterations. One hallmark of aging is cellular aging, also known as cellular senescence. Although the precise definition

of cellular senescence is debated, it generally describes the irreversible arrest of the replicative cycle of a cell such that it no longer divides. The number of cell divisions in an organism is related to the organism's expected longevity. In addition to exhibiting a flattened and enlarged morphology, senescent cells express a specific set of genes, including negative regulators of the cell cycle. Senescent forms of endothelial progenitor cells and vascular endothelial cells, which have been found in atherosclerotic plaques, are likely facilitators of atherogenesis. Factors that predispose these vascular cells to premature aging are numerous and involve the attrition of basic cellular constituents and molecular mechanisms. These factors include telomere dysfunction, faulty DNA repair systems, insufficient endogenous antioxidants, dysregulation of the insulin/Akt pathway, and altered angiotensin-II signaling. Telomere dysfunction is of particular interest, since telomeres act as protective caps at the ends of chromosomes and are involved in cellular replication pathways. Shorter telomere length, a marker of cell turnover, has been associated with endothelial dysfunction, arterial stiffness, and the presence of traditional cardiovascular (CV) risk factors and clinically significant atherosclerotic disease. Whether owing to telomere shortening and/or other factors, aging of vascular cells is associated with processes that lead to altered vascular structure and function and, in turn, accelerated atherosclerosis. Senescent vascular endothelial cells are found to have upregulated adhesion molecules, proinflammatory cytokines, and decreased NO production. Senescence of endothelial progenitor cells is associated with decreased angiogenesis and impairment of the complex vascular repair system intended to attenuate the chronic vascular injury and inflammation that leads to atherosclerosis.

Clinical Manifestations of Vascular Aging and Atherosclerosis

Vascular aging confers an illness burden on the general population larger than that associated with any other disease process. Underlying this burden of illness are the physiologic changes the result from increasing arterial stiffness, a key manifestation of which is isolated systolic hypertension (ISH). In addition to the well-described consequences of coronary, cerebrovascular and peripheral arterial atherosclerosis, arterial aging is now increasingly recognized as an important factor underlying the key geriatric syndromes of cognitive impairment and frailty. As a result of the significant burden associated with these processes, which inevitably occur concurrently in single individuals, outcomes among older adults are significantly worse as well as more varied compared to those in younger adults (**Figure 76-3**).

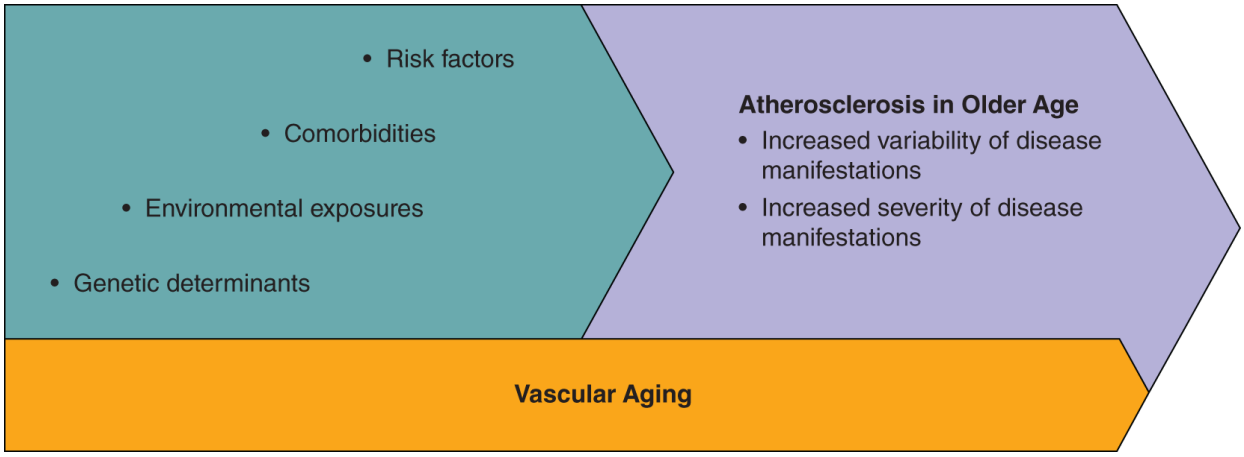


FIGURE 76-3. Contributors to the development of atherosclerosis interact with vascular aging to increase the variability and severity of disease manifestation in older age.

Arterial Stiffness and Isolated Systolic Hypertension

Arterial stiffness is a key risk factor for cardiac as well as vascular outcomes in older adults. Arterial stiffening in its early stages can be assessed across all age groups via noninvasive tonometry. A less direct and, thus, less sensitive but very specific measure of arterial stiffness is the finding of a widened pulse pressure detected from standard brachial blood pressure measurement. Increased pulse pressure, even in the absence of a frankly elevated mean and systolic pressures, is associated with adverse vascular remodeling and outcomes. The most common clinical manifestation of arterial stiffness is ISH, defined as a systolic pressure greater than 140 mm Hg and diastolic pressure less than 90 mm Hg. ISH is a key clinical consequence of increased arterial stiffness that can result from vascular aging and atherosclerosis of the central arterial system. The prevalence of ISH increases with age and peaks at the age of 70.

People who are not hypertensive at age 65 who achieve their average life expectancy have an almost 90% chance of developing ISH.

Young central arteries are elastic, which allows them to distend to absorb the pressure wave from left ventricular systole, and distal vascular beds are cushioned from excessively forceful pulsatile flow. The pressure wave is partially reflected at the bifurcations with elastic arteries with higher-resistance distal vessels. The reflected wave is impeccably timed to arrive back at the heart after the closure of the aortic valve, thus supporting diastolic pressure and coronary perfusion without contributing to left ventricular afterload. Increasingly stiff central arteries are progressively less able to cushion the pressure wave, leading to increased systolic pressure and more rapid distal transmission of a higher-amplitude pressure wave. This leads to a number of pathologic physiologic changes: (1) the increase in systolic pressure and associated shear stress accelerates and exacerbates the process of arterial aging and stiffness, and promotes the development of greater atherosclerosis; (2) the reflected pressure wave is of greater amplitude and arrives back to the heart before aortic valve closure, resulting in increased left ventricular afterload, left ventricular hypertrophy, diastolic dysfunction, relative coronary hypoperfusion, lower diastolic blood pressure, and increased pulse pressure; and (3) highly vascular end organs, such as the brain and the kidneys, are subjected to highly pulsatile flow, leading to vascular damage and predisposing to ischemic injury.

These physiologic changes imparted by a central arterial stiffness increase the vulnerability of older persons to atherosclerosis and its consequences. Stressors such as alterations in intravascular volume or tachycardia (from dehydration, fever, hyperthyroidism, arrhythmias, or deconditioning) can thus easily provoke symptoms or events in older adults. The co-occurrence of relative coronary hypoperfusion pressure, in addition to left ventricular hypertrophy, diminishes myocardial perfusion, resulting in ischemia often in the absence of discrete coronary lesions. Further, increased left ventricular pressures from augmented afterload exacerbate left atrial and pulmonary pressures, which lower the dyspnea threshold.

ISH is therefore a key risk factor for the development of atherosclerosis and associated events, including myocardial infarction (MI), heart failure, strokes, renal failure, total mortality, and dementia, and thus an important therapeutic target. The management of ISH is described further in Chapter 82.

Arterial Aging, Cerebrovascular Disease, and Cognitive Impairment

Stroke is arguably the most commonly recognized consequence of cerebrovascular atherosclerosis and a significant cause of morbidity, disability, and mortality in older individuals (see Chapter 65). Presenting complaints range from classical hemiplegic stroke to cognitive impairment resulting from often silent and chronic cerebral ischemia. Clinically occult cerebrovascular disease is common in older individuals, especially in those with orthostatic hypotension and hypertension independent of other risk factors.

However, arterial stiffness per se is increasingly recognized as an important risk factor for vascular cognitive impairment independent of cerebrovascular atherosclerotic burden. A recent systematic review of observational studies demonstrated a robust association between arterial stiffness and cognitive impairment in 14 of 15 cross-sectional studies, and an association between arterial stiffness and cognitive decline in six of seven longitudinal studies. This association appears to be mediated by an increased prevalence of ischemic white matter disease and lacunar infarctions in persons with arterial stiffness. The review suggests that arterial stiffness is a risk factor for incident vascular dementia, and that vascular stiffness may be associated with Alzheimer disease and mild cognitive impairment. Evidence suggests that ischemic injury may be mediated by increased pulse pressure and relatively lower diastolic blood pressure.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

More than half of older heart failure patients presenting with symptomatic heart failure with preserved ejection fraction (HFPEF, see Chapter 79). Characteristics associated with the clinical presentation of HFPEF include older age, female sex, atrial fibrillation, relative obesity, anemia, and renal insufficiency. The pathogenesis of HFPEF likely involves multiple factors, including long-standing hypertension, left ventricular hypertrophy (LVH), and impaired early diastolic relaxation. Preliminary evidence suggests that arterial stiffness may be a precursor to heart failure. The Multiethnic Study of Atherosclerosis (MESA) of 5960 subjects free of cardiovascular disease and followed 7.6 years found that increased central arterial pressure, a marker of arterial stiffness, was a strong predictor incident heart failure. Increased central pulse pressure has been associated with the development of LVH as well as heart failure events in older persons. LVH develops in response to increased ventricular afterload imposed by the consequences of increased

aortic stiffness and the early reflected pulse wave. In addition to LVH, isovolumic relaxation of the ventricle is prolonged, encroaching on diastole. Thus, increased central arterial stiffness exacerbates impaired early diastolic relaxation and filling. At rest, the ventricular and central vascular functions of the older adult remain fairly energetically coupled. Normally, ventricular-vascular coupling implies that the heart is functioning at maximum metabolic efficiency and can maintain blood pressure and cardiac output in a physiologic range. However, in the older adult, as both the myocardium and the central vasculature stiffen, the cardiovascular reserve mechanisms are challenged by stressors, resulting in labile blood pressure at higher cardiac work. Factors that can trigger an exacerbation of HFPEF are similar to those that can trigger systolic heart failure. However, HFPEF may be more afterload and preload dependent, necessitating tight blood pressure control and judicious use of diuretics as a part of long-term management. Interestingly, aortic stiffening may be greater in older women, thus explaining in part the increased prevalence of HFPEF in this population.

Coronary Artery Disease

The lifetime risk for symptomatic coronary artery disease (CAD—see Chapter 77) after the age of 40 is 49% in men and 32% in women, and the average age of patients suffering a first MI is 64.9 in men and 72.3 in women. Of those who die from CAD, over 80% are aged 80 and over. Arterial stiffness is an important risk factor in the development of CAD, as well as in determining patient outcomes. While classical risk factors (smoking, physical inactivity, hypertension, diabetes mellitus, hyperlipidemia) account for most cases of CAD, a significant proportion of people develop CAD despite a minimal burden of these risk factors. Arterial stiffness may precipitate this risk through the development of incident hypertension. A systematic review of 17 longitudinal studies of 15,877 older subjects followed for almost 8 years shows that increased arterial stiffness was associated with an increased risk of cardiovascular events (heart rate [HR] 2.26, 95% confidence interval [CI] 1.89–2.70), cardiovascular mortality (HR 2.02, 95% CI 1.68–2.42), as well as all-cause mortality (HR 1.90, 95% CI 1.61–2.24). The risk of poor outcomes was greatest among those with elevated baseline risk of events (eg, preexisting CAD).

PERIPHERAL ARTERIAL DISEASE

The prevalence of peripheral arterial disease (PAD—see Chapter 81) increases with age and in individuals older than 55 years is estimated at 16.9% in men and 20% in women, and is linked to both symptomatic and asymptomatic atherosclerotic disease, smoking, and hypertension. Measurement of the ankle-brachial index (ABI) is often used for the noninvasive identification of PAD, which is associated with significantly reduced quality of life and decreased functional performance. However, functional performance correlates less with the ABI than it does with arterial stiffness, which has been shown in patients with PAD to correlate with aerobic fitness. Underlying mechanisms associated with arterial stiffness may include coronary hypoperfusion and diastolic dysfunction that through microcirculatory dysfunction and endothelial dysfunction, may impair skeletal muscle function.

RENAL DISEASE

Similarly to the brain, kidneys are highly vascular organs and are thus highly susceptible to increased arterial and arteriolar pulsatility. Arterial stiffness has been associated with an increased risk of end-stage renal disease (ESRD—see Chapter 88), and has also been identified as a risk factor for more rapid progression of renal disease. In turn, ESRD is also a risk factor for arterial stiffness, which increases the risk for poor outcomes in patients with ESRD. In addition renal artery stenosis (RAS) is primarily caused by atherosclerosis, often characterized by plaque extending from the aorta into the renal artery lumen, creating an ostial lesion. The prevalence of RAS increases with age, especially in the setting of risk factors such as hypertension. Renal atrophy and ischemic changes may result from progressive reduction in renal blood flow or by microthromboembolism from unstable prothrombotic plaques. Progressive renal dysfunction, increased sympathetic nervous system activity by the ischemic kidney, and augmentation of the renin-angiotensin-aldosterone system can exacerbate preexisting hypertension, resulting in cardiac and cerebrovascular complications. The resulting severe hypertension from unilateral RAS can also lead to contralateral renal disease, and thus progress to end-stage renal failure. Atherosclerotic RAS may account for up to 15% of admissions with ischemic nephropathy leading to ESRD among older persons.

ABDOMINAL AORTIC ANEURYSMS

Abdominal aortic aneurysms are most commonly found incidentally on examination or imaging (see Chapter 81). Increased MMP activity and decreased tissue inhibition of MMPs are found in abdominal and thoracic atherosclerotic aneurysms compared with nonatherosclerotic lesions. In the setting of chronic inflammation and oxidative stress—which promote the progression of in situ atherosclerotic plaque—MMPs have been implicated in the degradation of structural proteins (eg, elastin, collagen, and laminin) that contribute to aneurysmal dilatation of the aortic wall. Small studies suggest that arterial stiffness also plays a role in the development of abdominal aortic aneurysms. Notably, older women tend to develop abdominal aortic aneurysm at a more advanced age than older men and are more likely than men to suffer aneurysmal rupture. However, the extent to which increased arterial stiffness contributes to higher rupture rates in women remains unknown.

ARTERIAL AGING AND FRAILTY

Aging is not a heterogeneous process, and while some older persons remain fully engaged in a variety of activities well beyond their 80s, others age less well, requiring caregiver support to remain in their own homes, or even institutional care. Much of this heterogeneity can be explained by the concept of frailty (see Chapter 46). Frailty is a state arising from reduced physiologic reserve across multiple systems—an accumulation of deficits—and renders an individual, usually but not exclusively of advanced age, highly vulnerable to poor outcomes when challenged by health stressors. A systematic review confirms that a strong association exists between frailty and a wide-range of chronic cardiovascular conditions, both clinical and subclinical. Several longitudinal studies also demonstrate that the greater the cardiovascular risk, the more likely an individual is to develop incident frailty. Furthermore, this association may be bidirectional: for example, frail persons may be more likely to develop incident heart failure, and persons with heart failure are more likely to develop frailty. The presence of frailty in a person with cardiovascular disease confers an increased risk of adverse outcomes, including mortality, morbidity, health-service utilization, and impaired quality of life.

Arterial stiffness can be associated with frailty through its association with cardiovascular disease. However, emerging evidence also suggests that abnormal arterial structure and physiology may be independently associated with frailty. Cross-sectional analysis of the Toledo Study on Healthy Aging showed that markers of endothelial dysfunction were associated with frailty, as measured by the Fried criteria. In the Health, Aging and Body Composition study, pulse wave velocity (a marker of arterial stiffness) was associated with decline in gait velocity (a marker of frailty) over 7 years in patients with established PAD; this relationship was not noted in otherwise health controls. Most intriguing given that frailty-associated sarcopenia has been associated with an increased risk of cardiovascular mortality is the result of a cross-sectional study of almost 500 middle-aged to older adults in whom increased arterial stiffness was associated with decreased thigh muscle volume, primarily in men.

IMPLICATIONS OF FRAILTY ON THE MANAGEMENT OF OLDER ADULTS WITH CARDIOVASCULAR DISEASE

Frailty occurs in up to 60% of older adults with cardiovascular disease, in whom it is associated with worse outcomes. Frailty is a better marker of risk than chronological age, and can thus help identify patients at lower risk despite a more advanced age, and persons at higher risk despite a lower chronological age. Frail individuals with certain conditions, particularly those with cognitive impairment, may have more to lose from undertreatment, and thus more to gain from more intensive interventions, such as heart failure management programs. Frail persons with acute cardiovascular conditions are more likely to present with nonspecific symptoms such as delirium, falls, or rapid functional decline; in such situations, clinicians must retain a high index of suspicion for conditions such as an acute coronary syndrome or heart failure. Frailty can be assessed and managed through comprehensive geriatric assessment (see Chapter 10), and potential stressors, such as nongeriatric friendly hospital care processes, anticipated and addressed (see Chapter 16). Finally, frailty may be so severe that the potential benefits of any proposed intervention, for example coronary artery bypass surgery or transcatheter aortic valve implantation, are outweighed by the risks related to the potential of a severe stressor on the frail individual, and, thus, help inform important discussions about treatment decisions with patients and their families.

PRINCIPLES OF MANAGING VASCULAR AGING AND AGE-RELATED ATHEROSCLEROSIS

The incremental vascular changes that precede clinical atherosclerosis and its varied manifestations—including endothelial dysfunction, arterial stiffness, and subclinical atherosclerosis—typically develop over the life course. Therefore, primordial prevention of vascular aging and age-related atherosclerosis ideally begins in youth, with maintenance of a healthy diet and lifestyle that includes regular physical activity and avoidance of traditional cardiovascular risk exposures such as tobacco. Nonetheless, slowing down or even reversing at least some aspects of vascular aging may yet be possible in middle or older adulthood. Despite lack of definitive evidence for specific therapies, research to date suggests the potential of certain approaches to optimizing vascular health with aging.

Endothelial dysfunction, considered one of the earliest precursors to atherosclerosis, is associated with a variety of pathologic stressors (eg, oxidative and inflammatory markers) that have been studied as therapeutic targets. To date, however, targeted antioxidant therapies (eg, vitamins C or E) have not been shown to offer any clear benefit on outcomes. Similarly, targeted anti-inflammatory agents have yet to demonstrate efficacy at ameliorating endothelial dysfunction or improving outcomes. In particular, low-dose aspirin has yet to be proven as a preferred agent for preventing new-onset vascular events in older adults, although large prospective trials are currently underway. Alternately, endothelial dysfunction has been shown in experimental studies to improve in the setting of administering newer-generation β-blockers (nebivolol, carvedilol), calcium channel blockers, ACE inhibitors, angiotensin receptor blockers (ARBs), and particularly statins. Some studies suggest that statins not only provide anti-inflammatory effects but can also augment the production or release of endothelial progenitor cells, which may offer endothelial reparative and regenerative properties. At present, however, there is only scant clinical evidence to suggest that these therapies might improve endothelial function and, in turn, add benefit incremental to the blood pressure and lipid-lowering effects with respect to clinical outcomes. Interestingly, physical activity, and particularly aerobic fitness, has been associated with better endothelial function, even in persons with overt clinical atherosclerotic disease (eg, patients with peripheral arterial disease). Maintenance or increase in lean body mass might attenuate ROS accumulation and, in turn, contribute to vascular health.

Arterial stiffness, considered a hallmark of vascular aging, has been the target of numerous clinical studies. Data from multiple studies suggest that arterial stiffness is associated not only with typical cardiovascular outcomes but also with the accelerated development of milder as well as more severe forms of cognitive impairment. Data from studies including the Hypertension in the Very Elderly Trial (HYVET) suggest that arterial stiffness (assessed by pulse pressure) may be a central factor that mediates the potential relationship between hypertension and dementia. Nonpharmacologic therapies that have shown promise for reducing arterial stiffness include exercise and weight loss. Garlic powder, α-linoleic acid, and fish oil treatments have also been studied. Although some studies suggest that arterial stiffness is difficult to reverse with diet and exercise, especially in the setting of cardiometabolic risk factors, other studies have observed that resistance and particularly aerobic exercise training is associated with improved arterial compliance in postmenopausal women and even in individuals with established clinical atherosclerotic disease. Pharmacologic therapies that appear able to reduce arterial stiffness include all the major antihypertensive medication classes particularly calcium channel blockers, ACE inhibitors, ARBs, and aldosterone antagonists, which may act by reducing arterial collagen deposition. ACE inhibitors and ARBs may also serve to inhibit the expression of proinflammatory mediators and, in turn, attenuate adverse vascular remodeling. Arterial stiffness may also be reduced with the use of statins and targeted AGE breakers such as alagebrium (ALT-711). However, the extent to which therapy-related reduction in arterial stiffness translates into a reduction in clinical events has yet to be determined in long-term trials.

Subclinical atherosclerosis has been the subject of much research with respect to its potential as a therapeutic target in persons of all ages. Several trials have shown that reducing low-density lipoprotein (LDL) cholesterol with statin therapy is associated with significant reductions in the rates of subclinical coronary and carotid atherosclerosis disease progression. The extent to which statin therapy targeted to lower either LDL cholesterol or C-reactive protein is effective at reducing both atherosclerosis and adverse events as part of primary prevention, particularly in older adults, is not yet clear (Chapter 111). However, a subanalysis of the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study did show even greater clinical risk reduction in adults age 70 and older compared to younger adults. The majority of these individuals were known to have high baseline Framingham risk score as well as hypertension, suggesting a high prevalence of subclinical atherosclerosis in this

cohort. Importantly, the vast majority of clinical trials including JUPITER did not enroll many adults over age 80, and so it remains unclear if therapies for potentially slowing the progression of atherosclerosis and lowering its associated risk can also be extended to very old adults.

SUMMARY

Vascular aging is a highly prevalent life course process that strongly predisposes to the development of atherosclerotic disease, as well as to other important geriatric syndromes. Research to date reveals that the relationship between vascular aging and atherosclerosis is complex and multifaceted. Accordingly, the clinical implications of vascular aging and atherosclerosis in older compared to younger individuals are more varied and more severe, involving more than just the heart and vasculature, but also the brain, the kidneys, and the overall fitness, or frailty, of the individual. Although novel therapies to target vascular aging and atherosclerosis are being tested, the most effective approach to reducing the overall atherosclerotic disease burden in aging adults remains a focus on lifelong risk factor modification for primordial prevention. Traditional and readily available nonpharmacologic as well as pharmacologic therapies for risk factor modification remain underused in older adults, and this should be emphasized to both patients and providers as evidence-based guidelines for older cardiovascular patients continue to evolve.

ACKNOWLEDGMENTS

This chapter is dedicated with gratitude to Dr. Irene Turpie.

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Chapter 77

Coronary Heart Disease

Karen P. Alexander, Eric D. Peterson

Learning Objectives

- Understand the prevalence of coronary heart disease (CHD) in older adults.
- Describe the clinical features—including symptoms, signs, and results of diagnostic tests—that distinguish CHD in older adults from that occurring during middle age.
- Understand current treatment of CHD in older adults.

Key Clinical Points

1. **CHD is common in older adults; more than 80% of CHD deaths occur in persons older than 65 years.**
2. **Overt CHD represents the tip of the coronary disease iceberg; many older patients have asymptomatic, subclinical disease.**
3. **The prevalence of angina increases with age, but older individuals also complain of atypical features such as dyspnea, abdominal pain, fatigue, confusion, or malaise.**
4. **Delay in recognizing symptoms contributes to later presentation in older patients.**
5. **Older patients with symptoms suggestive of CHD should undergo a similar assessment for coronary disease as younger patients. Yet, older patients frequently experience difficulty with exercise testing and may need modified protocols or pharmacologic-based stress tests.**
6. **Without high-risk features, an initial attempt to manage symptoms with medical therapy is warranted.**
7. **Management of coronary heart disease must be individualized in older patients with competing morbidities and in accordance with goals of care.**

DEFINITION

Coronary heart disease (CHD) describes the spectrum of clinical presentations resulting from insufficient oxygen supply for the demands of the myocardium. Atherosclerosis in the coronary circulation causes luminal narrowing and provides the substrate for vascular dysfunction and thrombosis. The clinical manifestations of CHD include stable ischemic heart disease as well as unstable angina and acute myocardial infarction (MI).

EPIDEMIOLOGY

Despite a decline in mortality from coronary heart disease during the past three decades, it remains the leading killer of both men and women in the United States. More than 80% of CHD deaths occur in persons older than 65 years. In addition, 37% of recognized acute MIs occur in those older than 75 years, and, although these account for roughly 6% of the US population, 60% of all MI-related deaths affect patients 75 years or older.

The spectrum of CHD includes asymptomatic or subclinical CHD, stable angina, unstable angina, and acute MI. In the United States, the prevalence of CHD, MI, and angina all increase with age in both men and women (**Figures 77-1** and **77-2**). The initial manifestation of CHD may be an acute MI, occurring in about in 40% of cases, or sudden death in 10% to 20% of cases. Furthermore, despite the fact that women typically have a 10-year lag in CHD manifestations as compared with men, the majority of patients with CHD older than 75 years are women because of survival biases.

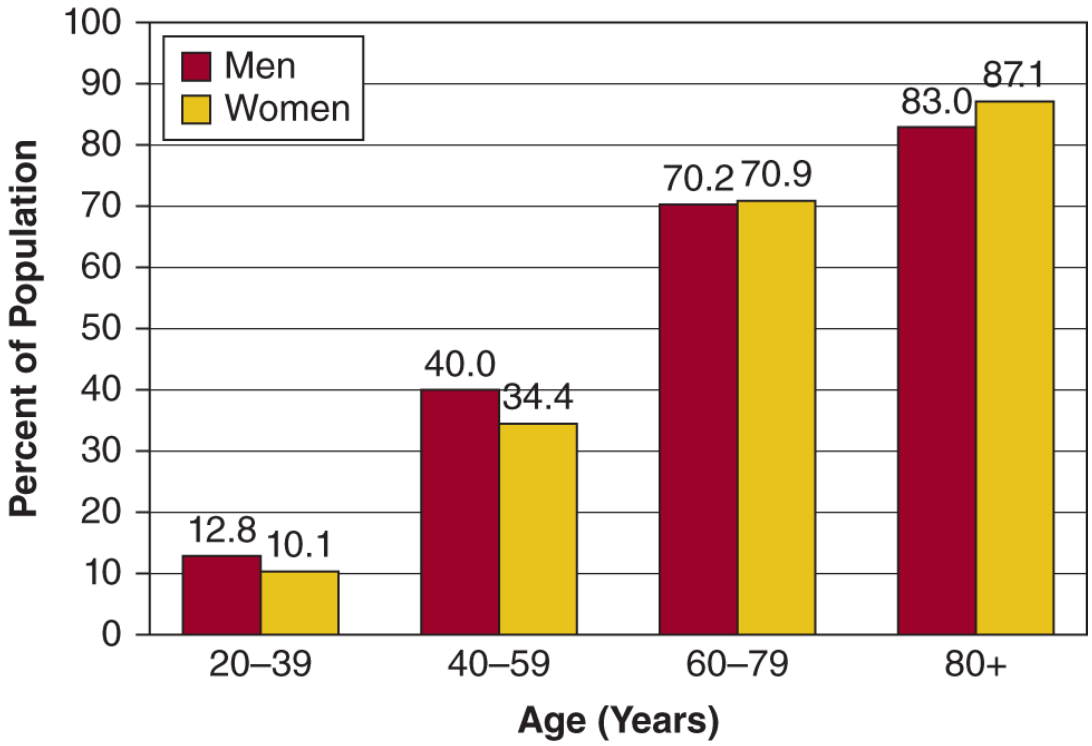


FIGURE 77-1. Estimated prevalence of coronary heart disease by age and sex. (Adapted with permission from Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update. *Circulation*. 2014;129:e28–e292.)

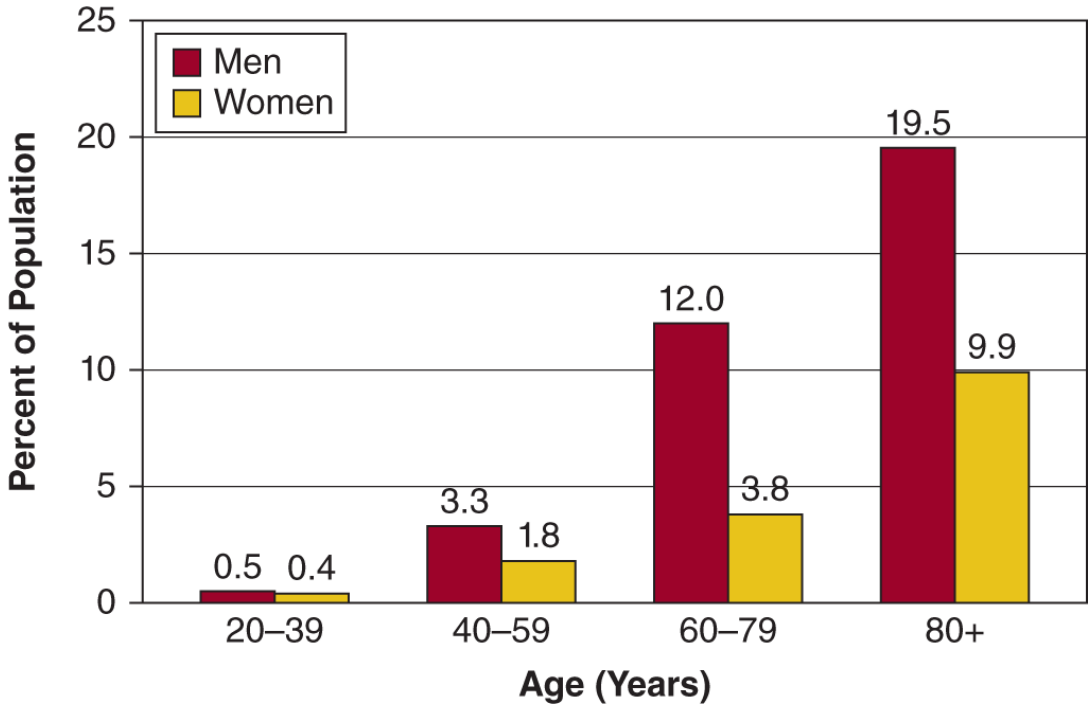


FIGURE 77-2. Estimated prevalence of myocardial infarction by age and sex. (Adapted with permission from Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update. *Circulation*. 2014;129:e28–e292.)

Overt CHD represents the tip of the coronary disease iceberg and a great number of older patients have asymptomatic, subclinical disease. Researchers for the Cardiovascular Health Study examined the prevalence of both clinical and subclinical cardiovascular disease (CVD) in a large community-dwelling Medicare population by using a composite measure of MI on electrocardiogram (ECG) or echocardiography and abnormal carotid artery wall thickness or ankle-brachial blood pressure index and found that disease frequency increased from 22% in women aged 65 to 70 to 43% in those aged 85 or older. Similarly, the frequency of subclinical vascular disease in men increased from 33% to 45% in these age groups, respectively.

PATHOPHYSIOLOGY (CLASSIFICATION)

Cardiovascular changes are seen commonly with advancing age. Arterial stiffening is prevalent and results in isolated systolic hypertension and widened pulse pressures, factors known to be associated with an increase in cardiovascular events. Elevated end-diastolic pressures that accompany heart failure with preserved ejection fraction (EF) further impair the diastolic filling of the coronary circulation. The aging of the vasculature also heralds blunted responses to protective vasodilatory mediators and progressive endothelial dysfunction. This endotheliopathy results in increasing numbers and severity of atherosclerotic plaques. The composition of these lesions also changes with age, with reduction in the soft lipid core and an increase in calcification and fibrosis. While more advanced calcified plaques are actually less likely to rupture, the sheer increase in lesion numbers leads to an increased overall likelihood for CHD events in the older patient.

CHD is defined by a diagnosis of a cardiovascular event, ischemia on noninvasive testing, or obstructive coronary artery disease (CAD), which can exist together or in isolation. In addition, angina, a patient-reported experience, may or may not occur with these other identifiers of coronary disease. Some examples of presentation types include evidence of prior silent MI on ECG, stable angina without ischemia on noninvasive testing, or asymptomatic ischemia found on noninvasive testing. The presence of obstructive CAD may also vary across these presentations. Findings of coronary calcification on imaging mark the presence of CAD, and should trigger evaluation and management of risk factors and/or symptoms.

The pathophysiology underlying the acute coronary syndromes (ACSs) involves atherosclerotic plaque rupture, platelet activation/aggregation and embolization, endothelial dysfunction, inflammation, and thrombus formation. If a clot completely occludes a coronary artery, the patient suffers an acute MI, and an injury pattern (eg, ST elevation) is often seen on the ECG. In contrast, patients with plaque rupture can also form a nonocclusive thrombus, resulting in subendocardial ischemia. Acute coronary syndromes include unstable or new-onset angina and MI defined by myocardial necrosis as evidenced by elevated cardiac markers. The separation between unstable angina and MI has shifted with the advent of high sensitivity troponins, now identifying very low levels of circulating cardiac troponin. This has increased the number of patients previously identified as unstable angina now in the category of MI. Even low levels of circulating troponin are associated with increased risk, although there is ongoing debate about the diagnosis of MI as opposed to myocardial injury without infarction at the low end of the spectrum of detection. MI type is also stratified by ECG findings of ST-segment elevation MI (STEMI) or nondiagnostic ECG considered non-ST–segment elevation MI (NSTEMI). These are related to the extent of transmural injury and may or may not result in Q-wave infarction after treatment and symptom resolution (**Figure 77-3**).

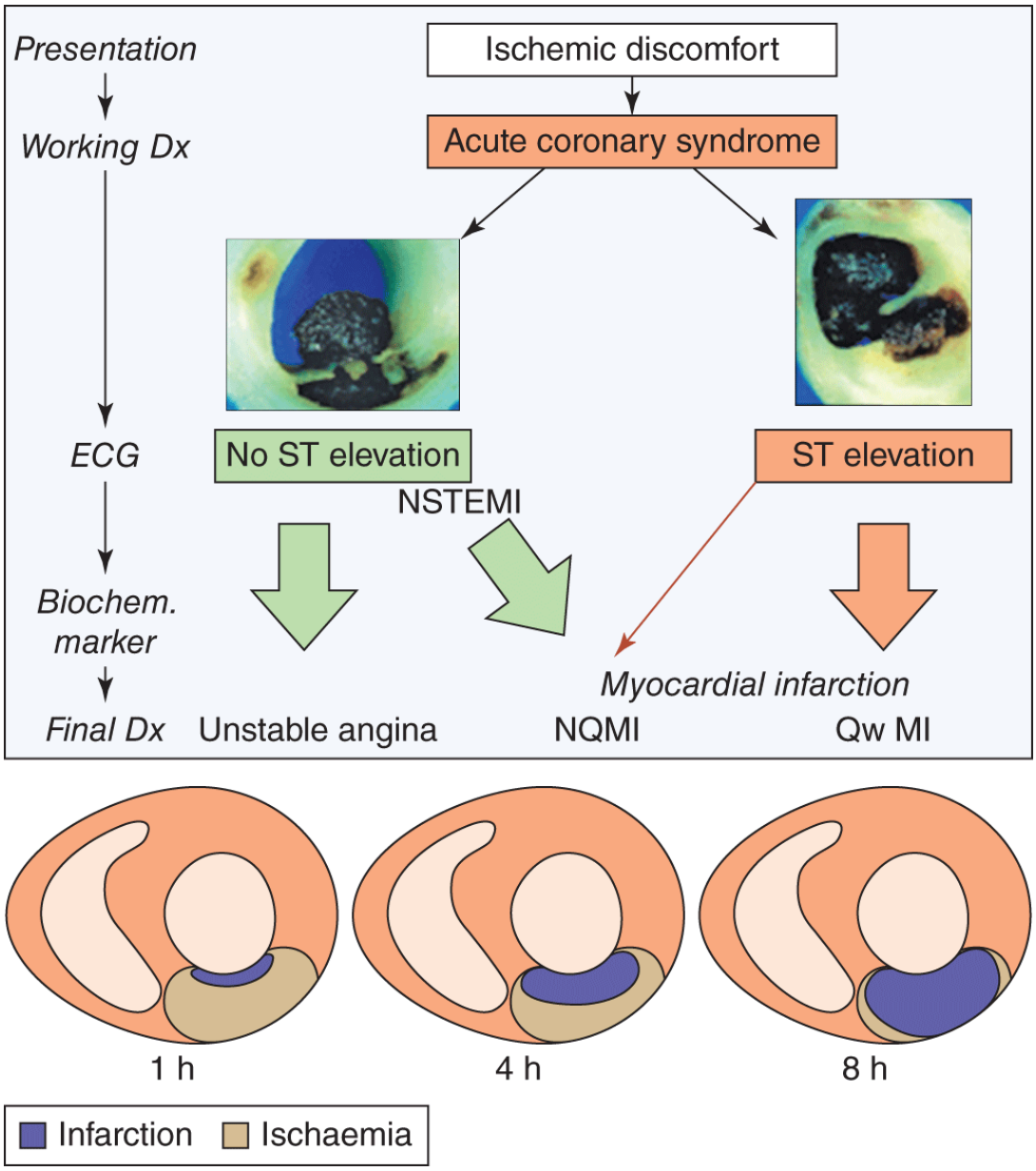


FIGURE 77-3. Myocardial infarction classification by ECG findings and pathophysiology. (Adapted from Hamm CW, Bertrand M, Braunwald E. Acute coronary syndrome without ST elevation: implementation of new guidelines. *Lancet*. 2001;358:1533–1538; MJ Davies: Heart 83:361, 2000; with permission from the BMJ Publishing Group.)

PRESENTATION

The prevalence of angina increases with age in the general population (**Figure 77-4**). It is also the case that older individuals more often complain of atypical features such as a vague feeling of dyspnea, abdominal pain, fatigue, confusion, or malaise that may be misinterpreted as consequences of aging or other comorbid illness. Findings from the Global Registry of Acute Coronary Events, a large, prospective, multinational registry of ACSs, demonstrated that patients presenting with atypical symptoms were less likely to receive appropriate cardiac medications, undergo cardiac catheterization, and were at higher risk of in-hospital morbidity and mortality. Older people can also have an impaired ischemia warning system. In a series of patients with CHD undergoing treadmill testing, researchers found that patients aged greater than 70 took more than twice as long as their younger counterparts to report angina symptoms after ECG-documented ischemia was noted.

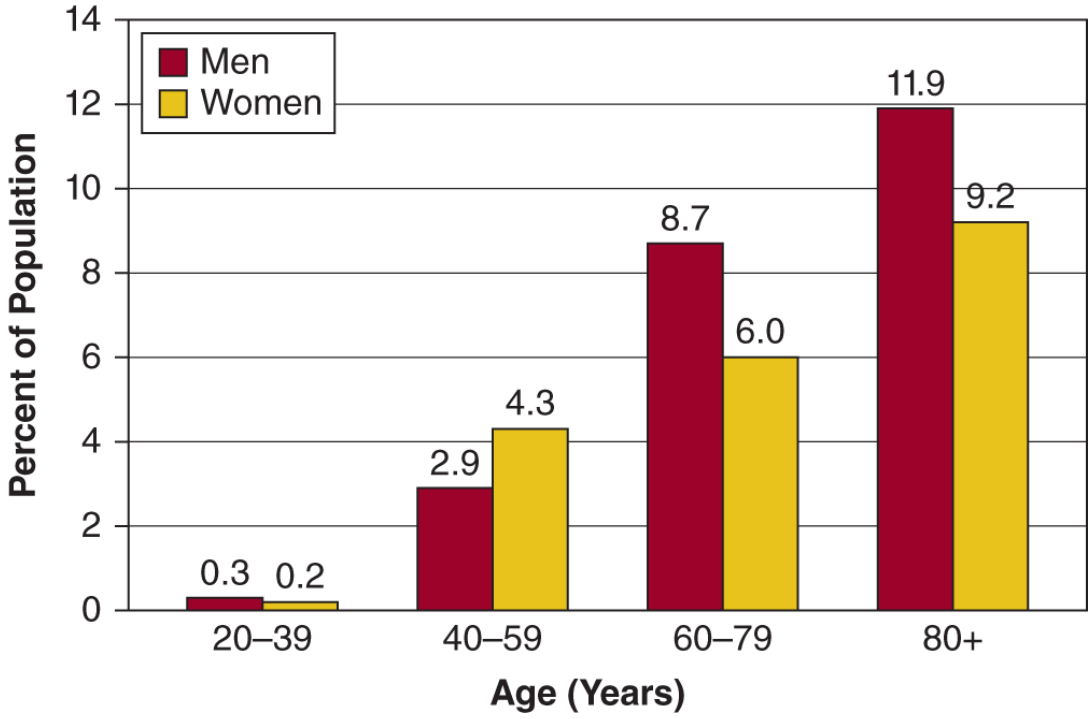


FIGURE 77-4. Estimated prevalence of angina pectoris by age and sex. (Adapted with permission from Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update. *Circulation.* 2014;129:e28–e292.)

Difficulty in recognizing symptoms contributes to later presentation of acute events in older patients. In fact, studies show that more than two-thirds of patients with MI, greater than 65 years old, fail to reach an emergency department within 6 hours after the onset of their symptoms. In the Worcester Heart Attack Study, patients 75 years and older had the longest prehospital delay of any age group, many outside the critical 6-hour window for fibrinolytic therapy. The Rapid Early Action for Coronary Treatment study quantified delay time as an additional 14 minutes for every 10-year increment in age, beginning with the age of 30. The significant prehospital delay among older patients is multifactorial and includes considerations such as atypical presentation, medical comorbidities, previous experiences within the health care system, socioeconomics, access to care, and cognitive and functional impairments. Importantly, delays in MI presentation have strong prognostic implications. Thus, clinicians should advise that cardiac symptoms can vary and patients should seek rapid medical attention if ischemic symptoms occur.

EVALUATION

Given its prevalence and often atypical presentation in older patients, clinicians must have a high index of suspicion for CHD to make the diagnosis. In taking a thorough history, with emphasis on prior CVD, clinicians must pay close attention to assessing a patient's major cardiac risk factors (smoking, hypertension, diabetes mellitus, and lipid status), as well as any symptoms suggestive of CHD. Eliciting the temporal course of these symptoms is also important. Patients with new, progressive, or refractory symptoms typically require an expedited—and possibly inpatient—evaluation, in contrast to those patients with chronic stable symptoms.

A systematic approach to the physical examination with awareness of age-related changes in the cardiovascular system may provide further clues to the presence of CHD. Some older patients develop calcific vascular disease, and pseudohypertension may be observed. Diminution of the femoral pulses or brachial-femoral delay may suggest the presence of atherosclerotic aortoiliac disease, and these findings may accompany observed dermatologic changes with lower extremity hair loss. Performing ankle-brachial indices remains a useful and sensitive screening tool for identifying patients with peripheral vascular disease, a known risk factor for increased cardiovascular events. The cardiac examination may include signs of left- or right-sided heart failure (pulmonary edema, displaced point of maximal impulse, an S_3, or peripheral edema) or characteristic murmurs of valvular heart disease. Once a thorough history and physical has been completed, further diagnostic evaluation should be based on the patient's symptoms as outlined below. Risk factors, particularly blood pressure and lipid screening, should be measured. Obtaining a baseline ECG is also reasonable because of the high prevalence of silent MIs in older individuals.

Beyond the standard history, physical examination, and simple laboratory tests, further diagnostic testing (carotid ultrasound, treadmill testing, echocardiography, or electron-beam computed tomography) in the asymptomatic older patient to detect occult or subclinical CHD remains controversial and is not generally recommended.

Older patients with symptoms suggestive of CHD should undergo a similar assessment for obstructive coronary disease as younger patients. These are based on algorithms that take into account symptom characteristics, including angina type (nonanginal, atypical, or typical), its course (stable, progressive, or unstable), and its duration. This initial assessment of a patient's pretest probability of disease should guide diagnostic testing. In particular, clinicians need to be cognizant that, according to Bayesian theory, the predictive value of a test is influenced by the disease prevalence in the population tested. For example, clinicians may interpret a negative stress test in a high-risk older woman (pretest probability of disease 80%) as "ruling out" the presence of CHD, whereas this patient's posttest likelihood remains more than 60% (**Table 77-1**). For these reasons, older patients with high pretest likelihood for coronary disease should be considered for direct referral for cardiac catheterization (if revascularization is an appropriate option). At the other extreme, patients with a low pretest probability for CAD less than or equal to 20% (ie, no risk factors, normal ECG, and very atypical symptoms) can often be followed clinically and/or be assessed for other etiologies of their symptoms (gastrointestinal, pulmonary, musculoskeletal, etc). Older patients with an intermediate pretest probability for CHD (between 20% and 70%) are those in whom stress testing has its greatest impact on clinical decision making.

TABLE 77-1 INFLUENCE OF AGE ON PREDICTIVE VALUE OF STRESS TESTING (BAYES THEOREM)

HISTORY	AGE (Y)	PRETEST LIKELIHOOD OF SIGNIFICANT CAD[a] (%)	TREADMILL TEST[b]	POSTTEST LIKELIHOOD OF SIGNIFICANT CAD (%)
Female, typical CP	45	30	Positive	56
			Negative	16
↑ Lipids	75	80	Positive	92
			Negative	63
Female, atypical CP	45	5	Positive	12
			Negative	3
No RF	75	35	Positive	62
			Negative	18

CAD, coronary artery disease; CP, chest pain; RF, risk factor.

[a]Based on CAD risk nomogram for predicting significant CAD.

[b]Sensitivity of treadmill test = 68%, specificity = 77%.

When a stress test is indicated, guidelines recommend standard exercise ECG as a first strategy for most patients. The exercise ECG provides important prognostic information (including exercise duration and hemodynamic response), as well as electrocardiographic indications of ischemia (ST depression). Older patients, however, frequently experience difficulty with exercise testing because of deconditioning or disability and may need modified protocols starting at lower levels with slower stage progression. Alternatively, for patients who cannot exercise, a pharmacologic-based stress test (dobutamine, adenosine, or dipyridamole) is warranted. In older patients with baseline ECGs abnormalities (resting ST depression, left bundle branch block, left ventricular hypertrophy with strain, or paced rhythms), imaging modalities, such as nuclear perfusion or stress echocardiography, are required. While these modalities significantly add to the cost of the test, these improve the diagnostic accuracy beyond stress ECG alone and provide information as to the location and extent of coronary disease. Thus, the choice of diagnostic test should consider the clinical setting as well as local availability and expertise (**Figure 77-5**). There is no need to repeat stress tests for asymptomatic patients with stable ischemic heart disease, and appropriateness criteria and guidelines advise against repeat testing within 2 years of percutaneous coronary intervention (PCI) and 5 years of coronary artery bypass graft (CABG).

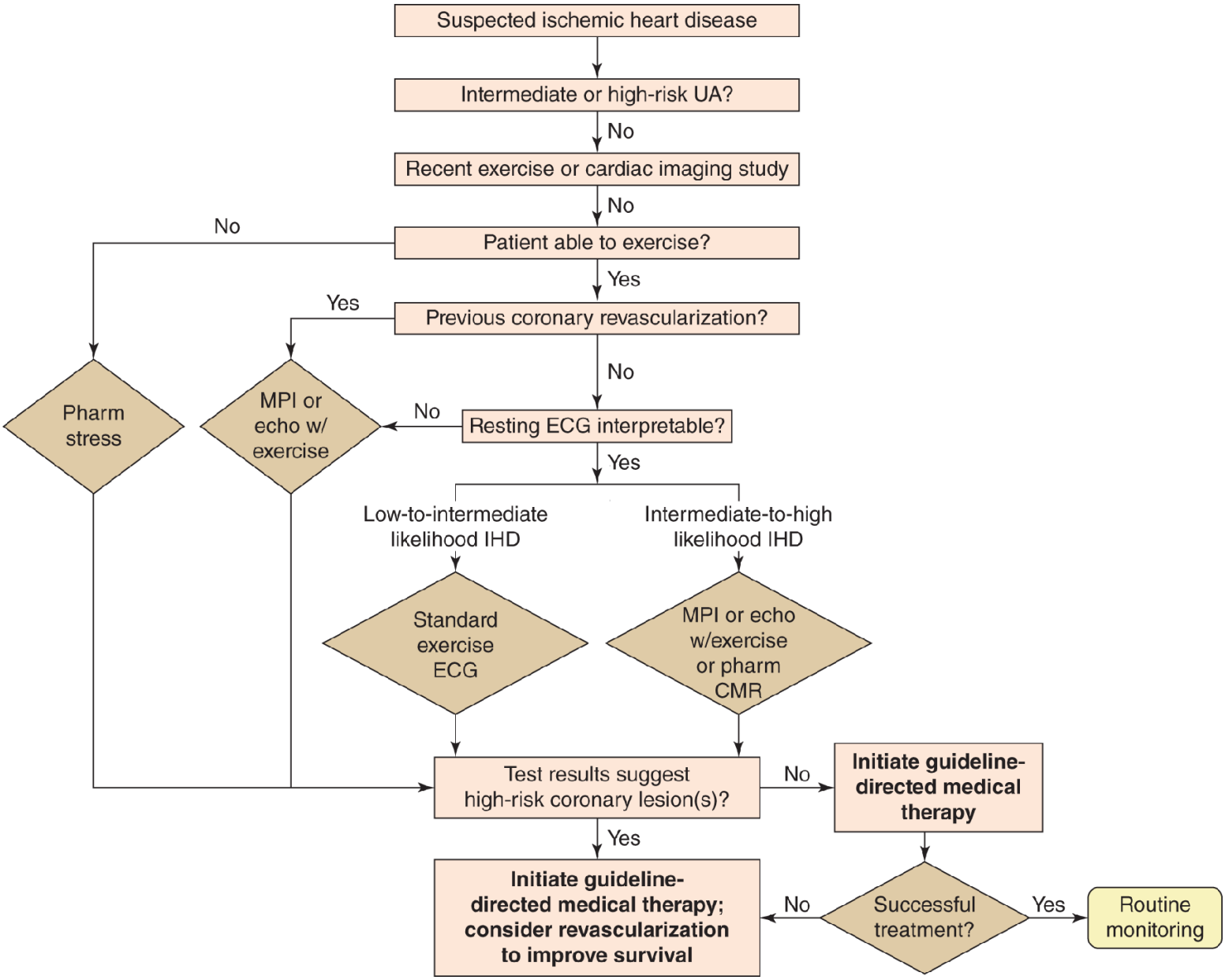


FIGURE 77-5. Stress testing strategy and treatment. CMR, cardiac magnetic resonance; IHD, Ischemic Heart Disease; MPI, myocardial perfusion imaging; UA, unstable angina. (Adapted from Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2012;126:e354–e471.)

Cardiac catheterization in older patients is informed by its risk-benefit ratio. Cardiac catheterization should be considered for those at high risk of severe coronary disease, or refractory ischemic symptoms despite maximally tolerated medical treatment. At the same time, the stable ischemic heart disease guidelines recommend it is safe to defer cardiac catheterization for initial medical management in patients with stable ischemic heart disease. This is a helpful clarification particularly for older patients with multimorbidity who may have stable symptoms. While cardiac catheterization has become commonplace and relatively safe in contemporary practice, vascular injury, bleeding, MI, stroke, and even mortality can result, albeit rarely. Advanced age increases these risks slightly; however, the risk to life remains less than 0.2%, and the risk of other serious adverse events is less than 0.5%, even in those aged greater than or equal to 75. Placing a patient even at minimal risk, however, is not worthwhile if the information obtained from a catheterization is unlikely to impact treatment decisions. For example, a cardiac catheterization may have limited impact on the management of an older patient who is not a candidate for coronary revascularization, based on medical comorbidity, cognitive decline, or personal preference. In addition, if symptoms can be managed with medical therapy, then a PCI is unlikely to add benefit for symptoms, and in stable patients without high-risk features, has not

been shown to improve mortality.

Patients with acute coronary syndromes often have an acceleration of chest pain symptoms (unstable angina) and may have more subtle changes on the ECG (eg, flipped T waves or ST depression). There is some evidence that plasma levels of procoagulation markers and coagulation factors are elevated in older patients, but it remains unclear whether these findings alone are responsible for increased thrombotic tendencies in older patients or alter risk when accompanied by other traditional risk factors for thrombotic events. There are also significant proportions of older patients who develop ACS secondary to exacerbations of chronic comorbid conditions or acute medical illnesses (**Table 77-2**). These type 2 (secondary) MIs occur in the setting of sepsis, acute blood loss or chronic anemia, pneumonia, pulmonary embolism, chronic obstructive pulmonary disease, congestive heart failure, dysrhythmias, or hypertensive urgencies. A retrospective study demonstrated that approximately 30% of patients present with an acute noncardiac condition concomitant with an MI, contributing to increased in-hospital mortality and variations in receipt of cardiac medications and invasive cardiac therapies. These secondary events usually occur in the context of increased myocardial oxygen demand or hemodynamic stress in patients with underlying CAD and represent a substantial number of cases. The distinction between a type 1, spontaneous MI, and a type 2, secondary MI, is helpful to determine best approach to management. In the latter, focus on supply-demand and risk stratification is warranted, where in the spontaneous MI group, more typical approach with anticoagulation and cardiac catheterization is warranted.

TABLE 77-2 UNIVERSAL MI DEFINITION—SPONTANEOUS AND SECONDARY MYOCARDIAL INFARCTION TYPES

Spontaneous MI (Type 1 MI)
• Spontaneous in onset usually due to plaque rupture, ulceration, fissuring, erosion, or dissection with complex plaque and coronary arterial thrombus often seen during coronary angiography.
• Ischemic chest discomfort or equivalent often present.
• Associated ECG changes such as ST-segment depression or elevation.
• Associated blood troponin levels tend to be higher than in type 2 MI, but not always.
• Treat with anticoagulants and antiplatelets; cardiac catheterization.
Secondary MI (Type 2 MI)
• Usually associated with conditions that lead to elevated myocardial oxygen demand (eg, tachycardia), or decreased myocardial oxygen supply (eg, hypotension or anemia).
• Ischemic chest discomfort or equivalent often absent.
• ECG changes are minimal, absent, or nonspecific.
• Associated blood troponin levels often but not always minimally elevated.
• Angiography often does not demonstrate plaque rupture with associated thrombus.
• Treat by addressing secondary causes, supportive care, antiplatelets; risk stratification prior to catheterization.

MEDICAL MANAGEMENT

Antiplatelet Therapy

There is strong support for the benefit of aspirin in secondary prevention, and for primary prevention, particularly in the presence of risk factors. The Antithrombotic Trialists' Collaboration, which performed a meta-analysis of aspirin trials and included more than 135,000 patients, identified a 25% risk reduction in cardiovascular events. In the Physician's Health Study of 44,000 men without known CHD, those randomized to aspirin had a 44% lower risk for subsequent MI versus those taking placebo.

Observational data from the Nurse's Health Study suggest similar benefits of aspirin for primary CHD prevention in women. The benefit is in reduction in nonfatal cardiovascular events and stroke, and is greater for secondary prevention than for primary prevention, particularly if at low risk. In general, primary prevention recommendations suggest treating men over age 55 and women over age 65, particularly in the presence of CHD risk factors, with daily aspirin. Although recommendations for primary prevention are indeterminate over age 80, similar benefits are observed in the older-aged patients. Concerns for bleeding with aspirin make individual decisions about treatment important.

Aspirin dose continues to be debated, but efficacy of aspirin does not appear to increase at doses greater than 150 mg/day, and higher doses increase the risk for bleeding. Thus, 81 mg of aspirin is the dose with the best evidence.

Clopidogrel, a thienopyridine that inhibits ADP-dependent platelet aggregation, adds incremental benefit to aspirin in the setting on NSTE-ACS with a 20% relative risk reduction in cardiovascular death, MI, or stroke in the clopidogrel in unstable angina to prevent recurrent events trial. The study found similar benefits in older patients; nevertheless, registry data suggest that the in-hospital use of clopidogrel in older patients after MI remains low. The use of clopidogrel is recommended as an alternative to aspirin in the small subset of patients who are aspirin allergic. Newer ADP-dependent platelet aggregation inhibitors are used in patients following interventions. Prasugrel has a black box warning against use in those age 75 and older or those with prior stroke or low body mass index due to increased risk of bleeding. Ticagrelor, with a different risk profile, seems safe for use in those over age 75 based on current evidence. Patients who require long-term dual antiplatelet therapy or oral anticoagulation with warfarin are advised to take a reduced aspirin dose of 81 mg daily, and all older patients should be on reduced aspirin dose, regardless of other agents.

Antithrombin Therapy

Clinical trials have demonstrated reduction of cardiovascular events with the use of antithrombotic therapies for patients with ACS, and these findings have been extended to the older population. Yet, registry data reflect a decrease in use of antithrombotic therapy in older patients when compared to their younger counterparts. Unfractionated heparin, in conjunction with antiplatelet therapy, is associated with significant reduction in death or MI in patients with ACS, but important considerations involving their use are necessary as aged patients are more often susceptible to overdosing, reflected by an elevated partial thromboplastin time, and bleeding. The use of low-molecular-weight heparin for ACS has also been supported by evidence from clinical trials, with some suggestion of improved clinical outcomes, when compared with unfractionated heparin. Subgroup analyses of these studies have demonstrated a greater relative benefit in older patients treated with low-molecular-weight heparin, but concerns remain over the dosing of low-molecular-weight heparin in older patients, as these therapies are renally cleared and have been associated with excessive dosing and bleeding complications, which have translated to increased adverse events. Bivalirudin has equivalent antithrombotic activity with less bleeding in several trials. This is used frequently in invasively managed ACS patients, often in conjunction with oral antiplatelet loading. There remains a need to further characterize the efficacy and safety of the combination of antithrombotic therapies in older patients with ACS. With the increase in type 2 MI in the older population, consideration for the likelihood of a thrombotic process and an invasive management strategy can help guide the approach to anticoagulation.

β-Blockers

β-Blockers decrease myocardial oxygen demand and improve coronary blood flow and are helpful medications in the care of older patients with chronic angina. A meta-analysis of 25 randomized control trials showed a 25% reduction from β-blockers in all-cause mortality and reinfarction in patients with prior MI. Data from an adjusted observational analysis demonstrated that older patients receiving β-blockers following acute MI had a 33% reduction in 1-year mortality compared with those not treated. A more contemporary analysis, divided patients from the REACH registry into three cohorts, CAD without MI, CAD with prior MI, and CAD risk factors only. The use of β-blockers was not associated with lower rates of death, nonfatal MI, or nonfatal stroke in any cohort. However, in those with recent MI (≤ 1 year), β-blocker use was associated with a 25% lower incidence of the composite which included cardiac rehospitalization. This suggests the greatest benefit for β-blockers in the contemporary era is in patients in the first year following an MI. Longer-term benefits are likely for symptom management, blood pressure treatment, or in those with CHD and heart failure and depressed left ventricular function.

Older patients are often vulnerable to drugs with hypotensive actions and have altered responses to β-blockers owing to conduction system deterioration and the physiologic desensitization of β-adrenergic receptor function. Additionally, a recent trial found that early use of β-blockers in patients with MI could worsen risks for congestive heart failure and result in poorer outcomes. Thus, medications should be administered to those with an identified potential for benefit and titrated with caution.

Secondary Prevention Strategies

Secondary prevention aims at reducing recurrent cardiovascular events in patients with known CAD. These therapies

are targeted toward control of known risk factors, such as hypertension, hyperlipidemia, and tobacco cessation. Older patients with CHD face higher overall risk, so benefits of prevention in absolute terms rises with age and corresponding "number needed to treat" for these prevention strategies falls. Exercise and lifestyle interventions should be universally applied, and are effective regardless of age. There is no upper age limit for the benefit of exercise, even if physical limitations modify the type of activity. Cardiac rehabilitation can be especially important following a cardiac event in assisting the older patient in selecting a comfortable exercise routine.

The renin-angiotensin-aldosterone system is a key determinant in hypertension, inflammation, atherosclerosis, and, ultimately, increased cardiovascular events. Angiotensin-converting enzyme (ACE) inhibitors have strong support for safe and effective treatment of hypertension, and improving survival post-MI with depressed heart function, heart failure, or anterior MIs. The Heart Outcomes Prevention Evaluation (HOPE) study extended the benefits of ACE inhibitors to all patients with known CHD or at high risk of CHD. In HOPE, patients with CHD and other patients with high CHD risk (eg, diabetes plus one or more cardiac risk factor) were randomized to 10 mg of ramipril daily versus placebo. After 5 years, treated patients had 26% lower risk of CHD death than those who were not treated. Rates of MI, congestive heart failure, stroke, renal dysfunction, and even development of diabetes were lower in the ACE-treated patient group. The treatment effects of ACE inhibition were greater in those patients aged greater than or equal to 65 than in younger patients. Current guidelines suggest consideration of ACE inhibitors in all patients having CHD with depressed ventricular function, diabetes, or hypertension. Some experts have suggested that these drugs be considered in all patients with known CHD regardless of other risk factors or left ventricular dysfunction, yet there remains conflicting evidence from clinical trials regarding this issue. ARBs, similar to ACE inhibitors, are designed to produce antihypertensive and anti-inflammatory effects within the cardiovascular system, and recent studies demonstrate that these agents translate to decreased cardiovascular events. Several randomized control trials have shown that the ARBs can slow the progression of nephropathy in patients with diabetes and microalbuminuria in a fashion similar to ACE inhibitors. Overall, the data favor the use of established ACE inhibitors for primary and secondary prevention of cardiovascular events, with the consideration of ARB substitution in patients who are intolerant of ACE inhibitors (most commonly from troublesome cough). When used in older patients, one should monitor serum electrolytes and creatinine, as these drugs can cause decreased renal function and hyperkalemia.

Cholesterol is a key determinant of risk, reflected by levels of low-density lipoprotein cholesterol (LDL-C) and non–HDL-C. Yet often, older patients with coronary artery disease have lower cholesterol levels than their younger counterparts despite having CAD. There are several classes of drugs for lowering serum cholesterol, including fibrates, bile acid sequestrants, niacin, fish oil, ezetimibe, and the hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Of these, only statins alone or in combination with ezetimibe, have evidence for efficacy in secondary CHD prevention. A meta-analysis done with pooled data from nine large statin randomized control trials for secondary prevention among those aged greater than 65 showed an average 22% relative risk reduction in all-cause death with statin compared to placebo. In addition, there was a 30% reduction in coronary heart disease mortality and a 26% reduction in nonfatal MI. Another meta-analysis of five randomized trials comparing intensive statin versus nonintensive statin therapy among those age greater than 65 found no difference in total mortality (heart rate [HR] 0.97; 95% confidence interval [CI] 0.87–1.09) but reductions in CVD events such as nonfatal MI, stroke, and coronary revascularization with intensive statin therapy. Intensive statin therapy reduced all-cause mortality in patients with recent ACS but not with stable CHD. The NCEP guidelines for lipid-lowering therapy do not include age cutoffs or age-specific treatment recommendations. The 2013 ACC/AHA guidelines recommend moderate statin if tolerated for those age 75 and above with coronary disease, as opposed to the recommendation for high-intensity statin in younger individuals. In patients with known CAD, there is no recommendation or evidence for treating based on LDL-C, which eliminates the need to intensify therapy. This is particularly helpful in older patients where low doses may be preferred and better tolerated. However, in the immediate post-MI period, intensive lipid-lowering therapy has demonstrated benefit in older patients to prevent recurrent cardiovascular events. In fact, in a post hoc analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction (PROVE IT-TIMI 22) trial, patients age 70 years and older were found to derive greater benefit than younger counterparts in terms of reduction in cardiovascular events. The IMPROVE-IT trial tested a long-term strategy of simvastatin alone or simvastatin with ezetimibe and found a lower achieved LDL-C level in the simvastatin/ezetimibe arm as well as a reduction in the primary end point of cardiovascular death, stroke, MI, or revascularization. While lipid-lowering drugs are generally safe in older patients, monitoring of liver function studies after initiation is recommended, and attention to cognitive impairment, myopathy, or myalgia is equally important.

CATHETERIZATION AND REVASCULARIZATION

Unstable Angina or Myocardial Infarction

The post-MI period requires continuation of evidence-based medical therapies already reviewed and assessment of an individual's risk for future cardiovascular events. Care guidelines recommend that all those diagnosed with an MI should have an assessment of both left ventricular function (via echocardiography or other means) and coronary disease severity. In patients with NSTE-ACS, the two options for assessment of post-MI risk are routine angiography with revascularization for all patients who have no contraindications or a conservative strategy of medical therapy with patient selection for angiography based on symptoms or demonstrable ischemia on investigation ("ischemia-driven" approach). While in the past it had been suggested that "early invasive" (cardiac catheterization) and noninvasive (stress testing) approaches represented equivalent strategies, recent clinical trials suggest that the early invasive approach might be preferable for patients at increased risk of recurrent cardiovascular events. With the introduction of contemporary trials, the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Ischemia/Infarction (TACTICS-TIMI)-18 trial randomized patients with unstable angina/NSTE-ACS to one or the other of these strategies and found that those in the early invasive arm (within 48 hours) had nearly 20% lower rates of death, nonfatal MI, or rehospitalization at 6 months than conservatively treated patients. Interestingly, the successful enrollment of older patients (40% of patients were 65 years or older) allowed the identification of a 44% relative risk reduction in 30-day death or nonfatal MI among patients 65 years or older (invasive 5.7% vs conservative 9.8%; $p < 0.05$) and a 56% relative risk reduction in patients older than 75 years (invasive 10.8% vs conservative 21.6%; $p < 0.05$) with the early invasive strategy, findings consistent with a greater benefit in older relative to younger patients.

Stable Ischemic Heart Disease

A major challenge in the care of older patients with stable CHD is related to who should undergo evaluation for coronary revascularization. In younger patients, randomized clinical trials have simplified this decision-making process by identifying subgroups in which PCI or CABG surgery improves survival and/or quality of life beyond medical therapy. However, patients older than 75 years were generally not represented in these pivotal trials, so clinicians and patients must rely on a careful comparison between the acute procedural risks and potential long-term benefits. Developments in the techniques of coronary catheterization, PCI, and CABG are changing the landscape for patient selection and outcomes for revascularization. Based on Medicare data, trends and outcomes in older patients after PCI were compared between the balloon angioplasty era (1991–1995), the bare metal stents (BMS) era (1998–2003), and the drug-eluting stents (DES) era (2004–2006). Despite a significant increase in comorbidity, the number of post-PCI adverse cardiovascular events decreased over time, including less death and MI at 3-year follow-up. The improved outcomes were due to reductions in the need for repeat target vessel/lesion revascularizations and CABG, highlighting the efficacy of evolving technologies and techniques, as well as improving adjunctive therapy.

The use of fractional flow reserve (FFR < 0.8) to identify lesions contributing to ischemia has been shown to improve associated PCI outcomes. The use of third-generation stents has also improved the outcomes of PCI among those with multivessel disease, although CABG continues to demonstrate superior survival and fewer events at 5 years compared with PCI. The selection of patients for CABG as the optimal revascularization strategy should include those with reduced ejection fraction (< 35% with viable myocardium), left main coronary artery disease or its equivalent, and diabetes.

Mortality rates following revascularization procedures rise dramatically and progressively with advancing age. Age-associated risk in procedural mortality is not strictly linear but rises rapidly beyond the age of 75. Additionally, at any age, patients with CABG face two- to threefold higher mortality risks than do patients receiving angioplasty. However, technological advances have led to improved procedural success rates and lower risks for both procedures. Thus, despite the fact that procedures were performed on patients with higher risk, the risk of death after CABG in patients aged 65 or older in the Society for Thoracic Surgery database declined nearly 20% between 1990 and 1999 and now rests at just above 4%. The Society for Thoracic Surgery has devised risk models that can be used to guide the impact of patient risk factors on operative morbidity and mortality and can be used in patient management. The web-based risk calculator can be found at http://www.sts.org.

Nonfatal procedural complications (stroke, MI, and renal failure) also rise in a curvilinear fashion with age and are higher in patients with CABG relative to those undergoing angioplasty. Of major importance to many older patients are the procedural risks of stroke and loss in mental acuity. Patients with CABG aged 75 or older have a reported 3% to

6% incidence of permanent overt stroke as compared with a less than 1% incidence for angioplasty. Additionally, by using highly sensitive neurocognitive testing, Newman and colleagues found that up to 50% of patients of all ages undergoing CABG had measurable impairments in neurocognitive function at hospital discharge. Although half of patients with initial impairment recovered by 6 months, cognitive deficits reappeared in many of them during long-term follow-up and portended an impaired functional status. However, one recent study that compared cognitive ability after CABG to angioplasty and age-matched controls noted no meaningful clinical deterioration of cognitive performance between groups. Similarly, the initial enthusiasm of improving neurocognitive outcomes by performing off-pump CABG versus traditional on-pump CABG has been tempered by findings from a recent randomized trial, which demonstrated comparable cognitive outcomes between the two groups, although long-term follow-up has yet to occur. While increasing age is generally a major risk factor for procedural complications or mortality, it is not the only factor to consider. For example, by using published risk models, one can stratify an octogenarian's likelihood for mortality with CABG from 2% to 3% for a "healthy" patient without other comorbidities, to greater than 30% for the patient with multiple risk factors such as diabetes or preexisting CVD.

As with reperfusion therapy, the risks of revascularization must be balanced against the potential benefits in terms of prolonged survival, improved functional outcomes, or both. The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease registry examined the care and outcomes of more than 6000 patients aged 70 to 79 who underwent cardiac catheterization. Compared with medical therapy, those receiving CABG or PCI had significantly higher adjusted 4-year survival rates (CABG 87%, PCI 84%, medical therapy 79%, $p < 0.001$). These survival benefits of revascularization also held for octogenarians and increased in all aged patients in proportion with the number of diseased vessels and the degree of left ventricular dysfunction. Results from the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease registry have been confirmed in other observational analyses. Together, these studies strongly suggest that older patients with multivessel coronary disease have higher survival rates if treated with PCI or CABG than if they are treated with medical therapy.

Beyond survival, there is also a growing body of literature to support the notion that PCI and CABG also reduce angina symptoms and improve functional outcomes of older patients with CHD. Initially, these results were reported in observational studies that adjusted for treatment-selection issues, as well as other baseline clinical factors. Most recently, similar results have been validated in the Trial of Invasive Versus Medical Therapy in Elderly Patients with Chronic Symptomatic Coronary Artery Disease trial. The Trial of Invasive Versus Medical Therapy in Elderly Patients with Chronic Symptomatic Coronary Artery Disease study randomized 305 patients with chronic angina, aged 75 or older, to diagnostic catheterization (followed by coronary revascularization as appropriate) or optimized medical therapy with intervention only for those with refractory symptoms. Of those randomized to catheterization and intervention as appropriate, 74% underwent CABG or PCI, while almost 33% of the conservative management arm crossed over to revascularization by 6 months. Patients in the early revascularization arm had significantly greater improvement in their symptoms and almost all aspects of functional status and quality of life when compared with medically treated patients. However, clinical end points in the trial were mixed, with a higher 6-month mortality rate but a lower incidence of nonfatal MI in the early invasive arm. While this randomized study was limited in sample size and presented several methodological challenges, its results do provide further support for the consideration of revascularization in the very old patient with CHD. While we await more representative randomized trials, the ACC/AHA guidelines stipulate that age should not be used as the sole criterion to rule out consideration of revascularization and that complex medical and surgical interventions have an adjunctive role in the care of older patients when in accordance with available scientific evidence and with the patient's goals of care.

Fibrinolysis and Primary PCI in Older Patients

The primary objective in the management of patients with STEMI is to provide early reperfusion therapy with either pharmacologic means (ie, fibrinolysis) or percutaneous intervention with balloon angioplasty. Numerous studies have confirmed that reperfusion therapy (fibrinolytic therapy or primary angioplasty) in patients presenting with acute STEMIs improves survival if performed in a timely fashion. An overview of the major thrombolytic trials from the Fibrinolytic Therapy Trialists' Collaborative Group, a meta-analysis that included more than 58,000 patients, demonstrated a 15% relative risk reduction in death for patients 75 years or older with STE MI or bundle branch block treated with fibrinolytics. Despite older patients achieving a smaller relative reduction in death than younger patients, the trend toward absolute benefit in terms of lives saved with fibrinolytics was threefold greater in patients older than 75 years compared with those younger than 55 years.

In addition, an observational analysis from the ACTION Registry–GWTG found that approximately 6% of patients

with STEMI treated in the community were greater than or equal to 85 years (median age 88). Compared to younger patients, the oldest old were more likely to be women, had more hypertension, and prior heart failure and stroke. More than 42% of the oldest old were also cited as having contraindications to reperfusion, but absolute or relative contraindications were only reported in 10%. Patient preference was the most common reason indicated (45%). Even in reperfusion-eligible patients, the oldest old were less likely to receive it with neither mortality benefit nor harm in those who did receive it. Similarly, in the Nationwide Inpatient Sample, STEMI patients coming from a nursing home were compared to those coming from the community. Compared with their community-dwelling counterparts, nursing home residents are less likely to receive reperfusion therapy for STEMI and had higher in-hospital mortality.

The possible benefits of thrombolysis must be weighed carefully against the risks, especially in the older population. Data from the Fibrinolytic Therapy Trialists' meta-analysis showed that patients aged greater than 70 had nearly a threefold higher relative risk of intracranial hemorrhage, the most feared complication in the postlytic period, after fibrinolysis than those aged less than 60. Bearing this in mind, clinicians should realize that intracranial hemorrhage is a rare event and the absolute risk of this complication after fibrinolysis in those older than 70 years remains between 0.7% and 2.1% in major trials and nearing 3% in those older than 85 years. The risk factors for intracranial hemorrhage include low body weight, elevated blood pressures, facial or head trauma, and dementia. Dementia was found in one trial to significantly increase the risk for intracranial hemorrhage by threefold.

In contrast with mixed results for fibrinolysis, timely reperfusion for STEMI with PCI is almost universally associated with improved outcomes in all age groups. For example, a randomized study of primary PCI versus thrombolysis in patients with STEMI showed a 40% relative risk reduction for death, MI, and stroke in patients treated within 3 hours of presentation with PCI. In the ACTION Registry, primary PCI was associated with lower 30-day and 1-year mortality when compared to no therapy or thrombolysis among older patients with acute MI. Over the past decade, the use of primary PCI overall, and in older patients, has dramatically increased, in-hospital mortality has been reduced, and complications are lower with direct revascularization. However, when percutaneous intervention is not available in a timely manner, thrombolytic therapy may improve outcomes when given in the right window of time.

The only caveat to the successes of primary PCI in older patients was seen in a trial of patients with very high-risk MI whose course was complicated by cardiogenic shock (ie, hypotension and signs of poor tissue perfusion). In one trial, those randomized to primary PCI had significantly higher survival rates; however, this effect was age dependent, and those older than 75 years had much higher mortality risk with PCI.

SPECIAL CONSIDERATIONS

Multimorbidity and Frailty

The diagnosis and care of older CHD patients invokes an interplay of biological differences, comorbid conditions, functional status, drug pharmacology, and the patient's goals of care. This complexity is compounded by the need to largely extrapolate evidence-based care from studies conducted in younger populations. The traditional approach of one disease at a time is of limited utility in the older patient population. Of Medicare beneficiaries, 68% have more than or equal to two chronic conditions, and 14% have more than or equal to six chronic conditions. Among those Medicare beneficiaries with a diagnosis of ischemic heart disease, 81% have hypertension, 69% have hyperlipidemia, 42% have diabetes, 41% have arthritis, 39% have anemia, 36% have heart failure, and 30% have chronic kidney disease. Frailty is also a common occurrence in patients with CHD, in part due to shared risk factors, and common end-organ manifestations. Frailty increases mortality and morbidity among those hospitalized with MI, with a twofold increased risk of mortality, rehospitalization, bleeding, stroke, or dialysis at 1 year. Similar increased risks are noted for frail elders following PCI and CABG.

While clinical trials should enroll populations similar to those treated to increase generalizability, almost all of the national guidelines have been based on trials performed predominately in younger patients. Patients older than 75 years comprise approximately 9% of the population enrolled in clinical trials of ACS therapies, but account for more than 37% of patients with ACS in the community. Despite calls for inclusion, this trend has shown little improvement over the last two decades. Given this knowledge gap as well as their inherent complexity, the approach to cardiac care of the older patient requires a *patient-centered* plan incorporating an individual's goals and health state.

Patient Preferences

Beyond physiologic and pharmacologic issues, cardiac treatment plans need to consider the patients' overall health, as

well as their preferences and willingness to accept risk. While some older individuals engage in very active, independent lives well into their advanced years, others are frail and suffer disabling physical and/or mental illnesses. Beyond this variability in health and functional status, there is great diversity in the health values of older patients. Some consider illness and disability to be inevitable and have no interest in extensive medical or surgical intervention. However, many older patients favor longevity if coupled with good cognitive ability and lack of neurologic disability. In hospital settings, many older patients feel vulnerable and abdicate decision making to family or physicians entrusted to act in the patient's best interest. It is incumbent on those caring for older patients to attempt to elicit preferences, while providing necessary information regarding potential risks and benefits of treatment options. Ethical mandates at the core of the patient-physician relationship include the desire to preserve autonomy and to "do no harm."

Renal Function and Pharmacology

Consistently, an individual's renal function remains a powerful predictor of cardiovascular morbidity and mortality. In the Cooperative Cardiovascular Project, renal dysfunction predicted adverse outcomes among an older post-MI population, such that 1-year mortality was 24% if serum creatinine was below 1.5 mg/dL and 66% if creatinine was above 2.5 mg/dL. The pitfalls attributed to using the serum creatinine as a surrogate for renal function are often compounded in the older patient population. Consistent with recommendations from the Panel on Acute Coronary Care in the Elderly, the creatinine clearance should be calculated on all patients 75 years or older who present with an ACS. In addition, the clinician should remain cognizant of changes in the creatinine clearance during the index hospitalization and after discharge, as several medications prescribed may have an impact on renal function. From the Global Registry of Acute Coronary Events study, a 10 mL/min decrease in creatinine clearance had the same impact on in-hospital mortality as a 10-year increase in age. The role of renal dysfunction in the management of older patients with ACSs cannot be overemphasized, as this entity plays a pivotal role at the interface of pharmacologic management.

Cardiovascular drugs are among the most commonly prescribed therapies in older patients, and altered pharmacokinetics (ie, drug distribution and metabolism) are frequently observed in older patients as a consequence of decreased lean body mass and volume of distribution. Combined, these factors lead to higher drug concentrations and prolonged half-lives. A drug's pharmacodynamics (ie, the effect of a drug on a target cell) can be considerably altered with age. For example, increased calcification of the cardiac conduction system can increase an older patient's sensitivity to atrioventricular nodal blocking agents and lead to profound bradycardia. Comorbid illness and frailty can also influence drug selection and safety. For instance, a frail older person may have a higher risk of falling, which can markedly increase the likelihood of bleeding complications with anticoagulants. Finally, polypharmacy is often a serious issue in older patients and can lead to life-threatening drug-drug interactions and poor adherence because of confusion over medications and/or prohibitive costs.

SUMMARY

Despite advances in prevention and treatment, CHD remains a major health problem for older patients. As the population ages, the need for evidence-based cardiac care for patients aged greater than or equal to 75 will increase. Older patients benefit as much, if not more, from existing therapies as do younger patients. However, the care of CHD in older patients takes place within the context of their multidimensional health status and requires awareness of atypical presentations of ACS, altered pharmacokinetics of therapy, and underlying cognitive and functional status. Bearing this in mind, treatment paradigms applied to younger patient groups are often appropriate when treating older patients, and adherence to guidelines translates into better outcomes. The classification of physiologic frailty may offer additional risk information for older patients considering revascularization. This information could identify a cohort who may benefit from a geriatric intervention before revascularization, or for whom alternate treatment is the preferred route. Finally, studies must focus on relative safety and efficacy of medical or procedural interventions when reporting results on older patients. Despite the significant challenges in cardiovascular care of the oldest old, redirecting efforts to a patient-centered model may provide the best opportunity to improve outcomes.

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Chapter 78

Valvular Heart Disease

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Learning Objectives

- Describe clinical features, diagnostic modalities, and therapeutic options for the most common valvular diseases in older patients.
- Identify when patients with valvular disease should be offered surgical intervention.

Key Clinical Points

1. **Aortic stenosis is very common in older patients and novel surgical approaches allow more older patients a surgical treatment option.**
2. **Transcatheter aortic valve replacement (TAVR)—an alternative to surgical aortic valve replacement—may be considered in older patients.**
3. **Aortic insufficiency is managed similarly in younger and older patients.**
4. **Mitral regurgitation may be structural or functional. Once symptomatic, it is best treated with mitral valve repair than replacement.**
5. **The primary treatment option for mitral stenosis is valvuloplasty. Surgical intervention is reserved for severely calcified valves and is associated with high risk.**
6. **Anticoagulation and risk of valve degeneration are the two important risks associated with mechanical and biological prostheses, respectively.**
7. **A multidisciplinary team approach is advocated in managing older patients with valvular heart disease.**

AORTIC STENOSIS

Definition

Aortic stenosis is the progressive narrowing of the aortic valve resulting in outflow obstruction during systole. This is in distinction to aortic valve sclerosis, where the valve leaflets are calcified or thickened, but do not cause a meaningful outflow obstruction.

Epidemiology

Aortic stenosis is present in 2% to 9% of older patients and is the leading clinically significant valvular disorder in older adults. Risk factors for developing aortic stenosis include age, bicuspid aortic valve, and rheumatic heart disease. In 90% of patients older than 65 years aortic stenosis is caused by the calcific degeneration of a tricuspid aortic valve. While bicuspid valves are relatively common (~ 2% of the population), patients with bicuspid valves are present with stenosis usually in the fourth to sixth decade of life. Similarly, rheumatic heart disease presents earlier in life and often in association with mitral valve disease.

Pathophysiology

Although the causes of aortic valve calcification in aging are unclear, the process bears many similarities to atherosclerosis—both diseases are characterized by lipid deposition, inflammation, neoangiogenesis, and calcification. Bicuspid aortic valves are characterized by accelerated calcification and progressive outflow obstruction in the majority of patients. Rheumatic fever results in progressive fusion of the aortic valve leaflets causing both aortic valve stenosis and regurgitation. Aortic stenosis is classified as mild, moderate, or severe based on the valve area, ejection velocity, and the pressure gradient that develops across the valve (**Table 78-1**).

TABLE 78-1 ECHOCARDIOGRAPHIC FINDINGS IN AORTIC STENOSIS

	MILD	MODERATE	SEVERE
Aortic valve area (cm^2)	> 1.5	1.0–1.5	< 1.0
Velocity (m/s)	< 3	3–4	> 4
Mean gradient (mm Hg)	< 25	25–40	> 40

Aortic valve sclerosis (valve thickening without outflow tract obstruction) is present in 25% of patients older than 65 years and 48% of those older than 75 years, and is associated with male gender, hypertension, smoking, diabetes, and lipid abnormalities. The rate of progression to frank stenosis is not clear, but the Cardiovascular Health Study has identified an increased incidence of adverse cardiovascular outcomes in patients with sclerotic valves even when corrected for other cardiovascular risk factors. The mechanism for this association is unclear, and there are currently no guidelines for intervention.

On average, aortic valve stenosis progresses at an estimated increase in jet velocity of 0.3 m/s/year and a reduction in valve area of 0.1 cm^2/year. Despite these average rates of disease progression, the rate for each individual is difficult to predict, therefore asymptomatic patients with mild-to-moderate disease should be followed on a regular basis.

Clinical Presentation

Aortic stenosis has a long asymptomatic latency period, when the only finding is a harsh, late-peaking, crescendo-decrescendo systolic murmur that radiates to the carotids and is best heard over the right, second interspace. The second heart sound may be paradoxically split. Aortic stenosis is associated with “pulsus parvus et tardus,” characterized by a weak and diminished pulse with a late upstroke that is most easily noted in the carotids. However, these physical findings may be less obvious in older adults, because of the effects of aging on the vascular bed.

Patients with aortic valve stenosis develop compensatory left ventricular (LV) hypertrophy, which can be seen on echocardiogram, on electrocardiogram and even on chest x-ray. The ventricular hypertrophy produces coronary malperfusion with subendocardial ischemia. Older women are prone to develop excessive ventricular hypertrophy, which may contribute to the higher perioperative morbidity and mortality in this patient cohort.

Although aortic stenosis has a long latency, once symptoms develop the progression to death is rapid. The three classic symptoms are angina, syncope, and heart failure. While sudden death occurs in patients with aortic stenosis and may be considered a fourth symptom group, this is rarely seen in asymptomatic patients (< 1%). Unfortunately, older adults often move into the symptomatic phase of aortic stenosis undetected because of the overlap of these major symptom constellations with other changes associated with aging.

Two-thirds of patients present with angina, which may be caused by concomitant coronary artery disease, although 40% do not have significant coronary artery disease. The most likely etiology for angina in the absence of coronary artery disease is subendocardial ischemia and the increased oxygen demands of the hypertrophied ventricle together with decreased coronary flow reserve. Untreated patients with aortic stenosis and angina have a 50% 5-year survival.

Syncope due to aortic stenosis may be caused by inadequate cardiac output to meet demands, by dysfunctional left ventricular baroreceptor response, or by arrhythmias, and is associated with a 50% 3-year mortality without valve replacement.

Aortic valve stenosis presenting with congestive heart failure carries the worst prognosis—50% mortality at 2 years without valve replacement. Typical symptoms include paroxysmal nocturnal dyspnea, orthopnea, and dyspnea on exertion, which may be associated with signs of peripheral edema, pulmonary edema, and rales. Thickening of the left ventricle due to aortic stenosis as well as the changes associated with aging both lead to diastolic dysfunction. Consequently, the older patient with aortic stenosis is more dependent on atrial contraction for ventricular filling.

Therefore, these patients often present with exacerbated or new onset of symptoms if they develop atrial fibrillation.

Impaired platelet function and decreased levels of von Willebrand (vW) factor are also associated with severe aortic stenosis, and 20% of patients may present with epistaxis or ecchymoses. Patients can also develop Heyde syndrome (gastrointestinal bleeding due to colonic angiodysplasias). Interestingly, these abnormalities resolve with valve replacement.

Evaluation

The American Heart Association recommends evaluation of early systolic, midsystolic grade 3 or greater, late systolic, or holosystolic murmurs with echocardiography. Older patients may present with ominous murmurs due to aortic valve sclerosis without significant valvular stenosis. Transthoracic echocardiography is the study of choice since it allows evaluation of valve morphology, severity of stenosis, and degree of left ventricular hypertrophy and function. Echocardiography is also useful for following disease progression.

Stress echocardiogram can be utilized in asymptomatic patients with severe aortic stenosis to assess for physiologic changes that may indicate the need for earlier intervention. Computed tomography (CT) angiography is routinely used in patients being considered for TAVR, but is not helpful in assessing severity of aortic stenosis. Cardiac magnetic resonance imaging (MRI) is sometimes helpful in evaluating the severity of stenosis but is not widely used. Cardiac catheterization is routinely performed in older patients who are scheduled for valve replacement, to diagnose concomitant coronary artery disease and to measure transvalvular gradients if there is a question of severity of stenosis.

Management

Asymptomatic patients Survival of asymptomatic patients is the same as age-matched individuals without aortic stenosis. However, given the significant decline in survival once symptoms develop, it is essential to consider surgical intervention and to confirm the absence of symptoms in patients who do not appear symptomatic. If a careful history fails to elicit symptoms in patients with severe aortic stenosis, exercise testing may be considered. However, exercise testing in symptomatic patients is contraindicated because of the high risk of complications.

Patients who are asymptomatic by history but who, on exercise testing, develop symptoms, fail to generate a 20 mm Hg increase in blood pressure, or develop ST-segment abnormalities, have a 19% 2-year symptom-free survival compared with 85% 2-year symptom-free survival for patients who do not manifest these abnormalities on exercise testing. Exercise testing may elicit symptoms in as many as a third of patients thought to be asymptomatic by history alone. Close supervision and prompt termination of the study at any decline in blood pressure, significant ST-segment depression, or onset of arrhythmia is strongly advocated. On average, the probability of a patient with severe aortic stenosis remaining symptom free at 5 years is only 50%, which has prompted some to recommend earlier surgery while the patient is “younger” and in better health.

If the patient is truly asymptomatic, continued frequent routine monitoring is reasonable, but patients should be instructed to report the development of angina, syncope, or any sign of congestive heart failure. Monitoring by echocardiography should include annual or biannual examinations for patients with severe aortic stenosis: every 1 to 2 years for patients with moderate aortic stenosis, every 3 to 5 years if the stenosis is mild, and should be performed as needed if the patient develops symptoms. Patients who are demonstrated to be symptom free need not restrict their activity and may exercise.

Medical management Once patients develop symptoms they should be considered for valve replacement. Currently, there is no documented medical treatment that will delay or reverse aortic valve stenosis. Medical management is palliative and consists mostly of antibiotic prophylaxis for endocarditis and blood pressure control. Although standard guidelines for the management of hypertension are recommended, β-blockers are salutary in patients with concomitant coronary artery disease, and angiotensin-converting enzyme (ACE) inhibitors may have a beneficial effect in LV fibrosis. Diuretics are discouraged if the LV is small due to the potential decrease in cardiac output. Statins have not demonstrated regression of stenosis in prospective studies, although they are indicated for patients with concomitant coronary artery disease.

The American Heart Association guidelines states that “patients who develop symptoms require surgery, not medical therapy.” If the patient is not a candidate for surgery, consideration should be given to TAVR. Every patient should be assessed based on their individual risks and benefits before advocating surgical aortic valve replacement (SAVR), TAVR, or medical management.

Percutaneous aortic valvuloplasty Balloon valvuloplasty is not a substitute for surgery but is a useful tool in the treatment armamentarium for temporary palliation of symptoms for nonsurgical candidates or as a bridge for patients with hemodynamically unstable aortic stenosis. The procedure uses transvalvular balloon inflations to crack the calcified aortic valve. Unfortunately, the maximum enlargement rarely exceeds 1.0 cm^2 (severe-to-moderate aortic stenosis), carries a 10% risk of complications, and results in restenosis within 6 months to a year. One-year actuarial mortality is 35% to 50%, which is no better than untreated aortic stenosis, but it can result in significant relief of symptoms and improvement in quality of life and can be a useful tool to optimize acutely decompensated patients prior to TAVR or SAVR.

Surgical management Aortic valve replacement is recommended for all symptomatic patients because of the improvement in both symptoms and survival. Current American Heart Association recommendations are listed in **Table 78-2**. Moreover, since there is an increased risk of sudden death, replacement should be performed as soon as feasible after the development of symptoms. Age alone is not a contraindication to surgery, and to date numerous studies have demonstrated outcomes in older patients to be comparable to those seen in younger patients. Operative mortality in older patients ranges from 3% to 4% to as high as 24%. The variability in published studies is the result of both patient selection and the definition of "older patient"—which varies from cohorts aged 65 to 80. Medicare outcomes data for 142,000 patients older than 65 years demonstrate an operative mortality of 8.8% overall, and 6.0% mortality in high-volume centers. , although individual patient risk can and should be calculated using the STS risk calculator.

TABLE 78-2 AMERICAN HEART ASSOCIATION RECOMMENDATIONS FOR VALVE REPLACEMENT IN AORTIC STENOSIS

Indications for valve replacement in aortic stenosis
• Symptomatic patients with severe aortic stenosis
• Patients with severe aortic stenosis undergoing other cardiac surgery
• Patients with severe aortic stenosis and left ventricular dysfunction (ejection fraction < 50%)
Considerations for valve replacement in aortic stenosis
• Patients with severe aortic stenosis and decreased exercise tolerance or a fall in blood pressure with exercise
• Symptomatic patients with low-flow/low-gradient severe aortic stenosis with left ventricular dysfunction and low-dose dobutamine stress study that shows aortic velocity of ≥ 4 m/s
• Symptomatic normotensive patients with low-flow/low-gradient severe aortic stenosis and LVEF > 50%, if clinical, hemodynamic and anatomic data support valve obstruction as the most likely cause of symptoms
• Patients with moderate aortic stenosis undergoing other cardiac surgery
Possible indications for valve replacement in aortic stenosis
• Asymptomatic patients with severe aortic valve stenosis with rapid disease progression and low surgical risk

LVEF, left ventricular ejection fraction.

Predictors of surgical mortality include emergent surgery, right heart failure, severity of symptoms (New York Heart Association [NYHA] class IV), renal insufficiency, female gender, depressed left ventricular function, associated coronary bypass, or concomitant mitral valve surgery. Emergent surgery increases the surgical risk substantially, and is often the result of not referring the patient for elective surgery because it is "too risky," but reconsidering surgery when the patient is critically ill and the medical options have dwindled to none. Unfortunately the result is a self-fulfilling prophecy that older patients will not do well with surgery. A European study of older patients with aortic stenosis provocatively demonstrated that 41% of patients older than 70 years were not offered surgery despite severe valve stenosis and symptoms. These findings were corroborated in a second study of 1200 patients from 92 centers in 25 countries. In this study, 33% of patients older than 75 years with severe symptomatic aortic stenosis were not offered valve replacement.

Although many studies have found that concomitant coronary artery bypass or mitral valve surgery increases the surgical risk, there is clear support for performing concomitant aortic valve replacement for any patient with severe aortic stenosis, who is undergoing any other cardiac surgical procedure, regardless of symptoms. Similarly, in patients with moderate stenosis, it is "accepted practice" to replace the aortic valve at the time of other cardiac surgery.

Simultaneous valve replacement in patients with mild aortic stenosis undergoing heart surgery is more controversial, although an argument can be made for concomitant replacement in patients with mild stenosis but moderate-to-severe valve calcification.

Transcatheter aortic valve replacement An alternative to surgical aortic valve replacement is transcatheter aortic valve replacement, in which a catheter-mounted bioprosthetic valve is deployed across the aortic valve. The valve can be introduced through the femoral artery, the apex of the heart, or the aorta via small incisions. Symptomatic patients with prohibitive or high surgical risk and a predicted postintervention life expectancy of more than 12 months may be eligible for TAVR. The surgical risk is assessed by predicted operative mortality scores (STS-PROM, EuroSCORE-II) and frailty scores to help determine which patients might be suitable TAVR candidates. Prohibitive risk is defined as combined predicted 30-day morbidity and mortality of over 50% due to comorbid disease or serious irreversible conditions. High risk is patients with a predicted operative mortality of 8% to 15% or anatomic factors or frailty that increases the surgical risk. Patients of moderate operative risk (predicted operative mortality 4%–8%) may qualify for TAVR based on frailty or anatomic risks. While the decision for SAVR versus TAVR is defined by the predicted risk for death, more frequently patients are also assessed by the likelihood of returning to an active lifestyle and the impact of the surgical technique to the overall postoperative activity. For example, patients dependent on the upper body for mobility may lose this ability following sternotomy. Such patients may be better candidates for alternative approaches including TAVR.

A multidisciplinary team approach is invaluable for optimal procedure selection (TAVR vs SAVR). This approach to individualized risk assessment is described later in this chapter.

AORTIC INSUFFICIENCY

Definition

Aortic insufficiency occurs when the aortic valve fails to close during diastole resulting in blood flow from the aorta back into the left ventricle.

Epidemiology

Acute aortic regurgitation is uncommon and presents a surgical emergency. Chronic aortic insufficiency occurs in 20% to 30% of individuals older than 65 years and like aortic stenosis has a long asymptomatic latency period. However, even asymptomatic patients with normal left ventricular function have a 0.2% incidence of sudden death, progress to symptomatic disease at a rate of approximately 3.5% per year, and develop either left ventricular dysfunction or symptoms at a rate of approximately 6% per year. Once patients develop left ventricular dysfunction, more than 25% each year will progress to symptomatic disease and, once symptomatic, the mortality rate for aortic regurgitation is more than 10% per year. Patients with NYHA class III or IV symptoms have an annual mortality rate of 25%, while patients with less severe symptoms (NYHA class II) have a 6% annual mortality rate.

Risk factors for the development of left ventricular dysfunction, symptoms, or death include age, left ventricular end-systolic dimension (LVESD)/volume, left ventricular end-diastolic dimension (LVEDD)/volume, and left ventricular ejection fraction with exercise. Each year 19% of patients with end-systolic size greater than 50 mm develop left ventricular dysfunction and symptoms or die. The rate of development of these same end points was 6% per year for patients with end-systolic size between 40 and 50 mm.

Presentation

The findings and eponyms associated with aortic insufficiency are a delight to lovers of medical trivia (**Table 78-3**). However, the most obvious physical findings are those of a diastolic murmur and a widened pulse pressure.

TABLE 78-3 EPONYMOUS SIGNS OF AORTIC INSUFFICIENCY

EPONYM	PHYSICAL FINDING
Austin Flint murmur	Low-pitched mid-diastolic rumble
Becker sign	Accentuated retinal artery pulsation

Corrigan pulses	Rapidly rising and falling pulse to palpation
de Musset sign	Bobbing of head
Duroziez sign	To-and-fro femoral artery murmur with compression
Gerhard sign	Pulsatile spleen
Hill sign	Higher BP in lower than upper extremity
Mayne sign	Decrease in blood pressure with arm elevated
Mueller sign	Pulsatile uvula
Quincke sign	Pulsatile nail beds
Rosenbach sign	Pulsatile liver
Traube sign	Double femoral artery pulse sound
Sherman sign	Dorsalis pedis pulse prominent in patients older than 75 y
Watson's water hammer pulse	Bounding peripheral pulse

Patients with acute aortic regurgitation usually present dramatically in cardiogenic shock. The most common causes are infective endocarditis and acute aortic dissection.

Chronic aortic regurgitation progresses slowly and insidiously. Occasionally palpitations or awareness of each heart beat may be the first signs owing to the large regurgitant volumes. Infrequently angina may develop due to coronary flow mismatch, and as the ventricle fails congestive heart failure develops with symptoms of dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and lower extremity edema.

Evaluation

Echocardiography is the diagnostic modality of choice for both initial evaluation as well as routine follow-up. It provides both diagnostic confirmation, assessment of the severity of valve regurgitation, as well as evaluation of left ventricular function and the aortic root. It can also help determine the etiology of the aortic regurgitation (eg, infective endocarditis or aortic dissection). The clinical stages and management recommendations are defined by symptomatic status, severity of the regurgitation, LV volume, and LV systolic function (**Table 78-4**). Transesophageal echocardiography may improve sensitivity and specificity.

TABLE 78-4 SEVERITY OF AORTIC REGURGITATION

	MILD	MODERATE	SEVERE
Ratio of width of regurgitant jet to left ventricular outflow (%)	< 25	25–64	≥ 65
Vena contracta (cm)	< 0.3	0.3–0.59	≥ 0.6
Regurgitant volume (mL/beat)	< 30	30–59	≥ 60
Regurgitant fraction (%)	< 30	30–49	≥ 50
Effective regurgitant orifice area (mm^2)	< 10	10–29	≥ 30

Exercise testing may be reasonable for asymptomatic patients who wish to initiate an exercise regimen, but the results have not been consistently useful in predicting outcomes for asymptomatic patients with normal resting cardiac function. It may also be used to objectively assess exercise capacity in otherwise asymptomatic patients or patients with equivocal symptoms.

CT angiography is useful for the diagnosis and follow-up of patients with aortic dissections, aneurysms, or annuloaortic ectasia. MR angiography similarly allows for evaluation and follow-up of aortic disease and also provides quantitative assessment of aortic regurgitation, which can be helpful in patients with suboptimal echocardiographic images or if there is discordance between clinical assessment and noninvasive studies.

Cardiac catheterization is routinely performed in patients being evaluated for aortic valve replacement, and provides intraventricular pressure measurements, but is not recommended for routine quantification of aortic regurgitation. It is contraindicated in acute aortic dissection or when there are large mobile vegetations on the aortic valve.

Management

Medical management Surgery is indicated for patients who develop either angina or signs of congestive heart failure, since the mortality for patients with angina is more than 10% per year and for heart failure is more than 20% per year. Medical management in symptomatic patients results in poor outcomes even if the left ventricular function is normal. Patients older than 75 years are more likely to develop either symptoms or ventricular dysfunction at earlier stages of the disease, and have a poorer prognosis once they develop ventricular dysfunction.

The medical management of aortic insufficiency is best achieved with vasodilators that reduce afterload and wall stress. Since symptomatic disease carries such a poor prognosis without surgery, medical management is primarily indicated for patients who are not surgical candidates because of comorbidities, to preoperatively optimize hemodynamics, or for asymptomatic hypertensive patients with normal ventricular function. Conflicting data exist as to the benefits of hydralazine, ACE inhibitors, and calcium channel blockers, which suggest that vasodilator therapy is not indicated for asymptomatic, normotensive patients with normal ventricular function. However, once symptoms or ventricular dysfunction develops, the patient should be considered and evaluated for surgery. Although β-blockers are not recommended as first-line medication for management of hypertension due to its bradycardic effect, they may benefit those patients who have LV dysfunction.

The absence of data indicating that exercise contributes to the progression of aortic insufficiency suggests that the asymptomatic patient with normal left ventricular function may participate in the full range of physical activities, with the exception of isometric exercises, which are contraindicated. However, it is prudent to exercise test patients to the anticipated level of activity to assess tolerance prior to initiating an exercise regimen.

Patients with aortic regurgitation should have regularly scheduled follow-up. Mild regurgitation with normal ventricular function can be followed clinically on an annual basis with biennial or triennial echocardiograms; more severe valvular regurgitation should be followed with annual or even biannual echocardiograms depending on the presence of ventricular dilatation (60 mm). Asymptomatic patients with more severe dilatation (> 70 mm) should be followed with echocardiograms every 4 to 6 months because the likelihood of developing symptoms or ventricular dysfunction is as high as 20% per year. Asymptomatic patients with normal left ventricular function and dilated ventricles (LVESD > 50 mm) may be candidates for early valve replacement.

Surgical management Surgery is not indicated for asymptomatic patients with normal ventricular function and minimal ventricular dilatation regardless of the severity of valvular regurgitation. However, once symptoms or left ventricular dysfunction develop in patients with severe aortic regurgitation, the patient should be considered for surgery (**Table 78-5**). Patients with severe left ventricular dysfunction have a high operative mortality (at least 10%) and a lower postoperative survival; therefore, asymptomatic patients should be closely followed for the development of left ventricular dysfunction.

TABLE 78-5 RECOMMENDATIONS FOR SURGERY IN AORTIC INSUFFICIENCY

Indications for valve replacement in aortic insufficiency
• Symptomatic patients with severe aortic regurgitation regardless of LV function
• Asymptomatic patients with severe aortic regurgitation and left ventricular ejection fraction < 50%
• Patients with severe aortic regurgitation undergoing other cardiac surgery
Considerations for valve replacement in aortic insufficiency
• Asymptomatic patients with severe aortic insufficiency, normal left ventricular function and dilated ventricle—LVESD > 50 mm
• Patients with moderate aortic insufficiency undergoing other cardiac surgery
Possible indications for valve replacement in aortic insufficiency
• Asymptomatic patients with severe aortic regurgitation, normal cardiac function, but progressive left ventricular dilatation > 65 mm if surgical risk is low

LVESD, left ventricular end-systolic dimension.

In older patients with severe compensated aortic insufficiency, the onset of symptoms can be hard to ascertain, since mild dyspnea on exertion and fatigue often mimic the effects of aging. However, once ventricular dysfunction develops, the older patient is more likely to have persistent postoperative ventricular dysfunction and symptoms, as

well as decreased postsurgical survival. Therefore, in patients without comorbidities that contraindicate surgery, an earlier commitment to surgery is generally the preferred strategy.

If the patient is asymptomatic but the LVESD exceeds 65 mm, surgery should be considered if it is low risk, because of the high risk of sudden death. Although the surgical treatment of asymptomatic patients with severe aortic regurgitation and left ventricular dilatation is controversial, if surgery is planned based on ventricular size or function, two consecutive studies should confirm the findings.

Surgical valve replacement is the treatment of choice for symptomatic patients with aortic insufficiency. Patients with annuloaortic ectasia or concomitant ascending aortic aneurysms may be candidates for aortic valve repair and replacement of the ascending aorta (David procedure), although such procedures are usually reserved for experienced centers. This procedure should be judiciously used in older adults, in whom the operative risk is usually higher and aortic valve replacement alone is simpler and carries a more predictable result. TAVR is currently not recommended in patients with aortic insufficiency.

MITRAL STENOSIS

Definition

Mitral valve stenosis is the progressive narrowing of the orifice of the mitral valve with a resultant increase in left atrial, pulmonary artery, and right ventricular pressures.

Epidemiology

The overwhelming majority of mitral stenosis is caused by rheumatic heart disease which causes thickening and calcification of the leaflets and chordae as well as shortening of the chordae and fusion of the commissures. While this tends to occur in the younger patients and is rarely seen in older patients, the number of older patients may be increasing. In developed countries, most patients present in their forties and fifties, but some studies note that a third of patients are older than 65 years. Only 60% of patients presenting with mitral stenosis recall a history of rheumatic fever, the disease progresses very slowly, and it is estimated that mitral valve area, which normally measures 4.0 to 5.0 cm^2, decreases by 0.09 to 0.32 cm^2/year. When the valve area is reduced to 2.5 to 1.5 cm^2, patients usually develop symptoms. Significant valvular disease lags the development of rheumatic fever by 20 to 40 years. However, once symptoms start, the 10-year survival is only 50% to 60%. Patients who are asymptomatic or with minimal symptoms have an 80% 10-year survival, and 60% have no progression of symptoms. Patients that meet criteria for surgery but do not get operated on, have a 10-year survival below 30%. Patients with severe pulmonary hypertension usually live fewer than 3 years, and most patients will die from progressive pulmonary hypertension, congestive heart failure, systemic emboli, pulmonary emboli, or infection.

Senile calcific mitral stenosis is becoming more common in the United States. This is usually associated with mitral annular calcification that extends into the leaflets and is prevalent in patients with decreased renal function, elevated inflammatory markers, and in patients with senile aortic stenosis. Although not all patients develop progressive stenosis, the rate of progression, when it occurs, is accelerated compared to rheumatic disease.

Other rarer causes of mitral stenosis include intracardiac clot, intracardiac tumor (such as myxoma), or congenital malformations.

Presentation

Mitral stenosis often presents with new-onset atrial fibrillation or an embolic event; sometimes patients come to medical attention because of fatigue or dyspnea and rarely due to hemoptysis. The left recurrent laryngeal nerve can be compressed by the enlarged left atrium, causing hoarseness (Ortner syndrome). The onset of atrial fibrillation sometimes results in pulmonary edema and death. On physical examination an opening snap may be noted to the first heart sound as well as a diastolic rumble.

Diagnosis

Evaluation of patients with suspected mitral stenosis includes an echocardiogram, both to confirm the diagnosis and assess the severity of the disease and therapeutic options (**Table 78-6**). Patients have mild mitral stenosis if the valve area is greater than 1.5 cm^2, moderate if the valve area is 1.0 to 1.5 cm^2, and severe if the mitral valve area is less than

1.0 cm . Additionally, pulmonary pressures should be assessed, since this determines the disease severity.

TABLE 78-6 ECHOCARDIOGRAPHIC FINDINGS IN MITRAL STENOSIS

	MILD	MODERATE	SEVERE
Mitral valve area (cm^2)	> 1.5	1.0–1.5	< 1.0
Pulmonary artery pressure (mm Hg)	< 30	30–50	> 50
Mean gradient (mm Hg)	< 5	5–10	> 10

Transesophageal echocardiography is useful when transthoracic echocardiography provides limited images, when the presence of left atrial thrombus needs to be excluded, or when valvuloplasty is contemplated.

Cardiac catheterization is rarely used to facilitate assessment of mitral valve gradient. It is however recommended in assessing the coronaries as part of preoperative work-up. Stress testing has a value when there is discrepancy between echocardiographic severity of mitral stenosis at rest and clinical symptoms. CT scanning is valuable in patients with senile mitral stenosis, especially those considered for surgical intervention as it complements the echocardiographic assessment of mitral annular and leaflet calcification.

Management

Medical management It should be emphasized that medical management cannot reduce a mechanical narrowing like mitral stenosis. However, increasing diastolic filling time by slowing the heart rate with β-blockade may be helpful in patients in sinus rhythm and exertional symptoms. The addition of sodium restriction and a diuretic ameliorates pulmonary edema. Additionally, patients with mitral stenosis should receive antibiotic prophylaxis before high-risk procedures (**Tables 78-7A** and **B**). Asymptomatic patients should be followed closely for the development of symptoms, at which time they should be assessed by echocardiogram.

TABLE 78-7A ENDOCARDITIS PROPHYLAXIS PROCEDURES

	ENDOCARDITIS PROPHYLAXIS IS RECOMMENDED	ENDOCARDITIS PROPHYLAXIS IS NOT REQUIRED
Respiratory procedures	• Oral surgery including tonsillectomy and adenoidectomy • Respiratory tract surgery involving mucosal surfaces • Rigid bronchoscopy	• Intubation • Flexible bronchoscopy
Gastrointestinal procedures	• Esophageal procedures—sclerotherapy and dilatation • Biliary tract surgery or instrumentation—ERCP • Gastrointestinal surgery or procedures that violate the intestinal mucosa	• Transesophageal echocardiogram • Endoscopy without mucosa violation
Genitourinary procedures	• Prostate surgery • Urethral instrumentation—including dilatation	• Transvaginal surgery • Urethral catheterization in uninfected patient

ERCP, endoscopic retrograde cholangiopancreatography.

TABLE 78-7B PROPHYLACTIC ANTIBIOTIC RECOMMENDATIONS

	ANTIBIOTIC	DOSAGE
Standard	Amoxicillin	2 g PO 1 h before procedure
Penicillin allergic	Clindamycin	600 mg PO 1 h before procedure 2 g PO 1 h before procedure

	Cephalexin	
Unable to take oral medicines and penicillin allergic	Ampicillin	2 g IV or IM 30 min before procedure
	Clindamycin	600 mg IV 30 min before procedure
	Cefazolin	1 g IV or IM 30 min before procedure

A substantial number of older patients (30%–40%) will present with atrial fibrillation. Both, age and left atrial size, are predictive of the developing atrial fibrillation. Unfortunately, atrial fibrillation carries a guarded prognosis, since only 25% of mitral stenosis patients with atrial fibrillation will survive 10 years compared to 46% of those who remain in sinus rhythm. Treatment includes anticoagulation, rate control, and electrical or chemical cardioversion, especially if associated with hemodynamic instability. Patients who remain in atrial fibrillation for more than 24 to 48 hours are at increased risk of embolic complications and should be promptly anticoagulated. Electrical cardioversion may be used but only after confirming the absence of a left atrial thrombus by echocardiogram. If a thrombus is present, treatment may include 3 weeks of anticoagulation, followed by confirmation of the absence of thrombus by repeat echocardiography and subsequent defibrillation. In this setting, transesophageal echocardiography is the diagnostic tool of choice.

Patients with paroxysmal or persistent atrial fibrillation, prior emboli or left atrial thrombus should be anticoagulated. Systemic emboli occur in 20% of patients and age and atrial fibrillation are predictive of embolization.

Exercise is not contraindicated in asymptomatic patients with mild mitral stenosis. In patients with more severe stenosis, exercise is often limited by symptoms. Therefore exercise regimens for patients with more symptomatic or severe disease should be individually tailored.

Percutaneous mitral valvuloplasty Percutaneous mitral valvuloplasty is successful in select patients and often doubles the valve area with a substantial decrease in valve gradient. The selection of patients for this treatment option is determined by echocardiographic assessment of the valve, and is based on leaflet mobility, subvalvular apparatus, leaflet thickening, and the presence of calcification. The lowest scores are assigned to valves with the greatest leaflet mobility, the least subvalvular thickening, the most normal leaflet thickness, and the least calcium deposition. Patients with these valve characteristics (lowest scores) have the best response to balloon valvuloplasty. The majority of patients (90%) will see symptomatic relief, with a freedom from valve-related complications or death of between 50% and 65% at 7 years and as high as 80% to 90% in patients with favourable (low) preprocedural echocardiographic scores.

Symptomatic patients or patients with pulmonary hypertension, those with favourable echocardiographic mitral valve scores and without atrial thrombi, should be referred for mitral valvuloplasty. The risks for percutaneous mitral valvuloplasty are low (**Table 78-8**). Therefore, even patients with less favourable echocardiographic scores who are at high surgical risk may be considered candidates for this approach. However, it is contraindicated in patients with moderate-to-severe mitral regurgitation and/or the presence of left atrial clot. Unfortunately, patients older than 65 years have a lower success rate, higher incidence of complications, and shorter duration of symptom relief with this approach.

TABLE 78-8 COMPLICATIONS OF PERCUTANEOUS MITRAL VALVULOPLASTY

COMPLICATION	PROCEDURAL RISK (%)
Left ventricular perforation	0.5–4.0
Systemic embolization	0.5–3.0
Myocardial infarction	0.3–0.5
Death	1.0–2.0

Surgical management As a result of the success of balloon valvuloplasty in patient with favourable valve morphology, surgery is usually indicated only if the patient has failed percutaneous intervention or if the valve has unfavourable characteristics for balloon valvuloplasty. Patients with mitral stenosis ineligible for valvuloplasty are best treated surgically, as are patients with left atrial thrombus. Since balloon valvuloplasty requires a significant level of

expertise and the outcomes are related to experience, the American Heart Association recommends surgery if this experience is not available.

Patients with mild symptoms, severe pulmonary hypertension, and moderate-to-severe mitral stenosis may also benefit from surgery if balloon valvuloplasty is not appropriate or available. Similarly, patients with recurrent systemic emboli despite therapeutic anticoagulation may benefit from surgical intervention if ineligible for percutaneous treatment (**Table 78-9**). Notably, surgery is not recommended for patients with isolated mild mitral stenosis.

TABLE 78-9 SURGICAL RECOMMENDATIONS FOR MITRAL STENOSIS

Indications for valve intervention in mitral stenosis
• Percutaneous mitral balloon valvuloplasty is recommended in symptomatic patients with severe mitral stenosis, favorable morphology, and absence of contraindications
• Severely symptomatic patients (NYHA class III–IV) who are unable to undergo balloon valvuloplasty (owing to unavailability, contraindications, or unfavorable valve score) and are not high risk for surgery
• Patients with severe stenosis undergoing other cardiac surgery
Considerations for valve intervention in mitral stenosis
• Mildly symptomatic patients with severe mitral stenosis and severe pulmonary hypertension if ineligible for balloon valvuloplasty
• Percutaneous mitral balloon valvuloplasty is reasonable in asymptomatic patients with very severe mitral stenosis (MVA $\leq$ 1.0 cm^2), favorable morphology, and absence of contraindications
Possible indications for valve intervention in mitral stenosis
• Patients with moderate mitral stenosis undergoing other cardiac surgery
• Patients with severe mitral stenosis and recurrent emboli despite anticoagulation
• Percutaneous mitral balloon valvuloplasty may be considered in patients with severe mitral stenosis, new onset of atrial fibrillation with favorable morphology, and absence of contraindications
• Percutaneous mitral balloon valvuloplasty may be considered in symptomatic patients with severe mitral stenosis, suboptimal morphology who are not candidates for surgery or at high risk for surgery
• Percutaneous mitral balloon valvuloplasty may be considered in patients with mitral stenosis less than severe if there is evidence of hemodynamically significant stenosis during exercise

MVA, mitral valve area; NYHA, New York Heart Association.

The surgical options include open repair with commissurotomy or valve replacement with either a mechanical or a bioprosthetic valve. The surgical risk increases with decreased preoperative functional status, age, cardiac function, pulmonary hypertension, and the presence of coronary artery disease. Operative mortality can be as high as 20% in the older patient with significant comorbidities and pulmonary hypertension. Nonetheless, it is not recommended to wait until the patient becomes severely symptomatic (NYHA class IV), since this results in a substantial increase in the surgical risk. Conversely, surgery should be considered despite severe symptoms, since both quality of life and survival are exceedingly poor without surgical intervention.

Patients with senile calcific mitral stenosis often present a surgical challenge, because the calcification involves the annulus and the base of the leaflets. Valve replacement is complex and often involves annular debridement with reconstruction, which significantly increases the operative risk. Therefore intervention is often delayed until symptoms are severely limiting and cannot be managed medically.

MITRAL REGURGITATION

Definition

Mitral valve regurgitation is the inability of the mitral valve to close properly resulting in regurgitation of volume into the left atrium during systole. It is important to distinguish between primary (organic) and secondary (functional) mitral regurgitation as this has implications in treatment and prognosis.

Epidemiology

Significant mitral regurgitation occurs, equally in males and females, in about 2% of the population. The most common cause is mitral valve prolapse, which is present in 1% to 2.5% of the population and can occur either spontaneously or as a familial disorder. The latter is associated with a low but significant incidence of sudden death, presumably due to ventricular arrhythmias.

Acute mitral regurgitation is caused by disruption of the valve apparatus (leaflet perforation, chordal rupture, or papillary muscle rupture) and is often caused by endocarditis or myocardial infarction.

Chronic mitral regurgitation can be either primary (organic) regurgitation, which can be caused by mitral valve prolapse, rheumatic heart disease, endocarditis, and coronary artery disease with associated damage to the valve leaflets, chordae, papillary muscles, or mitral annulus. Secondary (functional) regurgitation is due to left ventricular dysfunction and annular dilation.

Chronic regurgitation is better tolerated, but when severe, especially in association with a flail leaflet, is associated with a 7% per year mortality. Patients with severe mitral valve regurgitation and a low ejection fraction have a particularly poor prognosis. The 10-year survival for patients with ejection fractions less than 50% is 32%, compared to a 70% 10-year survival for patients with ejection fraction greater than 60%. Even patients with borderline normal ejection fraction (50%–60%) have a decreased 10-year survival (53%) if untreated.

Presentation

Patients with chronic mitral valve prolapse may present with palpitations, panic attacks, atypical chest pain, dyspnea, easy fatigue, volume overload, or congestive heart failure. Palpitations may be caused by the onset of atrial fibrillation. Cessation of caffeine, tobacco, alcohol, and other stimulants may help control the anxiety in some patients. Acute mitral regurgitation usually presents either with shock or respiratory distress.

Physical examination reveals a holosystolic murmur, which is best heard at the apex of the heart with radiation to the left axilla. If the mitral regurgitation is severe and the atrial and ventricular pressure start to equalize, the murmur may be diminished. With cardiac enlargement, a third sound may also be heard.

Evaluation

As with other cardiac valvular problems, the diagnosis is best confirmed and quantified by echocardiogram (**Table 78-10**), which allows assessment of the severity of regurgitation, putative causes of the valve dysfunction, as well as assessment of left ventricular function. Transesophageal echocardiography often provides an even better assessment of the mitral valve. Cardiac catheterization, cardiac MRI, and viability studies can help identify those patients with functional ischemic MR who might benefit from surgical intervention.

TABLE 78-10 SEVERITY OF MITRAL REGURGITATION

	MILD	MODERATE	SEVERE
Color Doppler jet area	Small central jet	Jet greater than small, but no criteria for severe mitral regurgitation	Large jet filling large portion of atrium or wall impinging jet
Vena contracta (cm)	< 0.3	0.3–0.69	≥ 0.7
Regurgitant volume (mL/beat)	< 30	30–59	≥ 60
Regurgitant fraction (%)	< 30	30–49	≥ 50
Regurgitant orifice area (cm^2)	< 0.20	0.20–0.39	≥ 40

Management

Medical management Asymptomatic patients with mild primary mitral regurgitation may be followed with echocardiograms every 3 to 5 years while those with moderate mitral regurgitation should be followed every 1 to 2 years. Asymptomatic patients with severe organic regurgitation should probably undergo exercise testing to confirm the absence of symptoms, and if truly asymptomatic, should undergo restudy by echocardiogram every 6 to 12 months. The asymptomatic patient with organic mitral regurgitation, a normal ejection fraction without pulmonary hypertension, or left ventricular dilation may exercise without restriction.

Medical management consists of blood pressure control with vasodilators and diuretics. Asymptomatic patients

with normal blood pressure and LV function do not require treatment, and endocarditis prophylaxis is recommended for all patients with mitral valve prolapse and patients with moderate or severe organic mitral regurgitation.

Surgical management The surgical options consist of either repair or replacement (**Table 78-11**). All patients should be considered for valve repair because of the marked improvement in survival, left ventricular function, and the avoidance of long-term anticoagulation with valve repair compared to replacement. Although durability of repair is excellent, with freedom from reoperation equaling that of valve replacement (7%–10% at 10 years), the freedom from reoperation is dependent on the adequacy of the repair, whether the repair involved the anterior or the posterior valve leaflets, and whether chordal replacement was necessary. Patients with isolated posterior leaflet pathology are more likely to have long-term success compared to patients with anterior or bileaflet repairs.

TABLE 78-11 SURGICAL RECOMMENDATIONS FOR MITRAL REGURGITATION

Indications for valve repair or replacement in mitral regurgitation
• Symptomatic patients with chronic severe primary mitral regurgitation and left ventricular function > 30%
• Asymptomatic patients with severe regurgitation and decrease left ventricular dysfunction (EF 30%–60%) and/or ventricular dilatation (≥ 40 mm)
• Mitral repair is recommended in preference to replacement when surgery is indicated and regurgitation is limited to the posterior leaflet
• Mitral repair is recommended in preference to replacement when surgery is indicated and regurgitation involves the anterior leaflet or both leaflets and successful and durable repair can be accomplished
• Patients with severe primary mitral regurgitation undergoing other cardiac surgery
• Acute mitral regurgitation
Considerations for valve repair or replacement in mitral regurgitation
• Repair may be considered in asymptomatic patients with severe regurgitation and normal left ventricular size and function if the valve can be repaired with a high degree of certainty and low mortality
• Repair may be considered in asymptomatic patients with new-onset atrial fibrillation or pulmonary hypertension at rest with severe nonrheumatic regurgitation and normal left ventricular size and function
• Repair may be considered in patients with chronic moderate primary mitral regurgitation undergoing other cardiac surgery
• Patients with severe secondary chronic mitral regurgitation
Possible indications for valve repair or replacement in mitral regurgitation
• Symptomatic patients with chronic severe primary mitral regurgitation and EF ≤ 30%
• Repair may be considered in patients with rheumatic mitral valve disease if there are indications and durable repair is likely or long-term anticoagulation management is questionable
• Severely symptomatic patients (NYHA class III–IV) with chronic severe secondary mitral regurgitation
• Patients with chronic moderate secondary mitral regurgitation undergoing other cardiac surgery
Not indicated for valve replacement in mitral regurgitation
• Replacement should not be performed in patients with isolated primary mitral regurgitation limited to less than one-half of the posterior leaflet unless repair has been attempted and was unsuccessful.

EF, ejection fraction; NYHA, New York Heart Association.

When mitral replacement is necessary, the procedure should strive to retain as much of the mitral valve apparatus as possible. Preservation of these structures results in improved left ventricular function, exercise tolerance, and survival. The choices for mitral valve replacement include bioprosthetic or mechanical valves. Bioprosthetic valves in the mitral position are not as durable as in the aortic position, however, this option avoids the risks of lifelong anticoagulation. Conversely, a mechanical valve has the advantage of durability but requires a commitment to lifelong anticoagulation.

Mitral valve repair or replacement is indicated for all patients with symptoms (NYHA class II–IV) and severe regurgitation even in the face of normal cardiac size and function. Asymptomatic patients benefit from surgical intervention if they develop atrial fibrillation, pulmonary hypertension, left ventricular dysfunction (ejection fraction <

60%), or dilation (> 40 mm). In patients with atrial fibrillation, an intraoperative maze or modified maze procedure combined with suture closure of the left atrial appendage should be considered, in order to reestablish sinus rhythm and possibly reduce the risk of systemic embolization, respectively. Once left ventricular dysfunction develops, patient survival, even after repair or replacement, is compromised. Therefore, patients who are asymptomatic, with normal left ventricular size and function, should be followed closely, and, if necessary, exercise testing should be considered to confirm the absence of symptoms. Surgical intervention may be warranted for asymptomatic patients with severe mitral regurgitation with none of the noted indications for surgery if and only if the mitral valve can be repaired.

Operative mortality varies based on the procedure. Mitral valve repair is associated with a 2% perioperative mortality compared to 6% for valve replacement. Patients with ischemic and functional mitral regurgitation do much worse than the patients with organic regurgitation. A study of 292 patients older than 70 years demonstrated an in-hospital mortality of 0.7% for mitral repair compared to 13.9% for replacement. A study comparing cohorts of patients older than 75 years, between 65 and 75 years, and younger than 65 years, demonstrated an increased operative risk for older patients. However, restoration of life expectancy following surgery is the same for older as for younger patients. Current data suggest that in patients with functional mitral regurgitation there is no improvement in survival by performing a concomitant mitral repair with coronary artery bypass. Nonetheless, there may be an improvement in postoperative symptoms.

Percutaneous options Several percutaneous techniques for repair or replacement of the mitral valve are under investigation. Percutaneous approaches to the mitral repair includes a clip that provides an edge-to-edge repair for both functional and organical mitral regurgitation. Other repair devices include a mitral annular constraint device placed into the coronary sinus and artificial cord implantation. There are several other repair devices as well as transcatheter valves that are at different phases of development that will broaden the armamentarium of treatment options available for the next generation of older patients.

GENERAL CONSIDERATIONS

Evaluation of Surgical Risk

Society of thoracic surgeons predicted risk of mortality Many older patients have multiple comorbidities that impact the decision to operate. There are however, a number of statistical models that can be helpful in weighing the impact of individual comorbidities on operative outcome. The two most widely used are the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score and the EUROpean Score for Cardiac Operative Risk Evaluation (EuroSCORE-II), which is derived from a European surgical population. The STS-PROM, derived from a rolling cohort of North American patients, analyses the impact of preoperative variables of patients undergoing coronary artery bypass surgery and valve surgery (with or without concomitant coronary artery bypass) on 30-day mortality and postoperative complications. It is important to recognize that these data are derived only from patients who were operated on, and therefore do not provide insight into patients who were considered for surgery but did not undergo an operation. These risk models, though very informative, are not to be relied on as the only indicator for surgery (**Table 78-12**).

TABLE 78-12 PREOPERATIVE RISK ASSESSMENT

	LOW RISK	INTERMEDIATE RISK	HIGH RISK	PROHIBITIVE RISK
STS-PROM[a]	< 4% *and*	4%–8% *or*	> 8%	Surgical risk of death or major morbidity > 50%
Frailty	None *and*	1 index *or*	≥ 2 indices	
Major organ dysfunction that will not improve postoperatively	None *and*	1 organ system	No more than 2 organ systems	≥ 3 organ systems
Procedure-specific impediment	None	Possible	Possible	Severe

[a]Society of Thoracic Surgeons Predicted Risk of Mortality.

Frailty Traditionally physicians have guesstimated the probability of patient survival based on clinical judgment. In an

attempt to quantify these parameters there has been an increasing study of frailty as a measure of survivability. For example, one frailty index that incorporates a combination of five domains (nutritional status, activity, mobility, strength, and energy) has been evaluated for its ability to predict postsurgical survival (see Chapter 46)

Multidisciplinary team approach As diagnostic methods and treatment options become more sophisticated, and patients present with more comorbities, the optimal therapeutic choice is more complex and less clear. Assessing patients using a formal "heart valve team" has proven to improve outcomes. The heart valve team is comprised of a multidisciplinary team of clinicians that include cardiologists, cardiac surgeons, structural valve interventionalists, cardiovascular imaging specialists, anaesthesiologists, nurses, and often a geriatrician. The team reviews the patient and collaboratively discusses the therapeutic options, and then works with the patient and their family to arrive at a decision tailored for each individual patient that is consistent with the patient's goals of care.

Endocarditis Prophylaxis

Although there is surprising dearth of data supporting or refuting the use of antibiotic prophylaxis for patients with valvular disease, the American Heart Association recommends antibiotic coverage for a variety of dental and surgical procedures.

Prophylactic antibiotics are recommended for patients with prosthetic cardiac valves, prior endocarditis, cardiac transplants with abnormal valves, and complex congenital repairs or defects (**Table 78-13**). Standard antibiotic prophylaxis is orally administered, penicillin based, and given 1 hour before the procedure (see **Table 78-7B**). Patients with repaired valves usually do not require endocarditis prophylaxis as the incidence of infective endocarditis is estimated to be very low. Patients at risk of endocarditis should be covered for dental procedures that involve manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa. Nondental procedures in absence of active infection do not require prophylaxis (see **Table 78-7A**).

TABLE 78-13 INDICATIONS FOR ENDOCARDITIS PROPHYLAXIS

Patients for whom endocarditis prophylaxis is recommended
• Patients with any prosthetic valve—either mechanical or bioprosthetic
• Patients who have had valve repair procedures
• Patients with abnormal native valves—eg, bicuspid aortic valve
• Mitral valve prolapse with clinical findings of regurgitation or leaflet abnormalities by echocardiogram
Endocarditis prophylaxis is not required
• Mitral valve prolapse without regurgitation or abnormal leaflets
• Aortic valve sclerosis if jet velocity < 2 m/s
• Physiologic mitral regurgitation with normal valve leaflets
• Physiologic tricuspid regurgitation with normal valvular apparatus
• Physiologic pulmonary valve regurgitation with normal valvular apparatus

Anticoagulation

Anticoagulation has a significant associated morbidity particularly in the older patient. Consequently, the need for anticoagulation plays a pivotal role in the choice of valve. Patients with mechanical valves require lifelong anticoagulation, while patients with bioprosthetic valves are often anticoagulated for only 3 months (**Table 78-14**). If there is no contraindication to antiplatelet therapy, low-dose aspirin is also recommended for all patients with valve replacement.

TABLE 78-14 ANTICOAGULATION FOR PROSTHETIC VALVES

	MECHANICAL VALVE	BIOPROSTHETIC VALVE
Aortic	INR 2–3	INR 2–3 *for 3 mo*
	Aspirin 75–325 mg daily	Aspirin 75–100 mg daily
[a]		

Aortic with risk factors	INR 2.5–3.5	INR 2–3
	Aspirin 75–325 mg daily	Aspirin 75–100 mg daily
Mitral	INR 2.5–3.5	INR 2–3 *for 3 mo*
	Aspirin 75–325 mg daily	Aspirin 75–100 mg daily
Mitral with risk factors[a]	INR 2.5–3.5	INR 2.5–3.5
	Aspirin 75–325 mg daily	Aspirin 75–100 mg daily

[a]Risk factors: atrial fibrillation, prior thromboembolism, LV dysfunction (ejection fraction < 30%), and hypercoagulable condition.

Novel anticoagulation agents are not approved for anticoagulation in valve replacement patients—therefore, chronic anticoagulation requires warfarin therapy. The recommended international normalised ratio (INR) for patients with mechanical aortic valves is between 2 and 3; however, if the patient has a history of prior thromboembolism, LV dysfunction, atrial fibrillation, or hypercoagulability, the INR should be maintained between 2.5 and 3.5. Patients with mechanical mitral valves should have their INR maintained between 2.5 and 3.5, and those with bioprosthetic valves are often anticoagulated (INR 2.0–3.0) for the first 3 months following implantation.

The risk of thromboembolism for anticoagulated patients with mechanical valves is approximately 1% to 2% per year. The risk is lower in bioprosthetic valves (0.7%), and lower in patients with aortic prosthetic valves compared to mitral valves, regardless of the type of prosthetic valve implanted.

Hemorrhagic complications are more likely if the INR is greater than 5. Patients with an INR between 5 and 10 can be treated by holding warfarin and administration of 1 to 2.5 mg of oral vitamin K. However, the INR should be monitored daily until the INR is below 5, at which time warfarin can be reinitiated at adjusted doses. Of note, it is often harder to manage anticoagulation in the older patient as a result of polypharmacy in this patient population. An acute reduction in the INR for patients who are actively bleeding may be achieved by administering intravenous fresh frozen plasma. Vitamin K can also help reduce a dangerously high INR, but complicates re-anticoagulation.

Temporary cessation of anticoagulation in patients with mechanical valves is sometimes medically necessary. Patients with mechanical aortic valves (without risk factors) can have warfarin held 48 to 72 hours preoperatively and restarted within 24 hours following surgery without the need for bridging heparin anticoagulation. However, patients with mechanical mitral or mechanical aortic valves and high-risk factors should be bridged with heparin when the INR falls below 2. The heparin may be held 4 to 6 hours before surgery and restarted as soon as possible when the immediate postoperative risk of bleeding allows. For emergent procedures, it is preferable to administer fresh frozen plasma to reverse the effects of warfarin, since the administration of vitamin K will make re-anticoagulation difficult and increases the risk of a hypercoagulable state.

Prosthetic Valve Choices

All prosthetic valves fall into two broad groups: biological and mechanical valves. Mechanical valves have the advantage of durability but the disadvantage of requiring lifelong anticoagulation; bioprosthetic valves do not require anticoagulation but are limited by a finite durability.

Notably the risk of embolization and the durability is determined, in part, by valve location. Biological aortic valves are more durable than the same valve in the mitral position, and mechanical valves in the aortic position have a lower risk of thromboembolism than in the mitral position.

Within each class of valve, mechanical and bioprosthetic, there are numerous types of prostheses; each type of valve is available in different forms (eg, porcine vs bovine pericardial or bileaflet vs tilting disc).

The choice of replacement valve is sometimes determined by the contraindication to anticoagulation (which would necessitate the implantation of a bioprosthetic valve). Otherwise, the choice resides with the patient. There are some data to suggest that the rate of bioprosthetic valve deterioration is attenuated in older patients, prompting many surgeons to recommend bioprosthetic aortic valves for patients older than 65 years and bioprosthetic mitral valves for patients older than 70 years.

Other indirect factors may impact the choice of valve: atrial fibrillation, multiple valve replacement, prior mechanical valve, prior cardiac surgery, and annulus size may argue in favor of a mechanical valve. Essentially, the risk of a mechanical valve is that of anticoagulation and embolization, while the risk of a bioprosthetic valve is that of valve failure and reoperation. In the end, the choice of valve—unless there are contraindications to anticoagulation—belongs to the patient, since ultimately she or he must live with the perils of anticoagulation or the threat of reoperation.

Mechanical valves The original mechanical valve was the ball-caged design, which, while durable, has inefficient flow characteristics and requires higher levels of anticoagulation than the current generation of valves. The bileaflet mechanical valve is the most commonly used valve in the aortic position because of its superior flow characteristics. The risk of thromboembolism with anticoagulation is approximately 1% to 2% per year.

Bioprosthetic valves Stented and nonstented porcine valves and bovine pericardial valves are available, and like homografts, do not require immunosuppression or anticoagulation. The risk of embolism for this class of valves is approximately 0.7% per year without anticoagulation. However, all the biological valves are prone to structural deterioration. The rate of deterioration is slower in older patients—at 15 to 20 years, patients at age 70 have a 90% freedom from structural valve deterioration and patients older than 75 years have freedom from reoperation of 90% to 95%. Stentless valves do not have the valve mounting and are therefore more hemodynamically efficient, but this does not increase survival in the older patient.

Aortic homografts Cadaveric valves do not provide improved durability, but are particularly useful in patients with endocarditis and tissue loss. The rate of thromboembolism is low, and, like the stentless porcine valves, they are hemodynamically efficient especially at small sizes. Although there is no need for antirejection medications, the valve has a propensity to become heavily calcified, making re-replacement much more challenging.

Pulmonary Valve Autotransplants (Ross Procedure)

Mr. Donald Ross devised an operation to excise the patient's own pulmonary valve, which is used to replace the aortic valve, and then to replace the pulmonary valve with a homograft or bioprosthetic valve. Conceptually, the lower-pressure pulmonary circuit will allow for longer durability of the homograft or bioprosthetic valve in this circuit, and the aortic valve, which is now an autologous valve, would, therefore, also have increased durability. The operative morbidity and mortality for this procedure, especially in inexperienced hands, are higher than bioprosthetic replacement. The increased procedural risk and limited benefit in the older patient make it rarely indicated in this population. A variation of this operation is also available for mitral replacement, but it is currently investigational and has the same limitations for use in the older patient.

Valve repair Repair of the aortic or mitral valves is ideal. The ability to maintain ventricular geometry, to accommodate natural annular motion and the durability makes mitral valve repair the best option for suitable patients, since these advantages translate to lower operative mortality for mitral repair compared to replacement—1% to 2% versus 5.4% to 6.4%, respectively. Aortic valve repair for calcific disease is less durable and is rarely indicated; however, in the setting of normal leaflets, the aortic valve is repairable with excellent results (85% freedom from reoperation at 10 years).

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Chapter 79

Heart Failure

Michael W. Rich

Learning Objectives

- Understand the effects of aging on cardiovascular structure and function, and how these changes predispose to the development of heart failure.
- Describe the clinical features—including symptoms, signs, and results of diagnostic tests—that distinguish heart failure in older adults from heart failure occurring during middle age.
- Describe nonpharmacologic aspects of care for older adults with heart failure.
- Understand current treatment of heart failure with reduced and preserved ejection fraction in older adults.
- Discuss management of heart failure in patients approaching the end of life.

Key Clinical Points

1. **Cardiovascular aging is associated with extensive changes in cardiac and vascular structure and function that predispose older adults to the development of heart failure.**
2. **The clinical features of heart failure, including symptoms, signs, and diagnostic test results, often differ in older adults with heart failure compared to those in younger patients.**
3. **Management of heart failure with reduced ejection fraction (HFREF) is generally similar in older and younger patients, but must be individualized in older patients with competing morbidities and in accordance with goals of care.**
4. **To date, no pharmacologic agents have been shown to reduce mortality or substantially improve clinical outcome in patients with heart failure and preserved ejection fraction (HFPEF); therefore, treatment of this condition remains empiric.**
5. **Nonpharmacologic therapies, including lifestyle changes and multidisciplinary care interventions, play a fundamental role in optimizing care and outcomes for older patients with heart failure.**
6. **The overall prognosis for heart failure in older adults is poor, and it is therefore essential to incorporate goals of care and end-of-life planning into the clinical decision-making process, especially as symptoms progress and quality of life declines.**

INTRODUCTION

Heart failure may be defined as an inability of the heart to pump sufficient blood to meet the metabolic needs of the body's tissues or the ability to do so only at the expense of elevated intracardiac pressures. Heart failure represents a clinical syndrome rather than a specific diagnosis, and, to a large extent, it is a geriatric syndrome in much the same way that dementia and incontinence are geriatric syndromes. Indeed, heart failure may be viewed as the quintessential disorder of cardiovascular aging since, as discussed later in this chapter, extensive age-related changes in cardiovascular structure and function, in conjunction with the rising prevalence of cardiovascular diseases with advancing age and declines in premature cardiovascular deaths, all contribute to an exponential rise in heart failure

with advancing age. Thus, although the clinical syndrome of heart failure has been recognized by physicians for more than 2000 years, it has only been within the past three decades that it has been identified as a major public health concern, a development that is largely attributable to the aging of the population.

EPIDEMIOLOGY AND ECONOMIC IMPACT

Despite progressive declines in age-adjusted mortality rates from coronary heart disease and hypertensive cardiovascular disease, both the incidence and the prevalence of heart failure are increasing, and it is projected that these trends will continue for the next several decades. As shown in **Table 79-1**, several factors have contributed to the progressive rise in heart failure. Foremost among these is the increasing number of older adults who, by virtue of advanced age and the high prevalence of hypertension, coronary heart disease, and cardiac valvular disorders in older individuals, are predisposed to the development of heart failure. In addition, advances in the treatment of other acute and chronic cardiac and noncardiac conditions, most notably atherosclerotic heart disease, hypertension, renal failure, cancer, and infectious diseases, have paradoxically contributed to the increasing burden of heart failure. Thus, individuals who 20 years ago might have died in middle age from acute myocardial infarction are now surviving to older age only to develop heart failure in their later years. Similarly, improved blood pressure control has led to a 60% decline in stroke mortality over the last 30 years, yet these same patients remain at risk for the subsequent development of heart failure as a complication of hypertension and left ventricular hypertrophy.

TABLE 79-1 FACTORS CONTRIBUTING TO THE RISING INCIDENCE AND PREVALENCE OF HEART FAILURE

Aging of the population
• Age-related cardiovascular changes
• High prevalence of cardiovascular disease
Improved therapy for coronary heart disease and hypertension
• Decline in coronary mortality
• Fibrinolytic therapy
• Coronary angioplasty, stents, and bypass surgery
• Aspirin, β-blockers, and converting enzyme inhibitors
• Statins
• Decline in stroke mortality
• More widespread use of antihypertensive agents
• Beneficial effects of treating hypertension
• Fibrinolytic therapy
Improved therapy for other disorders
• End-stage renal disease
• Cancer
• Pneumonia and other infections

Heart failure affects approximately 5.7 million Americans, and it is projected that by 2030 the prevalence of heart failure in the United States will exceed 8 million, largely owing to the aging of the population. In addition, over 850,000 new cases are diagnosed each year. Moreover, both the incidence and the prevalence of heart failure are strikingly age dependent (**Figures 79-1** and **79-2**). Thus, heart failure is relatively uncommon in individuals younger than 40 years, but the prevalence doubles for each decade thereafter and exceeds 10% in both men and women older than 80 years. Similarly, heart failure mortality rates increase exponentially with advancing age in all major demographic subgroups of the US population.

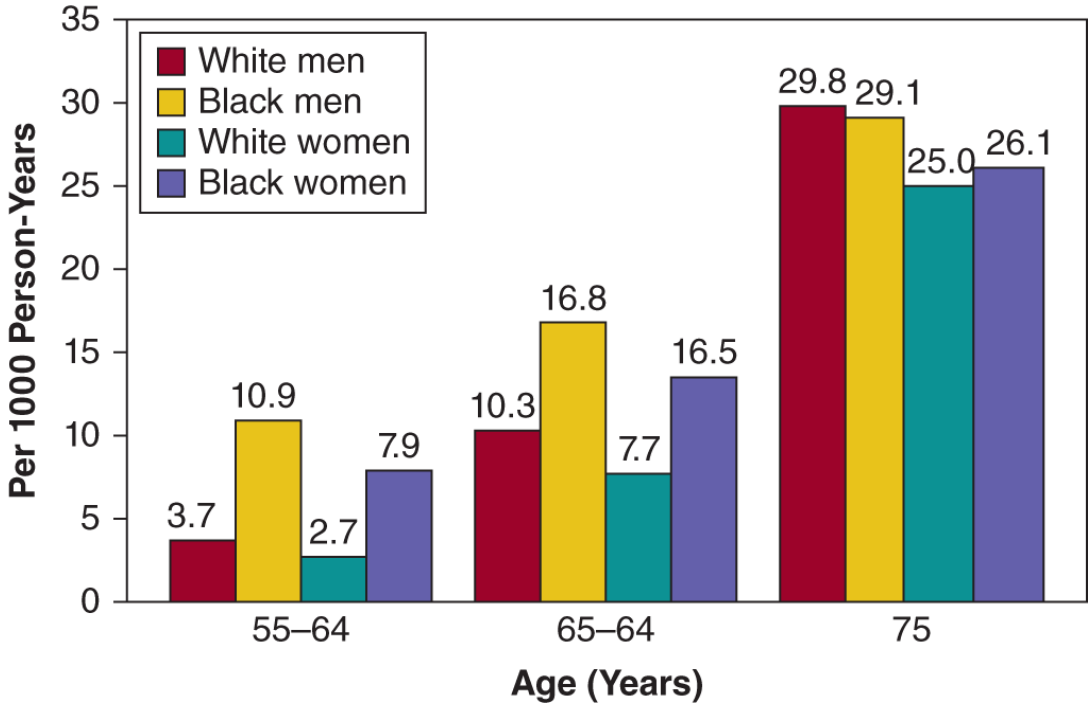


FIGURE 79-1. Incident heart failure hospitalizations in the United States by age, gender, and race, 2005–2011: the Atherosclerosis Risk in Communities Study. (National Heart, Lung, and Blood Institute; *Circulation*. 2015;131:e276.)

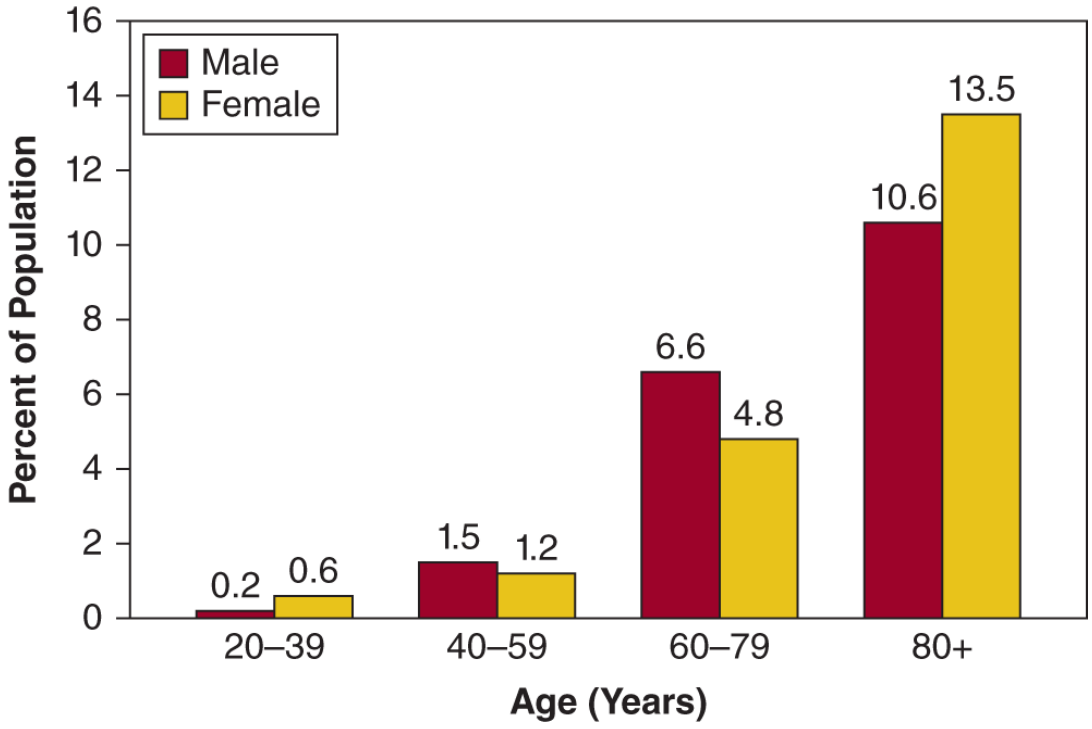


FIGURE 79-2. Prevalence of heart failure in the United States by age and gender: National Health and Nutrition Examinations Survey, 2009–2012. (National Center for Health Statistics and National Heart, Lung, and Blood Institute; *Circulation*. 2015;131:e275.)

Heart failure is also a major source of chronic disability and impaired quality of life in older adults, and it is the leading indication for hospitalization in individuals older than 65 years. Moreover, the number of hospital discharges for heart failure increased by more than twofold from 1979 to 2004, primarily owing to the aging of the population. In 2010, there were 1 million hospital admissions in the United States with a primary diagnosis of heart failure (**Table 79-2**). Of these, 71% were in patients older than 65 years, 53% were in patients 75 years or older, and 25% occurred in the 2% of the population greater than or equal to 85 years (**Figure 79-3**). The majority of heart failure patients younger than 65 years are males, but women comprise more than half of heart failure admissions after the age of 65, and the

proportion of females continues to rise with advancing age. The prevalence of heart failure in older Caucasians and African Americans is similar, but hospital admission rates are lower in Hispanics and Asians. Whether this represents a true difference in population prevalence or a cultural difference in the likelihood that affected individuals will seek medical attention is unknown. Heart failure is also a common reason for ambulatory care visits, with 1.8 million physician office visits with a primary diagnosis of heart failure in 2010. In this regard, heart failure ranks second only to hypertension among cardiovascular causes for outpatient physician visits.

TABLE 79-2 EPIDEMIOLOGY OF HEART FAILURE IN THE UNITED STATES

POPULATION GROUP	PREVALENCE[a] (AGE ≥ 20)	INCIDENCE (AGE ≥ 55)	MORTALITY[a] (2011, ALL AGES)	HOSPITAL DISCHARGES (2010, ALL AGES)	COST[b]
Both sexes	5.7 million (2.2%)	870,000	58,309	1.023 million	$30.7
Men	2.7 million (2.3%)	415,000	24,609 (42%)	501,000	
Women	3.0 million (2.2%)	455,000	33,700 (58%)	522,000	
Race/ethnicity					
NH white men	2.2%	365,000	21,802		
NH white women	2.2%	395,000	30,036		
Black men	2.8%	50,000	2371		
Black women	3.2%	60,000	3143		
Hispanic men	2.1%	NA	NA		
Hispanic women	2.1%	NA	NA		

NA, not available; NH, non-Hispanic.

[a]Based on 2012 data.

[b]Estimated for 2012, in billions of dollars.

Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation. 2015;131:e29–e322.

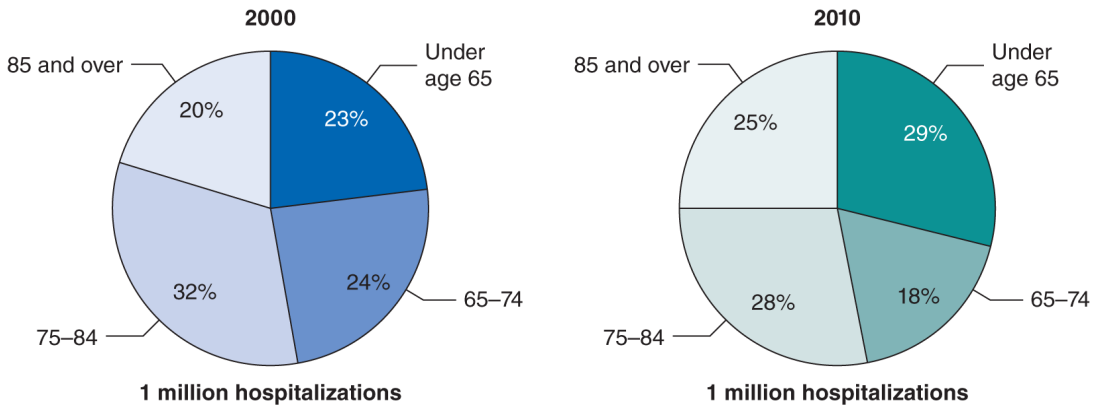


FIGURE 79-3. Distribution of hospitalizations for heart failure in the United States by age, 2000–2010. (National Center for Health Statistics, Data brief no. 108, October 2012.)

As a result of its high prevalence and the need for intensive resource use in both the inpatient and the outpatient settings, it is not surprising that the economic burden of heart failure is very high. Heart failure is one of the most costly diagnosis-related groups in the United States, with estimated total annual expenditures in excess of $30 billion. Overall, heart failure accounts for about 6% of Medicare expenditures for inpatient care.

PATHOPHYSIOLOGY

Heart failure represents the prototypical disorder of cardiovascular aging in that age-related changes in the cardiovascular system in concert with an increasing prevalence of cardiovascular diseases at older age conspire to produce an exponential rise in heart failure prevalence with advancing age.

Aging is associated with extensive changes in cardiovascular structure and function (see Chapter 75). However, in the absence of coexistent cardiovascular disease, resting cardiac function is well preserved even at very old age. Thus, the resting left ventricular ejection fraction, an index of left ventricular systolic performance, is unaffected by age in healthy individuals. Similarly, most studies indicate that resting cardiac output is either maintained or declines minimally with normal aging.

From the clinical perspective, the changes associated with cardiovascular aging result in an impaired ability of the heart to respond to stress, whether that stress is physiologic (eg, exercise) or pathologic (eg, hypertension or myocardial ischemia). Four principal changes in the cardiovascular system contribute directly to the heart's attenuated capacity to augment cardiac output in response to stress. First, aging is associated with reduced responsiveness to β-adrenergic stimulation. The mechanism underlying this change has not been fully elucidated, but is likely related to increased sympathetic nervous system activity and circulating catecholamine levels resulting in β-adrenergic receptor desensitization, rather than decreased β-receptor density on cardiac myocytes or altered responsiveness to intracellular calcium. In any case, the diminished response to β-adrenergic stimulation limits the heart's capacity to maximally increase heart rate and contractility in response to stress, and β_2-mediated peripheral vasodilatation is also impaired.

A second major effect of aging is increased vascular stiffness, primarily because of increased collagen deposition and cross-linking and degeneration of elastin fibers in the media and adventitia of the large- and medium-sized arteries. Increased vascular stiffness results in increased impedance to left ventricular ejection (ie, increased afterload), and it also contributes to the increased propensity of older individuals to develop isolated systolic hypertension.

A third major effect of aging is altered left ventricular diastolic filling. Diastole is characterized by four phases: isovolumic relaxation, early rapid filling, passive filling during mid-diastole, and late filling owing to atrial systole. The first two phases, isovolumic relaxation and early rapid filling, are largely dependent on myocardial relaxation, an active, energy-requiring process, whereas filling during the latter two phases is governed principally by intrinsic myocardial "stiffness," or compliance. Aging is associated with impaired calcium release from the contractile proteins and reuptake by the sarcoplasmic reticulum at the end of systole, leaving the heart in a state of "partial contraction" at the onset of diastole and inhibiting early diastolic relaxation. In addition, increased interstitial connective tissue content and collagen cross-linking reduce ventricular compliance. Compensatory myocyte hypertrophy in response to increased ventricular afterload and myocyte loss due to apoptosis further compromises left ventricular compliance. Thus, normal aging is associated with important changes that impair both relaxation and compliance, adversely impacting all four phases of diastole and substantially altering the pattern of left ventricular diastolic filling.

Age-related changes in diastolic filling and atrial function can be evaluated noninvasively using Doppler echocardiographic techniques to examine diastolic inflow across the mitral valve (**Figure 79-4**). In healthy young persons, the transmitral inflow pattern is characterized by a large E-wave, with a rapid upstroke representing rapid filling of the ventricle immediately following the opening of the mitral valve and corresponding to active ventricular relaxation (**Figure 79-4A**). This is followed by a period in which the rate of filling slows (the downslope of the E-wave), mid-diastolic diastasis (in which left atrial and left ventricular pressures are essentially equal), and a second burst of flow at the end of diastole corresponding to atrial contraction (the A-wave, or atrial "kick"). Importantly, the majority of ventricular filling occurs in the first half of diastole in young individuals, with a relatively small contribution from atrial contraction.

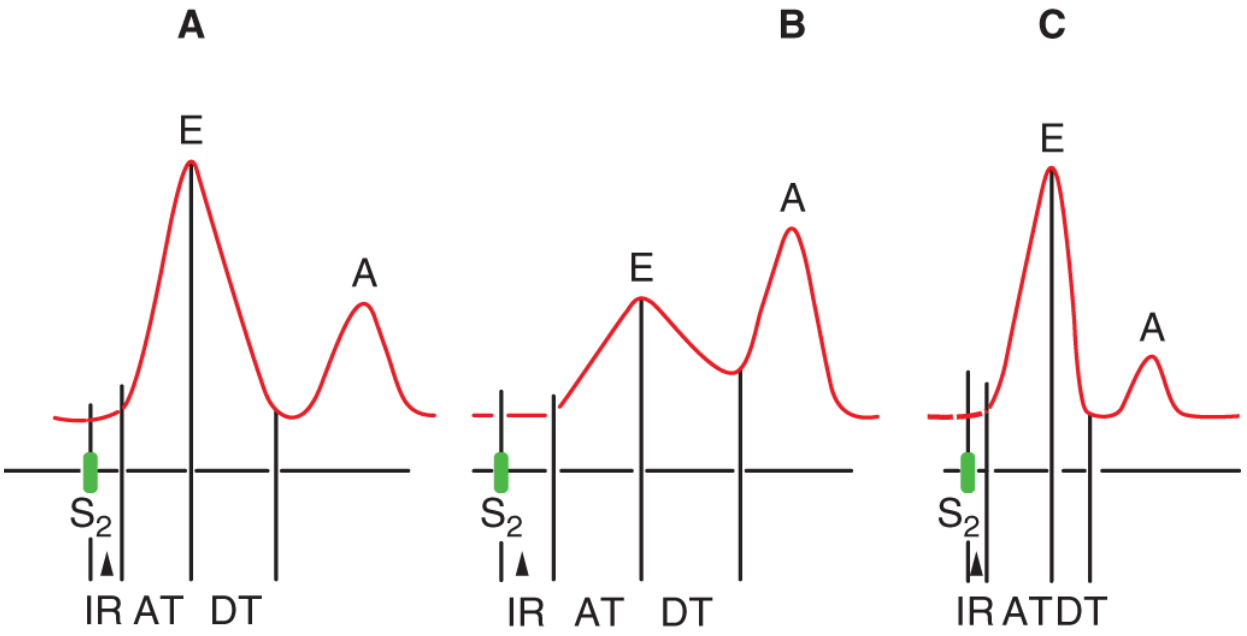


FIGURE 79-4. Schematic diagram of Doppler echocardiographic mitral valve inflow patterns. **A.** Normal pattern. **B.** Impaired filling pattern. **C.** Restrictive pattern. AT, acceleration time; DT, deceleration time; IR, isovolumic relaxation; S_2, aortic valve closure. (Adapted with permission from Feigenbaum H. *Echocardiography*. 5th ed. Philadelphia,PA: Lea & Febiger; 1994:152.)

In older persons, alterations in cardiac relaxation and compliance result in characteristic changes in the pattern of diastolic filling (**Figure 79-4B**). Early filling is impaired, and the upstroke of the E-wave is delayed. Similarly, the downslope of the E-wave is less steep, as it takes a longer time to achieve diastasis. In order to compensate for increased resistance to emptying, the left atrium enlarges and hypertrophies. This results in a more forceful left atrial contraction and an augmented A-wave. As a result of these changes, a greater proportion of filling occurs in the second half of diastole in older individuals, and as much as 30% to 40% of left ventricular end-diastolic volume may be attributable to atrial contraction. Thus, older individuals become increasingly reliant on the atrial "kick" to maximize left ventricular filling.

A third pattern of diastolic filling, referred to as the restrictive pattern, occurs when the left ventricle's ability to accept blood becomes severely compromised. In this situation (**Figure 79-4C**), very little flow occurs after the rapid filling phase in early diastole. This pattern is characterized by a tall, narrow E-wave with a rapid downslope, as diastasis is achieved early in diastole. Little additional flow occurs during mid-diastole, and the A-wave is typically small, with an amplitude that is less than 50% of the E-wave. A restrictive pattern usually indicates marked elevation of the left ventricular diastolic pressure, and it tends to be associated with a poor prognosis, particularly in patients with concomitant systolic dysfunction. The restrictive pattern almost always occurs in patients with advanced cardiac disease, and it is rarely attributable to aging alone.

Age-related changes in diastolic filling have several important clinical implications. First, inability to distend the cardiac myocytes to an optimal fiber length results in a failure of the Frank-Starling mechanism, one of the cardinal adaptive responses (along with sympathetic activation) to acutely increase cardiac output. Second, impaired diastolic filling results in a shift to the left in the normal ventricular pressure-volume relationship; that is, a small increase in diastolic volume is associated with a greater increase in diastolic pressure in older compared to younger individuals. This increase in diastolic pressure is transmitted back to the left atrium, and left atrial myocytes become "stretched." This, in turn, increases the likelihood of atrial ectopic beats and atrial arrhythmias, especially atrial fibrillation. This accounts, in part, for the fact that atrial fibrillation, like heart failure, increases in prevalence with advancing age. In addition, atrial fibrillation itself is a common precipitant of heart failure in older adults for two reasons. First, the absence of a coordinated atrial contraction substantially compromises late diastolic filling as a result of loss of the atrial "kick." Second, the rapid, irregular ventricular rate associated with acute atrial fibrillation shortens the diastolic filling period, which further attenuates ventricular filling.

A third effect of altered diastolic filling is an increased propensity for older adults to develop HFPEF, previously referred to as diastolic heart failure. Because of the altered left ventricular pressure-volume relation, increases in left ventricular pressure owing to ischemia or uncontrolled hypertension may lead to pulmonary congestion and edema. Moreover, individuals with impaired diastolic function are often "volume sensitive"; that is, small increments in

intravascular volume, as may occur with a dietary salt load or intravenous fluid administration, are poorly accommodated by the noncompliant ventricle. As a result, intraventricular pressure rises abruptly and heart failure ensues. Conversely, intravascular volume contraction, which may arise from poor oral intake or overdiuresis, can cause a marked fall in left ventricular volume, which in turn leads to a fall in stroke volume and cardiac output.

The fourth major effect of cardiovascular aging is altered myocardial energy metabolism at the level of the mitochondria. Under resting conditions, older cardiac mitochondria are able to generate sufficient quantities of adenosine triphosphate (ATP) to meet the heart's energy requirements. However, when stress causes an increase in ATP demands, the mitochondria are often unable to respond appropriately. Although the precise mechanism underlying this mitochondrial failure is unclear, the defect adds to the heart's inability to maintain normal function under stress.

To summarize, four major age-related changes in cardiovascular structure, function, and physiology combine to reduce cardiovascular reserve and greatly increase the risk of heart failure in older adults. Recalling that cardiac output is determined by four primary factors (heart rate, preload, afterload, and contractile state), and recognizing that each of these factors is adversely affected by one or more of the four major effects of aging on the heart, and that superimposed upon these changes is the high prevalence of cardiac disease in older adults, it is indeed not surprising that the incidence and prevalence of heart failure rise exponentially with advancing age.

It is also important to note that aging is associated with significant changes in other organ systems, which impact directly or indirectly on the development and/or management of heart failure. Aging is accompanied by a decline in glomerular filtration rate, and the aging kidney is less able to maintain intravascular volume and electrolyte homeostasis (see Chapter 86). The reduced capacity of the kidneys to respond to intravascular volume overload or dietary sodium excess further increases the risk of heart failure in older individuals. In addition, older patients are less responsive to diuretics and more likely to develop diuretic-induced electrolyte abnormalities than younger patients, factors that may complicate the management of heart failure in the older age group.

Aging is also associated with numerous changes in respiratory function, which serve to diminish respiratory reserve (see Chapter 83). Some of these effects, such as *V/Q* mismatching and sleep-related breathing disorders, may contribute directly to the development of heart failure by producing hypoxemia or pulmonary hypertension. Other changes reduce the capacity of the lungs to compensate for the failing heart by increasing tidal volume and minute ventilation, thereby contributing to the patient's sensation of dyspnea. In more severe cases of cardiac failure, such as pulmonary edema, acute respiratory failure may ensue, partly as a consequence of the inability of the lungs to maintain oxygenation and effective ventilation.

Age-related changes in nervous system function include an impaired thirst mechanism, which may contribute to dehydration and intravascular volume contraction in patients treated with diuretics, and reduced capacity of the central nervous system's autoregulatory mechanisms to maintain cerebral perfusion in the face of changes in systemic arterial blood pressure. The latter effect may contribute to subtle changes in cognitive function in older heart failure patients treated with vasodilators. Aging is also associated with widespread changes in reflex responsiveness. For example, impaired responsiveness of the carotid baroreceptors to acute changes in blood pressure may cause orthostatic hypotension or syncope, and these effects may be further aggravated by many of the drugs used to treat heart failure.

Finally, as is well recognized, aging is associated with significant changes in the pharmacokinetics and pharmacodynamics of almost all drugs. In addition, older patients tend to be at increased risk of both drug-drug and drug-disease interactions as a result of the high prevalence of comorbid conditions and the use of multiple pharmacologic agents. These factors often lead to alterations in drug efficacy and an increased side effect profile, and these effects must be taken into consideration when designing therapy for older heart failure patients (see Chapter 24).

ETIOLOGY AND PRECIPITATING FACTORS

In general, the etiology of heart failure is similar in older and younger patients (**Table 79-3**), but heart failure in older individuals is more often multifactorial. As in younger patients, hypertension and coronary heart disease are the most common causes of heart failure, accounting for more than 70% of cases. Hypertensive hypertrophic cardiomyopathy represents a more severe form of hypertensive heart disease most commonly seen in older women and often accompanied by calcification of the mitral valve annulus. These patients often manifest severe diastolic dysfunction and may exhibit dynamic left ventricular outflow tract obstruction indistinguishable from that seen in classical hypertrophic cardiomyopathy.

TABLE 79-3 ■ COMMON ETIOLOGIES OF HEART FAILURE IN OLDER ADULTS

Coronary artery disease
• Acute myocardial infarction
• Ischemic cardiomyopathy
Hypertensive heart disease
• Hypertensive hypertrophic cardiomyopathy
Valvular heart disease
• Calcific aortic stenosis
• Mitral regurgitation
• Mitral stenosis
• Aortic insufficiency
• Prosthetic valve dysfunction
Cardiomyopathy
• Dilated (nonischemic)
• Alcohol
• Chemotherapeutic agents (eg, anthracyclines, trastuzumab)
• Stress cardiomyopathy (takotsubo cardiomyopathy)
• Idiopathic
• Hypertrophic
• Restrictive (especially amyloid)
Infective endocarditis
Myocarditis
Pericardial disease
High-output failure
• Chronic anemia
• Thiamine deficiency
• Hyperthyroidism
• Arteriovenous shunting
Age-related increase in arterial stiffness and diastolic dysfunction

Valvular heart disease is an increasingly common cause of heart failure at older age. Calcific aortic stenosis is now the most common form of valvular heart disease requiring invasive treatment, and aortic valve replacement is the second most common major heart procedure performed in patients older than 70 years (after coronary bypass grafting). Mitral regurgitation in older individuals may be caused by myxomatous degeneration of the mitral valve leaflets and chordae tendineae (mitral valve prolapse), mitral annular calcification, valvular vegetations, ischemic papillary muscle dysfunction, or altered ventricular geometry owing to ischemic or nonischemic dilated cardiomyopathy. Importantly, mitral regurgitation may be acute (eg, following acute myocardial infarction), subacute (eg, endocarditis), or chronic (eg, myxomatous degeneration), and the clinical manifestations may vary widely in each of these settings. In the United States, rheumatic mitral stenosis is a less common cause of heart failure in older adults, but it is still occasionally seen. Functional mitral stenosis owing to severe mitral valve annulus calcification with encroachment on the mitral valve orifice is an uncommon cause of heart failure, but it is associated with a poor prognosis. Aortic insufficiency may be either acute (eg, because of endocarditis or type A aortic dissection) or chronic (eg, annuloaortic ectasia or syphilitic aortitis), but it is a relatively infrequent cause of heart failure in older adults. Finally, prosthetic valve dysfunction should be considered as a potential cause of heart failure in any patient who has undergone previous valve repair or replacement.

Cardiomyopathies are classified into three categories: dilated, hypertrophic, and restrictive. In older adults,

ischemic heart disease with one or more prior myocardial infarctions is the most common cause of dilated cardiomyopathy. Nonischemic dilated cardiomyopathy is less common in older than in younger individuals; when present, it is most often either idiopathic in origin or attributable to chronic ethanol abuse or cancer chemotherapy (eg, anthracyclines or trastuzumab). Stress cardiomyopathy (also known as takotsubo cardiomyopathy) is a relatively recently recognized cause of acute heart failure usually precipitated by physical or psychological stress. The majority of patients are women and most cases resolve within days to weeks. Classical hypertrophic cardiomyopathy, once thought to be rare in the geriatric age group, has been increasingly recognized in older adults since the advent of echocardiography. Similarly, restrictive cardiomyopathy, most commonly owing to amyloid deposition, is an occasional cause of heart failure. In one autopsy series, cardiac amyloid deposition was thought to be clinically important in approximately 10% of individuals 90 years or older. Recently there has been increased interest in "senile cardiac amyloid," which has been linked to mutations in the gene coding for the protein transthyretin (previously known as prealbumin). Genetic abnormalities in transthyretin are present in up to 4% of African Americans, who are at increased risk for developing cardiac amyloid. While the genetic defect is present from birth, clinical manifestations typically do not become apparent until after age 60. Novel therapies that inhibit production or promote stabilization of transthyretin amyloid, such as diflunisal and tafamidis, are currently being evaluated in clinical trials.

Infective endocarditis is an uncommon but important cause of heart failure in older patients because it is one of the few etiologies for which curative pharmacologic therapy is available. Endocarditis should be strongly suspected in any patient with persistent fever and either a prosthetic heart valve or a preexisting valvular lesion. It should also be considered in any patient with fever, recent dental work or other procedure, and a new or worsening heart murmur. It is important to recognize, however, that the clinical manifestations of endocarditis are often protean, and the absence of fever or a heart murmur does not exclude this diagnosis in older individuals.

Myocarditis is a relatively rare cause of heart failure in older adults. It may be infectious (eg, postviral) or noninfectious (eg, owing to sarcoid or collagen vascular disease). Pericardial effusions, for which there are numerous etiologies, occasionally present with heart failure symptomatology, including fatigue, exertional dyspnea, and edema. Constrictive pericarditis may be infectious (eg, tuberculous) or noninfectious (eg, postradiation), but it is a rare cause of heart failure in older patients.

High-output failure is an uncommon cause of heart failure in older adults, but when present the diagnosis is frequently overlooked. Potential causes of high-output failure include chronic anemia, hyperthyroidism, thiamine deficiency, and arteriovenous shunting (eg, owing to a dialysis fistula or arteriovenous malformations).

Finally, in a small percentage of older heart failure patients, detailed investigation may fail to identify any primary cardiovascular pathology. In cases with a normal left ventricular ejection fraction, heart failure may be attributed to age-related diastolic dysfunction.

Precipitating Factors

In addition to determining the etiology of heart failure, it is important to identify coexisting factors that may have contributed to the acute or subacute exacerbation (**Table 79-4**). The most common precipitant in patients with preexisting heart failure is nonadherence to medications and/or diet. Indeed, nonadherence may contribute to as many as two-thirds of heart failure exacerbations. In hospitalized patients, iatrogenic volume overload (eg, in the perioperative period) is also an important precipitant of heart failure.

TABLE 79-4 COMMON PRECIPITANTS OF HEART FAILURE IN OLDER ADULTS

Myocardial ischemia or infarction
Dietary sodium excess
Excess fluid intake
Medication nonadherence
Iatrogenic volume overload
Arrhythmias • Atrial fibrillation or flutter • Ventricular arrhythmias • Bradyarrhythmias, especially sick sinus syndrome

Associated medical conditions
• Fever
• Infections, especially pneumonia or sepsis
• Hyperthyroidism or hypothyroidism
• Anemia
• Renal insufficiency
• Thiamine deficiency
• Pulmonary embolism
• Hypoxemia from chronic lung disease
• Uncontrolled hypertension
Drugs and medications
• Alcohol
• β-Blockers (including ophthalmologic agents)
• Calcium channel blockers
• Antiarrhythmic agents
• Nonsteroidal anti-inflammatory drugs
• Corticosteroids
• Estrogen preparations
• Antihypertensive agents (eg, clonidine and minoxidil)

Among cardiac factors, myocardial ischemia or infarction and new-onset atrial fibrillation or flutter are the most common causes of an acute episode of heart failure. Other cardiac causes include ventricular arrhythmias, especially ventricular tachycardia, and bradyarrhythmias, such as marked sinus bradycardia or advanced atrioventricular block. Sick sinus syndrome, which is common in older adults, is a frequent cause of bradyarrhythmias in this population.

As previously discussed, older patients have limited cardiovascular reserve and they are less able to compensate in response to increased demands. As a result, heart failure in older adults is often precipitated by acute or worsening noncardiac conditions. Patients with acute respiratory disorders, such as pneumonia, pulmonary embolism, or an exacerbation of chronic obstructive lung disease, are particularly prone to exhibit deterioration in cardiac function. Other serious infections, such as sepsis or pyelonephritis, may also lead to heart failure exacerbations. In patients with hypertension, inadequate blood pressure control is a common cause of worsening heart failure. Thyroid disease, anemia (eg, owing to gastrointestinal bleeding), and declining renal function may also contribute directly or indirectly to the development of heart failure.

Finally, numerous drugs and medications may contribute to heart failure exacerbations. Alcohol is a cardiac depressant, and it may also precipitate arrhythmias, especially atrial fibrillation. β-Blockers (including ophthalmologic agents) and calcium antagonists are widely used in older individuals with cardiovascular disease, but both classes of agents are negatively inotropic and may exacerbate heart failure. Class Ia (eg, quinidine, procainamide, and disopyramide) and Ic (eg, flecainide and propafenone) antiarrhythmic agents have important myocardial depressant effects that may worsen cardiac function. Nonsteroidal anti-inflammatory drugs (NSAIDs), which are widely used by older adults, impair renal sodium and water excretion and may, therefore, contribute to intravascular volume overload. In addition, NSAIDs antagonize the effects of angiotensin-converting enzyme (ACE) inhibitors, thereby limiting the efficacy of these agents. Corticosteroids and estrogen preparations may cause fluid retention and an increase in total body water. Fluid retention is the most important side effect of the insulin-sensitizing thiazolidinediones (rosiglitazone and pioglitazone), and worsening heart failure may occur with these agents. The antihypertensive agent minoxidil also promotes fluid retention, and several other antihypertensive drugs (eg, clonidine and guanethidine) may have unfavorable hemodynamic effects.

CLINICAL FEATURES

Symptoms

As in younger patients, the most common symptoms of heart failure in older adults are exertional shortness of breath, orthopnea, dependent edema, fatigue, and exercise intolerance. However, there is an increased prevalence of atypical symptomatology in older patients, particularly those older than 80 years (**Table 79-5**). As a result, heart failure in older adults is paradoxically both over- and underdiagnosed. Thus, shortness of breath and orthopnea in an older individual may be attributed to heart failure when the underlying cause is chronic lung disease, pneumonia, or pulmonary embolism. Similarly, fatigue and reduced exercise tolerance may be caused by anemia, hypothyroidism, depression, or poor physical conditioning. On the other hand, sedentary individuals and those limited by arthritis or neuromuscular conditions may not report exertional dyspnea or fatigue, and atypical symptoms such as those listed in **Table 79-5** may be the first and only clinical manifestations of heart failure. In such cases, the physician must maintain a high index of suspicion or the diagnosis of heart failure may be readily overlooked.

TABLE 79-5 ATYPICAL MANIFESTATIONS OF HEART FAILURE IN OLDER PERSONS

Nonspecific systemic complaints
• Malaise
• Lassitude
• Weight loss
• Declining physical activity level
Neurologic symptoms
• Confusion
• Irritability
• Sleep disturbances
Gastrointestinal disorders
• Anorexia or early satiety
• Abdominal discomfort
• Nausea
• Diarrhea or constipation

Signs As with symptoms, the physical findings in older heart failure patients may be nonspecific or atypical. The classic signs of heart failure include moist pulmonary rales, an elevated jugular venous pressure, abdominojugular reflux, an S_3 gallop, and pitting edema of the lower extremities. However, pulmonary rales in older individuals may be due to chronic lung disease, pneumonia, or atelectasis, and peripheral edema may be caused by venous insufficiency, renal disease, or medication (eg, calcium channel blockers). Conversely, older patients may have an essentially normal physical examination despite markedly reduced cardiac performance. Alternatively, impaired sensorium or Cheyne-Stokes respirations may be the only findings to suggest the presence of heart failure.

Heart failure with reduced versus preserved ejection fraction

Current nomenclature distinguishes two forms of heart failure—HFREF, usually defined as ejection fraction less than 40%–50% and HFPEF. The clinical manifestations of both forms of heart failure are similar, and no single clinical feature can reliably distinguish patients with HFREF from those with HFPEF. Nonetheless, certain features tend to favor one form or the other (**Table 79-6**). Based on the presence or absence of specific features, the probability of normal or reduced systolic function can be estimated, and there have been several attempts to develop algorithms for distinguishing these syndromes. Unfortunately, the predictive accuracy of these algorithms has been modest, and additional testing is essential in order to reliably differentiate HFREF from HFPEF.

TABLE 79-6 CLINICAL FEATURES OF HEART FAILURE WITH REDUCED VERSUS PRESERVED EJECTION FRACTION

	HFREF	HFPEF
Demographics	Age < 60 y Male gender	Age > 70 y Female gender
Comorbid illnesses	Prior myocardial infarction	Chronic hypertension

	Alcoholism Valvular insufficiency	Renal disease Obesity Aortic stenosis
Physical examination	May be normotensive or hypotensive Jugular venous distention Displaced PMI S_3 gallop Pitting edema	Usually hypertensive Jugular venous distention often absent Sustained PMI S_4 gallop Peripheral edema often absent
Electrocardiogram	Q waves due to prior myocardial infarction	Left ventricular hypertrophy

HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; PMI, point of maximum impulse.

DIAGNOSTIC EVALUATION

Heart failure may be difficult to diagnose in older patients with multiple comorbid conditions and either vague or nonspecific symptoms and signs. Thus, the first task facing the physician is to establish whether or not heart failure is present. This begins with a careful history and physical examination, giving due consideration to potential alternative etiologies for the patient's findings. As discussed in the previous section, physical signs may be unreliable in older patients. Nonetheless, certain findings, including pulsus alternans, an S_3 gallop, and the presence of jugular venous distension at rest or in response to the abdominojugular reflux maneuver, are highly specific signs of heart failure in older patients. In the absence of these findings, the diagnosis often remains in doubt, and additional laboratory studies are required.

To differentiate shortness of breath attributable to heart failure from that owing to other causes, the level of B-type natriuretic peptide (BNP—a 32-amino acid hormone released by the cardiac ventricles in response to increased wall tension) or its precursor N-terminal pro-BNP (NT–pro-BNP) is the single most useful test. However, BNP levels increase modestly with age, especially in women (**Figure 79-5**), and with declining renal function, but tend to be lower in the presence of obesity. Therefore, the specificity of an elevated BNP level for clinical heart failure declines with age. BNP levels in excess of 500 pg/mL in the appropriate clinical context are highly suggestive of active heart failure, whereas a normal value (< 100 pg/mL) in a nonobese older adult makes the diagnosis of heart failure much less likely. In addition to the BNP level, the chest radiograph remains useful for establishing the presence of active pulmonary congestion. In patients with moderate or severe heart failure, the chest film will usually demonstrate typical findings of cardiomegaly, pulmonary vascular engorgement, parenchymal edema, and pleural effusions. However, in patients with mild heart failure or coexisting pulmonary disease, the chest radiograph may be nondiagnostic.

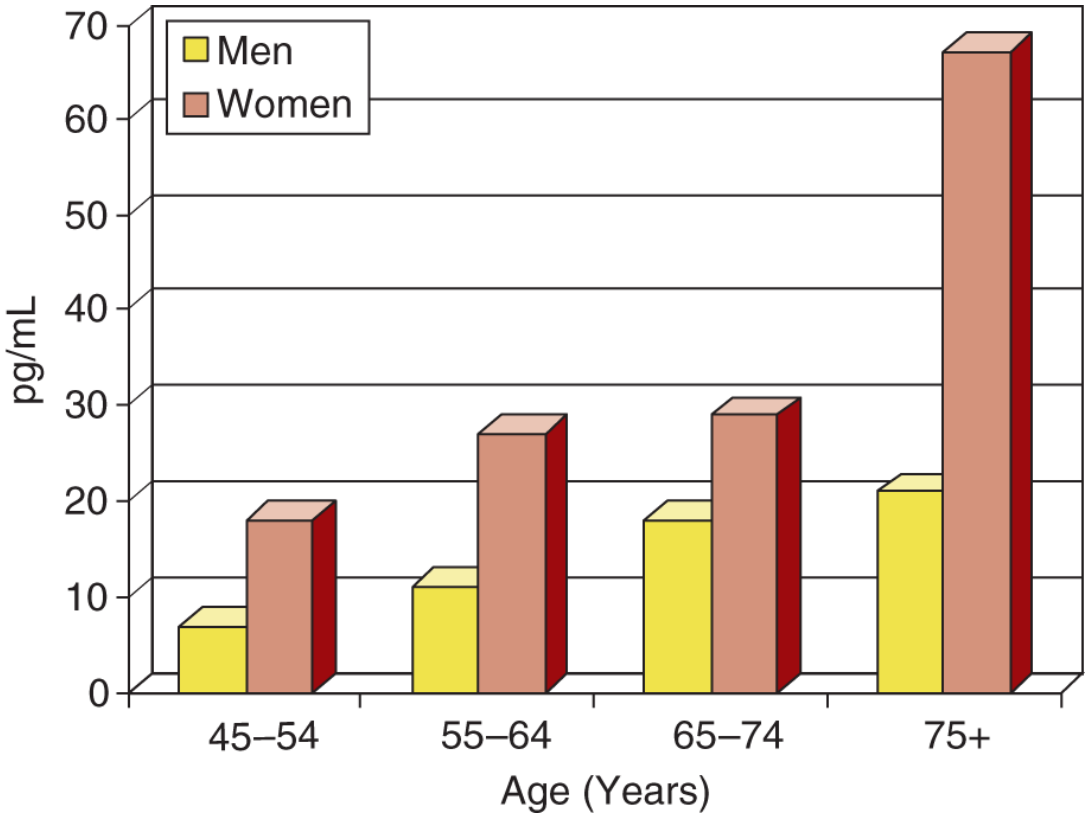


FIGURE 79-5. B-type natriuretic peptide levels by age and gender (mean values in healthy volunteers). (Adapted with permission from Redfield MM, Rodeheffer RJ, Jacobsen SJ, et al. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002;40:976–982.)

Once the presence of heart failure has been established, the physician must address two crucial questions, the answers to which will serve as the basis for selecting appropriate therapy:

1. What is the underlying etiology and pathophysiology of heart failure (see **Table 79-3**)?
2. What additional factors, if any, contributed to or precipitated the development of heart failure (see **Table 79-4**)? Often, one or more precipitating factors can be identified, and alleviating these factors may significantly improve symptoms and reduce the likelihood of subsequent heart failure exacerbations.

In 2013, the American College of Cardiology and American Heart Association Task Force on Practice Guidelines published revised guidelines for the diagnosis and management of heart failure. **Table 79-7** outlines an appropriate initial diagnostic assessment for patients with new-onset heart failure. Class I studies are defined as those that are indicated in most patients, class II procedures are acceptable in some patients but are of unproven efficacy and may be controversial, and class III studies are not routinely indicated and in some cases may be harmful. Briefly, basic laboratory studies, a thyroid function test, a chest radiograph, an electrocardiogram, and an echocardiogram with Doppler are recommended in all patients. Cardiac catheterization and coronary angiography are appropriate in patients with angina or significant ischemia on noninvasive testing, and in those who require surgical correction of a noncoronary cardiac lesion (eg, aortic stenosis), unless the patient is not a suitable candidate for coronary revascularization.

TABLE 79-7 ■ DIAGNOSTIC EVALUATION OF PATIENTS WITH HEART FAILURE

Class I (indicated in most patients)

- Complete blood count
- Blood chemistries: electrolytes, creatinine, blood urea nitrogen, glucose, magnesium, calcium, liver function tests, and lipid profile
- Thyroid-stimulating hormone (TSH)
- B-type natriuretic peptide (BNP) or N-terminal pro-BNP level
- Urinalysis

• Chest radiograph and electrocardiogram (ECG)
• Echocardiogram: two-dimensional with Doppler
• Cardiac catheterization and coronary angiography in patients with angina or significant ischemia unless the patient is not eligible for revascularization
Class II (acceptable in selected patients; see text)
• Serum iron and ferritin
• If suspected, assessment for rheumatologic disease, human immunodeficiency virus, amyloidosis, or pheochromocytoma
• Screening for sleep-disordered breathing
• Stress test to evaluate for ischemia in patients with unexplained heart failure who are potential candidates for revascularization
• Coronary angiography if ischemia may be contributing to heart failure in patients who are potential candidates for revascularization
• Endomyocardial biopsy when a specific diagnosis is suspected that would influence therapy
Class III (not routinely indicated)
• Routine repeat measurement of left ventricular function in stable patients
• Endomyocardial biopsy as a routine procedure in the evaluation of patients with heart failure

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. J Am Coll Cardiol. 2013;62:e147–e239.

The recommendations outlined in **Table 79-7** are targeted toward a broad range of adult heart failure patients, and most are applicable in patients at an advanced age. Nonetheless, in older patients it is appropriate to consider the potential risks and benefits of each diagnostic procedure on an individualized basis, taking into account comorbid conditions, the extent of cardiac and noncardiac disability, and the patient's goals of care. For example, in a frail 85-year-old individual with diabetic nephropathy, the risk of precipitating dialysis-dependent end-stage renal disease as a complication of coronary angiography must be carefully weighed against the potential benefits to be derived from a successful revascularization procedure. Similarly, patient autonomy must be respected in all cases, and it is inappropriate to exert pressure on an older patient to undergo a procedure that the patient clearly does not desire. In this regard, it is imperative to discuss the therapeutic implications of specific procedures (especially invasive procedures) with respect to the patient's subsequent care (eg, need for coronary bypass surgery) prior to performing the diagnostic assessment.

HFREF Versus HFPEF

An important goal of the diagnostic evaluation, apart from determining the etiology of heart failure, is differentiating HFREF from HFPEF, since the management of these two syndromes differs. As noted earlier, it is difficult to make this distinction on clinical grounds alone, and it is therefore essential to evaluate left ventricular function directly by echocardiography, radionuclide angiography, magnetic resonance imaging, or contrast ventriculography. In general, transthoracic echocardiography is the most useful technique because it is noninvasive, relatively inexpensive, and, in addition to providing information about systolic and diastolic function, it is helpful in evaluating chamber size, wall thickness and motion, valve function, pulmonary artery pressure, and pericardial disease. Thus, transthoracic echocardiography is appropriate in virtually all older patients with newly diagnosed heart failure and in those with an unexplained change in symptom severity. The principal limitation of echocardiography is that adequate visualization of the heart may be unobtainable in a small percentage of patients, although the availability of echocontrast agents has minimized this problem. Alternatively, radionuclide angiography can provide an accurate assessment of left ventricular function, as well as information about cavity size and regurgitant valvular lesions. Magnetic resonance imaging provides much the same information as echocardiography and radionuclide angiography but is more expensive and contrast administration may be contraindicated in patients with impaired renal function. For those patients who require cardiac catheterization, contrast left ventriculography is an excellent method for evaluating ventricular function.

Based on the results of echocardiography, radionuclide angiography, magnetic resonance imaging, or contrast ventriculography, heart failure may be classified as HFREF or HFREF (in the ensuing discussion HFREF is defined as ejection fraction < 45%, HFPEF is defined as ejection fraction ≥ 45%). However, it must be emphasized that systolic and diastolic dysfunction are not mutually exclusive. Indeed, almost all patients with significant systolic dysfunction also have concomitant diastolic dysfunction. Conversely, systolic dysfunction may play a role in the development of

heart failure even when the ejection fraction under resting conditions is normal or near normal. Despite these limitations, the classification of heart failure as HFREF or HFPEF is useful in guiding therapy.

MANAGEMENT

The primary goals of heart failure therapy are to improve quality of life, reduce the frequency of heart failure exacerbations, and extend survival. Secondary goals include maximizing independence and exercise capacity, enhancing emotional well-being, and reducing resource use and the associated costs of care.

To achieve these goals, optimal therapy in older patients comprises three principal components: correction of the underlying etiology whenever possible (eg, aortic valve replacement for aortic stenosis or coronary revascularization for severe ischemia), attention to the nonpharmacologic and rehabilitative aspects of treatment, and the judicious use of medications.

As will be discussed in the section on Prognosis, the outlook for patients with established heart failure is poor. Therefore, the importance of effectively treating the primary etiology and all comorbid conditions predisposing to heart failure cannot be overemphasized. Since coronary heart disease and hypertension are the most common causes of heart failure in older adults, primary and secondary prevention of these conditions are critical if the development of heart failure is to be forestalled. Indeed, it has now been shown in multiple clinical trials that effective treatment of hypertension can reduce the incidence of heart failure by 50% or more. Similarly, appropriate management of other coronary risk factors, particularly hyperlipidemia, sedentary lifestyle, and cigarette smoking, will undoubtedly further reduce the burden of heart failure through the primary prevention of coronary heart disease.

Nonpharmacologic Therapy

Despite recent advances in the pharmacotherapy of heart failure, repetitive heart failure exacerbations are common and are more often precipitated by behavioral and social factors than by either new cardiac events (eg, ischemia or an arrhythmia) or progressive deterioration in ventricular function. In one study, lack of adherence to prescribed medications and/or diet contributed to 64% of heart failure exacerbations among urban blacks, while emotional and environmental factors contributed to 26% of hospital readmissions. In another study involving 140 patients 70 years or older hospitalized with heart failure, 47% were readmitted at least once during a 90-day follow-up period. Behavioral and social factors contributing to readmission included medication and dietary nonadherence (15% and 18%, respectively), inadequate social support (21%), inadequate discharge planning (15%), inadequate follow-up (20%), and failure of the patient to seek medical attention promptly when symptoms recurred (20%). These findings suggest that interventions directed at behavioral and social factors could potentially reduce readmissions and improve quality of life in patients with heart failure, and this hypothesis has now been confirmed in numerous prospective randomized trials. In a meta-analytic review of 33 such trials, heart failure readmissions were reduced by 42%, all-cause readmissions were reduced by 24%, and mortality was reduced by 20% in patients with heart failure enrolled in a disease management program relative to conventional care.

Components of a comprehensive nonpharmacologic treatment program are listed in **Table 79-8**. As with other aspects of geriatric care, it is important to structure the treatment program in order to accommodate the needs of each individual patient. Clearly, not every patient will require all of the components listed in the table. Similarly, the optimal intensity of any given component, for example, patient education or follow-up care, will vary substantially. For these reasons, it is desirable to designate a single individual, such as a nurse case manager, to coordinate all aspects of the patient's care.

TABLE 79-8 NONPHARMACOLOGIC ASPECTS OF HEART FAILURE MANAGEMENT

Patient education
• Symptoms and signs of heart failure
• Detailed discussion of all medications
• Emphasize importance of adherence
• Specific information about when to contact nurse or physician for worsening symptoms
Daily weight chart

• Specific directions on when to contact nurse or physician for changes in weight • Self-management of diuretic dosage based on daily weights in selected patients • Involve family/significant other when feasible
Dietary consultation • Individualized and consistent with needs/lifestyle • Avoidance of excess sodium intake (> 2.3 g/d) • Avoidance of excess fluid intake (> 2 L/d) • Weight loss, if appropriate • Low fat, low cholesterol, if appropriate • Adequate caloric intake • Emphasize adherence while allowing flexibility
Medication review • Heart failure therapy in accordance with guidelines • Eliminate unnecessary medications • Simplify regimen whenever possible • Consolidate dosing schedule
Social services • Assess social support structure • Evaluate emotional and financial needs • Intervene proactively when feasible
Intensive follow-up • Telephone and/or telemedicine contacts • Home health visits as needed • Outpatient clinic
Palliative care consultation in patients with advanced symptoms or frequent hospitalizations
Contact information • Names and phone numbers of nurse and physician • 24-hour availability

Physical Activity and Exercise

Traditionally, patients with heart failure have been advised to restrict physical activity on the grounds that rest is beneficial for the heart and that exercise could potentially worsen cardiac function or precipitate arrhythmias. However, it is now recognized that although some degree of activity restriction may be appropriate, excessive limitation of physical activity may contribute to a progressive decline in functional capacity as a result of cardiovascular and muscular deconditioning. In addition, several studies have demonstrated that participation in an appropriately structured exercise program may result in significant improvements in functional capacity and quality of life in patients with heart failure. In the largest of these trials, HF-ACTION, 2331 patients with stable heart failure and an ejection fraction less than or equal to 35% were randomized to a supervised exercise program or usual care. The mean age was 59 (25% were ≥ 68) and 28% were women. After a median follow-up of 30 months, patients randomized to the exercise intervention experienced a 7% reduction in the primary end point of all-cause mortality or all-cause hospitalization, but the difference was not significant ($p = 0.13$). After adjusting for highly prognostic baseline characteristics, exercise was associated with an 11% reduction in the primary end point ($p = 0.03$). In addition, exercise was associated with improved health status beginning at 3 months and persisting for up to 4 years. Based on these findings, current guidelines recommend regular exercise for the majority of patients with heart failure. In addition, in 2014 the Centers for Medicare and Medicaid Services approved structured cardiac rehabilitation and exercise training for heart failure patients similar to those enrolled in the HF-ACTION trial.

While data on exercise training in older adults are limited, a randomized trial involving 200 patients 60 to 89 years

(mean 72 years, 66% male) with New York Heart Association (NYHA) class II to III HFREF evaluated the effects of exercise prescription, education, occupational therapy, and psychosocial counseling. At 24 weeks of follow-up, intervention group patients experienced significant improvements in NYHA class, 6-minute walk distance, and quality of life, whereas control-group patients demonstrated no change from baseline in any of these parameters. Patients receiving the intervention also had significantly fewer hospital admissions relative to the control group. In addition, two small randomized trials in older patients with HFPEF have demonstrated that exercise training is safe and results in improved exercise capacity and quality of life. These data provide support for a beneficial effect of exercise and cardiac rehabilitation in older patients with either HFREF or HFPEF. Nonetheless, additional studies are needed to evaluate the safety and efficacy of regular exercise in older heart failure patients, especially those older than 75 years, and patients with frailty or multiple comorbid conditions.

Exercise prescription A comprehensive exercise and conditioning program is appropriate for most older patients with mild-to-moderate heart failure symptoms and no contraindications to exercise (**Table 79-9**). **Table 79-10** outlines the basic components of such a program. In general, patients should try to exercise every day. A typical session should include some gentle stretching exercises as well as strengthening exercises using elastic bands or light weights and targeting all of the major muscle groups. Suitable forms of aerobic exercise for older patients include walking, stationary cycling, and swimming. The choice of aerobic exercise should be tailored to the patient's wishes and abilities. When initiating an exercise program, the duration and intensity of the aerobic activity should be well within the patient's comfort range. The activity should be enjoyable, not stressful, and after completing the activity the patient should feel "positive" about the experience and not unduly fatigued. For many older patients with heart failure, this may mean starting with as little as 2 to 5 minutes of slow-paced walking. Once the patient feels comfortable exercising, the duration of exercise can be gradually increased over a period of several weeks. Weekly increases of 1 to 2 minutes per session are appropriate for most patients. Once the patient can exercise continuously and comfortably for 20 to 30 minutes, the intensity of exercise may be increased, if desired. For example, if the patient is walking a half-mile in 30 minutes, he or she may gradually reduce the half-mile time to 20 minutes, while maintaining a total exercise duration of 30 minutes. More recently, high-intensity interval training, in which short bursts of higher-intensity exercise are incorporated into the exercise regimen, has been shown to be safe and to result in more rapid increases in exercise capacity in heart failure patients. These findings, while encouraging, should be regarded as preliminary, and high-intensity training should only be initiated in a monitored setting.

TABLE 79-9 CONTRAINDICATIONS TO EXERCISE IN OLDER PATIENTS

Recent myocardial infarction or unstable angina (within 2 wk)
Severe, decompensated heart failure (New York Heart Association class IV)
Life-threatening arrhythmias not adequately treated
Severe aortic stenosis or hypertrophic cardiomyopathy
Any acute serious illness (eg, pneumonia)
Any condition precluding safe participation in an exercise program

TABLE 79-10 EXERCISE PRESCRIPTION FOR OLDER PATIENTS WITH HEART FAILURE

Components of conditioning program • Flexibility exercises • Strengthening exercises • Aerobic conditioning
Frequency of exercise: daily, if possible
Duration of exercise: individualized; start low, go slow
Intensity of exercise: low to moderate (see text for details)
Rate of progression: gradual over weeks to months
Monitoring: heart rate, perceived exertion (see text)

The two most common techniques for monitoring exercise intensity are the target heart rate method and the patient's subjective assessment of perceived exertion. For patients not taking medications that lower heart rate (eg, β-blockers), the maximum attainable heart rate in beats/min can be estimated from the formula: 220 – age. The patient's resting heart rate is then subtracted from this figure to determine the *heart rate reserve*. A suitable target heart rate for low-intensity exercise can be calculated as the resting heart rate *plus* 30% to 50% of the heart rate reserve. For moderate-intensity exercise, the target range is the resting heart rate plus 50% to 70% of the heart rate reserve. For example, an 80-year-old individual has a predicted maximum heart rate of 220 – 80 = 140 beats/min. If the resting heart rate is 80, the heart rate reserve is 60 (ie, 140 – 80). For low-intensity exercise, 30% to 50% of the heart rate reserve would be 18 to 30 beats/min. Adding this to the resting heart rate of 80 would yield a range for the target heart rate of 98 to 110 beats/min.

For many older patients, calculating the target heart rate may be difficult. In addition, it may not be possible to accurately determine heart rate during exercise (unless a heart rate monitor is used). For these reasons, the patient's subjective assessment of perceived exertion is often the most practical method for monitoring exercise intensity. In addition, perceived exertion correlates reasonably well with exercise heart rate. A simple perceived exertion scale comprises five levels: very light, light, moderate, somewhat heavy, and heavy. Older patients with heart failure should begin with very light exercise, progressing to the light range as tolerated. After several weeks, some patients may wish to increase their perceived exertion level into the moderate range, but more strenuous exercise is not recommended for patients with heart failure.

Treatment of Heart Failure with Reduced Ejection Fraction

In general, the treatment of HFREF in older patients does not differ substantially from that in younger patients.

ACE inhibitors Numerous prospective randomized clinical trials using multiple different angiotensin-converting enzyme (ACE) inhibitors in a variety of clinical settings have conclusively demonstrated that these agents significantly reduce mortality and hospitalization rates and improve exercise tolerance and quality of life in patients with impaired left ventricular systolic function, even in the absence of clinical heart failure. Although none of these studies included patients older than 80 years, available evidence indicates that ACE inhibitors are as effective in older patients as in younger ones. Based on these findings, ACE inhibitors are now considered first-line therapy for all patients, regardless of age, with left ventricular systolic dysfunction with or without overt heart failure.

ACE inhibitors approved for use in the United States for the treatment of heart failure include captopril, enalapril, lisinopril, ramipril, trandolapril, quinapril, and fosinopril. In older patients, therapy should be initiated with a low dose (eg, captopril 6.25–12.5 mg TID or enalapril 2.5–5 mg BID), and the dose should be gradually increased as tolerated. In hospitalized patients who are hemodynamically stable, the dose may be increased daily; in outpatients, the dose should be increased weekly or biweekly. Throughout the titration period, blood pressure, renal function, and serum potassium levels should be monitored.

For maintenance therapy, ACE inhibitor dosages should be commensurate with those used in the clinical trials. Recommended "target" doses for selected ACE inhibitors are as follows: captopril 50 mg TID, enalapril 10 to 20 mg BID, lisinopril 20 to 40 mg daily, ramipril 10 mg daily, trandolapril 4 mg daily, quinapril 40 mg BID, and fosinopril 40 mg daily. In patients unable to tolerate full therapeutic doses of ACE inhibitors, lower doses may be used; however, it must be recognized that clinical benefits may be attenuated. In addition, although captopril is an excellent agent for use during the titration phase, once the maintenance dose has been reached, it may be desirable to change to a once-daily ACE inhibitor at equivalent dosage for reasons of convenience, adherence, and cost.

The most common side effect from ACE inhibitors is a dry, hacking cough, which may be severe enough to require discontinuation of therapy in 5% to 10% of patients during long-term use. Less common but more serious side effects include hypotension, a decline in renal function, and hyperkalemia. These side effects tend to occur shortly after initiation of therapy and may be aggravated by intravascular volume contraction as a result of overdiuresis. Indications for downward titration or discontinuation of an ACE inhibitor include symptomatic hypotension, persistent increase in serum creatinine of 1 mg/dL or greater, or a rise in the serum potassium level above 5.5 mEq/L. Note that asymptomatic low blood pressure does not mandate dosage reduction.

Although ACE inhibitors are generally well tolerated and can be taken safely in combination with most other medications, it is important to recognize that NSAIDs, which are widely used by older adults (both by prescription and over the counter), are potent ACE inhibitor antagonists. In addition, NSAIDs promote sodium and water retention and may adversely affect renal function. Therefore, NSAIDs should be avoided whenever possible in patients with heart failure. The use of low-dose aspirin in combination with an ACE inhibitor appears to be safe and does not attenuate

the beneficial effects of the ACE inhibitor. Therefore, patients with a clear indication for aspirin therapy, such as coronary artery disease, peripheral arterial disease, cerebrovascular disease, or diabetes mellitus, should receive aspirin according to current treatment guidelines for these conditions. The value of prophylactic aspirin in older patients with heart failure without known vascular disease or diabetes is unknown, and additional study of this issue is needed.

Angiotensin II receptor blockers Angiotensin II receptor blockers (ARBs) bind directly to angiotensin II receptors on the cell membrane. Unlike ACE inhibitors, ARBs do not inhibit the breakdown of bradykinins, thus eliminating bradykinin-mediated side effects, including cough.

The use of ARBs for the treatment of heart failure, either alone or in combination with an ACE inhibitor, has been evaluated in several studies. In the second Evaluation of Losartan in the Elderly trial (ELITE-II), losartan 50 mg once daily was compared to captopril 50 mg TID in 3152 patients 60 years or older (mean age 71) with moderate heart failure and an ejection fraction of 40% or less. After a mean follow-up of 18 months, there was no statistically significant difference in mortality between the two treatments, although there were 12% more deaths in the losartan group (280 vs 250). As in the smaller ELITE-I trial, losartan was better tolerated than the ACE inhibitor captopril.

In the Valsartan Heart Failure Trial (Val-HEFT), 5010 patients with heart failure and an ejection fraction of less than 40% were randomized to valsartan or placebo in addition to standard care, which included an ACE inhibitor in 93% of patients and a β-blocker in 35%. During a 2-year follow-up period, mortality did not differ between patients treated with valsartan or placebo, but there was a significant 24% reduction in rehospitalizations for heart failure in the valsartan group, with similar effects in younger and older patients. However, patients receiving both an ACE inhibitor and a β-blocker as background therapy experienced an unexplained increase in mortality when valsartan was added.

In the Valsartan in Acute Myocardial Infarction trial, 14,703 patients with clinical heart failure and/or an ejection fraction less than 35% within 10 days of experiencing an acute myocardial infarction were randomly assigned to receive valsartan, captopril, or both drugs. More than 70% of patients were also receiving β-blockers. During a median follow-up of 24.7 months, there were no differences between groups with respect to all-cause mortality or the composite end point of fatal or nonfatal cardiovascular events. Median age was 65, and results were similar in older and younger patients. Hypotension and renal dysfunction were more common with valsartan, whereas cough, rash, and taste disturbances were more common with captopril. Limiting side effects were more common in patients receiving both drugs than in those receiving either drug alone.

The use of candesartan for the treatment of patients with heart failure and an ejection fraction of 40% or less has been evaluated in two large trials. In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)—Alternative study, 2028 patients intolerant to ACE inhibitors were randomized to candesartan or placebo and followed for a median of 33.7 months. Compared to patients in the placebo group, patients randomized to candesartan experienced a significant 30% reduction in the composite end point of cardiovascular death or hospitalization for heart failure. All-cause mortality was reduced by 17%, which was of borderline statistical significance. Hypotension, worsening renal function, and hyperkalemia, but not cough or angioedema, were more common in the candesartan group. The mean age of patients in the CHARM-Alternative study was approximately 66.5, and nearly one-fourth of patients were 75 years or older; however, subgroup analysis by age has not been reported.

In the CHARM-Added trial, 2548 symptomatic patients with heart failure and an ejection fraction of 40% or less who were receiving an ACE inhibitor were randomized to candesartan or placebo and followed for a median of 41 months. Compared to the placebo group, there was a significant 15% reduction in the composite end point of cardiovascular death or hospitalization for heart failure in patients randomized to candesartan. All-cause mortality was 11% lower in the candesartan group, but the difference was not significant. The mean age of patients in the CHARM-Added trial was 64, 19% of patients were 75 years or older, and similar results were reported in older and younger patients.

Combining the results of these two trials with a third study that compared candesartan with placebo in patients with HFPEF, a total of 7599 patients were enrolled, of whom 1736 (22.8%) were 75 years or older. Among the latter group, candesartan was associated with a significant 13.7% reduction in all-cause mortality or first admission for heart failure.

Based on these studies, ARBs are indicated for treatment of symptomatic heart failure in patients intolerant to ACE inhibitors and in patients with heart failure or left ventricular systolic dysfunction following acute myocardial infarction. In the United States, valsartan and candesartan are approved for the treatment of heart failure. The recommended starting dose of valsartan is 20 to 40 mg BID, and the dose should be titrated to 160 mg BID as tolerated. The starting dose of candesartan is 4 to 8 mg once daily, with titration to 32 mg once daily as tolerated. The major side effects of ARBs include hypotension, renal insufficiency, and hyperkalemia.

Hydralazine/nitrates In patients who are unable to tolerate an ACE inhibitor or ARB, the combination of hydralazine

with oral or topical nitrates provides an acceptable alternative. In the first Veteran's Administration Heart Failure trial (V-HeFT-I), the hydralazine/nitrate combination was associated with a 36% mortality reduction compared to prazosin and placebo in patients with HFREF. In a follow-up study (V-HeFT-II), patients with HFREF were randomized to receive hydralazine/nitrates or enalapril. Although hydralazine/nitrates and enalapril had similar effects on exercise tolerance and quality of life, mortality was lower in the enalapril group.

More recently, the African-American Heart Failure Trial (A-HeFT) randomized 1050 black patients with NYHA class III or IV heart failure to a fixed-dose combination of isosorbide dinitrate plus hydralazine or to placebo in addition to standard heart failure therapy. The study was stopped after an average follow-up of 10 months because of a significantly lower mortality rate in patients randomized to the intervention. Heart failure hospitalizations were also lower and quality of life was improved in patients randomized to hydralazine-nitrates relative to placebo. Based on the results of A-HeFT, the fixed-dose combination of isosorbide dinitrate and hydralazine has been approved for treatment of heart failure in black patients in the United States. Although there was no upper-age restriction for the A-HeFT study, the average age of patients enrolled in the trial was 57, so the efficacy of this therapy in older blacks remains unknown.

The dose of hydralazine used in the V-HeFT trials was 75 mg QID, and nitrates were administered as isosorbide dinitrate 40 mg QID. In A-HeFT, the total daily dose of hydralazine was 225 mg and of isosorbide dinitrate 120 mg. For older patients, treatment should begin with lower dosages (eg, hydralazine 12.5–25 mg TID–QID; isosorbide dinitrate 10 mg TID–QID), followed by gradual upward titration to achieve the doses used in the trials. The most common side effects associated with hydralazine/nitrates in the V-HeFT and A-HeFT studies included headache and dizziness. A small percentage of patients in V-HeFT developed arthralgias or other symptoms suggestive of hydralazine-induced lupus.

β-Blockers As recently as 20 years ago, β-adrenergic blocking agents were considered contraindicated in patients with heart failure owing to their negative inotropic and chronotropic effects, both of which serve to diminish cardiac output. However, it is now recognized that persistent activation of the sympathetic nervous system is detrimental in patients with heart failure because it exacerbates ischemia, aids in arrhythmogenesis, promotes β-receptor desensitization, and contributes to a progressive decline in ventricular function. Furthermore, several large prospective randomized clinical trials have now confirmed that long-term β-blockade improves left ventricular function and reduces both total mortality and sudden cardiac death in a broad spectrum of patients with HFREF.

In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure trial (SENIORS), 2128 patients 70 years or older (mean age 76, 37% women) were randomized to nebivolol or placebo. During a mean follow-up of 21 months, the primary composite outcome of death or cardiovascular hospitalization was significantly lower in patients randomized to nebivolol, with similar results in younger and older patients, including those older than 85 years. Based on these studies, β-blockers are now recommended as a standard therapy, along with ACE inhibitors, in almost all patients with symptomatic HFREF in the absence of contraindications.

In the United States, carvedilol and metoprolol succinate have been approved for the treatment of heart failure. Starting dosages are carvedilol 3.125 mg BID and metoprolol succinate 25 mg once daily. The dose should be gradually increased at approximately 2-week intervals as tolerated to achieve maintenance dosages of carvedilol 25 to 50 mg BID or metoprolol 100 to 200 mg daily.

Contraindications to the use of β-blockers include severe decompensated heart failure, significant bronchospastic lung disease, marked bradycardia (resting heart rate < 50/min), systolic blood pressure less than 90 to 100 mm Hg, advanced heart block (> first degree), and known intolerance to β-blockade. In addition, as a result of the potential for significant adverse effects, it is important to monitor heart rate, blood pressure, clinical symptoms, and the cardiorespiratory examination during initiation and titration of therapy. Patients should be advised that they may experience a modest deterioration in heart failure symptoms during the first few weeks of β-blocker therapy, but that in most cases these symptoms resolve and the long-term tolerability of β-blockers is excellent. However, if severe adverse effects occur, dosage reduction or discontinuation of treatment may be necessary.

Mineralocorticoid antagonists The mineralocorticoid antagonists spironolactone and eplerenone are relatively weak potassium-sparing diuretics that interfere with the effect of the neurohormone aldosterone. In the Randomized Aldactone Evaluation of Survival trial, spironolactone 12.5 to 50 mg once daily reduced mortality by 30% and heart failure hospitalizations by 35% in patients with NYHA class III or IV heart failure and a left ventricular ejection fraction less than or equal to 35%, in addition to therapy with an ACE inhibitor, digoxin, and loop diuretic. Moreover, the beneficial effects of spironolactone were at least as great in older as in younger patients. In the Eplerenone Post-

Acute Myocardial Infarction Heart Failure Efficacy and Survival study, eplerenone 25 to 50 mg once daily significantly reduced mortality by 15% over a mean follow-up period of 16 months in patients with clinical evidence for heart failure and an ejection fraction of 40% or less within 3 to 16 days following acute myocardial infarction. Sudden death from cardiac causes and cardiovascular hospitalizations were also reduced in the eplerenone group. Compared to placebo, hyperkalemia occurred more commonly but hypokalemia occurred less frequently with eplerenone. The average age of patients in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study was 64, and although the relative benefit of eplerenone was somewhat less in older compared to younger patients, the difference was not statistically significant.

More recently, the EMPHASIS-HF trial randomized 2737 patients with NYHA class II heart failure and a left ventricular ejection fraction less than or equal to 35% to eplerenone at a dose of up to 50 mg or matching placebo. The mean age was 68.7 and 24% of patients were 75 years or older. The primary outcome was death from cardiovascular causes or hospitalization for heart failure. The study was stopped prematurely after a median follow-up of 21 months because eplerenone was associated with a marked reduction in the primary end point relative to placebo (18.3% vs 25.9%, hazard ratio 0.63, $p < 0.001$). Results were similar in patients over or under age 75. Eplerenone was also associated with significant reductions in all-cause mortality, all-cause hospitalizations, and heart failure hospitalizations (hazard ratios 0.76, 0.77, and 0.58, respectively).

Based on the results of these studies, a mineralocorticoid antagonist is recommended in patients with NYHA class II to IV heart failure symptoms and left ventricular ejection fraction less than or equal to 35%, and in patients with heart failure and an ejection fraction of 40% or less following myocardial infarction. These agents are contraindicated in patients with significant renal dysfunction (creatinine ≥ 2.5 mg/dL) or preexisting hyperkalemia. Older patients are at increased risk of adverse effects, and renal function as well as serum potassium levels should be monitored closely during initiation and titration of therapy. In addition, up to 10% of patients receiving long-term treatment with spironolactone may experience painful gynecomastia requiring discontinuation of the drug; this side effect occurs rarely with eplerenone.

Diuretics Diuretics are the most effective agents for relieving pulmonary congestion and edema, and for this reason they remain a key component of heart failure management. However, neither thiazide nor loop diuretics have been shown to alter the natural history of heart failure, and their beneficial effects are primarily palliative.

In patients with mild chronic heart failure, a thiazide diuretic may be sufficient for relieving congestive symptoms and maintaining fluid homeostasis. However, most patients will require a more potent agent, and the “loop” diuretics, including furosemide, bumetanide, and torsemide, are the drugs most widely used. For optimal effectiveness, patients should be instructed to maintain a low sodium diet (< 2.3 g/day) and to avoid excessive fluid intake. Typical daily doses of “loop” diuretics range from 20 to 160 mg for furosemide, 0.5 to 5 mg for bumetanide, and 5 to 100 mg for torsemide. In patients hospitalized with an acute episode of heart failure, intravenous administration may be more effective than the oral route in promoting diuresis, in part due to bowel wall edema which may decrease the drug’s absorption. In patients who fail to respond adequately to a loop diuretic, the addition of metolazone 2.5 to 10 mg daily often leads to a brisk diuresis.

The most common and important side effects of diuretics are electrolyte disturbances, including hypokalemia, hyponatremia, hypomagnesemia, and increased bicarbonate levels indicative of metabolic alkalosis. Owing to age-related changes in renal function as well as a higher prevalence of comorbid illnesses such as diabetes, older patients are at increased risk of serious diuretic-induced electrolyte abnormalities. For this reason, electrolytes should be monitored closely when diuretic therapy is being adjusted. This is particularly true when using metolazone, which can cause life-threatening hyponatremia after relatively short-term use.

Digoxin Digoxin inhibits the sodium-potassium exchange pump located within the myocyte membrane, producing a rise in intracellular sodium concentration. This facilitates sodium-calcium exchange, leading to an increase in intracellular calcium. Calcium binds with troponin C, which initiates the process of contraction by allowing myosin to bind with actin. By increasing calcium availability, digoxin induces a modest increase in the force of myocardial contraction (positive inotropic effect). This effect occurs whether or not heart failure is present, and it does not appear to be affected by age.

In 1997, the Digitalis Investigation Group (DIG) reported the results of a prospective randomized trial involving 6800 patients with HFREF. Patients were randomized to receive digoxin or placebo in addition to diuretics and an ACE inhibitor, and the average duration of follow-up was 37 months. Overall mortality did not differ between digoxin and placebo (34.8% vs 35.1%), but there were 28% fewer hospitalizations for heart failure in the digoxin group, and

the combined end point of death or hospitalization for heart failure was significantly reduced. In addition, the beneficial effects of digoxin were similar in younger and older patients, including octogenarians. Subsequent analyses based on data from the DIG trial suggest that digoxin administered at low dosages to achieve serum concentrations in the range of 0.5 to 0.9 ng/mL may be associated with improved survival as well as a reduction in all-cause hospitalizations. These findings confirm that digoxin is beneficial in controlling heart failure symptoms and support the use of low-dose digoxin in patients who remain symptomatic despite appropriate dosages of an ACE inhibitor, β-blocker, mineralocorticoid antagonist, and diuretic.

Side effects from digoxin fall into three major categories: cardiac, neurologic, and gastrointestinal. In the DIG study, side effects that occurred more frequently in patients receiving digoxin included nausea and vomiting, diarrhea, visual disturbances, supraventricular and ventricular arrhythmias, and advanced atrioventricular heart block. Although not reported in the DIG trial, older patients may be at increased risk of digoxin toxicity, especially cardiac toxicity, in part owing to a decreased volume of drug distribution. Patients with chronic lung disease, amyloid heart disease, and other conditions may also be at increased risk of digoxin toxicity.

In most older patients with relatively normal renal function, a digoxin dose of 0.125 mg daily is usually sufficient to achieve a therapeutic effect. Patients with renal impairment or small body habitus may require a lower dose. Serum digoxin concentration should be measured 2 to 4 weeks after initiating therapy, and periodically thereafter, to ensure that the level is in the therapeutic range of 0.5 to 0.9 ng/mL. It is also appropriate to measure the digoxin level whenever digitalis intoxication is suspected. In addition, since diuretic-induced hypokalemia and hypomagnesemia potentiate digoxin's cardiotoxic effects, including proarrhythmia, it is important to maintain normal serum concentrations of these electrolytes in all patients receiving digoxin.

Calcium channel blockers First-generation calcium channel blockers, including nifedipine, diltiazem, and verapamil, are contraindicated in patients with systolic heart failure because each of these agents has been associated with adverse clinical outcomes. The third-generation calcium channel blockers amlodipine and felodipine have been studied in prospective randomized trials involving patients with HFREF. Although the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) suggested that amlodipine might be beneficial in patients with nonischemic HFREF, this was not confirmed in PRAISE-2. Similarly, the V-HeFT-3 trial failed to demonstrate a significant benefit in patients with HFREF treated with felodipine. Thus, there are no approved indications for the use of calcium channel blockers in patients with heart failure, and their use in this condition is not recommended. However, in patients with heart failure and active anginal symptoms not controlled with β-blockers and nitrates, the addition of a long-acting calcium channel blocker is reasonable. Similarly, diltiazem or verapamil may be used in heart failure patients with rapid atrial fibrillation who do not respond adequately to β-blockers and other interventions.

Antithrombotic therapy Patients with left ventricular systolic dysfunction are at increased risk for thromboembolic events, including stroke. However, in the absence of atrial fibrillation, rheumatic mitral valve disease, or a history of prior embolization, the value of antithrombotic treatment for the prevention of embolic events is unproven. In the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, 1587 patients with NYHA class II or III HFREF were randomized to receive aspirin 162 mg/day, clopidogrel 75 mg/day, or warfarin to maintain an international normalized ratio (INR) of 2.5 to 3.0. After a mean follow-up of 23 months, there were no differences between the three groups in the primary composite end point of death, myocardial infarction, or stroke. Hospitalizations for heart failure occurred more frequently in the aspirin group than with either clopidogrel or warfarin, whereas bleeding complications were more common with warfarin. The mean age of patients in the WATCH trial was 63; subgroup analysis by age has not been reported.

In the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) study, 2305 patients with heart failure, a left ventricular ejection fraction less than or equal to 35%, and sinus rhythm were randomized to warfarin (target INR 2.0–3.5) or to aspirin 325 mg daily. The primary outcome was all-cause mortality, ischemic stroke, or intracerebral hemorrhage. The mean age was 61 and 80% of participants were men. After a mean follow-up of 3.5 years, there was no difference between groups in the primary outcome. Warfarin was associated with fewer ischemic strokes but more major bleeding events. Intracranial hemorrhage was infrequent and did not differ between groups. As with WATCH, subgroup analysis by age has not been reported.

Based on currently available data, anticoagulation with warfarin to achieve an INR of 2 to 3 is recommended in heart failure patients with chronic or paroxysmal atrial fibrillation or atrial flutter, rheumatic mitral valve disease with left atrial enlargement, prior stroke or unexplained arterial embolus, a mobile left ventricular thrombus (as demonstrated by echocardiography or other imaging modality), or a left atrial appendage thrombus identified by transesophageal echocardiography. Routine use of warfarin in other circumstances is not recommended. In patients

with nonvalvular atrial fibrillation, one of the newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban) may be used as an alternative to warfarin.

Aspirin is justified in patients with known coronary heart disease, particularly those with recent myocardial infarction, unstable angina, percutaneous coronary intervention, or bypass surgery. Aspirin is also recommended for older patients with peripheral arterial disease or diabetes. In addition, aspirin is appropriate in high-risk patients (as listed earlier) who are not suitable candidates for warfarin. As noted previously, additional study is needed to determine the value of aspirin in older patients with heart failure without established vascular disease or diabetes. The need for "triple therapy" with aspirin, clopidogrel, and warfarin in patients with indications for both dual anti-platelet therapy and systemic anticoagulation has recently been questioned, with at least one randomized trial showing that eliminating aspirin from the regimen reduces bleeding without increasing ischemic events.

Statins Statins reduce mortality and nonfatal cardiovascular events in patients up to age 82 with coronary artery disease, peripheral arterial disease, or diabetes. However, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), in which 5011 patients 60 years or older (mean age 73, 24% female) with ischemic cardiomyopathy and an ejection fraction of 40% or less were randomized to rosuvastatin or placebo and followed for an average of 33 months, failed to show a significant benefit of rosuvastatin on either the primary outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, or on total mortality. Hospitalizations for cardiovascular causes occurred less frequently in patients randomized to rosuvastatin. Based on these findings, rosuvastatin is not recommended for older patients with HFREF. The role of other statins in this population requires further investigation.

Device Therapy

Device therapy, including implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT), is playing an increasing role in the management of patients with HFREF. ICDs reduce mortality from sudden cardiac death in patients with NYHA class II to III HFREF and a left ventricular ejection fraction less than or equal to 35% (primary prevention), and in patients resuscitated from cardiac arrest attributable to ventricular tachyarrhythmias (secondary prevention). However, although current HF guidelines do not incorporate age into the recommendations for ICD therapy, very few patients greater than or equal to 75 years were enrolled in clinical trials evaluating these devices. In addition, a comprehensive meta-analysis suggested that the benefit of ICDs declines with age, most likely due to competing risks for mortality. Patients with life expectancies of less than 12 to 18 months are unlikely to benefit from an ICD, and patients greater than or equal to 80 years are twice as likely as younger patients to experience major complications related to device implantation. Thus, the benefit-to-risk relationship is modified by age, and consideration of ICD therapy must be individualized based on life expectancy, prevalent comorbidities, and patient goals of care using a process of shared decision making. In patients who choose to undergo placement of an ICD, management of the ICD at end of life, including circumstances under which the patient would want to have the device disabled in order to avoid painful shocks, should be clearly articulated prior to implantation. Similarly, if a generator change is needed due to battery depletion, the option of foregoing the procedure, along with the implications of this decision, should be discussed.

In contrast to ICDs, which reduce the risk of sudden death but do not improve quality of life, CRT improves symptoms, exercise tolerance, quality of life, and survival in carefully selected patients with HFREF, including octogenarians. CRT involves placement of a biventricular pacemaker with one lead in the right ventricle and a second lead inserted into the coronary sinus in a retrograde fashion to pace the left ventricle. As the name implies, the goal of CRT is to "resynchronize" myocardial contraction, thereby increasing stroke work, ejection fraction, and cardiac output. CRT is indicated in patients with NYHA class II to IV HFREF, left ventricular ejection fraction less than or equal to 35%, and QRS duration greater than or equal to 150 milliseconds by electrocardiogram. Patients with left bundle branch block, which is present in 20% to 30% of patients with HFREF, derive the greatest benefit from CRT, and there is evidence that the benefits tend to be greater in women than in men. CRT can be performed with or without concomitant ICD therapy (CRT-D and CRT-P, respectively), and patients greater than or equal to 80 years are proportionately more likely than younger patients to receive a CRT-P device. As with ICDs, selection of patients for CRT should involve shared decision making with appropriate consideration of the potential salutary effects on quality of life in older patients who are significantly limited by persistent heart failure symptoms despite optimal medical therapy.

Treatment of Heart Failure With Preserved Ejection Fraction

Despite the fact that approximately 50% of older patients with heart failure have preserved left ventricular systolic function (ie, HFPEF), no large-scale clinical trials have documented major beneficial effects for any pharmacologic agents (**Table 79-11**). As a result, therapy for HFPEF remains largely empiric.

TABLE 79-11 PHARMACOTHERAPY TRIALS FOR HEART FAILURE WITH PRESERVED EJECTION FRACTION

TRIAL[a]	PATIENTS	TREATMENT	LVEF[b]	AGE	OUTCOMES COMPARED TO PLACEBO[c]
PEP-CHF	850	Perindopril	65 (56–66)	75 (72–79)	Death/hospitalization by 1 y—HR 0.69 (0.47–1.01, p = 0.055). HF hospitalization by 1 y—HR 0.63 (0.41–0.97, p = 0.033)
CHARM-Preserved	3023	Candesartan	54 ± 9	67 ± 11	CV death/HF admission—HR 0.89 (0.77–1.03, p = 0.118). HF admission—HR 0.85 (0.72–1.01, p = 0.072)
I-PRESERVE	4128	Irbesartan	60 ± 9	72 ± 7	Death/hospitalization—HR 0.95 (0.86–1.05, p = 0.35)
SENIORS (EF > 35% subgroup)	643	Nebivolol	49 ± 10	76 ± 5	All cause death/CV hospitalization—HR 0.81 (0.63–1.04)
TOPCAT	3445	Spironolactone	56 (51–62)	69 (61–76)	CV death/HF hospitalization/aborted SCD—HR 0.89 (0.77–1.04, p = 0.14). HF hospitalization—HR 0.83 (0.69–0.99, p = 0.04)
Aldo-DHF	422	Spironolactone	67 ± 8	67 ± 8	Reduced E/e' avg 1.5 ($p < 0.001$)
RELAX	216	Sildenafil	60 (56–65)	69 (62–77)	No difference in Δ VO_2 peak at 24 wk
ESS-DHF	192	Sitaxsentan	61 ± 12	65 ± 10	Median 43 s relative increase in Naughton treadmill time (p = 0.03)
DIG Ancillary	988	Digoxin	55 ± 8	67 ± 10	HF hospitalization—HR 0.79 (0.59–1.04, p = 0.09). Hospitalization for unstable angina—HR 1.37 (0.99–1.91, p = 0.06)
SWEDIC	113	Carvedilol	> 45	66 (48–84)	No effect on primary composite end point of diastolic function; improved *E/A* with carvedilol
RAAM-PEF	44	Eplerenone	62	70	No effect on 6-min walk distance; collagen turnover and E/e' improved with eplerenone
ELANDD	116	Nebivolol	62.6	66	No effect on 6-min walk distance, peak VO_2, or quality of life

[a]Trial acronyms: PEP-CHF, Perindopril in Elderly People with Chronic Heart Failure; CHARM-Preserved, Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity—Preserved LVEF; I-PRESERVE, Irbesartan in Heart Failure with Preserved Ejection Fraction study; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist; Aldo-DHF, Aldosterone Receptor Blockade in Diastolic Heart Failure; RELAX, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction; ESS-DHF, Effectiveness of Sitaxsentan Sodium in Patients with Diastolic Heart Failure; DIG Ancillary, Digitalis Investigation Group Ancillary Trial; SWEDIC, Swedish Doppler-echocardiographic Study; RAAM-PEF, Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction; ELANDD, Effects of the Long-term Administration of Nebivolol in Diastolic Dysfunction.

[b]LVEF, left ventricular ejection fraction; E/e' avg, echocardiographic mitral inflow velocity/tissue Doppler velocity ratio; CV, cardiovascular; SCD, sudden cardiac death; HR, hazard ratio (with 95% confidence interval); HF, heart failure.

Age (in years) and LVEF (%) presented as mean ± SD or median (IQR).

[c]All-cause mortality was not significantly reduced in any trial.

At least 70% to 80% of older persons with HFPEF have hypertension, and coronary and valvular heart diseases are also highly prevalent in this population. Treatment for HFPEF begins with aggressive management of hypertension to target levels; that is, systolic blood pressure less than 140 mm Hg for most patients 60 to 79 years, less than 150 mm Hg for most patients greater than or equal to 80 years, and diastolic blood pressure less than 90 mm Hg for all older adults. Myocardial ischemia should be treated with antianginal medications and/or coronary revascularization as indicated. Resting and exercise heart rate should be adequately controlled in patients with atrial fibrillation. Patients with severe valvular heart disease should be considered for valve repair or replacement, and less severe regurgitant valvular lesions should be treated with unloading agents, such as ACE inhibitors. As with HFREF, nonpharmacologic

aspects of therapy, including regular physical activity and exercise as described earlier, should be appropriately addressed.

Diuretics Diuretics are an essential component of therapy for the relief of pulmonary and systemic venous congestion in most patients with HFPEF. However, such patients are often "volume sensitive." As a result, overly zealous diuresis can lead to a reduction in left ventricular diastolic volume, with a resultant decline in stroke volume and cardiac output, often manifested by increased fatigue, relative hypotension, and worsening prerenal azotemia. Thus, diuretics must be prescribed judiciously in order to relieve congestion while avoiding overdiuresis.

β-Blockers β-Blockers have little or no direct effect on diastolic function, but they may improve symptoms in patients with HFPEF by slowing heart rate and lengthening the diastolic filling period. In patients with left ventricular hypertrophy, long-term β-blockade and effective blood pressure control may aid in the regression of left ventricular hypertrophy, which in turn may be associated with improved diastolic function. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure trial, more than 20% of patients had relatively preserved left ventricular systolic function (ejection fraction ≥ 40%), and the benefits of nebivolol were similar in this group compared to those with ejection fractions less than 40%. These data provide some support for the use of β-blockers in patients with HFPEF.

The goal of β-blocker therapy in HFPEF is to reduce the resting heart rate to less than 65 beats/min. The initial β-blocker dose should be low and titration should be gradual. In the event that symptoms and exercise tolerance do not improve, alternative therapy should be considered.

ACE inhibitors ACE inhibitors may improve symptoms in HFPEF both directly (by improving diastolic function) and indirectly (by promoting regression of left ventricular hypertrophy). The use of ACE inhibitors for the treatment of HFPEF in patients of advanced age is supported by findings from the Perindopril in Elderly People with Chronic Heart Failure study, in which 850 patients greater than or equal to 70 years (mean age 76, 55% women) with heart failure and relatively preserved left ventricular systolic function (estimated ejection fraction ≥ 40%) were randomized to perindopril 4 mg once daily or placebo and followed for an average of 2.1 years. Overall, there was no significant difference between groups with respect to the primary outcome of death or unplanned hospitalization for heart failure. However, heart failure hospitalizations were significantly reduced by 78% during the first 12 months of follow-up in patients randomized to perindopril. Relative to placebo, perindopril-treated patients also experienced significant improvements in NYHA class and exercise tolerance during the first year of therapy. Perindopril is not approved for the treatment of heart failure in the United States, and none of the other ACE inhibitors are approved for the treatment of HFPEF.

Angiotensin II receptor blockers ARBs lower blood pressure and may have salutary effects on diastolic function similar to those observed with ACE inhibitors. In the CHARM-Preserved Trial, 3024 patients with NYHA class II to IV heart failure and an ejection fraction greater than 40% were randomized to candesartan or placebo and followed for a median of 36.6 months. The mean age was 67, 27% were 75 years or older, and 40% were women. Mortality did not differ between groups, but patients randomized to candesartan experienced a significant 16% reduction in the risk of hospitalization for heart failure and 29% fewer total heart failure admissions. Subgroup analysis by age was not reported. Hypotension, hyperkalemia, and worsening renal function occurred more frequently in the candesartan group.

Taken together, the findings of Perindopril in Elderly People with Chronic Heart Failure and CHARM-Preserve suggest that some ACE inhibitors and ARBs may reduce hospitalizations and improve symptoms in patients with HFPEF but have little or no effect on mortality. In contrast, the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial, which enrolled over 4000 patients greater than or equal to 60 years with HFPEF, showed that the ARB irbesartan was of no benefit in the treatment of this condition. Thus, the value of ACE inhibitors and ARBs in the management of patients with HFPEF remains uncertain.

Mineralocorticoid antagonists The mineralocorticoid antagonists spironolactone and eplerenone reduce myocardial hypertrophy and fibrosis in laboratory animals and small studies indicate that they have a favorable effect on left ventricular diastolic function in humans. In addition, as discussed previously, both of these agents have been shown to improve mortality and other outcomes in patients with HFREF. In a recently published trial, 3445 patients with symptomatic heart failure and an ejection fraction greater than or equal to 45% were randomized to spironolactone or placebo and followed for a mean of 3.3 years. The average age was 68.7 and 52% were women. The primary outcome, a composite of cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure, did not differ between patients randomized to spironolactone versus placebo. Similarly, total mortality and all-cause hospitalizations were not

different between groups. However, hospitalizations for heart failure were reduced 17% among patients randomized to spironolactone (p = 0.04). In addition, in a post hoc analysis of patients enrolled in North or South American (vs Russia or Georgia), spironolactone was associated with a significant 18% reduction in the primary end point, as well as a 26% reduction in cardiovascular mortality and 18% reduction in heart failure rehospitalization. Thus, although additional research is needed, this study suggests that spironolactone may be beneficial for patients with HFPEF.

Calcium channel blockers Calcium channel blockers decrease intracellular calcium and may have a modest beneficial effect on diastolic function. However, there have been no large clinical trials evaluating calcium channel blockers for the treatment of HFPEF, and calcium channel antagonists are not recommended for the treatment of this condition.

Nitrates In addition to relieving ischemia, nitrates are effective venodilators and thus lower pulmonary capillary wedge pressure. For these reasons, nitrates may serve as a useful adjunct to diuretics in relieving symptoms of pulmonary congestion, particularly orthopnea. However, nitrates have the potential for decreasing venous return to the heart, thereby reducing left ventricular diastolic volume and stroke volume. In addition, tolerance to the hemodynamic effects of nitrates occurs in the majority of patients. As a result, the value of nitrates in the long-term management of HFPEF is uncertain, and further study of these agents, alone or in combination with other drugs, is needed.

Digoxin Digoxin is usually considered contraindicated in patients with heart failure and normal systolic function. However, digoxin, as well as other inotropic agents, may exert a favorable effect on diastolic function by accelerating calcium reuptake by the sarcoplasmic reticulum at the onset of diastole. In the original DIG trial, 988 patients with heart failure and an ejection fraction of more than 45% were randomized to digoxin or placebo in an ancillary study. As in the main trial, digoxin had no effect on mortality. Hospitalizations for heart failure were reduced in patients with HFPEF receiving digoxin, but this effect was counterbalanced by increased hospitalizations for acute coronary syndromes. Thus, digoxin does not appear to be beneficial in patients with HFPEF and is not recommended except as an adjunct for controlling heart rates in patients with atrial fibrillation.

Other agents Preliminary studies of phosphodiesterase 5 inhibitors suggested that these agents may have favorable effects on exercise capacity in patients with HFPEF. In the RELAX trial, 216 patients (mean age 69, 48% women) with heart failure and a left ventricular ejection fraction greater than or equal to 50% were randomized to sildenafil or placebo and followed for 24 weeks. The primary end point was change in peak oxygen consumption; secondary outcomes included change in 6-minute walk distance and a composite clinical status score. The main findings were that sildenafil did not result in significant improvements in exercise capacity or clinical status compared to placebo.

Endothelin type A receptor antagonists have also shown promise for treating HFPEF in preliminary studies. In the Effectiveness of Sitaxsentan Sodium in Patients with Diastolic Heart Failure (ESS-DHF) trial, 192 patients (mean age 65, 63% women) with HFPEF and a left ventricular ejection fraction greater than or equal to 50% were randomly assigned in a 2:1 ratio to receive sitaxsentan or placebo for 24 weeks. The primary outcome was change in treadmill exercise time; secondary outcomes included changes in left ventricular mass, diastolic function, symptom severity, and quality of life. Sitaxsentan therapy was associated with a modest improvement in treadmill exercise time relative to placebo (37 seconds; p = 0.03), but there was no effect on any of the secondary outcomes.

Summary Studies published to date indicate that ACE inhibitors, ARBs, mineralocorticoid antagonists and β-blockers may have favorable effects on some outcomes in patients with HFPEF, but none of these agents are of proven benefit and none are recommended as standard therapy in current practice guidelines. Management of HFPEF should include aggressive treatment of the underlying cardiac disease, and a diuretic should be administered at low-to-moderate doses to relieve congestion and edema. The addition of an ACE inhibitor, ARB, mineralocorticoid antagonist, or β-blocker to improve symptoms and reduce the risk of hospitalization seems reasonable. However, if the patient fails to respond to initial therapy, alternative treatment should be considered. Additional studies are needed to evaluate novel therapies for this condition.

Isolated Right Heart Failure

While the most common cause of chronic right-sided heart failure is one or more abnormalities of left heart function, a small proportion of patients present with isolated right heart failure. Etiologies of isolated right heart failure in older adults include pulmonary arterial hypertension due to chronic lung disease, chronic pulmonary thromboembolic disease, sleep-disordered breathing, or primary pulmonary vascular disease, and disorders of the tricuspid or (less commonly) pulmonic valve (eg, infectious endocarditis, carcinoid heart disease). Rarely, right heart failure in older

patients may be attributed to congenital heart disease (eg, atrial septal defect), neoplasm (eg,. right atrial myxoma or rhabdomyosarcoma), or a primary cardiomyopathy involving the right ventricle (eg, arrhythmogenic right ventricular dysplasia). Acute right heart failure may be due to right ventricular infarction, massive or submassive pulmonary embolism, or severe lung disease (eg, pneumonia, acute respiratory distress syndrome). Symptoms of right heart failure include dyspnea, impaired exercise tolerance, dependent edema, and, in severe cases, abdominal discomfort and swelling. The physical examination is notable for signs of elevated right-sided pressures (jugular venous distension, abdominojugular reflux, right ventricular heave, hepatomegaly), lower extremity edema, and possibly ascites. Depending on the etiology, other symptoms and signs may be present. Treatment is directed primarily at the underlying cause(s) and secondarily at alleviating systemic congestion through the judicious use of diuretics. The value of other pharmacologic agents, such as β-blockers and renin-angiotensin system inhibitors, for the treatment of isolated right heart failure is unknown.

Refractory Heart Failure

Refractory heart failure may be defined as heart failure not amenable to primary corrective measures (eg, valve replacement or revascularization) and not responsive to aggressive nonpharmacologic and pharmacologic therapy as described earlier. However, before designating heart failure as refractory, it is important to perform a careful search for potentially treatable causes, to carefully review the patient's medication regimen to ensure that therapy is optimal, and to discuss the patient's diet and medication habits in detail with the patient and family to ensure that an appropriate level of adherence is being maintained. The latter issue is of particular importance, since many cases of refractory heart failure can be traced to nonadherence to dietary restrictions, medications, or both.

In most cases, refractory heart failure simply represents the final common pathway of end-stage heart disease. Under these circumstances, the value of highly aggressive treatment is questionable, and decisions regarding the appropriateness of specific therapeutic interventions must be made on an individualized basis (see also Chapters 9 and 55).

Table 79-12 lists treatment options for refractory heart failure. In patients with systolic heart failure, intensifying the vasodilator regimen by using high doses of ACE inhibitors (eg, up to 400 mg/day of captopril or 80 mg/day of enalapril), either alone or in combination with hydralazine/nitrates or an angiotensin II receptor blocker, may result in significant symptomatic improvement. This can often be accomplished in the outpatient setting, but titration must be very gradual, with frequent follow-up contacts to avoid adverse events. In patients who fail to respond to these measures, intravenous vasodilator therapy with nitroglycerin, nitroprusside, or nesiritide (recombinant BNP) may be considered and may lead to significant clinical and hemodynamic improvements.

TABLE 79-12 ■ TREATMENT OPTIONS FOR REFRACTORY HEART FAILURE

Heart failure with reduced ejection fraction
Intensive vasodilator therapy
• High-dose ACE inhibitors
• Combination therapy
• ACE inhibitor plus hydralazine/nitrates
• ACE inhibitor plus angiotensin II receptor blocker
• Intravenous agents (eg, nitroglycerin, nitroprusside, nesiritide)
Intensive diuretic therapy
• High-dose oral agents, especially in combination
• Continuous intravenous infusion
Chronic or intermittent inotropic therapy
• Dobutamine
• Milrinone
Cardiac resynchronization therapy
Dialysis
• Short-term or chronic dialysis

• Dry ultrafiltration
Left ventricular assist device
Heart transplantation
Heart failure with preserved ejection fraction
Intensive diuretic therapy
Dialysis

ACE, angiotensin-converting enzyme.

In patients with persistent pulmonary congestion or peripheral edema, high-dose oral diuretics (eg, furosemide 200 mg BID or bumetanide 10 mg daily), alone or in combination with metolazone, may be effective. Alternatively, a continuous intravenous infusion of furosemide 5 to 40 mg/h or bumetanide 0.5 to 1 mg/h may facilitate diuresis.

The use of intravenous inotropic agents in the management of chronic heart failure is somewhat controversial, since these agents have not been shown to improve outcomes and they may increase the risk of life-threatening arrhythmias. Nonetheless, extensive clinical experience indicates that intermittent or continuous infusions of dobutamine or milrinone may reduce symptoms and improve quality of life in selected patients with refractory heart failure.

As noted earlier, cardiac resynchronization therapy has been shown to improve symptoms, quality of life, and survival in patients with advanced heart failure and left bundle branch block or marked intraventricular conduction delay on the 12-lead electrocardiogram. This procedure should, therefore, be considered in appropriately selected patients with persistent class III or IV heart failure symptoms.

An emerging therapy for patients with end-stage refractory heart failure (primarily HFREF) is mechanical circulatory support through implantation of a left ventricular assist device (LVAD). LVADs improve symptoms, exercise tolerance, quality of life, and survival in selected patients with severe heart failure, including patients in their 70s and early 80s. Although LVADs were originally developed as a bridge to heart transplantation, with technological advances they are now commonly implanted as “destination therapy” in patients who are not transplant candidates. As a result, an increasing number of older adults are receiving LVADs, and this trend is likely to continue as the technology evolves. Older adults are at increased risk for gastrointestinal bleeding following LVAD implantation; other potential complications include infection, stroke, and pump thrombosis. Optimal patient selection is critical, and patients with advanced comorbidities or frailty may not be suitable candidates. To this end, a thorough discussion of goals of care, perhaps facilitated by a palliative care team consultation, is recommended as an integral component of the evaluation for LVAD therapy.

Heart transplantation is a highly effective therapy for patients with advanced heart failure, but its use is limited by the paucity of donor hearts. As a result, the number of heart transplants performed in the United States has remained stable at about 2000 to 2500 per year for more than a decade. In part due to limited availability, most transplant centers exclude patients over 70 to 75 years of age. Nonetheless, among patients greater than or equal to 65 years undergoing heart transplantation, outcomes are favorable and generally similar to those in younger patients.

For patients with refractory HFPEF, therapeutic options are limited (see **Table 79-12**). Intensive diuretic therapy may be attempted, but efficacy is often confounded by the development of progressive prerenal azotemia and/or worsening renal function. If satisfactory symptom control and an acceptable quality of life cannot be achieved, transition to a palliative care approach should be considered (see later).

PROGNOSIS

The long-term prognosis in patients with established heart failure is poor, and the 5-year survival rate among older adults is less than 50%. In patients greater than or equal to 80 years hospitalized with heart failure, fewer than 25% survive more than 5 years. In general, the prognosis is worse in men than in women, in patients with HFREF rather than HFPEF, and in patients with an ischemic rather than nonischemic etiology. Patients with more severe symptoms or exercise intolerance, as defined by the NYHA functional class or as assessed by a 6-minute walk test, also have a less favorable outlook. Other markers of an adverse prognosis include elevated plasma norepinephrine, BNP, tumor necrosis factor alpha (TNF-α), and endothelin 1 levels; low systolic blood pressure; hyponatremia; renal insufficiency; anemia; peripheral arterial disease; cognitive dysfunction; reduced heart rate variability; and the presence of atrial fibrillation or high-grade ventricular arrhythmias. In patients with chronic heart failure, 40% to 50% die from

progressive heart failure, 40% die from arrhythmias, and 10% to 20% die from other causes (eg, myocardial infarction or noncardiac conditions). Notably, the proportion dying from noncardiac causes is much higher among patients with HFPEF compared to those with HFREF.

ADVANCE CARE PLANNING AND END-OF-LIFE DECISIONS

Overall survival rates for patients with heart failure are lower than for most forms of cancer. In addition, once heart failure symptoms have reached an advanced stage (eg, NYHA class III or IV), quality of life is often severely compromised and therapeutic options are limited. Moreover, even patients with relatively mild or well-compensated heart failure are continually at risk of experiencing sudden cardiac arrest, and, if initial resuscitative efforts are successful, questions regarding life support and related issues may arise.

For these reasons, it is incumbent upon the physician to discuss the patient's wishes regarding the intensity of treatment and end-of-life care at a time when the patient is still capable of understanding the issues and making informed choices. In addition, since the patient's views may evolve over the course of illness, these issues should be readdressed at periodic intervals. The development of an advance directive and appointment of durable power of attorney should also be encouraged (see Chapters 9 and 12).

A related concern is the extent to which clinicians should offer aggressive or investigational therapeutic options that are unlikely to substantially alter the natural history of disease or significantly improve quality of life. This concern applies not only to many of the treatment modalities discussed in the Refractory Heart Failure section earlier, but also to such procedures as admission to an intensive care unit and endotracheal intubation. In many cases, these interventions not only fail to modify the clinical course but actually contribute to the patient's pain and suffering in the terminal stages of disease. Moreover, the suggestion that a given intervention may help stabilize the patient and slow disease progression may create false hopes in the minds of the patient and family, and subsequent failure of the intervention may compound the emotional suffering that both the patient and the family are forced to endure. For these reasons, it is essential that the clinician realistically appraise the potential benefits and attendant risks, both physical and emotional, prior to offering aggressive therapeutic options that may provide little or no hope of improving the patient's quality of life over a clinically important period of time. In this context, it is often appropriate to offer transition to a palliative care approach and to obtain consultation from a palliative care specialist.

Finally, as the patient approaches the terminal stages of disease, there should be discussions with the patient and family regarding where the patient would like to spend his or her final days. For many patients, the idea of dying at home surrounded by close family is comforting, and this desire should be honored whenever possible. Often home hospice affords optimal end-of-life care in the home environment by providing effective symptom control, as well as emotional, spiritual, and caregiver support. Home hospice is also associated with higher levels of patient and family satisfaction with care in most cases. For some patients, the hospital or an inpatient hospice may be the preferred environment for terminal care, but an attempt should be made to secure a private room with open visitation hours. The intensive care unit, with its austere, "high-tech" facade, may be the least desirable place to die, and this should be avoided whenever possible.

PREVENTION

In view of the exceptionally poor prognosis associated with established heart failure in older adults, it is essential to develop and implement preventive strategies. Appropriate treatment of hypertension has been repeatedly shown to reduce the incidence of heart failure by 50% or more. In the Hypertension in the Very Elderly Trial, for example, treatment of hypertension was associated with a 64% reduction in incident heart failure among patients 80 years or older (additional details in Chapter 82). Treatment of hyperlipidemia has also been shown to reduce the incidence of heart failure, most likely through prevention of myocardial infarction and other ischemic events. Likewise, smoking cessation and regular exercise reduce the risk of myocardial infarction and stroke in older adults and likely have similar effects on the development of heart failure. Unfortunately, despite abundant evidence that heart failure prevention is feasible through risk factor modification, such strategies are underused, especially in persons older than 80 years.

SUMMARY

Heart failure is an exceedingly common and important clinical problem in older adults, owing, in large part, to the complex interplay between age-related changes in the cardiovascular system, the high prevalence of cardiovascular and noncardiovascular diseases in the older population, and the widespread use of certain drugs and other therapies that may adversely affect cardiovascular physiology. As the world population continues to age, heart failure will exact a progressively greater toll on health care delivery systems. In addition, the impact of heart failure on quality of life and independence in the large number of older adults with this disorder is incalculable. Clearly, there is a compelling need to develop more effective strategies for the prevention and treatment of heart failure, with particular emphasis on the geriatric population.

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Chapter 80

Cardiac Arrhythmias

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Learning Objectives

- Understand the etiologies of bradyarrhythmias, indications for pacemaker placement, and selection of the pacemaker mode.
- Discuss the goals of rate and rhythm control and approach to anticoagulation in older patients with atrial fibrillation (AF).
- Understand the indications for cardioverter-defibrillator and cardiac resynchronization therapy.

Key Clinical Points

1. **Age-related changes throughout the heart and conduction system predispose older individuals to bradyarrhythmias, conduction disturbances, and supraventricular and ventricular tachyarrhythmias, all of which increase in incidence and prevalence with advancing age.**
2. **The indications for invasive electrophysiologic testing are generally similar in younger and older patients.**
3. **The indications for permanent pacing for treatment of bradyarrhythmia are similar in older and younger patients. More than 80% of permanent pacemakers are placed in patients 65 years or older, with sinoatrial dysfunction being the leading indication for pacemaker implantation in this age group.**
4. **Compared with single-chamber ventricular pacing, dual-chamber pacing reduces the risk of AF but does not affect mortality or the risk of stroke.**
5. **Age greater than 75 is a well-recognized risk factor for thromboembolism in patients with AF.**
6. **In asymptomatic or minimally symptomatic patients with AF, a strategy of rate control and anticoagulation is associated with equivalent or better outcomes than a strategy of rhythm control.**
7. **In patients with symptomatic AF refractory to pharmacologic treatment, various catheter-based ablation procedures, as well as the surgical maze procedure, provide effective control of rate and/or arrhythmia in a high proportion of patients.**
8. **The indications for implantable cardioverter-defibrillator and cardiac resynchronization therapy are similar in older and younger patients, as are the benefits in terms of reducing mortality and improving symptoms. However, few data are available on the use of these devices in patients older than 80 years.**

In older patients without apparent cardiovascular disease, the number of cardiac myocytes declines, while residual myocytes enlarge. Concurrently, there is an increase in elastic and collagenous tissue in all parts of the interstitial matrix and conduction system with advancing age. Calcification of the cardiac skeleton, which includes the aortic and mitral annuli, the central fibrous body, and the summit of the atrioventricular (AV) septum, also increases with age.

Due to its proximity to these structures, the conduction system is likewise affected by aging. Prolongation of action potential duration and diminished autonomic response also develop in conjunction with the aging process. Taken together, these changes provide the substrate for the age-related increase in propensity for chronotropic and dromotropic incompetence and for the development of atrial and ventricular arrhythmias.

BRADYARRHYTHMIAS AND CARDIAC PACEMAKER THERAPY

Sinus Node Dysfunction

Pacemaker therapy is indicated in patients with symptomatic bradycardia (syncope, presyncope, dyspnea, and exercise intolerance) correlated to sinus node dysfunction (SND), manifest as pauses, persistent bradycardia, or chronotropic incompetence. It is acceptable to proceed with implantation of a single chamber pacemaker (atrial lead, AAI or AAIR mode). However, it must be taken into consideration that concomitant AV conduction disease can be detected in up to 20% of patients with SND. Therefore, current guidelines suggest the implantation of dual-chamber pacemaker for these patients. In this case, the programming must be adjusted to minimize the chances of ventricular pacing to reduce the risk of pacing-induced cardiomyopathy or heart failure. The use of single-chamber pacemaker (ventricular only) is not recommended due to the risk of developing pacemaker syndrome and the potential risk of ventricular dysfunction induced by chronic pacing. Exclusive ventricular pacing has also been associated with increased chances of atrial fibrillation (AF).

In older patients, SND is often associated with atrial tachyarrhythmias, including AF. Current pacemaker technology allows effective recognition of fast atrial rhythms, which will trigger the temporary suspension of atrial lead function, switching from dual chamber to ventricular pacemaker until resolution of the atrial arrhythmia.

Acquired Advanced AV Block

Class I indications for permanent pacemaker implantation include third-degree AV block and advanced second-degree AV block in symptomatic patients. Pacing therapy is also recommended in patients with neuromuscular diseases such as myotonic dystrophy and Emery-Dreifuss muscular dystrophy and first- or second-degree AV block whether or not they are symptomatic, because progression of AV conduction slowing is not predictable in such patients.

The presence of second-degree AV block type II or alternating bundle branch block is an indication for pacing, even in asymptomatic patients. First-degree AV block is never an indication for pacing therapy, except for patients with associated neuromuscular disorders.

Pacemaker Therapy Single Versus Dual-Chamber Pacemaker

More than 80% of pacemaker recipients in the United States are older than 65 years. Several pivotal trials that address appropriate pacemaker mode selection are summarized in **Table 80-1**. The three largest trials (> 6500 patients) did not find a beneficial effect of dual-chamber pacing for the prevention of stroke or improvement in survival when compared with ventricular pacing. However, the incidence and progression to chronic AF were reduced with dual-chamber pacing. In addition, heart failure symptoms were reduced slightly and quality of life was better in patients receiving dual-chamber pacemakers for sinus node dysfunction, most likely because of the prevention of pacemaker syndrome.

TABLE 80-1 ■ RANDOMIZED CLINICAL TRIALS OF PACEMAKER MODE SELECTION IN OLDER PATIENTS

RELATIVE RISK WITH VENTRICULAR VERSUS ATRIAL OR DUAL-CHAMBER PACING											
TRIAL,[a] YEAR REPORTED	NO. ENROLLED	MEAN AGE (Y)	GROUP	FOLLOW-UP (Y)	MODE OF PACING	MORTALITY	CHF	HF HOSPITALIZATION	AF	TE	QOL
PASE, 1998	407	76	SND or AVB	2.5	VVIR versus DDDR	NS	NS	NS	↑	NS	NS,[b] ↓ in SND
CTOPP, 2000	2568	73	SND or AVB	3	VVIR versus DDDR or AAIR	NS[b]	NS	NS	↑	NS[b]	Not stated
MOST, 2002	2010	74	SND	2.7	VVIR versus DDDR	NS[b]	↑	NS	↑	NS[b]	↓
UK-PACE, 2003	2021	80	AVB	4.6	VVI/VVIR versus DDD/ DDDR	NS[b]	NS		NS	↑[b]	Not stated

AF, atrial fibrillation; AVB, atrioventricular block; CHF, congestive heart failure; HF, heart failure; NS, no significant difference; QOL, quality of life; SND, sinus node dysfunction; TE, thromboembolism; ↑, increased; ↓, decreased.

[a]CTOPP, Canadian Trial of Physiologic Pacing; MOST, Mode Selection Trial; PASE, Pacemaker Selection in the Elderly; UK-PACE, UK Pacing and Cardiovascular Events.

[b]Designated primary end point of the trial.

SYNCOPE

Hypersensitive Carotid Sinus Syndrome

Carotid sinus hypersensitivity (≥ 3-second pause or a decrease in systolic blood pressure ≥ 50 mm Hg during carotid sinus massage) predominantly affects older patients, although the prevalence in the general population has not been precisely defined. In older patients with recurrent syncope or falls, carotid sinus hypersensitivity has been reported in up to 35% of cases. Permanent pacing in patients with carotid sinus syndrome is indicated. Observational and randomized studies have shown that recurrent symptoms are significantly reduced after permanent pacemaker implantation in patients with carotid sinus syndrome. Dual-chamber pacing is considered the best choice for these patients, although data are lacking from randomized trials. Newer algorithms, such as the "rate-drop response" or "sudden-brady response," which accelerates the pacing rate when bradycardia is detected, are available. However, the clinical utility of these newer algorithms has not shown to be superior to conventional pacemakers.

Neurocardiogenic ("Vasovagal") Syncope

Vasovagal syncope is more common in younger patients but also should be considered in older patients with unexplained syncope. Although the triggering mechanisms are complex and may differ among young and older patients, the efferent responses generally can be categorized as cardioinhibitory (pauses of ≥ 3 seconds or heart rate < 40 beats/min for > 10 seconds), vasodepressor (systolic blood pressure falls by 50 mm Hg or more without symptoms or 30–50 mm Hg with symptoms of syncope or presyncope, and the heart rate does not decrease by > 10%), or mixed (heart rate decreases but the ventricular rate does not fall below 40 beats/min for > 10 seconds, and there are no pauses for > 3 seconds; blood pressure usually decreases before the heart rate drops). Of note, the vasodepressor component is frequently present in patients with vasovagal syncope, and pacing therapy does not necessarily eliminate or significantly reduce vasodepressor-mediated symptoms.

Studies comparing pacing with conventional therapy (conservative or drug) failed to confirm a beneficial effect from pacing therapy in patients with vasovagal syncope. In general, outcomes from pacing and drugs for treating vasovagal syncope reflect the heterogeneous patient population, complex underlying mechanisms, and sporadic nature of the neurocardiogenic reflex. On the basis of available evidence, it is reasonable to consider pacing as a class II indication in older patients who have recurrent syncope with documented bradycardia during a vasovagal response.

Older Patients With Syncope of Uncertain Cause

Syncope is a common cause of falls, injuries, and hospitalizations in older adults. Numerous age-related autonomic and humoral changes also predispose older patients to syncope. Decreased heart rate responsiveness to postural changes and diminished baroreceptor sensitivity impair the ability to adapt to orthostatic stress. Reduced concentrations of plasma aldosterone, coupled with impaired thirst, place older patients at risk of volume depletion. These age-related changes, in combination with comorbid medical conditions, increase the propensity for multiple potential etiologies of syncope in older patients. In turn, multiple-cause syncope is an independent predictor of poor clinical outcome.

Factors associated with an increased risk of cardiogenic syncope include a history of coronary artery disease, prior myocardial infarction, chronic heart failure, abrupt onset of symptoms (no prodrome), an event occurring in the supine position, older age, abnormal cardiovascular examination (aortic stenosis murmur and S_3 gallop), abnormal electrocardiogram (ECG) (Q waves, bundle branch block, or sinus bradycardia), and an abnormal echocardiogram (structural abnormality or reduced ejection fraction). Carotid sinus massage should be a routine part of examination in older patients presenting with syncope, unless there is a carotid bruit or prior history of stroke. An electrophysiologic study (EPS) should be considered in older patients with unexplained syncope and an increased risk of a cardiogenic cause. In patients at low risk of cardiogenic syncope, noninvasive cardiac monitoring or tilt-table testing may be appropriate. An implantable loop recorder should be considered in older patients with recurrent syncope of unknown cause, especially if structural heart disease is present. Empirical pacing is generally not recommended except for those patients with bundle branch block on ECG and recurrent syncope after nondiagnostic investigations. Once a cause of syncope has been established, treatment is similar in older and younger patients.

TACHYARRHYTHMIAS AND CARDIAC IMPLANTABLE DEFIBRILLATOR THERAPY

Atrial Fibrillation

AF affects approximately 2.3 million people in the United States and is the most common rhythm disorder among US patients hospitalized with a primary diagnosis of an arrhythmia. The median age of AF patients is 75; 84% are older than 65 years. AF has a substantial impact on both morbidity and mortality. It is a strong independent risk factor for stroke, responsible for an estimated 75,000 cerebrovascular accidents annually. AF is also associated with a more than twofold increase in all-cause mortality. Although AF frequently coexists with other medical conditions, especially cardiovascular and pulmonary disorders, mortality remains higher after adjusting for these and other conditions.

Stroke prevention in atrial fibrillation The annual incidence of stroke in older patients with nonvalvular, paroxysmal, persistent, or permanent AF is approximately 5% without anticoagulation, compared with approximately 1% for comparable populations in sinus rhythm. The $CHADS_2$ and CHA_2DS_2-VASc risk stratification schemes are summarized in **Table 80-2**. The most recent American Heart Association (AHA)/American College of Cardiology (ACC) guidelines have adapted the CHA_2DS_2-VASc score for clinical use that provides a more granular stratification of stroke risk, especially among patients with lower scores. Data from a pooled analysis of primary prevention studies indicate that the annual risk of stroke in patients with one or more clinical risk factors varies from 2% to 12% and that warfarin therapy reduces the risk by 60% to 70% (ie, down to 1%–4%).

TABLE 80-2 COMPARISON OF $CHADS_2$ AND CHA_2DS_2-VASC

Risk Stratification for Stroke Nonvalvular Atrial Fibrillation

	$CHADS_2$			CHA_2DS_2 VASC		
	$CHADS_2$ POINTS	TOTAL SCORE	ADJ RISK (%/Y)	CHA_2DS_2 VASC POINTS	TOTAL SCORE	ADJ RISK (%/Y)
Risk factors						
		0	1.9 (1.2–3.0)		0	0.0
CHF	1	1	2.8 (2.0–3.8)	1	1	1.3
HTN	1	2	4.0 (3.1–5.1)	1	2	2.2

Age ≥ 75	1	3	5.9 (4.6–7.3)	2	3	3.2
Diabetes	1	4	8.5 (6.3–11.1)	1	4	4.0
Stroke/TIA/thromboembolism	2	5	12.5 (8.2–17.5)	2	5	6.7
Vascular disease	–	6	18.2 (10.5–27.4)	1	6	9.8
Age 65–74	–			1	7	9.6
Female gender	–			1	8	6.7
					9	15.2
Maximum score	6			9		

ADJ, adjusted; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; TIA, transient ischemic attack.

It is well known that individuals younger than 60 years with CHA_2DS_2-VASc of 0 to 1 are at low risk of stroke, and the current recommendation for stroke prevention includes the use of aspirin alone or observation. Individuals with nonvalvular atrial fibrillation who are at higher risk of stroke should be placed indefinitely on chronic oral anticoagulation. The annual risk of embolic stroke increases proportionally to the CHA_2DS_2-VASc score, and current guidelines recommend chronic oral anticoagulation for individuals with a score greater than or equal to 2. The type of atrial fibrillation, paroxysmal, persistent or permanent, does not influence the assessment for risk of stroke or the decision for anticoagulation. Risk of bleeding can be assessed by the HAS-BLED scoring system. HAS-BLED includes seven clinical parameters (hypertension [uncontrolled], abnormal renal/liver functions, stroke, bleeding tendency or predisposition, labile international normalized ratio [INR], age > 65, and drugs [aspirin/nonsteroidal anti-inflammatory drug or alcohol]). One point is given to each risk factor. Patients with a score greater than or equal to 3 are considered to be at higher risk of bleeding while on anticoagulants. Nevertheless, the score should not be used alone to include or exclude patients from oral anticoagulant therapy, but rather allows clinicians to make an informed judgment as to the risk of bleeding and to identify modifiable bleeding risks that need to be addressed. The recommendations for stroke prevention according to the AHA/ACC 2014 guidelines are summarized in **Table 80-3**.

TABLE 80-3 STROKE PREVENTION IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION[a]

Class I recommendations

- Shared decision: risk of stroke vs bleeding, values and preferences
- CHA_2DS_2-VASc and HAS-BLED: risk assessment at periodical intervals
- Warfarin for mechanical prosthetic valves
- CHA_2DS_2-VASc ≥ 2: warfarin, dabigatran, rivaroxaban, or apixaban
- New agents preferred if INR is difficult to maintain; renal function needs to be assessed

Class IIa recommendations

- Reasonable to consider no therapy if CHA_2DS_2-VASc = 0
- Consider warfarin when CrCl < 15 cc/min

Class IIb recommendations

- ASA or no therapy when CHA_2DS_2-VASc = 1
- Reduced doses of direct antithrombin or factor Xa agents when renal insufficiency is present (safety and efficacy not yet established)
- ASA (< 100 mg/d) with or without clopidogrel, concurrently with AC after coronary intervention or CABG
- Bare metal stent may be considered in patients with ischemic heart disease
- Warfarin in renal failure or on dialysis

Class III recommendations: Harm

- Direct antithrombin or factor Xa agents should not be used in severe renal insufficiency

ASA, aspirin; CABG, coronary artery bypass grafting; CrCl, creatinine clearance; INR, international normalized ratio.

[a]Synopsis from AHA/ACC guidelines 2014.

For patients who are not able to safely manage oral anticoagulation, the use of aspirin (75–325 mg/day) is considered an alternative approach; however, the level of protection against embolic stroke is significantly lower when compared to warfarin. The combination of aspirin and clopidogrel has been studied in randomized trials. The aspirin and clopidogrel combination was inferior to warfarin for stroke prevention, but with better results when compared to aspirin alone. However, the risk of bleeding and particularly intracranial hemorrhage was comparable to warfarin. The concern of bleeding is the most common reason for the restriction to the use of warfarin, therefore, the combination of clopidogrel and aspirin would not be a replacement therapy for most cases.

Novel oral anticoagulants Warfarin has been the gold standard for treatment and prevention of thromboembolic events for decades. However, maintaining adequate time in therapeutic range with warfarin is a challenge because of frequent interactions with other medications and dietary choices, requirement of frequent blood tests and dose adjustments. A new class of drugs—direct thrombin inhibitors—has been developed, and all of these drugs have been shown to be noninferior when compared to warfarin in the role of stroke prevention in patients with nonvalvular atrial fibrillation. The common feature among these new agents is the quick onset and offset of drug action, fewer interactions with other drugs, no dietary restrictions and no need for routine blood work. The disadvantage of these drugs is the lack of appropriate reversal agent in case of hemorrhagic complication. The first drug released in the market was dabigatran. The recommended dose is 150 mg twice a day. The dose should be adjusted (75 mg twice a day) in patients with significant impaired renal function (ClCr < 50 mL/min), dabigatran should be avoided when ClCr is less than 30 mL/min. The reversal of dabigatran includes activated prothrombin complex concentrates, or recombinant factor VIIa, or concentrates of coagulation factors II, IX, or X, but their use has not been adequately evaluated.

Rivaroxaban, apixaban, and edoxaban share the same mechanism of action, and are classified as factor Xa inhibitors. The dose of rivaroxaban is 20 mg/day and the dose should be reduced to 15 mg/day in patients with decreased renal function (ClCr < 50 mL/min) and should be avoided if ClCr less than 30 mL/min. No antidote is available for this drug and rivaroxaban cannot be removed by hemodialysis. Apixaban is the latest oral anticoagulant approved for clinical use, with recommended dose of 5 mg twice a day. The dose should be reduced in half for patients who are more than 80 years, body weight less than 60 kg, or when creatinine levels are greater than 1.5 mg/dL. This drug is the only one that was shown to be superior to warfarin, mostly by having reduced number of bleeding events. Apixaban also lacks an antidote. Edoxaban is the newest oral anticoagulant, and is not yet approved in United States of America. However, clinical data have shown noninferiority when compared to warfarin.

Despite significantly fewer interactions with other drugs when compared to warfarin, all novel anticoagulants should be used with caution if the concomitant use of a P-glycoprotein inhibitor (dronedarone, quinidine, verapamil) or inducer (rifampin) is present. There is also a potential interaction with CYP3A4 inhibitors (ketokonazole, ritonavir, verapamil, diltiazem), resulting in increased serum levels of these novel agents.

Pharmacologic therapy for atrial fibrillation

Rate Control Although urgent cardioversion is required for patients with AF associated with hemodynamic instability, persistent angina, or critical aortic stenosis, most acute-phase symptoms can be controlled by prompt reduction of the ventricular rate. Digitalis glycosides decrease ventricular rate in AF by augmenting cardiac vagal tone and increasing the level of block at the atrioventricular node (AVN). However, in both acute and chronic settings, digoxin is generally less effective at controlling rate than either β-adrenergic blockers or calcium channel blockers (eg, diltiazem or verapamil). β-Blockers and calcium channel blockers reduce the ventricular rate in AF by slowing conduction through the AVN. β-Blockers are preferable for rate control of AF paroxysms precipitated by acute coronary ischemia, whereas calcium channel blockers are chosen in the setting of asthma. In older patients, optimizing rate control with drugs may be difficult because of presence of comorbidities and susceptibility to adverse effects. Clinical conditions such as sinus node dysfunction, AV conduction delay, and ventricular dysfunction may result in significant bradyarrhythmia or worsening heart failure when rate-controlling agents are administered. In addition, rate control alone may be insufficient to alleviate symptoms in some patients, such as those with hypertrophic cardiomyopathy, in whom restoration of sinus rhythm may be beneficial.

Rhythm Control In the acute setting, rhythm control can be established by pharmacologic or nonpharmacologic cardioversion. The efficacy of intravenous and oral antiarrhythmic drugs for cardioversion of AF is highly variable, ranging from 30% to 75%. Efficacy also varies with the age of the patient, duration of the arrhythmia, presence of atrial flutter, underlying left ventricular function, and left atrial size. Ibutilide, a class III drug, is more effective in restoring sinus rhythm in atrial flutter than AF. Dofetilide, another class III agent, is effective for oral prophylaxis and

safe in patients with left ventricular dysfunction. Single-dose oral propafenone has also been evaluated for AF cardioversion and has an excellent efficacy and safety profile. In general, higher cardioversion efficacy rates are reported for paroxysmal than for persistent AF. Older patients may be at increased risk of proarrhythmia with all of these agents, thus necessitating careful monitoring during and after cardioversion. The efficacy of intravenous amiodarone for termination of recent-onset AF is disputed. Although some studies suggest a high efficacy comparable to direct-current cardioversion, intravenous amiodarone was not more effective after 24 hours than placebo in a randomized trial of 100 patients with recent AF. This may be explained by the delayed onset of amiodarone's antiarrhythmic effects. Current data do not support the use of amiodarone for acute cardioversion.

External direct-current cardioversion can restore sinus rhythm in 75% to 90% of patients with AF. For maintenance of sinus rhythm in patients with recurrent AF, consideration is given to chronic antiarrhythmic therapy. Class Ia antiarrhythmic drugs such as quinidine, disopyramide, and procainamide; class Ic agents such as flecainide and propafenone; and class III agents such as sotalol, amiodarone, and dofetilide have all been used to prevent recurrent AF, with efficacy rates ranging from 30% to 80% during the first year of follow-up. Amiodarone is more efficacious and safer during short- and intermediate-term follow-up than class I agents, for which the risk of ventricular proarrhythmia must be carefully considered. The presence of structural heart disease, which is common in older patients, increases the risk of proarrhythmia with class I agents. However, amiodarone is associated with considerable noncardiac side effects during long-term use, resulting in drug discontinuation rates of up to 20% at 1 year. In general, drugs with substantial negative inotropic effects, including procainamide, disopyramide, and flecainide, are contraindicated in patients with left ventricular systolic dysfunction. Class 1c drugs should not be used in patients with underlying coronary artery disease. Class Ia and III agents prolong ventricular repolarization and the QT interval owing to potassium channel blockade. Propafenone, sotalol, and amiodarone have a β-blocking effect that could be clinically significant in older patients with sinus node or AVN conduction disease. In patients with His-Purkinje disease, class I agents should be used with caution because of their potential to slow infranodal conduction. Dofetilide, sotalol, and active metabolite of procainamide are predominantly excreted by the kidney and should be used with extreme caution in older patients with concomitant renal dysfunction. The target sites of the antiarrhythmic drugs are shown in **Figure 80-1**.

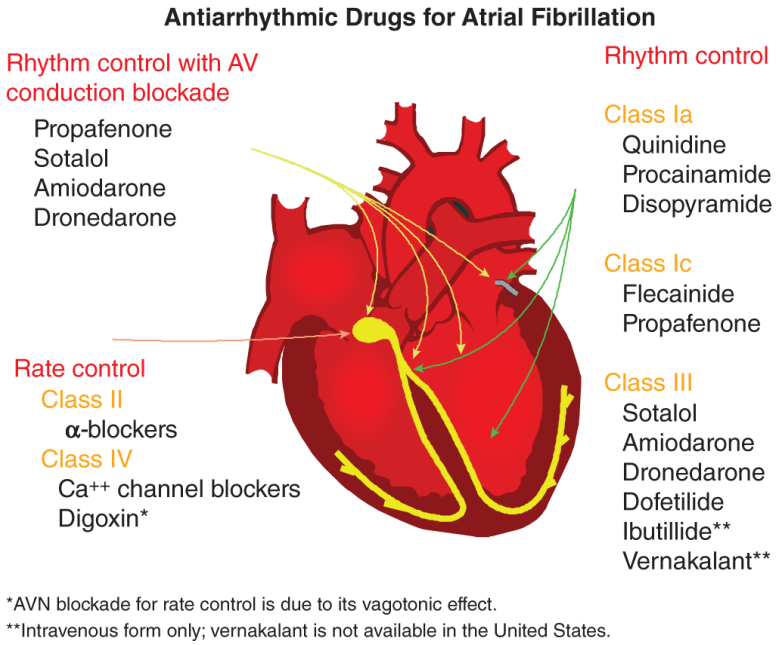


FIGURE 80-1. Therapeutic targets for antiarrhythmic drugs for atrial fibrillation.

Rate Versus Rhythm Control Ideally, the goal of treating AF is to restore and maintain sinus rhythm. This goal may be of greater importance among older patients in whom there is greater reliance on the atrial contraction to complete left ventricular filling during diastole. The challenge to meeting this goal is that all of the currently available therapeutic options are also associated with undesirable side effects. Several randomized trials compared the effectiveness of rate control (ie, controlling ventricular rate in AF) versus rhythm control (attempting to maintain sinus rhythm). These trials have consistently shown that mortality outcomes or composite end points of cardiovascular

events including stroke are not significantly different between these two treatment strategies. Hospital admissions are more frequent in patients randomized to rhythm control. These results support that medical therapy for rate control and chronic anticoagulation are the preferred approaches in asymptomatic or minimally symptomatic patients with persistent AF, especially in older patients. These studies also show that an optimal drug therapy regimen for rhythm control in AF is not currently available for the large population of patients with symptomatic AF, who are often older (estimated to be at least 40% of the entire AF population).

Nonpharmacologic therapy for atrial fibrillation In the absence of a simple and effective drug-based treatment strategy, major efforts are being undertaken to develop and evaluate nonpharmacologic methods for treating recurrent AF. Before wide application of these approaches can be recommended in older patients, clinically relevant end points, such as survival, stroke, major cardiovascular events, symptoms, and functional capacity, must be evaluated.

Rate Control In patients with severe symptoms and in whom drug therapy fails, ablation of the AVN and permanent pacing are effective for controlling ventricular rate. Although ablation of the AVN does not eliminate AF or the need for anticoagulation, it relieves symptoms and improves health-related quality of life, exercise tolerance, and left ventricular function. Biventricular pacing after AVN ablation is associated with improved 6-minute walk distance compared with conventional right ventricular apex pacing in patients with preexisting heart failure symptoms. Despite the efficacy of AVN ablation and pacemaker implantation for controlling symptoms in patients with AF, there is concern that the creation of complete AV block and the associated requirement for permanent pacing may have an adverse effect on long-term survival. However, in a large observational study, survival among patients who underwent ablation of the AVN to control ventricular rate for AF was similar to that among patients who received drug therapy.

Rhythm Control Despite antiarrhythmic drug therapy, recurrent and refractory symptomatic AF is common in patients of all ages. Nonpharmacologic treatment options are increasingly being used to maintain sinus rhythm in these patients. However, the projected benefits must be weighed carefully against the potential risk of invasive procedures, especially in older patients with other comorbid conditions. The surgical maze procedure is highly effective in the treatment of refractory AF and has become an important adjunctive procedure for patients with AF undergoing cardiac surgery for other reasons. The long-term success rate has been reported to be as high as 90% during 4- to 5-year follow-up. The surgical experience has also provided impetus to develop catheter-based ablative techniques for the treatment of AF.

The success rate for catheter ablation has been estimated in the range of 60% to 70% in patients with paroxysmal AF and 40% to 60% in patients with persistent or permanent AF during an average follow-up of 2 years. One should also be aware that the mean age of patients undergoing primary AF ablation in most studies has been in the range of 50 to 65 years. Whether similar outcomes can be obtained in older patients, namely those greater than or equal to 75 years, remains to be determined.

Major complications of AF ablation include death, stroke, tamponade, esophageal perforation or fistula, and pulmonary vein stenosis. The impact of AF ablation on stroke is also unknown. Therefore, continuation of anticoagulation is recommended guided by the patient's risk score.

Supraventricular Tachyarrhythmia

The principles of drug and nondrug management of supraventricular tachyarrhythmia (SVT) are similar to those outlined for AF. However, for most SVTs, the arrhythmogenic substrate is isolated and well defined. AV nodal reentrant tachycardia (localized to the region of AVN) is the most common type of SVT identified among older patients, followed by atrial tachycardia. β-Blockers and calcium channel blockers are considered the first line of therapy for treating SVTs. Class I and III antiarrhythmic agents are effective for treating SVTs involving conduction through an accessory pathway or atrial tissue. Ablative therapy is also highly effective for the treatment of SVTs.

The types of arrhythmias that are most likely to be eliminated by catheter ablation are (1) AV nodal reentrant tachycardia, (2) recurrent atrial flutter, (3) SVTs associated with an accessory pathway, and (4) atrial tachyarrhythmias. Indications for catheter ablation in older and very old patients have not been separately defined and are the same as those for the general population. Success rates for catheter ablation of SVT range from 75% to more than 95%, depending primarily on the nature of the arrhythmia and the experience of the operator. Notably, age is not predictive of procedural success. The incidence of major complications associated with SVT ablation is approximately 3%, and the risk of minor complications is approximately 8%.

Ventricular Tachyarrhythmia

The management of ventricular arrhythmias in older patients is similar to that in the general population. In patients with asymptomatic nonsustained ventricular tachyarrhythmia, a careful evaluation for the presence of cardiac disease, including occult coronary artery disease, structural heart disease, and left ventricular dysfunction, is required. Premature ventricular contractions and nonsustained ventricular tachyarrhythmia are associated with a benign prognosis in the absence of any significant heart disease. The risk of sudden cardiac death (SCD) is increased in patients with compromised left ventricular ejection fraction, whether due to ischemic or nonischemic heart disease. Preventing SCD entails optimizing therapy directed at the underlying disease and the use of implantable cardioverter-defibrillator (ICD) therapy in selected patients. Although none of the indications for ICDs exclude or allude to special considerations in older patients, individual assessment and determination of primary therapeutic objectives are particularly pertinent in this population because comorbid medical illnesses are frequently present and life expectancy is shorter in the very old.

Secondary prevention of sudden cardiac death Indications for implantation of a cardioverter defibrillator for secondary SCD prevention include (1) cardiac arrest owing to ventricular tachycardia or ventricular fibrillation not related to a transient or reversible cause (eg, acute myocardial infarction), (2) spontaneous sustained ventricular tachycardia in association with structural heart disease, and (3) syncope of undetermined origin with clinically relevant, hemodynamically significant sustained ventricular tachycardia or ventricular fibrillation induced at EPS when drug therapy is ineffective, not tolerated, or not preferred. Randomized, prospective clinical trials comparing antiarrhythmic drug therapy to ICD have demonstrated the usefulness of ICD in reducing the risk of SCD as a result of cardiac arrhythmias and total mortality in those at risk of or resuscitated from cardiac arrest or life-threatening ventricular arrhythmias. However, none of these trials have focused specifically on the efficacy of ICD in older patients. Overall, the average age of patients in the clinical trials of ICD has been in the sixties. Data on octogenarian and nonagenarian patients are scant. However, using pooled data from the three major randomized ICD secondary SCD prevention trials, no statistically significant reduction in all-cause mortality or arrhythmic death was noted among patients aged 75 or older randomized to ICD therapy compared with amiodarone. This highlights the importance of individualization when making decisions on ICD implantation in older patients, taking into account the current guidelines, patient's preference, biological age, functional capacity, cognitive function, and underlying comorbidities.

Primary prevention of sudden cardiac death In patients with coronary artery disease, prior myocardial infarction, and an ejection fraction of 30% or less, a survival benefit was found with prophylactic implantation of a cardioverter defibrillator compared with medical therapy. In patients with class II or III heart failure symptoms and an ejection fraction of 35% or less, an ICD was associated with improved survival compared with amiodarone or medical therapy, and the benefit was evident in patients with or without ischemia (48%).

An ICD is currently approved by Medicare for use in patients with ischemic or nonischemic cardiomyopathy, ejection fraction of 35% or less, and class II or class III heart failure symptoms based on randomized clinical trials. Patients who had a history of myocardial infarction (> 40 days after the event) and ejection fraction of 30% or less also qualify regardless of their functional status. In patients with ejection fractions between 35% and 40%, an ICD is indicated if a sustained ventricular tachyarrhythmia is inducible during EPS evaluation. The mean age of patients in the primary prevention trials ranged from 52 to 64. Data for primary SCD prevention in very old patients—octogenarians and older—are not available from randomized trials. Useful information from the older population could be derived from large national registries in the future.

Cardiac resynchronization therapy and implantable cardioverter-defibrillator Cardiac resynchronization therapy (CRT) improves functional capacity and quality of life in patients with persistent class III and IV heart failure despite optimal medical therapy, and there is also evidence that CRT may reverse structural remodeling in selected patients. Clinical trials have consistently shown that CRT reduces hospitalizations and that CRT with or without an ICD reduces mortality in chronic heart failure. However, it must be recognized that very limited data are available on the use of these devices in the very old. Therefore, recommendations for the use of CRT and ICDs in this age group must be individualized, taking into consideration the patient's life expectancy, concomitant medical illnesses, and therapeutic objectives.

AGING AND DRUG-INDUCED PROARRHYTHMIA

There are several important changes in pharmacokinetics associated with aging that predispose older patients to an

increased risk of drug-induced side effects including arrhythmia. Age-related changes in volume of distribution, drug metabolism, absorption, and elimination are discussed in detail in Chapter 24. Compounding the pharmacokinetic changes are intrinsic changes in the cardiac pacemaker cells and the cardiac conduction system associated with aging, which increase the propensity of the older population to develop chronotropic incompetence, conduction block, and bradycardia. In addition to bradyarrhythmias, older patients are also at risk of drug-induced tachyarrhythmias. Acquired long-QT syndrome or drug-induced torsades de pointes is a form of ventricular tachyarrhythmia that can potentially degenerate into ventricular fibrillation and is an often overlooked cause of syncope and SCD. The underlying mechanism of drug-induced torsades de pointes has been attributed to the ability of multiple drugs to increase cardiac action potential duration and QT interval, leading to increased intracellular calcium loading and the generation of early afterdepolarization activity. The increased exposure of the older population to drugs that lengthen the QT interval, from reasons described above, may increase their likelihood of developing this life-threatening arrhythmia.

SUMMARY

The genesis of arrhythmia is the result of complex interactions among aging-related physiologic changes, disease-dependent substrate, risk factors, and genetic predisposition as shown in **Figure 80-2**. Guidelines on the treatment of cardiac arrhythmias continue to evolve and being updated regularly. Although many well-designed clinical trials have provided solid evidences for our clinical practice, the small number of very old patients (octogenarians and nonagenarians) participating in clinical trials poses significant limitations on a more specific practice recommendation in the geriatric patient population. Perhaps more so than survival rates, clinical outcomes such as symptoms, quality of life, functional capacity, independent living, and hospitalization need to be critically addressed when treating arrhythmias in this fastest growing segment of our population.

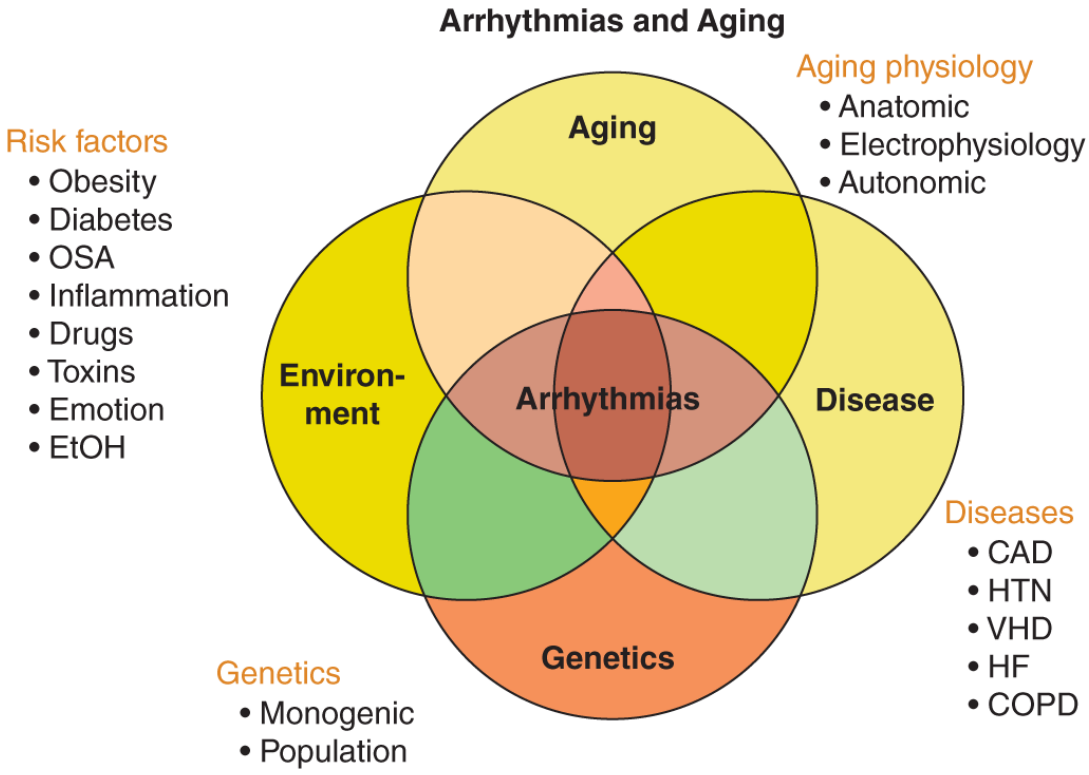


FIGURE 80-2. Risk factors related to genesis of arrhythmias in older patients.

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Chapter 81

Peripheral Vascular Disease

Jason Johanning

Learning Objectives

- Obtain a working knowledge of the most common sites of peripheral vascular disease (PVD), the initial diagnostic tests, and options for treatment as well as their outcomes.
- Understand the important role aging plays with regard to intervention in the PVD patient where the primary determination to intervene is based on risk-benefit ratio and the time to treatment equipoise.
- Describe the key indications with regard to intervention for the most common arterial diseases including claudication, critical limb ischemia, symptomatic and asymptomatic carotid artery stenosis, and abdominal aortic aneurysms (AAAs).
- Understand the role of minimally invasive endovascular intervention in comparison to open vascular surgery.
- Understand the key physiologic and nonphysiologic factors that affect surgical outcomes in vascular patients especially renal failure and functional status.

Key Clinical Points

1. **Peripheral arterial disease (PAD) is a common clinical condition in older adults with up to 20% of patients over the age of 70 having some form of PAD.**
2. **PAD can be diagnosed utilizing a simple and accurate test named the ankle-brachial index (ABI), which can be falsely elevated in diabetic patients.**
3. **The decision to intervene in a patient with claudication is a lifestyle choice and should be pursued only after a trial of exercise therapy has been performed as the risk of disease progression and amputation in this population is low.**
4. **Intervention for patients with asymptomatic carotid artery stenosis utilizing carotid artery stenting (CAS) is not currently indicated due to the significant risk of perioperative stroke except in unusual circumstances.**
5. **Carotid endarterectomy is the generally accepted intervention for older patients with both asymptomatic and symptomatic carotid artery stenosis with CAS acceptable for patients with specific indications.**
6. **Intervention of patients with AAA is generally accepted between 5 and 5.5 cm.**
7. **Outcomes for patients with acceptable anatomy for open or endovascular repair of infrarenal AAAs are similar based on current randomized trials, although short-term mortality appears to benefit patients undergoing endovascular repair.**
8. **Long-term follow-up of patients undergoing endovascular repair of AAA using computed tomographic scanning is currently recommended based on changing morphology of the residual aneurysm.**

Peripheral vascular disease (PVD) is primarily a disease of aging and is strongly associated with impaired quality of

life and increased cardiovascular mortality. The average age of patients seeking treatment is approximately 70. Various studies document a 15% to 20% prevalence rate in patients over the age of 70. With the increase in the older population, the diagnosis and treatment of PVD will become a priority. A working knowledge of the most common sites of disease, the initial diagnostic tests, and options for treatment as well as their outcomes are necessary to provide optimal guidance for these patients. This chapter is organized by the most commonly encountered arterial diseases of the geriatric patient. Although each has its unique presentation, treatment algorithms and nonoperative and operative management, it should not be forgotten that the underlying atherosclerotic process is a systemic disease and as such should be treated similar to coronary atherosclerotic disease with regard to risk factor management (see Chapter 75 for additional information).

PERIPHERAL ARTERIAL DISEASE

Definition

Lower extremity arterial disease is commonly referred to as peripheral arterial disease. As a whole this disease encompasses atherosclerotic narrowing of arteries from the infrarenal aorta to the level of the tibial arteries at the foot.

Epidemiology

Risk factors for peripheral arterial disease (PAD) are similar to those of coronary artery disease and include smoking history, advanced age, male gender, and positive family history. The prevalence of PAD increases with increasing age with up to 20% of patients over the age of 75 having some form of lower extremity arterial disease although classic claudication symptoms are present in less than half of patients.

Presentation

The presentation of PAD includes a range of symptoms. The most common presentation is that of claudication, or cramping of the lower extremity muscles. The cramping or aching is primarily in the calves and buttocks and is relieved within 10 minutes of cessation of activity. The above classic presentation of claudication has unfortunately been shown to be present in less than half of patients with documented PAD and leg symptoms. Therefore in the geriatric population, one must have a high index of suspicion for PAD as an underlying cause of ambulatory difficulties and leg symptoms. Additionally, in the older patient, coexisting conditions are common. The two most common conditions are osteoarthritis of the hip or knee and neurogenic claudication secondary to spinal stenosis. Osteoarthritis generally localizes to the joint, improves with pain medications, and has a varying course of improvement and worsening throughout the day. Neurogenic claudication is the most difficult to differentiate from vasculogenic disease because spinal stenosis is common in the older population. Neurogenic claudication most commonly presents with pain in the calves and posterior thigh and buttocks. In contrast to vasculogenic disease, neurogenic claudication has variable distance to onset, often takes 15 minutes to over hours to resolve, and claudication distance can be significantly increased with use of an assistive device such as a walker on which the patient can lean over and relieve the pressure on the spinal nerves.

A focused history of ambulation is usually sufficient to confirm or provide high suspicion for the diagnosis of claudication in the majority of patients and provide a differential as to arterial, spinal, or muscular/joint etiology. The patient with true vasculogenic claudication will complain of pain with ambulation that starts after a known, relatively fixed, distance (two to three blocks are common as this interferes with activities of daily living). Upon cessation of ambulation and rest, the pain will subside and upon resuming ambulation will reoccur at a similar distance. This cycle in vasculogenic claudication can be repeated indefinitely. Unfortunately, often all three conditions in the older patient can coexist and then diagnosis of the primary limiting condition is of utmost concern to achieve an optimal outcome and maintain ambulatory independence.

Although claudication secondary to arterial disease can cause the patient significant distress, the rate of disease progression to rest pain (severe ischemic pain due to insufficient arterial inflow), critical limb ischemia (gangrene, ulceration, or tissue loss), and subsequent amputation is low—on the order of 10% over 10 years or 2.5% annually given the high mortality rate in this cohort, even in the absence of any intervention. Thus, patients presenting to providers worried about amputation should be reassured that amputation is unlikely with appropriate noninterventional or nonoperative management strategies with the first and foremost being smoking cessation (**Figure 81-1**).

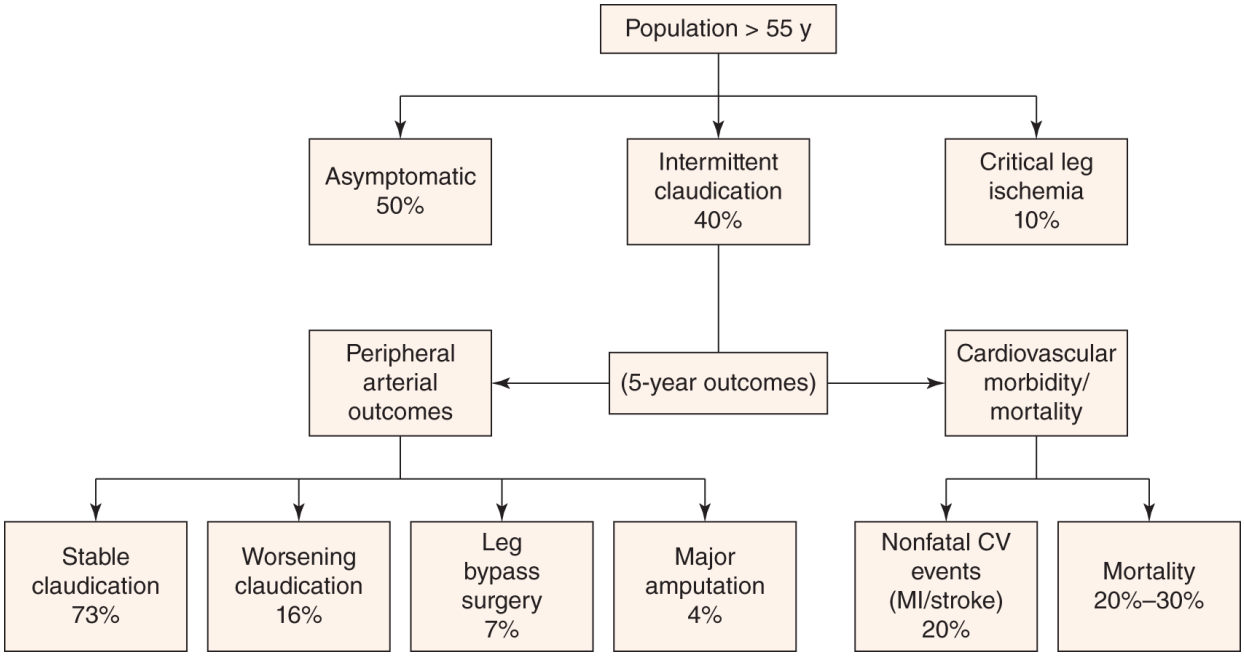


FIGURE 81-1. The natural history of patients with intermittent claudication including fate of the limb and the relationship to cardiovascular outcome. Note the benign nature of intermittent claudication with regard to the limb yet the high incidence of cardiovascular events. (Modified from Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation*. 1996;94[11]:3026–3049.)

Evaluation

Lower extremity examination and documentation include inspection of the legs to assess for and document lesions consistent with arterial ischemia. Arterial lesions are primarily located on the toes or distal foot and tend to be painful. Earlier presentation includes loss of hair on the toes and distal ankles. Palpation of pulses in the femoral, popliteal, and dorsalis pedis and posterior tibial distribution allows a gross determination of location of disease. Neuromotor functioning of the foot should be documented in the case of suspected acute or severe ischemia, as viability of the foot is determined not by pulse examination but retention of muscular and neurologic function.

The diagnosis of vascular disease relies heavily on the vascular laboratory. The initial and most important test is the ankle-brachial index (ABI). The ABI is a simple bedside examination that can be performed with a blood pressure cuff and handheld Doppler. It is defined as highest systolic blood pressure measured at the ankle divided by the highest systolic blood pressure measured in the arm (brachial artery).

The majority of the vascular system including retroperitoneal vascular structures can be imaged with high resolution using noninvasive techniques. Multiple radiologic studies can be used to assess the lower extremity arteries including duplex ultrasonography (DUS), computerized tomographic angiography (CTA) or magnetic resonance imaging (MRA), and conventional digital subtraction angiography (DSA). Each has utility in specific situations and should not be used interchangeably. However, DSA is typically reserved for situations when an intervention is planned. Invasive procedures are not commonly used as the initial diagnostic study due to the improvements in resolution and lack of morbidity for noninvasive evaluations.

Management

Lifestyle modification The most important initial management strategies for patients with PAD are smoking cessation and continued ambulation. It has been shown that among patients who are smokers who subsequently stop smoking, the risk of amputation becomes exceedingly low with stabilization of PAD progression and often improvement of walking distance. Also, patients should be encouraged to ambulate with the disease. There is no negative impact of ambulation on the musculature. In fact, ambulation is the first-line treatment for patients suffering from symptomatic PAD where supervised exercise therapy has been systematically shown to have a positive and sustainable improvement in ambulatory distances.

Exercise therapy Marked improvements in walking distances have been demonstrated in virtually all studies

examining exercise therapy with supervised exercise therapy providing consistently increasing walking distances compared to baseline. Exercise therapy is classically performed by having patients walk beyond the onset of pain for as long as they can safely tolerate and repeating a series of walking trials with each session lasting 30 minutes occurring three times a week. Patients should be reassured that walking to and through the onset of pain will not have any adverse effect on their legs or muscles but to the contrary this will promote and increase in walking distance. On average, walking distance can be increased on the order of 50% to 200% with a formal exercise program and in many patients this increase in distance will allow them to accomplish the tasks of daily living that prompted their presentation at the outset.

Pharmacologic Medical management should consist of an antiplatelet agent in conjunction with a statin agent. Antiplatelet agents may be prescribed; however, these agents have known and not insignificant side effects and contraindications. These agents have been variably shown to improve ambulation in patients with claudication; however, the maximal gain in walking distance is marginal compared to exercise therapy.

Interventional PAD treatment using a percutaneous endovascular approach has become the preferred initial treatment for those patients with both lifestyle-limiting claudication and rest pain or tissue loss. The approach is usually from the femoral arteries for both iliac and femoral/tibial lesions. Short focal stenosis responds very well to angioplasty and stenting where as long segment stenosis and occlusions are more challenging to treat and have a reduced patency rate approaching 50% at 6 months. Although generally believed to be less durable than open surgical approaches, the endovascular approach provides a lack of major complications compared to open surgery especially in the frail patient and can be repeated two to three times after the initial revascularization procedure while still maintaining the ability to perform open surgical bypass in the future. This minimally invasive approach has resulted in significant increases in the number of procedures in older patients but has also been associated with a concomitant reduction in number of amputations nationwide. As a geriatrician, however, one must always focus on the goal of care in the patient with rest pain or tissue loss where pain relief, infection treatment, and sustaining or improving ambulatory function are the primary end points.

Open surgical bypass of occluded or stenotic segments still remains the gold standard against which percutaneous interventions are gauged. Bypass of iliac stenosis using aortobifemoral bypass or bypass of the occluded superficial femoral artery or proximal tibial arteries are the most commonly performed procedures to provide pulsatile flow to the distal leg in the setting of ulcerated lesions or gangrene. The downside to open surgical revascularization is the definite risk of mortality and morbidity that accompanies these procedures despite the much more reliable provision of blood flow although contemporary quality databases have demonstrated that patients with advanced age greater than 80, renal failure, chronic obstructive pulmonary disease (COPD) requiring oxygen, and congestive heart failure are additive risk factors, and thus in high-risk patients, amputation may be the preferable option for treatment of pain and infection.

Complications associated with percutaneous intervention include vessel thrombosis, embolization, dissection, and rupture. The majority of these are tolerated due to the severity of the disease being addressed. Acute complications necessitating amputation can occur and the patient should be made aware of the potential for limb loss. Outcomes for percutaneous intervention are improving with patency rates of intervened segments approaching 80% at 2 years for iliac artery stents and 70% at 2 years for superficial femoral artery stents. Aortoiliac revascularization utilizing aortobifemoral bypass has a 90% 5-year patency while femoral popliteal and femoral tibial bypasses have 70% to 80% and 60% to 70% 5-year patency rates, respectively. More importantly, limb salvage is greater than 90% in the majority of patients at 2 years and this is confirmed by large-scale data documenting a reduction in amputation rates in population-based studies.

Knowledge of diagnosis and management of PAD is important for the geriatrician based on a high prevalence of the disease within the older population. A trend toward noninvasive diagnosis and minimally invasive approaches is noted. However, a treatment plan based on knowledge of current treatment paradigms with attention to provider and patient-specific factors should be taken into consideration to achieve optimal treatment outcome.

CAROTID ARTERY STENOSIS

Definition

Proper diagnosis, management, and treatment of carotid stenosis are critically important for reducing risk of ischemic stroke in older patients. Carotid stenosis is defined as atherosclerotic narrowing of the extracranial cervical arterial

circulation primarily located at the bifurcation and extending into the proximal internal carotid artery. The stenosis and subsequent plaque rupture, embolism of plaque fragments or platelet thrombi lead directly to the development of ischemic stroke primarily in the frontal and middle cerebral circulation.

Epidemiology

Stroke and its resultant disability are the third leading cause of death in the United States. In general 80% of strokes are ischemic and 20% hemorrhagic, and of those strokes that are ischemic, 20% to 30% are attributed to atheroembolic disease due to carotid artery stenosis. The presence of asymptomatic carotid artery stenosis of moderate degree is 7.5% and severe stenosis is 3.1% in patients 80 years and older.

Presentation

A complete history is required to definitively classify patients as either symptomatic or asymptomatic as the treatment and aggressiveness of intervention are markedly different. Neurologic symptoms including unilateral weakness, parasthesias, receptive or expressive aphasia, dysarthria, amaurosis fugax (transient unilateral loss of vision), as well as prior history of a documented transient ischemic attack (TIA) or stroke are significant findings to elicit. A clear understanding of the event's time course is key in determining symptomatic status. By definition, patients who experience any of the above symptoms in conjunction with an obstruction of 50% or greater of the corresponding carotid artery are considered symptomatic. Patients with confirmed amaurosis fugax, TIA, or stroke in the past 3 months are at greater risk for stroke. It is also important to note that the following symptoms are not usually associated with carotid stenosis—generalized weakness, vomiting, nausea, vertigo, ataxia, and diplopia.

Evaluation

Recommendations for screening of asymptomatic patients are in constant debate. Multiple societies and current guidelines recommend against the evaluation of the asymptomatic patient. In the case of the older patient, the do no harm imperative becomes even more pronounced, as older patients do not benefit from asymptomatic carotid intervention to the extent that younger patients may in either the immediate postoperative period and in the long term especially in frail patients and those with renal failure. It is generally agreed upon that population screening examinations are not cost-effective for asymptomatic patients and only beneficial in highly selective patient populations such as patients undergoing coronary artery bypass grafting. Screening is not recommended for patients based solely on presence of an AAA, presence of a carotid bruit, or prior head and neck radiotherapy. In contrast, a patient with clear unilateral signs and symptoms of ischemia should undergo imaging of the cervical carotid circulation due to the change in risk-benefit equation that favors intervention based on symptomatic status and long-term survival. The need to ensure long-term survival in patients undergoing intervention should be emphasized with the recognition that the benefit of treatment accrues over time and patients on average should be expected to live 4 to 5 years after treatment (**Table 81-1**).

TABLE 81-1 OUTCOMES AFTER CAROTID ARTERY STENTING IN MEDICARE BENEFICIARIES, 2005 TO 2009

MORTALITY	1 Y	2 Y	3 Y	4 Y
Asymptomatic	6.20%	13.10%	19.80%	27.90%
Symptomatic	10.00%	18.80%	27.10%	36.30%

Table created using data from Jalbert JJ, Nguyen LL, Gerhard-Herman MD, et al. Outcomes after carotid artery stenting in Medicare beneficiaries, 2005 to 2009. JAMA Neurol. 2015;72(3):276–286.

Complete physical examination is important to assess the potential subtle signs of neurologic ischemia. Focused physical examination includes auscultation of heart and detection of potential cardioembolic source from an arrhythmia, palpation of pulses, cranial nerve, and neurologic assessment to include examination of face for unilateral weakness or facial droop, musculoskeletal examination for overall strength and symmetry. Ophthalmic consultation for detection of Hollenhorst plaques may be indicated especially in the setting of amaurosis fugax.

Multiple noninvasive imaging studies can assess the carotid arteries including DUS, CTA, or magnetic resonance angiography (MRA). Invasive conventional DSA is reserved for the rare situation when noninvasive imaging is equivocal or if the patient is in need of an intervention to treat the stenosis utilizing an endovascular approach. Each

modality has utility in specific situations with each able to provide the degree of stenosis and characterization of the plaque's morphology and location. Even though DSA is considered the "gold standard," it is reserved only for questionable or contradictory findings on noninvasive imaging due to its inherent risk of stroke based on previous randomized trials.

DUS is an accurate, reliable, noninvasive imaging modality and is often the initial study to identify patients with disease. The degree of stenosis and plaque morphology of the carotids can be readily assessed but is operator dependent. CTA and MRA use contrast and can provide accurate imaging of the carotid arteries. Both tests are limited by allergic reactions with anaphylaxis or preexisting renal disease. However, both studies are very effective at imaging with high resolution both the cervical and intracranial carotid and vertebral circulation in addition to the brain itself. Both imaging modalities are more expensive than duplex imaging and both suffer from artifact such that an experienced interpretation is needed to accurately assess carotid plaque morphology and stenosis. DSA or catheter-based digital angiography provides excellent images which are easy to interpret regarding degree of stenosis, location, and plaque morphology. Again, it is reserved in patients with conflicting imaging prior to operation with limitations including risk of stroke, cost, and morbidity.

Management

Pharmacologic Initial management of both symptomatic and asymptomatic patients includes maximizing medical therapy with appropriate antiplatelet agents to prevent platelet aggregation and embolization in conjunction with lipid-lowering agents to stabilize the at-risk plaque in the carotid distribution. For patients who smoke, the risk of stroke nearly doubles with continuance and cessation will markedly reduce stroke risk. For the asymptomatic patient, aggressive medical management is thought to be equivalent to invasive intervention and ongoing trials are underway to address this issue. For symptomatic patients, in addition to medical management, the next step is confirming the presence of significant stenosis that would benefit from invasive intervention.

Interventional Once a diagnosis of carotid stenosis is made, several factors are taken into account when considering optimal treatment. One must consider multiple factors before embarking on interventional treatment including whether the stenosis is symptomatic or asymptomatic, degree of stenosis and anatomic ease of intervention, anticipated mortality rate over the upcoming years by assessment of medical comorbidities, and frailty and patient preferences regarding stroke risk reduction in the asymptomatic setting. Generally medical management is advised for low-grade stenoses (< 50%) in both asymptomatic and symptomatic patients. Intervention is recommended in symptomatic patients with more than 70% stenosis and in asymptomatic stenosis with more than 80% stenosis in centers with a track record of excellent outcomes and in patients with an anticipated lifespan exceeding 5 years. In symptomatic patients with 50% to 69% stenosis, risk-benefit analysis should be given careful consideration prior to intervention as studies support intervention, but only in centers that have excellent perioperative outcomes.

CAS via percutaneous approach is an acceptable approach to treating carotid stenosis in selected patients based on specific indications. CAS is less invasive allowing for intervention in poor surgical candidates, especially those with cardiac disease. CAS also allows for angiography, angioplasty, and stent placement all with one procedure. It is indicated in patients with prior neck radiation, prior surgical treatment of the carotid artery or neck lesions, contralateral vocal cord injury, significant coronary artery disease, or congestive heart failure. CAS can be anatomically challenging due to aortic arch anatomy, especially in older adults where calcific lesions and poor arch anatomy due to natural aortic remodeling are present. In addition, significant controversy exists on the benefit and outcomes in octogenarians and older patients as multiple studies have documented increased stroke rates in older patients such that trials to date have excluded this population from inclusion due to poor outcomes compared to younger patients.

Carotid endarterectomy (CEA) is the gold standard operative procedure for treatment of carotid stenosis. It has been shown to reduce stroke risk in multiple well-done randomized trials compared against medical management. For patients with asymptomatic stenosis, CEA is the currently indicated procedure except in select circumstances. A patient with a life expectancy of greater than 5 years should generally—except when there are neck anatomic concerns—be advised to undergo a CEA for asymptomatic disease. Additionally, it is now becoming accepted that CAS in general carries a greater stroke risk compared to CEA. For both CEA and CAS, patients are monitored overnight in the hospital and can be discharged the following day barring any complications or concerns. Antiplatelet agents are generally continued during the perioperative period to inhibit platelet adhesion and embolization as studies have shown decrease in stroke risk with an antiplatelet regimen.

Complications associated with CAS and CEA include stroke, hematoma, and death. CEA is unique in risk for cranial nerves although current studies document a low rate of permanent injury with recovery the norm. As noted above, risk of myocardial infarction is higher with CEA whereas perioperative stroke rates are higher in CAS. Accepted 30-day stroke and death risk is less than 3% for asymptomatic patients and less than 6% for symptomatic patients.

AORTIC ANEURYSM

Definition

AAA is a degenerative disease of the aorta characterized by inflammation and arterial wall degradation that lead to dilatation and possibly rupture. AAA is defined by increase in vessel diameter by more than 50%, generally over 3 cm in men. The majority of AAA remains asymptomatic until which time rupture or less commonly rapid expansion occurs leading to severe and unrelenting abdominal pain radiating to the back or a pulsatile abdominal mass.

Epidemiology

Aortic aneurysms occur 95% of the time in the infrarenal location and in 1% to 3% of subjects depending on the population screening criteria. Men commonly present starting at the age of 65 with women having a noted delay in presentation. This results in a male-to-female ratio of AAA in patients less than 80 years of 2 to 1, whereas in patients greater than 80 years the incidence is equal. Racial differences are present too with Caucasians having a greater than threefold incidence of AAA compared to non-Caucasians.

Pathophysiology

AAA is often thought to be caused by atherosclerosis, but no specific cause and effect has been demonstrated; rather a strong correlation exists. In contrast, some inciting event—generally thought to be smoking since greater than 95% of patients have a smoking history—is believed to trigger an inflammatory state where there is an unchecked proinflammatory process that is present within the media and adventitia of the aortic wall that results in degradation of the wall's structure by matrix metalloproteinases (MMPs). The end result is loss of structural integrity of the aortic wall with dilation and weakening leading to rupture.

Presentation

Multiple studies have now documented that detection of AAA in men over the age of 65 reduces overall AAA mortality and is cost-effective. A thorough history is required in determining a patient's risk for developing an AAA since the patient should ideally have their AAA detected when in the asymptomatic status as the risk of repair is markedly less than in patients with symptomatic unruptured and ruptured AAA. AAA risk factors include advanced age, coronary artery disease, atherosclerosis, high cholesterol, hypertension, first-degree relative affected, and male gender. Risk factors for expansion include advanced age, severe cardiac disease, prior stroke, and tobacco use. Independent risk factors for AAA rupture include female gender, large initial diameter, low forced expiratory volume in 1 second (FEV_1), current smoking, and elevated mean blood pressure. Patients with family history for inherited connective tissue disorders such as Marfan syndrome or Ehlers-Danlos are also at increased risk for developing AAA albeit at younger age.

A complete physical examination is critical to assess overall patient function. Abdominal examination can be difficult especially with extreme obesity and may not reveal a pulsatile mass in the mid abdomen. AAAs over 5 cm can be detected on careful examination 76% of the time, whereas smaller AAAs between 3 and 3.9 cm are only detected 29% of the time thus reinforcing the need for screening examinations. In addition to abdominal examination, femoral and pedal pulses and cardiac and pulmonary examination should be performed at a minimum as these systems are commonly involved with atherosclerosis and end-organ dysfunction from long-term smoking.

Evaluation

Current screening recommendations are to obtain an abdominal ultrasound (US) examination on men over 65 years who have any smoking history or over 55 years with family history. Women should be screened with US at age 65 if there is a family history or smoking history. Currently Medicare offers US screening as part of their Welcome to

Medicare Physical Examination to men who have smoked at least 100 cigarettes over their lifetime or any patient with a family history.

No definitive recommendations exist for surveillance once an AAA is detected. Current common practice for 3.5 to 4.4 cm AAA is to monitor every 12 months and for 4.5 to 5.4 cm AAA every 6 months. For smaller aneurysms in the 2.6- to 3.3-cm range, a 2- to 5-year follow-up is reasonable. The above recommendations are based on an average growth rate of 0.30 cm per year for all aneurysms with smaller aneurysms growing at a lesser rate. Any symptoms potentially related to the aneurysm should prompt a repeat study to ensure absence of rapid expansion as staccato growth of AAA is the norm rather than linear growth.

As noted above, the initial screening study and the preferred method of surveillance is ultrasound. This is a simple, noninvasive, and painless test with no risk to the patient. However, the US is unable to fully image the aneurysm for screening purposes in many obese patients. Alternative modalities include both computed tomography (CT) and magnetic resonance imaging (MRI), which do not require dye to assess the presence of an aneurysm or its size.

Current CT imaging in the form of CT angiography provides excellent detail of the aortic aneurysm in addition to other potential intra-abdominal processes. CT is also more reproducible than US with more consistent measurements between examinations with operator variation removed. Additionally, if performed as an initial scan, CT also allows examination of the entire aorta from aortic root to bifurcation and provides for 3D reconstruction of vessels which is key for planning both open and endovascular intervention. As CT has become more accessible, it is more commonly used to follow patients after intervention but exposes the patient to dye and radiation hence the preference to use DUS whenever feasible. MRI can also be used to evaluate AAA, however due to expense, time, and limited access, MRI should not be first-line imaging for AAA. Its use should be reserved for patients in whom a CT scan is otherwise contraindicated.

Management

Pharmacologic Optimal medical management is directed at controlling comorbidities in patients with AAA. This includes smoking cessation, hypertension control, lipid control, diabetes management, diet and exercise, lifestyle modifications, and regular follow-up with primary care provider. It should be noted that exercise and transient increases in blood pressure are not predictors or causes of rupture and therefore patients with an AAA diagnosis should continue to be active while being surveyed. Standard medical therapy for atherosclerotic occlusive disease should be provided including antiplatelet agents and statin therapy when indicated. Although it would seem β-blockade would reduce vessel stress and thus rupture, this has not been the case and antihypertensive regimens should follow accepted guidelines. Recently new evidence also suggests that small asymptomatic AAA may be amenable to medical therapy by addressing the end effector of aneurysm formation, namely MMP. Doxycycline has been shown both in vitro and in vivo to inhibit MMP activity. Randomized trials are currently ongoing to address this potential intervention.

Interventional The single goal of AAA management is to reduce the chance of AAA rupture. As this is purely a risk-benefit analysis, knowledge of rupture and subsequent death risk at given AAA sizes is necessary to make appropriate recommendations for intervention. The size of the AAA is the major determining factor for risk of rupture and thus the major indicator dictating the timing of an intervention. Less commonly, rapid rate of expansion—generally agreed to be greater than 0.50 cm in 6 months—is an indication for intervention. The risk of rupture correlates directly with size. AAA less than 4 cm having 0% to 0.5% yearly rupture risk, 5 to 6 cm having 3% to 15% yearly rupture risk, and AAA greater than 8 cm having a 50% yearly rupture risk. It is generally accepted that AAA between 5 and 5.5 cm for men and 4.5 and 5 cm for women have a high enough yearly risk for rupture that elective surgical intervention is indicated in good-risk patients. This recommendation is based on current data supporting a mortality risk of AAA repair of approximately 1% to 2% for both endovascular and open aneurysm repair.

Repair of infrarenal AAA is commonly approached by either endovascular or open surgical repair. Now two decades old, the endovascular approach uses femoral artery access for a graft placement under fluoroscopic guidance. Benefits of endovascular repair include less postoperative pain, shorter hospital stay, and lower 30-day mortality. Additionally these benefits allow expansion to candidates who would not tolerate an open procedure. In spite of these immediate perioperative benefits, numerous studies have documented similar quality of life, long-term morbidity and mortality comparing the endovascular to open repair. However, the gain of 6 to 8 weeks of pain-free recovery and similar outcomes leads to utilization of the endovascular approach especially in the geriatric population with 80% to 90% of patients now anatomically suitable for graft placement.

Open repair of an AAA requires either a transperitoneal or retroperitoneal approach, with midline laparotomy

common. Open approach is generally used for patients who do not meet anatomic specifications for endovascular aneurysm repair (EVAR), specifically those with a poor segment of aorta immediately distal to the renal arteries. Thus, the patients undergoing open repair in today's era are generally at more risk than a standard AAA patient due to need for suprarenal clamping and concomitant risk of renal failure and complex anatomic characteristics that preclude endovascular repair. This generally includes renal artery involvement or complex pelvic anatomy that increases the risk of morbidity and mortality.

With proper diagnosis, surveillance, and medical management, patients can be monitored for years without needing surgical repair for their AAA, and with appropriate intervention, patients can have similar life expectancies compared to matched controls (**Table 81-2**).

TABLE 81-2 AAA SURVEILLANCE IMAGING RECOMMENDATIONS[a]

Surveillance imaging at 12-mo intervals is recommended for patients with an AAA of 3.5–4.4 cm in maximum diameter	
Level of recommendation:	Strong
Quality of evidence:	Low
Surveillance imaging at 6-mo intervals is recommended for those patients with an AAA between 4.5 and 5.4 cm in maximum diameter.	
Level of recommendation:	Strong
Quality of evidence:	Low
Follow-up imaging at 3 y is recommended for those patients with an AAA between 3 and 3.4 cm in maximum diameter.	
Level of recommendation:	Strong
Quality of evidence:	Low
Follow-up imaging at 5-y intervals is recommended for patients whose maximum aortic diameter is between 2.6 and 2.9 cm.	
Level of recommendation:	Weak
Quality of evidence:	Low

[a]Optimal frequency of follow-up of a once detected abdominal aortic aneurysm has not been defined by a randomized study, yet reasonable recommendations from the literature and expected growth rates can be made based on natural history studies.

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Chapter 82

Hypertension

Mark A. Supiano

Learning Objectives

- Understand what key age-related physiologic changes account for the progressive increase in the prevalence of hypertension with age.
- Explain the mechanisms for greater blood pressure variability with age, and understand why a hypertension diagnosis should never be based on a single elevated measurement.
- Determine the benefit-based systolic blood pressure (SBP) treatment goal based on age, comorbidities, and cardiovascular risk factors.
- Understand that arterial stiffness is an independent cardiovascular risk factor.
- Select the best thiazide-type diuretic to treat geriatric hypertension.

Key Clinical Points

1. **The prevalence of hypertension increases steadily with age.**
2. **Older people develop systolic hypertension due to the age-related increase in arterial stiffness. Systolic blood pressure and pulse pressure, both closely associated with arterial stiffness, confer the greatest significance as cardiovascular and cerebrovascular risk factors.**
3. **Age-related changes in systems that regulate blood pressure result in greater blood pressure variability. Therefore, careful attention is needed to accurately measure and diagnose hypertension, as well as monitoring for adverse drug events—especially postural hypotension—throughout treatment.**
4. **The diagnosis of hypertension should be based on the average of a minimum of nine blood pressure readings that have been obtained on three separate office visits or derived from 24-hour ambulatory or home blood pressure monitoring results.**
5. **Older hypertensive individuals commonly have physiologic characteristics that respond effectively to lifestyle modifications.**
6. **The focus of therapy should be on lowering the systolic blood pressure to the patient's benefit-based target goal. Applying benefit-based therapy to the majority of adults age 60 to 80 who are at high cardiovascular disease risk would in general favor a systolic blood pressure goal of less than 140 mm Hg, and for some a goal of 120 mm Hg may be considered.**
7. **Thiazide-type diuretic drugs—notably chlorthalidone—are preferred as the initial drug in most patients. Combination therapy with low doses of one or more agents should be considered if needed to control blood pressure below the target level.**
8. **Current blood pressure control rates are inadequate. Systems approaches that incorporate geriatric approaches to team care combined with quality improvement strategies need to be adopted to improve treatment outcomes.**

INTRODUCTION

High blood pressure has the greatest impact on global attributable mortality of any risk factor and accounts for the third leading cause of global burden of disease—64 million disability-adjusted life-years lost. The age-associated increase in blood pressure combined with the worldwide demographic increase in the aging population translates to an enormous emerging public health problem. In addition to the well-ascribed hypertension risk for cardiovascular disease (CVD) and stroke, it is also a significant risk factor for chronic kidney disease, atrial fibrillation, congestive heart failure (CHF) with both reduced and preserved left ventricular ejection fraction, and cognitive impairment—each with a relative risk between 2.0 and 4.0. A reduction of 10 mm Hg systolic and 5 mm Hg diastolic at age 65 is associated with a reduction of up to 25% in myocardial infarction, 40% in stroke, 50% in CHF, and 10% to 20% overall decrease in mortality. Despite this knowledge, current rates of hypertension control are extremely low, especially among older women. In addition to illustrating the clinical importance of hypertension, these data are compelling in a call to improve both our knowledge concerning the mechanisms that underlie the age-associated increase in blood pressure to aid in its prevention as well as to implement changes in the systems of care necessary to improve blood pressure control among those with hypertension.

EPIDEMIOLOGY

Although high blood pressure should not be construed to be a normal aspect of aging, there is clearly an age-associated increase in blood pressure and in the prevalence of hypertension. The National Health and Nutrition epidemiologic surveys have documented that hypertension is a very prevalent condition among older Americans (**Figure 82-1**). Based on this study's definition of hypertension—the average of three readings greater than or equal to 140 mm Hg systolic and/or greater than or equal to 90 mm Hg diastolic or those receiving an antihypertensive medication—the overall prevalence for hypertension among those aged 65 or older exceeds 60%. For women aged 75 and older, the prevalence is 80%. Of note, there is an age-gender interaction in hypertension prevalence across age. At younger ages, prevalence rates are higher among men while above the age of menopause the prevalence in women surpasses that of men.

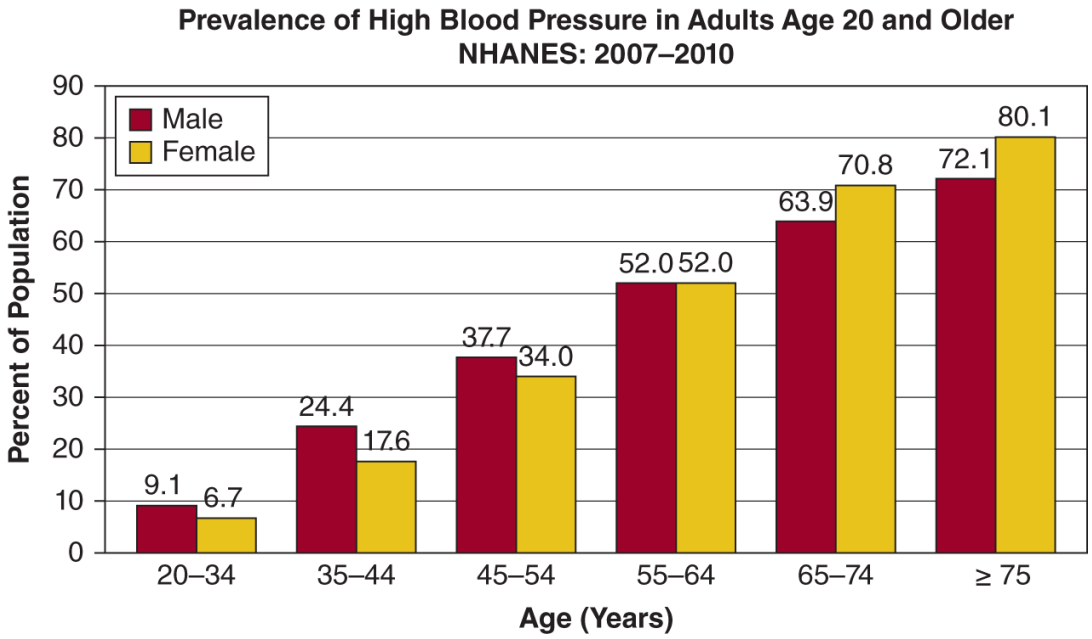


FIGURE 82-1. Prevalence of high blood pressure in adults age 20 and older. NHANES: 2007–2010. (NCHS and NHLBI. Hypertension is defined as SBP 140 mm Hg or DBP 90 mm Hg, taking antihypertensive medication, or being told twice by a physician or other professional that one has hypertension.)

Another perspective on epidemiology is to examine the lifetime risk of developing hypertension as has been done in participants in the Framingham Heart Study. This study identified that among men and women participants who had normal blood pressure readings at age 55, nearly 90% developed hypertension over 20 to 25 years of follow-up.

CLASSIFICATION

Classification schemes that define prehypertension (systolic from 120–139 mm Hg or diastolic from 80–89 mm Hg) and stage 1 (between 140 and 159 mm Hg systolic) and stage 2 (≥ 160 mm Hg systolic) hypertension levels make no adjustment for age. These definitions incorporate evidence that the cardiovascular risks associated with high blood pressure are continuous beginning at a level of 115/75 mm Hg. The definitions also emphasize that SBP is a more important CVD risk factor than diastolic blood pressure (DBP)—especially for individuals older than 50 years. Finally, since isolated diastolic hypertension is so uncommon among older patients, one may correctly classify an older patient's hypertension in almost all cases based entirely on the level of their systolic blood pressure.

PATHOPHYSIOLOGIC CHARACTERISTICS

A single factor is unlikely to explain the cause of essential hypertension regardless of its age of onset. However, a number of age-related changes in physiology have been identified and summarized in **Table 82-1** that likely contribute to the age-associated increase in blood pressure and to the prevalence of hypertension. Lifestyle factors such as obesity, especially central adiposity, being sedentary, and eating a diet high in sodium content are also contributors commonly identified among older individuals.

TABLE 82-1 AGE-RELATED PHYSIOLOGIC CHANGES THAT CONTRIBUTE TO ELEVATED BLOOD PRESSURE

- Arterial stiffness
- Decreased baroreceptor sensitivity
- Increased sympathetic nervous system activity
- Decreased α- and β-adrenergic receptor responsiveness
- Endothelial dysfunction
- Decreased ability to excrete sodium load (sodium sensitivity)
- Low plasma renin activity
- Resistance to insulin's effect on carbohydrate metabolism
- Central adiposity

Homeostatic regulation of blood pressure within its relatively narrow normal range while continuously maintaining adequate cerebral perfusion requires intricate and dynamic coordination of several complex interacting physiologic systems. Under resting conditions, despite age-related physiologic changes that occur in these systems, older individuals experience little difficulty maintaining their blood pressure and cerebral perfusion. However, when this balance is placed at risk by perturbations imposed by the intravascular volume shifts that occur with upright posture or following a meal, or the stimulus of exposure to one or more vasodilating medications, the older patient is less able to adapt and significant declines in blood pressure and inadequate cerebral perfusion may ensue.

Arterial stiffness, especially in the large arteries, is the pathophysiologic characteristic that best exemplifies geriatric hypertension. The age-related increase in arterial stiffness is responsible for the type of hypertension most commonly encountered in older patients, namely, systolic hypertension with high pulse pressure (the difference between systolic and diastolic blood pressure). Moreover, several longitudinal studies have demonstrated that an individual's pulse wave velocity—a marker of arterial stiffness—is a predictor for the subsequent development of hypertension. In addition to age, body mass index and type 2 diabetes, insulin resistance also appears to be independently related to increased arterial stiffness.

Beyond this structural change in the arteries, the regulation of vascular resistance is also affected by age-related changes in the autonomic nervous system and in the vascular endothelium. There is an age-associated decline in the sensitivity of the arterial baroreceptor. This effects the regulation of vascular resistance in two important ways. First, a larger change in blood pressure is required to stimulate the baroreceptor to invoke the appropriate compensatory response in heart rate. This contributes to the age-related increase in blood pressure variability and likely explains the greater prevalence of postural and postprandial hypotension observed in older individuals. Second, the decrease in

baroreceptor sensitivity leads to relatively greater activation of sympathetic nervous system outflow for a given level of blood pressure. An age-associated increase in sympathetic nervous system activity has been demonstrated by higher plasma norepinephrine levels, rates of norepinephrine release derived from tracer kinetic studies, and muscle sympathetic nerve activity. Moreover, in older hypertensive subjects, arterial α-adrenergic receptor responsiveness has been shown to be elevated in relation to their high level of sympathetic nervous system activity possibly contributing to their higher blood pressure.

Regulation of vascular resistance by the vascular endothelium is also changed in relation to age. Endothelial dysfunction demonstrated by a decrease in the production of endothelial-derived nitric oxide has been identified to accompany aging as well as hypertension. Impaired nitric oxide–mediated vasodilation is another potential contributor to the age-related increase in peripheral vascular resistance.

Age-related changes in renal function and in particular in renal regulation of sodium balance may also contribute to an increase in blood pressure. Decreased renal blood flow and glomerular filtration rate impair the aging kidney's ability to excrete a sodium load. These renal changes in the regulation of sodium balance create a tendency for sodium retention. This likely plays a part in the finding that a high proportion of older hypertensive individuals, perhaps as high as two-thirds, are characterized as having salt sensitivity. Salt sensitivity is operationally defined as an increase in mean arterial blood pressure, commonly 5 mm Hg or more, during a high compared to a low dietary sodium intake.

Aging also alters the renin-angiotensin-aldosterone system in ways that may contribute both to elevated blood pressure as well as sodium sensitivity. In general, older hypertensive subjects are characterized by having low levels of plasma renin activity. A direct relationship between plasma aldosterone levels within the physiologic range of normal and the future development of hypertension has been shown in normotensive individuals. Since higher levels of aldosterone have also been linked with central obesity, vascular stiffness, blunting of baroreceptor sensitivity, impaired endothelial function, insulin resistance, and sodium sensitivity, it seems very possible that aldosterone may prove to be a unifying factor that accounts for many of the age-related changes in these physiologic features that also contribute to elevated blood pressure.

Abnormalities in glucose homeostasis and, in particular, resistance to insulin's effects on metabolism are evident with aging as well as in hypertension. Insulin resistance has been grouped together with a constellation of other characteristics—obesity, central adiposity (commonly measured as increased waist circumference), hyperlipidemia, and hypertension—referred to as the metabolic syndrome. Studies that have been careful to control for the confounding factors of obesity, central adiposity, physical inactivity, and hypertension demonstrate that age is not independently associated with insulin resistance. Therefore, although many older hypertensive individuals will be insulin resistant, and many may have impaired glucose tolerance if not meet criteria for type 2 diabetes, an isolated age-related change in insulin resistance appears not to directly contribute to elevated blood pressure in aging.

DIAGNOSTIC EVALUATION

Measurement Considerations

The first and most critical step in the diagnostic evaluation of hypertension among older individuals is the accurate measurement of blood pressure. In addition to the standard measurement instructions dictating cuff size and type of instrument, several factors regarding appropriate blood pressure measurement deserve emphasis. First, as a result of the observation that blood pressure is more variable in older people, the dictum that "hypertension should never be diagnosed on the basis of a single blood pressure measurement" is especially true. Studies have documented that there is considerable overdiagnosis of hypertension among older people. For example, up to one-third of subjects who were receiving antihypertensive therapy when they enrolled in the Systolic Hypertension in the Elderly Program failed to meet entry blood pressure criteria for the study after their medications had been withdrawn. The diagnosis of hypertension should be based on the average of a minimum of nine blood pressure readings that have been obtained on three separate office visits or derived from 24-hour ambulatory or home blood pressure monitoring results.

Second, there is a strong association between arterial stiffness and the presence of an auscultatory gap. For this reason, if the blood pressure cuff is initially not inflated to a pressure above the true systolic pressure but falls within the range of the individual's auscultatory gap, the systolic pressure will be underestimated. One may palpate the systolic pressure by recording the pressure at which the radial artery pulse is first appreciated as the cuff is deflated to ensure that the true systolic pressure is obtained.

Third, while not directly related to the classification of hypertension, another important factor in blood pressure

measurement is to always obtain supine and upright standing readings to determine if there is evidence for an orthostatic or postural decrease in blood pressure. The commonly used definition of postural hypotension is a decrease in systolic blood pressure of 20 mm Hg or more from supine to upright positions within the first several minutes of standing. Elevated supine systolic blood pressure is one of the strongest predictors of postural hypotension. The presence of postural hypotension is an important risk factor for falls and may be exacerbated by almost all antihypertensive medications. Therefore, identifying those patients with postural hypotension at the outset and during therapy is of critical importance.

Fourth, some individuals may have in-office blood pressure readings that are markedly elevated compared with their in-home, self-taken readings, commonly referred to as white coat hypertension. For these individuals, it is worth considering further evaluation with carefully taken home readings using an appropriately calibrated instrument or obtaining 24-hour ambulatory monitoring. The 24-hour blood pressure monitor approach has an added advantage of defining both daytime and nocturnal as well as the overall average blood pressure values. The 24-hour average provides a good measure of the blood pressure load and correlates well with indicators of target organ damage. The circadian blood pressure pattern may also be informative in that individuals who fail to decrease their nocturnal blood pressure by at least 10% relative to their daytime blood pressure, referred to as “nondippers,” have been shown to have greater cardiovascular disease risk compared to those with the normal, dipper pattern.

A final point concerning blood pressure measurement is to emphasize the primacy of systolic over diastolic blood pressure as the pressure that confers the most significance with respect to cardiovascular risk. Moreover, the pulse pressure, the difference between systolic and diastolic pressure, appears to outweigh either systolic or diastolic blood pressure as a cardiovascular risk factor.

Evaluation

Similar to younger patients, more than 90% of older hypertensive patients have essential hypertension. A diagnostic evaluation for secondary and potentially reversible causes of hypertension should be completed following the standard guidelines that have been developed for younger patients. There are several factors that deserve special attention in an older patient population. First, since the majority of hypertension in this population is systolic hypertension, older patients who present with primarily diastolic hypertension merit a careful evaluation with a focus on a renovascular cause. This is especially true for those who present with relatively abrupt onset of diastolic hypertension. Second, older patients are likely to be receiving a number of medications, some of which could be contributing to elevated blood pressure. A complete medication review is warranted to search for medications that may be implicated, for example, corticosteroids and nonsteroidal anti-inflammatory drugs including COX-2 inhibitors. Third, the prevalence of sleep apnea among older patients with hypertension is high and may be an important pathophysiologic explanation for their elevated blood pressure. Fourth, although the incidence of pheochromocytoma is rare, there is a suggestion from an autopsy study that the incidence of this condition increases with increasing age.

Target Organ Damage and Risk Factor Assessment

The evaluation should also include a determination of target organ damage, a cardiovascular risk factor assessment, and identification of comorbid conditions that may impact antihypertensive drug selection. Determining the extent of hypertension-related target organ damage may be complicated by the confounding effects of concurrent age- or disease-related changes. It is important to assess whether the patient has evidence of renal impairment, proteinuria, hypertensive retinopathy, electrocardiographic abnormalities, or left ventricular hypertrophy. An assessment of overall cardiovascular risk—smoking history, alcohol intake, dietary salt and fat intake, and level of physical activity—should also be completed. Older patients presenting with hypertension are likely to have other conditions included among a group of abnormalities described collectively as the metabolic syndrome. Therefore, it is important to consider the coexistence of abdominal obesity; insulin resistance, impaired glucose tolerance, or overt type 2 diabetes; and hyperlipidemia and incorporate screening for these conditions into the diagnostic evaluation. Finally, the presence of other comorbid conditions (eg, dementia, chronic kidney disease, chronic obstructive pulmonary disease [COPD]) and comorbidities such as frailty may influence antihypertensive medication selection as well as an individual’s blood pressure target goal.

APPROACH TO TREATMENT

Treatment Effectiveness

Results from meta-analyses of numerous placebo-controlled randomized clinical trials that have been conducted in older hypertensive patients have confirmed that significant reductions in cardiovascular and cerebrovascular morbidity and mortality occur with antihypertensive therapy and that the treatments are also safe. Active treatment leads on average to a 12% to 25% decrease in the rate of death, a 35% reduction in stroke, and a 25% reduction in myocardial infarction in addition to significant decreases in the development of chronic kidney disease and congestive heart failure. Treatment may also be associated with a decreased rate in the development of dementia. Depending on the individual group's additional cardiovascular risk factors and assuming a 12 mm Hg decrease in systolic blood pressure for 10 years, between 9 (the highest risk group) and 81 (lowest risk group) patients would need to be treated to prevent one death. For these reasons, there is a clear consensus that treating hypertension in older patients is safe and effective.

Therapeutic Goals and Monitoring

In accordance with general geriatric principles, it is important to establish individualized patient treatment goals utilizing therapies that are least likely to produce adverse side effects or have a negative impact on quality of life. The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (also known as JNC-8) recommended a goal BP of less than 150/90 mmHg for patients between the ages of 60 and 80—a deviation from the SBP target level of less than 140 mm Hg that was previously recommended. However, significant controversy surrounds this recommendation. A dissenting minority opinion from this group argued for maintaining this goal below 140 mm Hg. Applying benefit-based therapy to adults age 60 and older with systolic hypertension who are at high CVD risk is one of the points emphasized by this group in support of their view that the appropriate SBP goal for this group should remain below 140 mm Hg. In addition, the JNC-8 recommendation is at odds with target goals published in clinical guidelines from many other organizations. The inherent complexity and heterogeneity of older adults with multiple comorbidities that may include cognitive impairment and frailty who also have elevated SBP likely explains why it is proving to be so challenging to apply "one size fits all" treat-to-target therapy to this population.

The optimal SBP treatment goal for patients older than 80 years was not addressed in detail in the JNC-8 recommendations. Prior to the completion of the Hypertension in the Very Elderly Trial (HYVET) in 2007, very few subjects aged 80 or older had been included in the controlled clinical trials of hypertension treatment. The HYVET study recruited 3845 hypertensive individuals aged 80 and older and randomized them to receive either active treatment with a target SBP goal of less than 150 mm Hg (a thiazide diuretic plus an angiotensin-converting enzyme [ACE] inhibitor if needed) or a placebo and followed outcomes (stroke and mortality rates were the primary outcomes) for 5 years. The HYVET study's Data Safety Monitoring Board ended the study early when an unexpected significant —21% reduction—in overall mortality in the active treatment group was identified. In the intention-to-treat analysis, the treatment group also had a 30% reduction in fatal and nonfatal stroke, and a 64% decrease in the rate of congestive heart failure. Moreover, active treatment was associated with fewer adverse events than placebo. While this trial's results clearly demonstrate the beneficial effects of antihypertensive therapy in patients 80 years and older, it is important to emphasize that its results may not generalize to older patients who would not have met the study's entry criteria. For example, the trial excluded those with dementia, who had an inability to walk or who resided in nursing homes. With that being said, the distribution of frailty among the HYVET subjects determined from a deficit accumulation approach has been found to be very similar to that of comparably aged community-based populations. Moreover, both frail and nonfrail HYVET subject groups benefited from active treatment. Finally, results from an open-label extension study in which placebo subjects switched to active treatment demonstrated that the prior-placebo group achieved the same reduction in stroke by 12 months, suggesting that the time to treatment benefit in this age group is relatively short.

The most common treatment-related adverse side effect, shared by all antihypertensive medications, is the development of postural hypotension. Patients may present with atypical symptoms such as generalized weakness or fatigue rather than noting postural light-headedness or dizziness. For this reason, it is important not to treat blood pressure too aggressively and also to always determine supine and upright blood pressure measurements during monitoring of all older patients. If a patient's seated systolic blood pressure cannot be lowered to below 140 mm Hg without the development of postural hypotension, it is prudent to consider modifying that patient's target blood pressure goal to instead focus on their standing blood pressure. This may be more important from an overall perspective to minimize the patient's fall risk.

When patients present with markedly elevated blood pressures in the absence of a true hypertensive emergency

(eg, signs of target organ damage, hypertensive encephalopathy, intracranial hemorrhage, acute heart failure with pulmonary edema, dissecting aortic aneurysm, or unstable angina), it is not necessary and may in fact be deleterious to reduce blood pressure to normal values too rapidly. Setting an intermediate treatment goal of 160 mm Hg may be appropriate for these patients. Dosage adjustments or additions of new therapies should be made gradually over time to avoid overtreatment. Similarly, once patients have reached their therapeutic target and have been maintained on stable therapy, their need for continued treatment should be periodically reassessed. Many patients will tolerate a dosage reduction or medication discontinuation during a carefully monitored withdrawal period, especially if they have been successful in achieving lifestyle modifications.

Lifestyle Modifications

Based on the physiologic profile of the typical older hypertensive patient described in the preceding section—overweight, sedentary, and salt-sensitive—lifestyle modifications directed toward these characteristics would be predicted to be especially efficacious. Additional reasons to focus attention on lifestyle modification are that they will be adjunctive if medications are also needed, will lead to improvements in other cardiovascular risk factors (eg, lipids), are associated with other salutary outcomes (notably exercise), and are associated with minimal adverse effects. For patients with stage 1 hypertension (systolic levels between 140 and 160 mm Hg) who do not have diabetes, a 6-month treatment intervention with appropriate lifestyle modifications is the recommended first step in the treatment algorithm. Randomized controlled trials of multifactorial lifestyle interventions have been conducted and demonstrated the benefit in blood pressure reduction that is achieved as well as sustained in the intervention groups. A meta-analysis of 105 such trails (although few were directed solely to older subjects), demonstrated the overall benefits of weight reduction, aerobic exercise, and decreased intake of sodium and alcohol. Each of these modifications was associated on average with a 5 mm Hg reduction in systolic blood pressure, comparable to the reduction achieved with a single antihypertensive medication.

The Trial of Nonpharmacologic Intervention in the Elderly (TONE) targeted the effect of dietary sodium restriction and weight loss in older hypertensive patients. In this study, the intervention led to fairly modest declines in dietary sodium intake (average of 40 mmol/day) and body weight (average 4 kg), but there was a 30% decrease in the need to reinitiate antihypertensive therapy among the intervention group.

Pharmacologic Therapies

Overview Currently available evidence supports two general principles with respect to antihypertensive medication selection: one, that the level of blood pressure reduction achieved is more important than which drug is used, and two, that all classes of antihypertensive medications have been demonstrated to be equally efficacious in older patients. Following these principles, the initial antihypertensive drug selection should be based on patient-specific factors. For example, drug selection will depend on whether the patient's hypertension is simple or complicated by another comorbid condition. The presence of a coexisting condition will often dictate the optimal medication (eg, an ACE inhibitor for patients with type 2 diabetes or CHF). Beyond these factors, medications that are least likely to produce adverse effects should receive first priority. For this reason, as a general statement, centrally acting antihypertensive medications and direct vasodilators are best avoided in older hypertensive patients due respectively to concerns regarding central nervous system sedating effects and their association with marked postural hypotension. In addition, attention should be paid to selecting a once-daily medication to promote adherence and to avoiding any medication interactions with the patient's other medications.

The 2014 JNC-8 guidelines modify the previously recommended approach to initial antihypertensive therapy for patients older than 60 years. Instead of suggesting that the initial drug be a thiazide-type diuretic, its recommendation is to select a drug from one of four general classes—ACE inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic. General treatment recommendations for stage 1 hypertension are summarized in **Table 82-2**. For patients with stage 1 hypertension in whom a 6-month lifestyle modification intervention strategy has failed to lower blood pressure to the goal level, a thiazide-type diuretic is the most commonly recommended initial medication. Patients who present with stage 2 hypertension will almost certainly require at least two drugs to control their blood pressure—consequently, two antihypertensives should be begun at the outset. Most often one of these two is a thiazide-type diuretic with the second agent selected either on compelling indications or on the basis of synergy with the initial agent (eg, combined with ACE inhibitor). It should be noted that regardless of the drug choice, in general the starting dose should be reduced in older patients and dosage titration be carried out gradually.

TABLE 82-2 ■ GENERAL TREATMENT RECOMMENDATIONS FOR STAGE 1 HYPERTENSION

- Begin with nonpharmacologic lifestyle modifications—weight loss, exercise, salt restriction for 6-mo period.
- Focus treatment goal on systolic blood pressure reduction to below 140 mm Hg.
- If target blood pressure is not met, consider low-dose thiazide-type diuretic—typically chlortalidone—as initial drug selection.
- Base alternative drug selection on individual patient characteristics.
- Consider combination of low doses of one or more agents if goal blood pressure not met with a single drug.
- When initiating drug therapy, begin at half of the usual dose, increase dose slowly, and continue nonpharmacologic therapies.
- Aggressive therapy is not appropriate if adverse side effects (eg, postural hypotension) cannot be avoided.

There are three additional general considerations to be made before a brief review of each of the major antihypertensive classes. (1) β-Receptor antagonists are not recommended as an appropriate choice for the initial antihypertensive drug, especially among older patients. Results from a meta-analysis concluded that unless there is a compelling indication for their use, β-blockers should not be considered as a first-line antihypertensive agent in older (60 years and older) patients. Whereas β-blockers were found to be equally efficacious in younger patient populations, this was not the case among the older population in whom compared with other agents, β-blocker therapy was associated with an increased risk of a composite outcome of death, stroke, or myocardial infarction. (2) Patient-specific factors that directly impact adherence also need to be taken into account. For example, thiazide diuretics are considered to be first-line agents, but persistence rates with their continued use are lower than with angiotensin receptor blockers. As with any prescribed medication, cost, simplicity of the regimen, and absence of side effects are important factors impacting rates of adherence. (3) Especially for stage 2 patients, currently available data are suggesting that prescribing a fixed and especially low-dose combination capsules may be associated with improved outcomes. Although the concept of a single multiple-medication capsule seems to contradict the general geriatric principle of avoiding polypharmacy, there appear to be benefits to this approach both with respect to improved efficacy and lower rates of side effects. This evidence suggests that it may be preferable to add a second agent in lower dose rather than titrating up the dosage of the first medication if a patient is not at target blood pressure in response to the starting dose of the first agent.

Diuretics **Table 82-3** summarizes the advantages and disadvantages for each of the major drug classes from the geriatric patient perspective. There are several reasons why thiazide-type diuretics are considered to be the preferred initial antihypertensive agent for most older patients. The primary pathophysiologic explanation is that diuretic therapy has been noted to reduce systolic blood pressure to a greater extent than diastolic blood pressure, and also achieves greater reductions in systolic pressure relative to other antihypertensive agents. Moreover, the majority of large-scale randomized controlled trials have utilized a thiazide-type diuretic in the treatment arm and there exist an abundance of outcome data demonstrating their therapeutic effectiveness in older hypertensive populations. Additional benefits include low cost, once-daily dosing, and a favorable side effect profile. The most common adverse drug events are metabolic abnormalities, especially hypokalemia, as well as hyperuricemia and impaired glucose intolerance; and urinary frequency or incontinence. However, these side effects are quite uncommon at lower doses. Within the thiazide diuretic class, chlorthalidone is the recommended medication. In addition to evidence of its efficacy from many randomized controlled trials, it has greater potency and a longer half-life than hydrochlorothiazide. When equipotent doses are compared, the incidence of hypokalemia is comparable. Finally, there is good synergy with most of the other commonly used medications, such that adding a second drug if needed to a thiazide-type diuretic is a reasonable approach.

TABLE 82-3 ■ ADVANTAGES AND DISADVANTAGES OF ANTIHYPERTENSIVE MEDICATION CLASSES SPECIFIC TO OLDER PATIENTS

ANTIHYPERTENSIVE CLASS	POTENTIAL ADVANTAGES	POTENTIAL DISADVANTAGES	CLINICAL SITUATIONS TO RECOMMEND USE	CLINICAL SITUATIONS TO RECOMMEND AGAINST USE, OR WHICH REQUIRE MONITORING
Thiazide-type diuretics	• Documented benefit in	• Metabolic	• Systolic hypertension	• Hyponatremia

	clinical trials • Produce greater reduction in systolic than diastolic blood pressure • Improve bone mineral density • Inexpensive	abnormalities (eg, hypokalemia) • Urinary frequency		• Gout
ACE inhibitors and angiotensin receptor blockers	• Absence of CNS effects • Preservation of renal function • Decrease proteinuria	• Hyperkalemia, cough	• CHF, type 2 diabetes	• Renal insufficiency or renal artery stenosis
Calcium channel antagonists	• Benefit documented in clinical trials • Absence of CNS or metabolic effects	• Peripheral edema, constipation, heart block	• Systolic hypertension • Coronary artery disease	• Left ventricular dysfunction
β-Adrenergic receptor antagonists	• Not recommended as monotherapy	• May increase peripheral vascular resistance • Metabolic abnormalities • CNS effects	• Postmyocardial infarction	• COPD, peripheral vascular disease, heart block, glucose intolerance, type 2 diabetes, hyperlipidemia, depression
α-Adrenergic receptor antagonists	• Improve urinary symptoms in BPH	• Increased rate of CHF hospitalizations as monotherapy relative to thiazide-type diuretics	• Prostatism	• Left ventricular dysfunction

ACE, angiotensin-converting enzyme; BPH, benign prostatic hypertrophy; CHF, congestive heart failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease.

Nonthiazide-type diuretics have been less well studied. Owing to the similarities observed between the physiologic effects of aldosterone and the age-related contributors to elevated blood pressure listed in **Table 82-1**, aldosterone receptor blockers (spironolactone or eplerenone) are other alternatives to consider.

Angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists ACE inhibitor agents and angiotensin receptor antagonists are choices for initial therapy or as second agents in combination with a thiazide-type diuretic. Their advantages include the absence of central nervous system or metabolic side effects and overall favorable side effect profile. They are also often used owing to the recommendations for their use in the setting of coexisting type 2 diabetes or systolic dysfunction. Another consideration favoring the use of these agents is the evidence that their use is associated with preservation of renal function and decreases in proteinuria in several clinical conditions.

Calcium channel antagonists All three chemical classes of calcium channel antagonists have been shown to be effective in treating older hypertensive patients. Their mechanism of action—decreased peripheral vascular resistance—and lack of significant central nervous system or metabolic side effects provide a good match with the characteristics of the geriatric patient. Age-related changes in the pharmacokinetics of these drugs (decreased clearance and increased plasma levels) mean that lower doses need to be used in older patients. The longer-acting agents in the dihydropyridine class of calcium channel antagonists have been the most widely studied in randomized controlled trials where their effectiveness in treating older patient populations has been demonstrated.

Adrenergic receptor antagonists As discussed previously, β-receptor antagonists are not an appropriate choice for

monotherapy for older patients with uncomplicated hypertension. β-Receptor antagonists should be reserved for patients with a compelling indication for their use, namely, as secondary prevention for those patients who have had prior myocardial infarction or have coronary artery disease or in some patients with systolic dysfunction.

Several observations have limited the adoption of α_1-receptor antagonists as first-line treatment for older hypertensive patients. In addition to their predilection to produce postural hypotension, subjects who received an α_1-receptor antagonist as monotherapy in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) were found to have a twofold higher risk of being hospitalized for heart failure relative to the subjects randomized to the diuretic arm of the study. Based on these observations, α_1-receptor antagonist therapy should be considered for use as monotherapy only in men in whom their use may be beneficial for symptoms related to benign prostatic hypertrophy, or in combination with another antihypertensive agent.

Barriers to Improving Blood Pressure Control

Since there is no cure for this chronic condition, effective treatment of hypertension requires a lifelong commitment to its management. For this reason, an approach that engages and sustains the patient's motivation and adherence over time is needed. Several methods may be recommended to promote the patient's efforts such as providing patient education materials appropriate for the patient's health literacy level, clear instructions for diet and exercise lifestyle recommendations, and prescribing once-daily medications to facilitate adherence. Some patients may benefit from the feedback and engagement that accompany home or self-taken blood pressure monitoring, although the effectiveness of this approach has not been proven. Another patient factor is the likelihood that the older hypertensive patient will have two or more additional chronic conditions. The complexity imposed by concurrently managing these comorbid conditions becomes extremely challenging. This is especially the case when treating a frail older individual when it is not clear how to best prioritize which of several guidelines should take precedence or for that matter if the guideline is still applicable to the patient's clinical situation.

In addition to these patient-specific factors, a number of barriers have been identified in the health care system that may impede progress in achieving better success in blood pressure control rates in the older population. The underdetection, undertreatment, and inadequate control of hypertension, especially among older patients, are well documented. Some of these system factors are limited access, lack of a team approach to care, constraints imposed by limited patient visit times, and the reimbursement system. Physician factors—the failure to modify treatment when the patient's target blood pressure goal has not been achieved—also contribute to this situation. Results from the TONE study demonstrated for example that there is systematic underutilization of the recommended thiazide-type diuretic among hypertensive patient populations. Moreover, many physicians overestimate their compliance with guidelines as well as the proportion of their patient populations who have blood pressure levels below their target. However, solely providing education appears not to be an effective solution to changing physician behavior in this regard. The Assessing Care in the Older Vulnerable Elders (ACOVE) project has demonstrated that hypertension is one of many conditions for which quality indicators are not being met in this patient population. However, some quality improvement strategies have been demonstrated to be effective in improving hypertension management. The most effective strategies in this regard have involved a multidisciplinary team approach (assigning a nonphysician member of the team to assume responsibility for management), home blood pressure monitoring, and patient education. Thus, it appears that incorporating a geriatrics approach to hypertension management in the context of a quality improvement program is one effective way to eliminate some of the barriers to improving hypertension control in older patient populations.

UNANSWERED QUESTIONS AND FUTURE RESEARCH DIRECTIONS

Future research directions should target our understanding of the mechanisms underlying the age-associated increase in blood pressure, with important implications for prevention and management. For example, it seems clear that understanding the predictors and modifiers of vascular stiffness is of critical importance in preventing the age-associated development of hypertension. Similarly, although none of the currently available antihypertensive agents specifically targets vascular stiffness, future advances in drug development aimed at preventing hypertension will likely address decreasing vascular stiffness as a mechanism of action.

Balancing the competing risks between the SBP-related risk of stroke, heart failure, and other cardiovascular events and the treatment-related risks, including adverse medication events, falls, and fall-related injuries, in a patient-centered approach remains a challenge that merits further research. Recently published results from the Systolic Blood

Pressure Intervention Trial (SPRINT) which compared usual (< 140 mm Hg) with intensive (< 120 mm Hg) SBP targets (ClinicalTrials.gov, NCT01206062) suggest that a lower SBP target may be recommended for some patients with high CVD risk. SPRINT included 2,636 community living subjects aged 75 and older (28% of the entire study population) who were assessed for frailty status including usual gait speed, orthostatic hypotension, adverse events including injurious falls and nursing home placement, and, in the SPRINT-MIND subset, comprehensive cognitive evaluations and brain imaging. In the group of older subjects randomized to the intensive arm there was a 34% reduction in the primary composite CVD outcome and a 33% reduction in all-cause mortality at 3.14 years of follow-up when the trial ended early due to its highly positive outcome (numbers needed to treat 27 and 41, respectively). These results did not differ for the most frail subgroup nor for those with impaired gait speed. While some adverse events were higher in the intensive group, there was no difference observed in serious adverse events including injurious falls and also no group difference in self-assessed health related quality of life regardless of frailty status. Additional information will be forthcoming from SPRINT – most notably the cognitive and brain imaging results – and future updates to clinical guidelines will no doubt recommend how the SPRINT data should be applied to establishing SBP treatment goals in clinical practice.

Finally, additional investigation will aim to elucidate why hypertension is a significant risk factor for cognitive impairment. Based on the results from several studies suggesting that antihypertensive therapy may help to prevent cognitive decline and decrease the incidence rate for dementia, controlling blood pressure may also confer beneficial effects in preserving cognitive function with aging. The interactions between elevated blood pressure, insulin resistance, and other aspects of the metabolic syndrome and cognitive function will be another area for future investigation.

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Chapter 83

Aging of the Respiratory System

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Learning Objectives

- Identify changes in lung physiology that occur with age and contrast those due to environmental influences.
- Differentiate chronic obstructive pulmonary disease (COPD) and asthma in older adults.

Key Clinical Points

1. **Age-related changes within alveoli account for "senile emphysema" characterized by alveolar dilatation without destructive changes to the alveolar walls. This causes reduced lung recoil, and increases dead space impairing gas exchange.**
2. **The mean maximal inspiratory pressure (MIP) is associated with decreased handgrip strength, lower body mass index, and current smoking status; for healthy 85-year-old men, it is approximately 30% lower than that of 65-year-old men.**
3. **Though total lung capacity (TLC), made up of the two components of vital capacity (VC) and residual volume (RV), does not change with age, age-related changes in lung physiology, bone, and muscle result in decreased VC with a corresponding increase in RV as measured by standard spirometry.**
4. **Aging results in a loss in forced expiratory volume in 1 second (FEV_1) of about one-third liter per decade, and the decline in FEV_1 with aging is greater than the decline in total forced vital capacity (FVC). Since FEV_1/FVC values below 0.65 are typically indicative of airway obstruction, this parameter may overestimate obstructive disease in extreme old age.**

INTRODUCTION

It is imperative to understand the changes that occur in the respiratory system with age because many disease processes have a direct correlation with age-related changes in respiratory physiology. Intrinsic aging alone produces changes, but there are also consequences of lifetime accumulation of insults by environmental factors and recovery from such insults. Cigarette smoke, accounting for the greatest population impact on the respiratory system, produces effects similar to aging and this is reflected in disease processes such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). The term "accelerated aging" is often encountered in studies of these chronic diseases in older adults so we try here to describe the changes in the respiratory system that occur in a healthy, nonsmoking individual as a result of age and compare them with the changes indicative of chronic diseases in older adults. This chapter deals with changes in (1) structure of the lung and chest wall, (2) lung volumes and lung capacities, and (3) respiratory mechanics. We further compare and contrast the features of normal aging, COPD, and

IPF to better understand the similarities and dissimilarities. Lastly, we address one of the most commonly encountered clinical dilemmas: attempting to differentiate COPD and asthma at the bedside; thus the chapter ends with a discussion on interpretation of spirometry results at baseline and with pharmacologic intervention in order to differentiate these diseases.

STRUCTURAL CHANGES

Structural changes associated with age occur most notably in the alveoli rather than the large airways. Alveoli are where gas exchange takes place. All the environmental lung insults accumulated over a lifetime affect the alveoli and change their structure. For example, alveoli lose their elastic recoil and enlarge with age, a phenomenon referred to as "senile emphysema." Unlike what occurs in other pathologic processes, "senile emphysema" results in alveolar dilatation without any destructive changes to the alveolar walls. Moreover, there is no reduction in the production of elastin, collagen, or surfactant. These characteristics lead us to believe that the increase in surface area is probably a result of changes to the structures surrounding the alveoli that accumulate over time, and result in reduced surface tension forces on the alveolar walls and in turn reduced lung recoil.

The next important change in lung function with age is attributed to the chest wall rather than the lung itself. The lungs are suspended within the chest wall which plays a crucial role in maintaining function. As noted in other chapters within this text, structural changes to bone are a common phenomenon of aging. Calcification of the articulating surfaces of the ribs and ossification of the cartilage make the chest wall stiffer. The vertebrae are also affected by a loss of intervertebral space and a compression of the vertebral bodies resulting in reduced vertebral height. These changes modify the shape of the thorax and result in kyphosis and a barrel-shaped chest. Such reshaping affects the outward force needed to keep the lung in shape during respiration and the next section addresses how spirometry readings reflect these changes.

Aging also affects muscle strength throughout the body, and the respiratory muscles are not spared. Expiration is largely a passive process, while inspiration depends mostly on the diaphragm. Compared to young adults, healthy older persons have approximately 25% lower diaphragmatic strength. Due to the age-related decline in muscle strength, there is a decline in the maximum inspiratory and expiratory pressures in the normal population. Further, as a result of the changes in the chest wall there is also an increased load on accessory muscles of respiration. The vital capacity is reduced when the diaphragm is weak and expiratory muscles of the abdomen and thorax cannot fully compensate to empty the lungs before reaching the resting respiratory position. Respiratory muscle strength is higher in men, but declines with age in both sexes. The mean MIP for healthy 85-year-old men is approximately 30% lower than that for 65-year-old men. A lower MIP is associated with many factors, including decreased handgrip strength, lower body mass index, and current smoking. A low MIP often causes a low functional vital capacity.

LUNG VOLUMES AND LUNG CAPACITIES

Total lung capacity (TLC) is the volume of air within the respiratory system when a subject makes a maximal voluntary inspiratory effort. It is a sum of RV, the volume of air remaining in the lungs when subjects have exhaled as much air as possible, and VC, the amount of air that a person can slowly exhale after inhaling maximally. TLC is determined by the balance of forces between the maximally activated inspiratory muscles and the elastic recoil of the lung and chest wall. As we discussed, the elastic recoil of lung tissue decreases with aging, which makes it easier for the lungs to expand with less effort, increasing TLC. However, the increased stiffness of the chest wall and the loss of motor power together decrease TLC. Thus, the two together result in an almost unchanged TLC with age.

Because lung recoil decreases with age and the muscles that oppose outward chest wall recoil weaken, RV and the ratio of RV to TLC increase from young adulthood to older age. Collapse of the alveoli with aging, which results in air trapping, also contributes to the increase in RV. Abnormally high RV/TLC is called hyperinflation, which can often be seen on a chest x-ray, and occurs with both asthma and COPD as well as advanced age. Because TLC is relatively constant while RV increases with age, the VC decreases with age.

Functional residual capacity (FRC) is the volume of air left at the end of normal respiration. This again is determined by the opposing factors of lung recoil and chest wall compliance. The increase in FRC with age, roughly 1% to 3% per decade, is a direct result of losing more lung recoil than chest wall compliance at the end of normal tidal expiration. Both FRC and RV increase with age, but RV increases more than FRC.

Expiratory reserve volume (ERV) is the difference between RV and FRC. Both FRC and RV increase with age, as discussed above, but RV increases more than FRC. With aging, expiratory airflow is impaired, and air is often trapped in the dependent alveoli. This is due to changes in the pressure dynamics across alveolar openings discussed earlier. Thus, there is a reduction in ERV over the normal process of aging.

Spirometry is easily performed on 9 of 10 older adults and measures dynamic lung function. Modern office spirometers use a flow sensor, connected to a microprocessor that determines the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC from the best maneuver, as well as the predicted values. FEV_1 is the most important value, representing the volume of air (in liters) exhaled during the first second. Guidelines for spirometry methods and instrument accuracy are available from the American Thoracic Society.

The presence of airways obstruction is indicated by a low FEV_1/FVC ratio and visualized on the flow-volume (F-V) curve as concavity toward the volume axis or tail at the end of the maneuver. The descending limb of the F-V curve of healthy young adults is a straight line at about a 45 degree angle until the end of the maneuver (shaped like a sail), corresponding to exponential emptying of the lungs. The shape of the F-V curve becomes progressively more curvilinear as a healthy adult becomes older, corresponding to decreases in expiratory flows at low lung volumes. The reduced flow at low lung volumes, even in healthy older adults, is a result of a decrease in the mean diameter of small airways.

Adults normally experience a loss in FEV_1 of about one-third liter per decade. The decline in FEV_1 with aging is greater than the decline in FVC, so that the FEV_1/FVC also declines with age. Values below 0.65 usually indicate airway obstruction in patients aged 65 years and older.

Many nonpulmonary factors contribute to the decline in the FEV_1 in older adult persons. The strongest factors are cigarette smoking; a diagnosis of COPD or asthma; workplace exposure to dust, chemicals, or smoke; and wheezing symptoms—all of which are known to cause airway obstruction (a low FEV_1/FVC ratio). The inability to take a deep breath (restriction) also reduces the FEV_1, a symptom seen in obesity, malnutrition, heart disease, and chest wall abnormalities. Lung volume restrictions can also be associated with ECG abnormalities, pitting angle edema, diabetes and past history of chest surgery. Further, for a given height, gender, and age, the FVC and FEV_1 of healthy older African Americans is approximately 12% lower than that of healthy older Caucasians, thus spirometry reference equations, which are race/ethnicity specific (as from the NHANES III study), are used to calculate predicted values. Since spirometry tests require athletic-type breathing maneuvers, poorly trained technologists in outpatient settings often do not obtain maximal patient effort during one or more of the three phases of the maneuver, causing misclassification of the results.

It is also important to note that maximal expiratory flow, as seen during spirometry tests, varies as a function of lung volume because higher flows are possible at a higher lung volume. For forced exhalation beginning from a deep inhalation (the first phase of a spirometry maneuver), the initial (peak) flow (phase 2) is determined by the recoil of the lung and chest wall and the degree of effort expended by the patient, as well as by the speed with which the patient's respiratory muscles can generate positive pleural pressure. Once maximal flow is achieved, maximal flow throughout the remainder of the VC (phase 3) is determined by the intrinsic properties of the lung.

Another important change to be studied in aging is the effect on closing volume (CV). It is measured at the point where basal airways close during normal expiration and is determined as the volume of gas that can be exhaled starting from the point of sharp change in alveolar concentration of the tracer gas after the alveolar plateau. This volume combined with RV from closing capacity (CC), which increases linearly with age from approximately 10% of TLC in young adults to approximately 30% of TLC by the age of 70. Increased CV is likely a result of reduced elastic recoil in the lung, which results in the collapse of the small airways.

RESPIRATORY MECHANICS

The ventilation of a respiratory zone must match its perfusion (V/Q matching) for optimal gas exchange. However, even in normal conditions, the ventilation of lung is not uniform and there is increased perfusion of the base of the lung, resulting in a low V/Q ratio in the sitting position. This difference is not significant enough to cause a disturbance in gas exchange under normal conditions.

This equilibrium is even more disturbed in aging. As discussed, the increased rigidity of the chest walls combined with reduced elastic recoil of the lung leads to an airflow limitation. This is seen as a decreased FEV_1/FVC, increased FRC, increased CV and increased RV. All of this combines and further reduces the ventilation at the bases of the lungs in comparison to perfusion, resulting in a much lower V/Q ratio in older adults. The lungs, however, are still

capable of a large physiologic reserve and therefore these changes are not evident in older adults unless they are affected by a pathologic process.

Curiously enough, there are also areas with an increased V/Q ratio in older adults due to the changes in perfusion of the lung. Under normal conditions, the area where such a mismatch happens is minimal. They have impaired clearance of CO_2 and are called "alveolar dead spaces," one of the components of physiologic dead space. This reduced perfusion results in an increased $PaCO_2$ (arterial partial pressure of carbon dioxide) and is thus an alternate form of peripheral alveolar hypoventilation.

With age, there is an increase in the pulmonary vascular resistance and decline in the density of lung capillaries. These changes result in increased pulmonary vascular pressure with aging, causing a heterogeneous pattern of lung perfusion with reduced flow to some areas that exhibit an increased V/Q ratio. Lung perfusion can also be reduced with aging because of lower cardiac output.

Reduction in lung capillary density, along with the reduction in the alveolar surface area leads to decline in other measurable lung functions, for example, the diffusion lung capacity for carbon monoxide (DLCO). DLCO is the amount of carbon monoxide (from a test gas containing 0.3% CO) that is absorbed into the blood during a 10-second breath-hold and a measure of the transfer capacity of the lungs across the alveolar-capillary interface. The test can be performed using a single-breath DLCO technique available at all hospital-based pulmonary function laboratories. A 15-minute noninvasive DLCO test is more expensive and skill-intensive, but may be clinically valuable for differentiating airway obstruction and restriction of lung volumes.

In healthy persons, the absolute value of DLCO in adults varies with height, age, gender, and race. As with spirometry, reference values from the healthy subset of large population studies are used to obtain percent predicted values for individual patients. DLCO is higher in very obese persons and lower in patients with anemia. The DLCO declines about 5% per decade after age 40 years, even in healthy adults.

Acid-base balance is tightly controlled, and therefore, normal values for arterial pH and $PaCO_2$ do not change throughout adult life in healthy persons. However, because of increased nonuniformity of ventilation with aging, mean arterial oxygen tension (PaO_2 [partial pressure arterial oxygen]) declines during middle life even in healthy never-smokers. Mean PaO_2 remains relatively constant at about 80 mm Hg from age 65 to 90 years in healthy older persons at sea level. This is probably because hemoglobin/oxygen (HbO_2) dissociation curve levels off at PaO_2 values greater than 60 mm Hg. So in areas with high V/Q ratio, there is no change in the O_2 content of the blood while the areas with decreased V/Q ratio will have a reduced O_2 content. This results in a combined reduction in PO_2 which becomes significant only when it falls below 60 mm Hg. However, CO_2 is linear in its relationship, therefore areas with increased V/Q ratio will have decreased $PaCO_2$ and areas with low V/Q ratio will have high $PaCO_2$ resulting in a net unchanged $PaCO_2$.

AGING IN IPF AND COPD

Aging is associated with an increased incidence of a number of diseases affecting all organ systems, from atherosclerosis to osteoporosis. Similarly, aging lungs are prone to diseases, and we know that COPD and IPF, two common chronic disorders of the lungs, are seen more frequently in older adults. What is interesting is that even though COPD and IPF are distinct disease entities, they share some similarities with each other and the normal process of aging. Both COPD and IPF occur late in life and are associated with enhanced deposition of collagen and subsequent fibrosis. Collagen deposition is seen in the small airways in COPD versus the lung parenchyma in IPF. In both diseases, there is a loss of alveolar parenchyma that leads to impaired respiratory function. IPF and COPD, which can occur in the same person, are associated with an increased incidence of lung cancer and most studies suggest that this is unrelated to the risk for cancer posed by smoking cigarettes. It is widely believed that abnormal regulation of the aging process contributes to the pathophysiology of these diseases. Further, many think that abnormal regulation, rather than aging acceleration, is responsible for both illnesses.

CONCLUSION

Healthy adults experience a number of changes in the structure of the lung and chest wall, lung volume, capacity, and mechanics. Although aging is pathologically distinct from a number of disease entities common in older adults (eg, IPF and COPD), aging reduces reserve in the respiratory system and confounds the diagnosis of numerous disease

processes. COPD and IPF exhibit abnormal regulation of the natural aging process, the exact results of which become clearer when contrasting the respiratory system of a healthy, nonsmoking adult and that of an older adult exhibiting a chronic respiratory disease.

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Chapter 84

Chronic Obstructive Pulmonary Disease

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Learning Objectives

- Identify the most common clinical definitions of chronic obstructive pulmonary disease (COPD) and their limitations in older adults.
- Establish goals of care in older adults with COPD, most often directed at relieving symptoms, improving exercise tolerance and health status, reducing the risk of disease progression and exacerbations, as well as managing comorbidities.
- Define the palliative care needs of older adults with advanced COPD, including symptom burden and potential indications for referral to hospice.

Key Clinical Points

1. **Age is a major risk factor for respiratory symptoms and the development of COPD due to age-related changes in lung physiology, and a greater exposure to COPD risk factors, particularly a higher prevalence of "ever smoking" in the older adult population.**
2. **Although symptoms consistent with COPD (eg, cough, hypersecretion of mucous) are common in seniors, two-thirds of persons who have symptoms of chronic bronchitis and half of those with physician-diagnosed emphysema/COPD have normal spirometry (ie, do not have COPD).**
3. **A reduced FEV_1/FVC establishes a diagnosis of airflow obstruction and limited reversibility is required to demonstrate chronic airflow obstruction, the hallmark of COPD. However, age-related airflow limitation is also characterized by a reduced FEV_1/FVC, and the threshold used to define COPD in seniors must account for normal aging.**
   a. **The most often used criteria for establishing and staging airflow obstruction are based on the Global Initiative for Obstructive Lung Disease (GOLD) criteria. The age-related limitations of the GOLD guidelines include two fundamental flaws: (1) GOLD defines a reduced FEV_1/FVC by a fixed ratio of 0.70, thus failing to distinguish between age-related airflow limitation and COPD-related airflow obstruction; (2) GOLD expresses the FEV_1 as a percentage of predicted value, thus failing to account for age-related variability in spirometric performance. The over-diagnosis of airflow obstruction (COPD) by GOLD in older adults is not associated with respiratory symptoms, exercise intolerance, impaired mobility, COPD hospitalization, or mortality.**
   b. **The Global Lung Initiative (GLI) has recommended the lower limit of normal be instead defined as the fifth percentile distribution of Z-scores (Z-score of –1.64), and use reference equations that include Americans and many other ethnicities (worldwide), as well as age range of up to 95 years. Prior work has shown that airflow obstruction defined by an FEV_1/FVC Z-score less than –1.64 is associated with respiratory symptoms, impaired mobility, frailty status, COPD hospitalization, and mortality.**
4. **Treatment of COPD in seniors is complicated by difficulty with drug administration (eg, due to cognitive impairment, physical disability) and may require additional teaching/coaching to achieve optimal outcomes.**
5. **Treatment of acute exacerbations includes:**

a. **Intensified bronchodilator therapy.**

b. **Corticosteroids should be considered for severe exacerbations, but side effects are common in seniors; for example, delirium is more common particularly at doses exceeding 60 mg daily.**

c. **Antibiotics should be considered only for moderate or severe exacerbations, not mild episodes. Older adult residents of skilled nursing facilities, or those who have spent time in acute-care or subacute-rehab facilities within 90 days of exacerbation, and persons with severe airflow obstruction (FEV_1 < 30% predicted or FEV_1 Z-score < –2.55) are more likely to be colonized with resistant organisms (methicillin-resistant *Staphylococcus aureus* and multidrug resistant gram negative organisms [eg, *Pseudomonas aeruginosa*]). Thus, these latter risk factors should guide choice of empiric therapy. The duration of antibiotic therapy, in the absence of complicating factors such as pneumonia, is typically 3 to 7 days.**

d. **Discharge planning should consider referral for pulmonary rehabilitation, the need for home oxygen, and a recalibration of maintenance therapy; because new treatment regimens increase the likelihood of medication nonadherence or errors, formal medication reconciliation and pharmacist-based review should be implemented.**

INTRODUCTION

Among older persons, respiratory symptoms are prevalent and associated with adverse outcomes. Dyspnea, for example, is reported in one-third of older persons and is associated with physical inactivity, impaired mobility, disability in activities of daily living, and death. Chronic bronchitis occurs in 15% of older persons and is associated with physical inactivity, reduced lung function, COPD exacerbations, and death. Wheezing occurs in 12% of older persons and is associated with physical inactivity and death.

The occurrence of respiratory symptoms frequently raises concerns regarding COPD, projected worldwide to be a leading cause of disability (fifth) and death (third) by 2030. Older persons are at high risk of developing COPD, given the age-related decline in physiologic capacity and the cumulative effect of frequent exposures to tobacco smoke, respiratory infections, air pollutants, and occupational dusts across the lifespan.

Epidemiologic surveys of COPD are often based on the symptoms of chronic bronchitis or physician-diagnosed emphysema/COPD, yielding prevalence rates of greater than or equal to 11.6% in US adults aged greater than or equal to 65. Alternatively, and more consistent with clinical guidelines, COPD is defined spirometrically as chronic airflow obstruction. When established by age-appropriate diagnostic thresholds, spirometry-confirmed COPD has a prevalence of 15.4% in US adults aged greater than or equal to 65.

PATHOPHYSIOLOGY

Aging Lung

As shown in **Table 84-1**, the aging lung is characterized by a reduced physiologic capacity, yielding multiple respiratory impairments that increase the vulnerability for developing COPD, including respiratory failure. The most pronounced of these impairments is in respiratory mechanics, including a progressive increase in the rigidity of the chest wall and decrease in the elastic recoil of the lung, further associated with a reduced diameter of the small airways and “senile” emphysema. The latter relates to the degeneration of elastic fibers around the alveolar duct that result in homogeneous airspace enlargement, concurrent with a reduced alveolar surface area but in the absence of alveolar wall destruction. These respiratory impairments lead to (1) airflow limitation: defined by a decreased spirometric ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC); (2) air trapping and hyperinflation: defined by an increased residual volume (RV) and functional residual capacity (FRC), respectively; (3) reduced maximum breathing capacity (MBC): defined by a decline in the maximal attainable minute ventilation, strongly correlating with a decrease in FEV_1 of ~30 mL/y; and (4) ventilation-perfusion mismatch: defined by an increased closing volume that approaches the FRC, leading to premature closure of the small airways and widening of the alveolar-arterial oxygen gradient. Other age-related respiratory impairments that increase the vulnerability for developing COPD, including respiratory failure, relate to reductions in pulmonary capillary density, mucociliary

clearance efficiency, respiratory muscle strength, and cerebrovascular responsiveness to carbon dioxide (CO_2) (tightly linked to the CO_2 ventilatory response).

TABLE 84-1 RESPIRATORY IMPAIRMENTS OF THE AGING LUNG AND COPD

DOMAIN	AGING LUNG[a]	COPD[b]
Respiratory mechanics	• ↑ chest wall rigidity, ↓ elastic recoil of the lung, ↓ small airway diameter, "senile" emphysema *Contributing to:* • Airflow limitation (↓FEV_1/FVC and FEV_1) • ↓ mucociliary clearance efficiency • ↑ prevalence of chronic bronchitis • Air trapping (↑ RV) • Hyperinflation (↑ FRC, unchanged TLC) • ↑ closing volume (approaching FRC) • ↑ dead space ventilation[c] • ↓ maximum breathing capacity[d]	• Progressive small airways disease, emphysematous destruction of the alveolar-capillary interface *Contributing to:* • Airflow obstruction (↓↓ FEV_1/FVC and FEV_1) • ↓↓ mucociliary clearance • ↑↑ prevalence of chronic bronchitis • Air trapping (↑↑ RV) • Hyperinflation (↑↑ FRC, ↑↑ TLC) • ↑↑ closing volume (exceeding FRC) • ↑↑ dead space ventilation[c] • ↓↓ maximum breathing capacity[d]
Respiratory muscles	• Impaired respiratory mechanics/sarcopenia, leading to ↓ inspiratory and expiratory muscle strength	• Impaired respiratory mechanics/sarcopenia, leading to ↓↓ inspiratory and expiratory muscle strength
Ventilatory control	• ↓ cerebrovascular response to CO_2 (tightly linked to the CO_2 ventilatory response) *Other putative mechanisms:* • ↓ peripheral chemoreflex CO_2 sensitivity • ↓ feedback from peripheral mechanoreceptors • ↓ number of medullary ventral respiratory neurons	• Impaired respiratory mechanics leads to ↓↓ ventilatory responsiveness to elevations in CO_2 *Other putative mechanisms:* • ↓↓ central chemosensitivity (chronic hypercapnia) • ↓↓ intrinsic ventilatory drive
Gas exchange	• ↑ closing volume • ↓ alveolar surface area and density of lung capillaries • ↑ pulmonary vascular resistance • ↓ cardiac output response to exercise *Contributing to:* • ↑ ventilation-perfusion mismatch, including ↓ $_a$/ ratio and ↑ dead space ventilation[c] • ↑ PA pressure, ↓D_{LCO}, ↓PaO_2, normal $PaCO_2$	• ↑↑ closing volume • ↓↓ alveolar surface area and density of lung capillaries • ↑↑ pulmonary vascular resistance • ↓↓ cardiac output response to exercise *Contributing to:* • ↑↑ ventilation-perfusion mismatch, including ↓↓ $_a$/ ratio and ↑↑ dead space ventilation[c] • ↑↑ PA pressure, ↓↓ D_{LCO}, ↓↓ PaO_2, normal to ↑ $PaCO_2$
Exercise	• Reduced exercise capacity due to: • ↓ V_{Emax}, including flow and volume limited, dynamic hyperinflation with ↑ PEEPi • ↓ PaO_2,[e] ↑ dead space ventilation,[c] normal $PaCO_2$[f]	• Reduced exercise capacity due to: • ↓↓ V_{Emax}, including flow and volume limited, and dynamic hyperinflation with ↑↑ PEEPi • ↓↓ PaO_2, ↑↑ dead space ventilation,[c] normal to ↑ $PaCO_2$[g]

D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; PA, pulmonary arterial; PEEPi, intrinsic positive end-expiratory pressure; RV, residual volume; TLC, total lung capacity; $_a$/, ventilation to perfusion ratio; $_{Emax}$, minute ventilation at maximal exercise.

[a] The noted impairments occur in an otherwise healthy older person.

[b] The noted impairments occur most often in patients who have moderate-to-severe airflow obstruction.

[c] Dead space refers to wasted ventilation ($_d$), including regions that are ventilated but poorly perfused. This increases ventilatory demand (and dyspnea), as an increase in total ventilation ($_T$) is required to maintain alveolar ventilation ($_a$), where $_a = _T - _d$.

[d] Maximal attainable minute ventilation in liters/min, estimated as follows: $FEV_1 \times 40$ for males or $FEV_1 \times 35$ for females. It may also be directly measured by a 12-second maximum voluntary ventilation maneuver.

[e] PaO_2 declines from an average of 100 mm Hg in young adults (18–24 years) to 89 mm Hg in older adults (≥ 65 years).

[f] The $PaCO_2$ response to exercise remains normal, despite the increase in dead space, because the maximum breathing capacity remains adequate for a compensatory increase in total ventilation ($_T$) to maintain alveolar ventilation, where $_a = _T - _d$.

[g] A combined COPD-level increase in dead space and decrease in maximum breathing capacity, when severe, can lead to alveolar hypoventilation ($\downarrow_T - \uparrow_d = \downarrow_a$), resulting in higher $PaCO_2$ levels (normally decrease in response to exercise).

Risk Factors

Advancing age is also accompanied by a high frequency of COPD risk factors. The most important of these is tobacco smoke, accounting for the majority of COPD cases. In recent cohorts of older Americans, the prevalence of ever-smokers was 56%, including 9% as current smokers, and, among never-smokers, 32% had exposure to second-hand smoke. Respiratory infections also contribute to the onset and progression of COPD. About one-quarter of older Americans report a prior pneumonia, and those aged greater than or equal to 75 have a 10-fold increased rate of influenza hospitalization. Outdoor air pollution is another COPD risk factor. In 2009, 34% of older Americans lived in a major city, a surrogate for exposure to outdoor air pollution. Other COPD risk factors include occupation (freight, stock, and material handlers, and metal and wood workers) and use of biomass fuel for indoor cooking or heating—the prevalence of these exposures are 12% and 18%, respectively, among older nonsmoking Americans.

Pathogenesis

The pathogenesis of COPD is poorly understood, especially in the context of the aging lung. The long-standing paradigms of COPD pathogenesis generally fall into two categories: (1) antioxidant/oxidant and (2) antiprotease/protease imbalance. This dual categorization was a result of early, compelling animal models in which candidate gene identification included α_1-antitrypsin (α1-AT), macrophage elastase, surfactant D, microsomal epoxide hydrolase, Nrf2, matrix metalloproteases, as well as cathepsins.

Most of these studies addressed the early, initiating phases of COPD development. However, COPD develops over decades despite smoking cessation, thought to be due to “progression” and “consolidation” phases of disease in genetically susceptible hosts. **Table 84-2** summarizes our current understanding of COPD pathogenesis, in which aging and aberrant immune responses have emerging roles.

TABLE 84-2 ■ SUMMARY OF COPD PATHOGENESIS

PROCESS	GENES AND PROTEINS
Protease/Anti-Proteases	• Neutrophil elastase • MMPs (1, 2, 9, 12) • Cathepsins (L, S, E) • Serpine2 • TIMPs
Oxidants/Anti-Oxidants	• General oxidants: OH^-, H_2O_2 • Intrinsic oxidant production: NADPH oxidase, xanthine oxidase, myeloperoxidase, mitochondrial oxidants • Antioxidants: NRF-2, HMOX-1, catalase, SOD2, SOD3, glutathione S-transferase
Immune Responses	• Cytokines: TNF-α, IL-6, IL-8, IL-1α, IL-1β, IL-13, IL-17 • Chemokines: IL-8, MCP-2, MIP-1α, MIP-3α, CCL-18 • Toll-like receptors • Leukotrienes: LTE4, LTB4 • Autoreactive T cells • Antitissue antibodies
Growth & Repair Factors	• MIF • VEGF

	• HGF • MTOR
DNA Damage, Cellular Senescence, & Telomere Shortening	• $_{\gamma}$-H2AX • p16, p21, p53 • XRCC5 • FOXO3 • RORα
Epigenetics	• HDAC2 • DNA methylation • Sirtuins
Cell Death, Metabolism & Organelle Homeostasis	• Ceramides • Leptins/Adiponectin • Autophagy • Mitochondrial fission-fusion

CCL, chemokine (C-C motif) ligand; FOXO3, forkhead box O3; γ-H2AX, phosphorylated Histone 2A family member X; HDAC, histone deacetylase; HGF, hepatocyte growth factor; HMOX, heme-oxygenase; IL, interleukin; MCP, monocyte chemoattractant protein; MIF, macrophage migration inhibitory factor; MIP, macrophage inflammatory protein; MMP, matrix metalloproteases; MTOR, mammalian target of rapamycin; NRF-2, nuclear factor erythroid 2–related factor 2; RORα, retinoid orphan receptor alpha; Serpine, serpin peptidase inhibitor; SOD, superoxide dismutase; TIMP, tissue inhibitors of MMPs; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Telomere length, which is a biomarker of cell aging, is shorter in lung cells from COPD patients compared with age-matched individuals without COPD. Genetic mouse models of accelerated aging also show chronic lung disease. Mutant *Klotho* mice, which have a shortened lifespan and manifest signs of accelerated aging, exhibit emphysema despite normal lung development. Expression of the NAD-dependent deacetylase, SIRT1, a member of the sirtuin family that is implicated in caloric restriction-mediated lifespan extension and proinflammatory signaling, is decreased in emphysematous lungs. Cellular senescence and apoptosis are two age-related processes that occur in COPD. Multiple studies have documented increased apoptosis in the lungs of patients with COPD and the resultant imbalance between apoptosis and tissue repair may underlie the development of emphysema.

Recent reports have identified innate immune molecules to be key regulators of age-related emphysema. There is functional overlap between immune responses to environmental and to invasive pathogens. The innate response constitutes the first phase of the immune response and is triggered by pattern-recognition receptors. Three main classes of recognition receptors activate the innate system: (1) the membrane-associated toll-like receptors (TLRs) recognize microbial components and ligands from damaged cells, (2) the NOD-like receptors (NLRs) are activated when stimuli enter the cytoplasm, and (3) the RIG-I-like receptors (RLRs) mediate cytoplasmic recognition of viral nuclei acids. Because immunosenescence contributes to susceptibility to infection and decreased vaccine responses in older adults, significant emphasis has been placed on immunology in understanding how aging affects the innate immune system. The roles of innate immune receptors in age-related lung disease have been reviewed elsewhere (see Further Reading).

Age-related loss of endogenous, protective immune molecules such as macrophage migration inhibitory factor (MIF) has recently been identified as a mechanism of emphysema in smokers and corroborated in mouse models. MIF exerts pleiotropic protective effects by modulating cellular senescence molecules, antioxidants (such as NRF-2), apoptosis, and key growth factors (such as VEGF). The loss of trophic factors (such as VEGF and Wnt signaling) found in lung samples from COPD patients are thought to lead to alveolar destruction and, potentially, the disappearance of the terminal airways in COPD. In addition to enhanced tissue destruction, the role of lung cell apoptosis has been highlighted by multiple studies. Enhanced cell death and inadequate regenerative responses are pivotal to the progressive loss of gas exchange surface area in emphysema.

Most studies of COPD pathogenesis have focused primarily on emphysema rather than chronic bronchitis, but the same processes are likely involved (**Figure 84-1**). The paucity of animal models for chronic bronchitis has been a barrier. Mice, for instance, do not exhibit significant airway mucus secretion or airway remodeling typical of chronic bronchitis despite chronic cigarette exposure. However, studies of IL-13, VEGF, and IL-18 lung-targeted overexpressing mice in combination with clinical evidence of increased levels of these cytokines in smokers' lungs have provided new venues for further study.

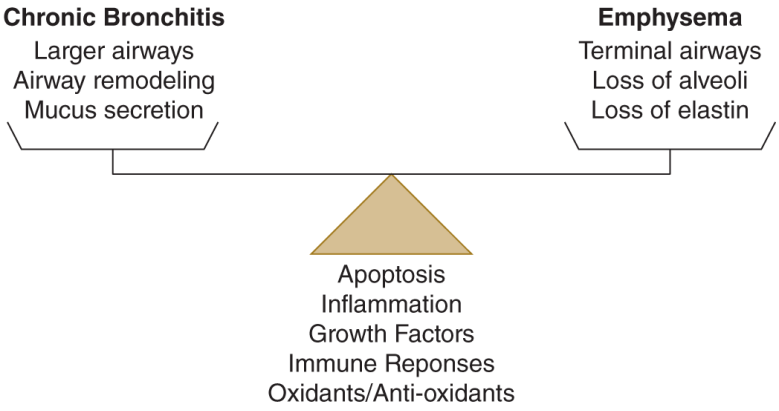


FIGURE 84-1. Cellular processes determining chronic bronchitis and emphysema.

Impairments

Because of progressive airways disease and emphysematous destruction of the alveolar-capillary interface, the respiratory impairments of COPD overlap with those of the aging lung, although to a more severe extent (see **Table 84-1**). The most important of these COPD-based respiratory impairments include (1) mucus hypersecretion, (2) chronic airflow obstruction, (3) air trapping and hyperinflation, and (4) gas exchange abnormalities.

Mucus hypersecretion is the hallmark of chronic bronchitis, defined as chronic cough and sputum production for at least 3 months per year for 2 consecutive years. These clinical features result from persistent airway inflammation, including goblet cell hyperplasia in large and small airways, and mucociliary dysfunction. Mucus hypersecretion worsens airflow obstruction and predisposes to bacterial infection. Because it is also associated with COPD, bronchiectasis is an additional mechanism that may underlie chronic cough and sputum production.

Chronic airflow obstruction is most often established by serial spirometry (confirming limited reversibility), with the major site of obstruction being the smaller bronchi and bronchioles less than 2 mm in diameter. The obstruction is due to mucus-containing inflammatory exudates that occlude the airway lumen, and due to a tissue-repair process that thickens the walls and narrows airway lumen. In addition, emphysematous destruction of alveoli increases airflow obstruction, through loss of alveolar attachments and a decrease in the elastic recoil of the lung.

Chronic airflow obstruction makes alveolar emptying increasingly difficult, resulting in air trapping and hyperinflation (measured clinically by helium dilution or whole-body plethysmography). In combination, these impairments adversely affect (1) breathing patterns: flow and volume limited, including dynamic hyperinflation with an increase in the intrinsic positive end-expiratory pressure (PEEPi); (2) respiratory muscle strength: the curvature of the diaphragm is reduced, shortening length-tension relationships and thus decreasing the force generating capacity of the diaphragm; and (3) maximum breathing capacity (MBC): the maximal attainable minute ventilation is reduced, strongly correlating with a decrease in FEV_1. The net effect is exercise intolerance, symptom-limiting dyspnea, and an increased risk of respiratory failure.

Gas exchange abnormalities are characterized by ventilation-perfusion mismatch, involving lung regions with a low ventilation-to-perfusion ratio or an increase in dead space (ventilated but underperfused)—these abnormalities relate to chronic airflow obstruction and alveolar-capillary destruction. Clinically, gas exchange abnormalities are initially identified by a reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) (adjusted for hemoglobin), suggesting emphysema when coexisting with airflow obstruction and hyperinflation. In advanced COPD, based on the relative contributions of impairments in respiratory mechanics, respiratory muscle strength, and central chemosensitivity (see **Table 84-1**), gas exchange abnormalities may progress to hypoxemia and hypercapnia, yielding a reduction in arterial oxygen content and an acute/chronic respiratory acidosis—these abnormalities define respiratory failure.

COPD can also yield extrapulmonary impairments, mainly involving the cardiovascular and musculoskeletal systems, and these also overlap with those of normal aging (**Table 84-3**). In particular, destruction of the alveolar-capillary interface and hypoxic pulmonary vasoconstriction can lead to pulmonary hypertension and right ventricular failure (cor pulmonale). Moreover, ventricular interdependence (right ventricular pressure and volume overload) and marked intrathoracic pressure swings (increased work of breathing, hyperinflation, air trapping, and PEEPi) can decrease left ventricular preload and increase left ventricular diastolic dysfunction, ultimately reducing the cardiac

output. The latter amplifies the ventilation-perfusion mismatch of COPD and reduces systemic oxygen delivery, thus increasing the risk of exercise intolerance and respiratory failure. Lastly, the systemic inflammation, immune response, anorexia, and severe deconditioning of COPD, most often seen with the emphysema phenotype, can lead to osteoporosis and sarcopenia, further impairing exercise capacity through reductions in lower extremity function and respiratory muscle strength.

TABLE 84-3 CARDIOVASCULAR AND MUSCULOSKELETAL IMPAIRMENTS OF THE AGING PERSON AND COPD

DOMAIN	AGING PERSON[a]	COPD[b]	COMMENT
Cardiovascular	• ↓ heart rate • ↓ cardiac contractility • ↑ cardiac dilatation • ↑ arterial stiffness *Contributing to:* • ↓ cardiac output[c] • ↑ peripheral vascular resistance[d]	• Cor pulmonale • Ventricular interdependence • Intrathoracic pressure swings • Comorbid cardiovascular disease *Contributing to:* • ↓↓ cardiac output[c] • ↑↑ peripheral vascular resistance[d]	• Adverse effects on gas exchange at the lung and in (systemic) oxygen delivery • Leads to an earlier exercise-induced lactic acidosis (at a lower workload), increasing CO_2 flux (bicarbonate buffering of lactate) to the lung, ventilatory demand, and, ultimately, exercise intolerance and dyspnea
Musculoskeletal	• ↑ osteopenia • ↑ sarcopenia[e] *Contributing to:* • ↓ musculoskeletal capacity • ↓↓ peripheral oxygen extraction	• Osteoporosis • ↑↑ sarcopenia[e] *Contributing to:* • ↓↓ musculoskeletal capacity • ↓↓ peripheral oxygen extraction	• Adverse effects on mobility • Leads to earlier exercise-induced lactic acidosis (at a lower workload), increasing CO_2 flux (bicarbonate buffering of lactate) to the lung, ventilatory demand, and, ultimately, exercise intolerance and dyspnea

[a] The noted impairments occur in an otherwise healthy older person.
[b] The noted impairments occur most often in patients who have moderate-to-severe airflow obstruction.
[c] The predominant mechanism is an age-related reduction in sympathetic modulation, inclusive of adaptive cardiac structural and functional alterations in response to increased vascular stiffness.
[d] Includes less efficient redistribution of blood flow to the exercising muscle.
[e] Loss of skeletal muscle mass and function, accompanied by reduced physical performance.

Accordingly, the impairments imposed by advancing age and COPD (see **Tables 84-1** and **84-3**) collectively increase the risk of having respiratory symptoms (dyspnea, chronic bronchitis, and wheezing), exercise intolerance, disability, hospitalization, respiratory failure, and death.

DIAGNOSIS

Epidemiologic Surveys

Epidemiologic surveys of COPD are often based on symptoms of chronic bronchitis or physician-diagnosed emphysema/COPD. Prior work has shown, however, that two-thirds of persons who have symptoms of chronic bronchitis and half of those with physician-diagnosed emphysema/COPD have normal spirometry (do not have COPD). This relates to symptoms of chronic bronchitis (cough in particular) also occurring with other conditions (postnasal drip, acid reflux, etc) or being drug-induced, and to a low-spirometric utilization in primary care settings.

Spirometry Given the above concerns, and because pathologic confirmation is invasive and not routinely available, the clinical strategy for establishing COPD is based on spirometry-confirmed chronic airflow obstruction (less than fully reversible). Spirometry can be conveniently performed with a portable, handheld device, using protocols from the American Thoracic and European Respiratory Societies (ATS/ERS). These protocols require performance of at least

two FVC maneuvers that meet ATS/ERS acceptability criteria—FVC maneuver is defined as the maximal volume of air that is exhaled with maximal effort starting from maximal inspiration.

The most common spirometric measures of interest are the FEV_1 and FVC, including its ratio (FEV_1/FVC). An additional measure is the forced expiratory volume in 6 seconds (FEV_6), used as an estimate of FVC. Although the FEV_6 is more reproducible and less physically demanding than the FVC, it is limited when distinguishing normal spirometry from a restrictive impairment, and predicted values are currently unavailable for those aged greater than 80.

Establishing airflow obstruction A reduced FEV_1/FVC establishes *airflow obstruction*. However, given that age-related *airflow limitation* is also characterized by a reduced FEV_1/FVC, the threshold that establishes *airflow obstruction* must account for normal aging, including increased variability in spirometric performance (at least 50% greater in healthy 80-year-olds than healthy 40-year-olds).

To account for age-related changes in lung function, the ATS/ERS recommend that airflow obstruction be established by a lower limit of normal (LLN) threshold for FEV_1/FVC. The ATS/ERS approach currently defines the LLN as the fifth percentile distribution of reference values, calculated in a population of healthy never-smokers matched for age, height, sex, and ethnicity (these predict normal lung function). In the United States, reference values are often based on equations from the Third National Health and Nutrition Examination Survey (NHANES III). Although these account for age-related declines in lung function, the NHANES III equations are limited to those aged less than or equal to 80 and do not consider variability in spirometric performance. Hence, the GLI has recommended that the LLN be instead defined as the fifth percentile distribution of Z-scores (Z-score of –1.64) (**Table 84-4**). The GLI calculated Z-scores account for the age-related decline in lung function and increased variability in spirometric performance and use reference equations that include Americans and many other ethnicities (worldwide), as well as age range of up to 95. Prior work has shown that airflow obstruction defined by an FEV_1/FVC Z-score less than –1.64 is associated with respiratory symptoms, impaired mobility, frailty status, COPD hospitalization, and mortality. Moreover, Z-scores have a strong clinical precedence, given their use in bone mineral density testing and pediatric growth charts.

TABLE 84-4 SPIROMETRIC CRITERIA FOR ESTABLISHING AND STAGING CHRONIC AIRFLOW OBSTRUCTION

METHOD	CHRONIC AIRFLOW OBSTRUCTION[a,b]			COMMENT
	MILD	MODERATE	SEVERE	
American Thoracic and European Respiratory Societies (ATS/ERS)				
FEV_1/FVC	< LLN[c]			• Accounts for age-related airflow limitation, but not age-related variability in spirometric performance • LLN and %Pred calculations are often based on NHANES III reference equations, which are limited to age < 80 • Yields a COPD prevalence rate of 19.2%
FEV_1	≥ 70 %Pred	50-69 %Pred	< 50 %Pred	
Global Lung Initiative (GLI)				
FEV_1/FVC	Z-score < –1.64[d]			• Accounts for age-related airflow limitation and age-related variability in spirometric performance • GLI reference equations include ages up to 95 and multiple ethnicities (worldwide) • Strong clinical precedence: Z-scores used in bone mineral density testing and pediatric growth charts • Novel, not yet widely applied • Yields a COPD prevalence rate of 15.4%
FEV_1	Z-score[e]			
	≥ –1.64	< –1.64 but ≥ –2.55	< –2.55	
Global Initiative for Obstructive Lung Disease (GOLD)				
FEV_1/FVC	< 0.70			• Widely used in research and clinical practice • Does not account for age-related airflow limitation or age-related variability in spirometric performance • FEV_1/FVC fixed ratio of 0.70 will often misidentify COPD in aging populations • %Pred calculations are often based on NHANES III reference equations, limited to age < 80 • Yields a COPD prevalence rate of 37.7%
FEV_1	≥ 80 %Pred	50–79 %Pred	< 50 %Pred	

FEV_1/FVC, ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC); LLN, lower limit of normal; NHANES III, Third National Health and Nutrition Examination Survey; %Pred, percent predicted (measured/predicted x 100).

[a] Airflow obstruction is first established by FEV_1/FVC, with severity thereafter staged by FEV_1.

[b] The use of prebronchodilator spirometric measures provides a more reasonable approach when establishing and staging airflow obstruction in older persons, with reversibility best evaluated by serial spirometry over time.

[c] Defined by the fifth percentile distribution of reference values.

[d] Calculated as: $[(\text{measured } FEV_1/FVC \div \text{median } FEV_1/FVC)^{Lambda} - 1] \div (\text{lambda} \times \text{sigma})$, wherein (1) median represents how the spirometric variable changes with a predictor variable (age and height); (2) sigma is the coefficient of variation, which models the spread of spirometric reference values; and (3) lambda, which models the departure from normality (skewness). GLI equations provide values for the median, lambda, and skewness, and are specific to sex and ethnicity. An FEV_1/FVC Z-score of –1.64 defines the LLN as the fifth percentile distribution of Z-scores.

[e] Calculated as: $[(\text{measured } FEV_1 \div \text{median } FEV_1)^{Lambda} - 1] \div (\text{lambda} \times \text{sigma})$. An FEV_1 Z-score of –1.64 defines the LLN (fifth percentile), whereas –2.55 corresponds to the 0.5th percentile distribution of Z-scores.

Staging airflow obstruction After establishing a reduced FEV_1/FVC, current practice stages the severity of airflow obstruction based on FEV_1 expressed as percent predicted (%Pred): [measured/predicted] × 100%. The ATS/ERS, in particular, recommend the thresholds for FEV_1 of 70 and 50 %Pred when staging airflow obstruction (see **Table 84-4**). This approach has age-related limitations, however, since %Pred assumes incorrectly the equivalence of spirometric variability across the adult lifespan. To address this limitation, GLI-calculated FEV_1 Z-scores should be used to stage the severity of airflow obstruction (see **Table 84-4**). Prior work has shown that Z-score thresholds for FEV_1 have a graded association with respiratory symptoms, COPD hospitalization, and mortality.

Global Initiative for Obstructive Lung Disease Despite serious age-related limitations in methodology, the most

often used spirometric criteria for establishing and staging airflow obstruction is based on GOLD guidelines (see **Table 84-4**). The age-related limitations of the GOLD guidelines include two fundamental flaws. First, GOLD defines a reduced FEV_1/FVC by a fixed ratio less than 0.70, thus failing to distinguish between age-related airflow limitation and COPD-related airflow obstruction. In particular, an FEV_1/FVC less than 0.70 is frequently seen in otherwise healthy, asymptomatic never-smokers who are aged greater than or equal to 65. Second, GOLD expresses the FEV_1 as %Pred, thus failing to account for age-related variability in spirometric performance. It is therefore not surprising that the prevalence of airflow obstruction in older persons is more than twofold higher when defined by GOLD versus a Z-score approach (37.7% vs 15.4%, respectively). Prior work has shown that the overdiagnosis of airflow obstruction by GOLD is not associated with respiratory symptoms, exercise intolerance, impaired mobility, COPD hospitalization, or mortality.

Reversibility COPD is defined as chronic airflow obstruction, meaning less than fully reversible. Clinical guidelines therefore recommend that spirometry should be performed before and after administration of an inhaled bronchodilator (pre- and post-BD, respectively) in order to establish (1) reversibility (pre- vs post-BD values) and (2) diagnosis of COPD (using post-BD values). Among older persons, in particular, this approach has two disadvantages. First, older persons have limited capacity to perform multiple FVC maneuvers, and may have an adverse response to an inhaled BD. Second, post-BD values have limited clinical relevance in distinguishing COPD from asthma, and have low reproducibility over time. Hence, the use of pre-BD values provides a more reasonable approach when diagnosing and staging COPD, with limited reversibility best established by serial spirometry over time.

Additional Considerations

Although chronic airflow obstruction is a necessary and sufficient criterion for defining COPD, the diagnostic evaluation should assess additional respiratory impairments, as these further confirm COPD and are associated with adverse outcomes (**Table 84-5**). Combining these respiratory impairments with clinical and radiologic features further establishes clinical phenotypes that serve to inform COPD-related treatment options and prognosis (**Table 84-6**).

TABLE 84-5 RESPIRATORY IMPAIRMENTS THAT ARE COMMONLY EVALUATED TO ESTABLISH A DIAGNOSIS OF COPD

PHYSIOLOGIC IMPAIRMENT	CRITERIA	OUTCOMES
Chronic airflow obstruction	• See **Table 84-4** for spirometric criteria • Not fully reversible, as defined by serial spirometry over time • Necessary and sufficient criterion to establish a diagnosis of COPD	
Hyperinflation	• Static lung volumes (helium dilution or whole-body plethysmography): ↑↑ TLC and ↑↑ FRC	
Air trapping	• Static lung volumes (helium dilution or whole-body plethysmography): ↑↑ RV and ↑↑ RV/TLC	
Pulmonary hypertension	• Echocardiography estimates of ↑↑ pulmonary arterial systolic pressure • Presence suggested by exercise induced oxygen desaturation	
Gas exchange[b]	• Reduced D_{LCO}, adjusted for hemoglobin • Hypoxemia at rest, asleep, or with exercise: pulse oximetry • Hypercapnia while awake, asleep, or with exercise: arterial blood gases	• ↑↑ respiratory symptoms • ↓↓ functional status • ↑↑ risk of respiratory failure
Exercise intolerance	• Reduced 6-minute walk distance • Maximal cardiopulmonary stress test with gas exchange: • Pulmonary mechanical limitation: $V_{Emax} \geq 85\%$ of MBC,[a] expiratory flow limitation (over more than 80% of the tidal volume by peak exercise), inspiratory flow limitation (approach	

	those available over higher lung volumes), volume limitation (↑↑ end-inspiratory lung volume relative to TLC), dynamic hyperinflation (↑↑ end-expiratory lung volume, ↑↑ PEEPi) • Pulmonary vascular limitation: ↓↓PaO_2, ↑↑ dead space,[b] normal or ↑$PaCO_2$[c]	

D_{LCO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; MBC, maximum breathing capacity; PEEPi, intrinsic positive end-expiratory pressure; RV, residual volume; TLC, total lung capacity; $_{Emax}$, minute ventilation at peak exercise.

[a] Maximal attainable minute ventilation in liters/min, estimated as follows: $FEV_1 \times 40$ for males or $FEV_1 \times 35$ for females. It may also be directly measured by a 12-second maximum voluntary ventilation maneuver.

[b] Dead space refers to wasted ventilation ($_d$), including regions that are ventilated but poorly perfused. This increases ventilatory demand (and dyspnea), as an increase in total ventilation ($_T$) is required to maintain alveolar ventilation ($_a$), where $_a = _T - _d$.

[c] A combined COPD-level increase in dead space and decrease in maximum breathing capacity, when severe, can lead to alveolar hypoventilation ($\downarrow_T - \uparrow_d = \downarrow_a$), resulting in higher $PaCO_2$ levels (normally decrease in response to exercise).

TABLE 84-6 ■ COPD CLINICAL PHENOTYPES

CLINICAL PHENOTYPE[a]	CRITERIA	TREATMENT[b]
Airway Predominant		
Airflow obstruction	• Airflow obstruction, without chronic bronchitis, bronchiectasis, or emphysema • ↑ small airway wall thickness on volumetric chest computed tomography • Variable reversibility, but lack some features of COPD-asthma overlap (eg, sputum eosinophilia, high IgE)	Bronchodilator, anti-inflammatory[c]
Chronic bronchitis	• Airflow obstruction, with chronic cough and sputum production for at least 3 mo/y for 2 consecutive years, and with persistent airway inflammation and colonization/infection • ↑ small airway wall thickness on volumetric chest computed tomography	Bronchodilator, anti-inflammatory,[c,d] ± mucolytics[e]
Bronchiectasis	• Airflow obstruction (usually severe), with isolation of bacteria from sputum (especially pseudomonas), increased sputum inflammatory markers, and at least one COPD exacerbation in the prior year • ↑ small airway wall thickness and bronchiectasis on volumetric chest computed tomography	Bronchodilator, airway-clearance techniques
COPD-asthma overlap	• Airflow obstruction, with enhanced response to inhaled corticosteroids (but not fully reversible), eosinophilia in respiratory secretions, high IgE • History of smoking (≥ 10 pack-years), asthma, and/or atopy • ↑ small airway wall thickness on volumetric chest computed tomography	Bronchodilator, anti-inflammatory[c]
Emphysema Predominant		
Emphysema	• Airflow obstruction, with alveolar-capillary destruction and airspace enlargement • Moderate-to-severe hyperinflation and air trapping, reduced D_{LCO} (adjusted for hemoglobin), ± pulmonary hypertension, emphysema on volumetric chest computed tomography • Severe dyspnea and exercise intolerance, low BMI	Bronchodilator, anti-inflammatory,[c] lung volume reduction or transplantation surgery,[f] α_1-antiprotease[g]
Combined pulmonary fibrosis-emphysema syndrome (CPEFS)	• Includes both upper-lobe emphysema and lower-lobe fibrosis. Usually occurs in male smokers and associated with pulmonary	Bronchodilator, anti-inflammatory,[c]

	hypertension, acute lung injury, and lung cancer.	other[h]
Frequent Exacerbator	• Defined by two or more symptom-defined exacerbations per year • ↓ health-related quality of life and accelerated decline in lung function	Bronchodilator, anti-inflammatory[c,d]
COPD-OSA Overlap	• Worse nocturnal hypoxemia/hypercapnia than COPD and OSA alone • Severity of airflow obstruction and hyperinflation correlates with OSA severity	Positive airway pressure: may improve survival, pulmonary hypertension, hypoxemia, and risk of hospitalization

D_{LCO}, diffusing capacity of the lung for carbon monoxide; OSA, obstructive sleep apnea.

[a] Although defined by the predominant clinical phenotype, patients may have multiple features (eg, combined chronic bronchitis, emphysema, and frequent exacerbator).

[b] Apply to stable COPD (see Management section for indications and comprehensive treatment considerations).

[c] Most often an inhaled corticosteroid and indicated in severe airflow obstruction, chronic bronchitis and/or frequent exacerbator.

[d] In select cases, may also include roflumilast or a macrolide antibiotic.

[e] Includes thiols (eg, N-acetylcysteine), but indication limited to tenacious sputum production that is refractory to standard therapy.

[f] In selected patients (see Management section).

[g] Consider α_1-antitrypsin (AAT) deficiency as the underlying mechanism of emphysema, if the affected individual is aged ≤ 45, if a nonsmoker or minimal smoker, if the predominant distribution is basilar on chest imaging, if coexisting panniculitis or unexplained chronic liver disease, and/or if a family history of emphysema or liver disease. Treatment includes intravenous supplementation with pooled human α_1-antiprotease for those with a high-risk phenotype (PI*ZZ), a plasma AAT level < 11 micromol/L, persistent airflow obstruction, likely to comply with the treatment protocol, and aged ≥ 18.

[h] Immunosuppressive therapy for the fibrosis component is rarely indicated, as the pathology is typically end-stage usual interstitial pneumonia.

CLINICAL MANIFESTATIONS

Because of shared risk factors (eg, tobacco smoke) and sequelae of progressive chronic disease, COPD is often associated with a high medical burden, as shown in **Table 84-7**. The clinical course of COPD is further characterized by exacerbations that cycle between chronic and acute care settings, leading to accelerated declines in lung function and increases in medical burden. The prognosis of COPD is informed by the BODE Index, which includes the body mass index (B) as a measure of nutritional status, FEV_1 as a measure of the severity of airflow obstruction (O), Medical Research Council score as a measure of the severity of dyspnea (D), and 6-minute walk distance as a measure of exercise (E) capacity.

TABLE 84-7 ■ MEDICAL BURDEN OF COPD

- COPD patients average 3.7 chronic conditions and 35 filled prescriptions over a given year.
- Most frequent comorbidities in COPD are hypertension, diabetes mellitus, cardiovascular (heart failure, coronary artery disease, arrhythmias, stroke, and peripheral artery disease), psychiatric (depression and anxiety), sarcopenia (decreased skeletal muscle mass and function), osteoporosis, anemia, and lung cancer. Moreover, in response to untreated chronic hypoxemia, secondary erythrocytosis may also develop and contribute to pulmonary hypertension and reductions in cerebral and coronary blood flow.
- COPD-associated sequelae include severe deconditioning and weight loss (sarcopenia); disabling symptoms (dyspnea, chronic bronchitis, wheezing, and fatigue); multiple sensory, cognitive, and mobility impairments; limitations in activities of daily living; and social isolation. Regarding cognitive impairment, this is more prevalent in COPD patients who are oxygen dependent and have limitations in physical function (eg, difficulties in performing household chores).
- Clinical course of COPD is characterized by exacerbations that cycle between chronic and acute care settings, leading to progressive declines in lung function and further increases in medical burden.
- Advancing age further increases the likelihood of multimorbidity and polypharmacy, including the complicating sequelae of multifactorial geriatric health conditions.

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second.

Advancing age will additionally increase the likelihood that comorbidities unrelated to chronic airflow obstruction will complicate the clinical course of COPD. For example, a postmortem examination of the cause of death in 43 older

persons hospitalized for COPD exacerbation included heart failure in 16 (37%) and pulmonary thromboembolism in 9 (21%). The age-related predisposition for polypharmacy may also adversely affect COPD: (1) opiates and benzodiazepines may decrease ventilatory control and increase the risk of aspiration; (2) statins may have a myopathic effect on the muscles of respiration and ambulation, and (3) β-blockers may exacerbate underlying heart failure and bradycardia. The interaction between these adverse medication effects and age-related reductions in physiologic capacity, including respiratory and cardiovascular impairments (see **Tables 84-1** and **84-3**), may contribute to pneumonia (28%) and respiratory failure (14%), as additional causes of death among older persons hospitalized for COPD exacerbation.

Lastly, advancing age is characterized by multifactorial geriatric health conditions, such as cognitive and physical impairments (including delirium and injurious falls), sleep disorders, incontinence, frailty (sarcopenia), malnutrition, and chronic pain and dyspnea. These frequently represent sequelae of multimorbidity, polypharmacy, sedentary status, and social isolation, emphasizing the need for a comprehensive approach when managing COPD in older persons.

MANAGEMENT

The goals of care for stable COPD are most often directed at relieving symptoms, improving exercise tolerance and health status, and reducing the risk of disease progression, exacerbations, and mortality. The symptoms of interest include dyspnea, cough, sputum production, wheezing, fatigue, activity limitation, and sleep disturbances. To achieve the stated goals, decisions regarding treatment strategies should account for the predominant clinical phenotype of COPD (see **Table 84-6**), including the severity of corresponding impairments (see **Tables 84-3** through **84-5**), as well as the accompanying medical burden (see **Table 84-7**). Ultimately, treatment options are calibrated to patient preferences and advance directives, and appropriately modified when the clinical trajectory progresses to advanced COPD.

Pharmacologic

Treatment options Medication regimens should consider the patient's skills/abilities, including the questions in **Table 84-8** and the algorithm in **Figure 84-2**. Prioritization is given to once-daily administration, self-contained inhaler devices, and educating the patient/caregiver on medication administration. **Table 84-9** summarizes currently available medications, emphasizing benefits, side effects, and complexity. In stable COPD, pharmacologic therapy should follow a stepwise approach that for some patients may lead to triple-inhaler maintenance therapy, including two classes of long-acting inhaled bronchodilators (β_2-selective adrenergic agonist and anticholinergic) and an inhaled corticosteroid, as well as prn use of a rescue inhaler (short-acting β_2-agonist). Additional options include theophylline, roflumilast, macrolides, and mucolytics.

TABLE 84-8 DEVICE SELECTION CONSIDERATIONS IN OLDER PERSONS WITH COPD

- Who will be administering the dose?
- Can the patient demonstrate proper "press and breathe" technique?
- Can delivery devices be easily confused?
- Does the product require a spacer or "valved holding chamber" device?
- Can the patient afford this medication?
- Does the patient have existing problems with medication adherence?
- Does the device require adequate dexterity or grip strength to use?
- Can the patient manage complex tasks?
- Is the patient capable of maintaining and cleaning the delivery device?
- Does the patient have a sufficient peak inspiratory flow?

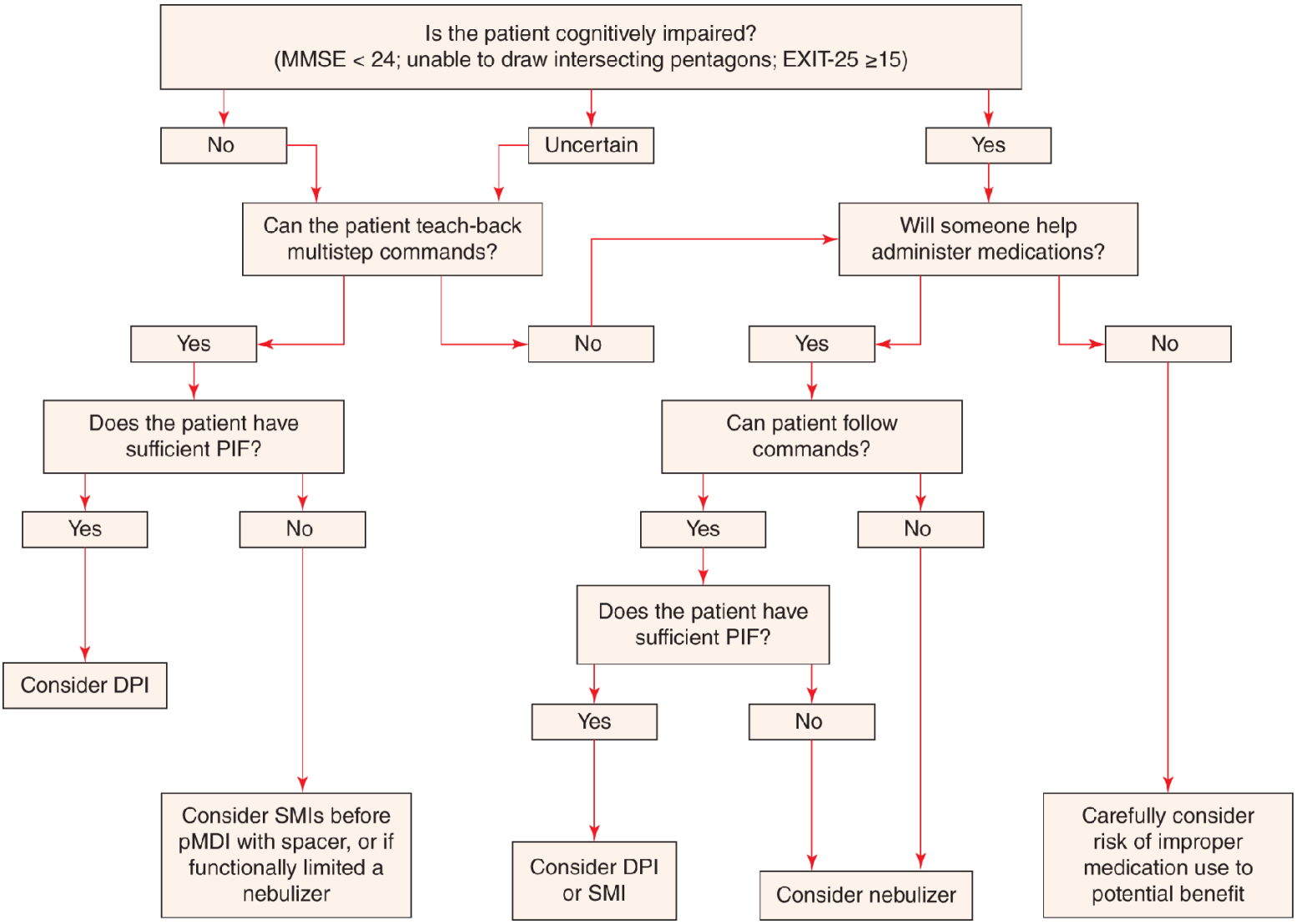


FIGURE 84-2. Algorithm for inhaler selection. DPI, dry powder inhaler; EXIT-25, a 25-item cognitive test (executive interview) that evaluates executive function (the higher the score, the worse the cognitive impairment); MMSE, Mini-Mental Status Examination (the lower the score, the worse the cognitive impairment); PIF, peak inspiratory fow; pMDI, pressurized metered-dose inhaler; SMI, soft-mist inhaler.

Short-Acting Bronchodilators Bronchodilators are fundamental to the treatment of stable COPD, irrespective of clinical phenotype, as they achieve improvements in symptoms, exercise capacity, and airflow obstruction. Inhaled bronchodilators are preferred over oral agents, based on efficacy and side effects, and aging itself does not reduce the bronchodilator response.

Albuterol is an inhaled short-acting β_2-agonist (SABA) with a fast onset of action. It is usually the first bronchodilator used, serving primarily as *rescue therapy* (as needed, rather than regularly scheduled), and is commonly prescribed as a handheld pressurized metered-dose inhaler (pMDI). Albuterol is also available as a nebulizer, an alternative for older patients who have difficulties using handheld inhalers. Patients/caregivers should be advised to always have albuterol readily available in the event of acute worsening of symptoms (dyspnea). Individuals with visual impairment should mark albuterol pMDIs to avoid confusion with other inhalers. Common side effects of SABAs are listed in **Table 84-9**, with concerns especially raised in COPD patients with cardiovascular disease, coexisting asthma (mortality), and excessive dosing.

TABLE 84-9 COPD PHARMACOLOGY [a]

MEDICATION (GENERIC/BRAND)	DOSAGE FORM/FREQUENCY	THERAPEUTIC BENEFITS	SIDE EFFECTS[b]	PATIENT TECHNIQUE INFLUENCES DRUG DELIVERY[c]	COMPLEXITY
Short-Acting β_2-Agonist (SABA) Bronchodilator—*rescue therapy*					
Albuterol (ProAir HFA and Ventolin HFA)	pMDI 1–2 puffs Q4–6 h prn	Improve respiratory symptoms, exercise capacity, airflow obstruction	Class effect: tremor, headache, insomnia, palpitations, reflex tachycardia, arrhythmia, mortality, ± hypokalemia, ± hyperglycemia	++++ (inhaler alone) +++ (if spacer used)	Prime before first use and if not used in > 2 wk
Albuterol (Accuneb)	Nebulizer 1 vial 3–4× daily prn			+ (if mask is used) ++ (if mouthpiece used)	Vials need to be opened and placed inside nebulizer
Levalbuterol Tartrate (Xopenex HFA)	pMDI 2 puffs Q4–6 h prn			++++ (inhaler alone) +++ (if spacer used)	Prime before first use and if not used in > 3 d
Levalbuterol Hydrochloride (Xopenex)	Nebulizer 1 vial Q6–8 h prn (max 3× daily)			+ (if mask used) ++ (if mouthpiece used)	Vials need to be opened and placed inside nebulizer
Long-Acting β_2-Agonist (LABA) Bronchodilator—*maintenance therapy*					
Formoterol (Foradil Aerolizer)	DPI 1 capsule (12 µg) Q12 h	Improve respiratory symptoms, exercise capacity, and airflow obstruction, in patients not controlled with a SABA Also improve adherence, health-related quality of life, and reduce exacerbations	See class effect: generally milder side effects than short-acting agents	+++	Capsules should be stored in blister pack and only removed before use
Arformoterol (Brovana)	Nebulizer 1 vial (15 µg) BID			+ (if mask used) ++ (if mouthpiece used)	Vials need to be opened and placed inside nebulizer
Formoterol (Peforomist)	Nebulizer 1 vial (20 µg) BID			+ (if mask used) ++ (if mouthpiece used)	Vials need to be opened and placed inside nebulizer
Indacaterol (Arcapta Neohaler)	DPI 1 capsule (75 µg) once daily			+++	Capsules should be stored in blister pack and only removed before use
Salmeterol (Serevent Diskus)	DPI 50 µg Q12 h			+++	Capsule has to be pierced before use
Olodaterol (Striverdi Respimat)	SMI 2 inhalations once daily			++	Prime prior to first use and if not used in > 21 d
Short-Acting Anticholinergic Bronchodilator—*maintenance therapy*					
Ipratropium (Atrovent HFA)	pMDI 2 puffs 4× daily (not to exceed 12 puffs in 24 h)	Improve respiratory symptoms, exercise capacity, and airflow obstruction	Class effect: headache, dry mouth, bad taste, pharyngitis, sinusitis, urinary retention, constipation, cardiovascular (arrhythmia, mortality), glaucoma, paradoxical bronchospasm	++++ (inhaler alone) +++ (if spacer used)	Prime prior to first use and if not used in > 3 d
Ipratropium (Atrovent)	Nebulizer 1 vial (500 µg) 3–4× daily			+ (if mask used) ++ (if mouthpiece used)	Vials need to be opened and placed inside nebulizer
Combined Short-Acting Anticholinergic + SABA Bronchodilator—*maintenance therapy*					
Albuterol+Ipratropium (Combivent Respimat)	SMI 2 inhalations 4× daily	Additive improvement	See corresponding class effects	++	Prime prior to first use and if not used in > 21 d
Albuterol+Ipratropium (DuoNeb)	Nebulizer 1 vial (3 mL) Q4–6 h			+ (if mask used) ++ (if mouthpiece used)	Vials need to be opened and placed inside nebulizer
Long-Acting Anticholinergic (LAMA) Bronchodilator—*maintenance therapy*					
Aclidinium bromide (Tudorza Pressair)	DPI 1 inhalation 2× daily	Improve respiratory symptoms, exercise capacity, airflow obstruction, adherence, and health-related quality of life; and reduce exacerbations	See class effect; generally milder side effects than short-acting agents *Note:* when LAMA is prescribed, the short-acting anticholinergic is discontinued	++	Need to press and release the green button prior to use, after correctly administering full dose the button should turn red
Tiotropium (Spiriva Handihaler)	DPI 1 capsule (18 µg) once daily			+++	Capsule has to be pierced before use, may need to repeat inhalation in order to get full dose
Umeclidinium (Incruse Ellipta)	DPI 1 inhalation once daily			++	No
Combined LABA + LAMA Bronchodilator—*maintenance therapy*					
Vilanterol+Umeclidinium (Anoro Ellipta)	DPI 1 inhalation once daily	Additive improvement, including increased adherence, and decreased polypharmacy and caregiver burden	See corresponding class effects	++	No

Inhaled Corticosteroid (ICS)—*maintenance therapy*					
Beclomethasone (Qvar)	pMDI 1 inhalation BID	Improve symptoms lung function, and health-related quality of life, and reduce exacerbations *Note:* single therapy with ICS is not recommended in COPD, as it is less effective than ICS+LABA	Class effect: dysphonia, oropharyngeal candidiasis, headache, skin bruising, pain in extremities, reduce bone mineral density, posterior subcapsular cataract, pneumonia	+++	Prime before first use or if not used > 10 d. Rinse mouth after use
Ciclesonide (Alvesco)	pMDI 1 inhalation BID			+++	Prime before first use or if not used in 7–10 d. Rinse mouth after use
Flunisolide (Aerospan HFA)	pMDI 1 inhalation BID			+++	Prime before first use or if not used in 2 wk. Rinse mouth after use
Fluticasone (Flovent Diskus)	DPI 1 inhalation BID			+++	Use in horizontal position. Rinse mouth after use
Fluticasone (Flovent HFA)	pMDI 1 inhalation BID			+++	Prime before first use, if not used in > 7 d, and if inhaler has been dropped. Rinse mouth after use
Mometasone (Asmanex Twisthaler)	pMDI 1 inhalation once daily in evening			+++	Twist to activate dose. Rinse mouth after use
Combined LABA Bronchodilator + ICS—*maintenance therapy*					
Formoterol+Budesonide (Symbicort)	pMDI 2 inhalations BID	Additive improvement, including increased adherence, and decreased polypharmacy and caregiver burden	See corresponding class effects	++++ (inhaler alone) +++ (if spacer used)	Prime before first use, if not used in > 7 d, and if inhaler has been dropped, wait 1 min between doses. Rinse mouth after use
Formoterol+Mometasone (Dulera)	pMDI 2 inhalations BID			++++ (inhaler alone) +++ (if spacer used)	Prime before first use and if not used in > 5 d, wait 30–60 s between doses. Rinse mouth after use
Salmeterol+Fluticasone (Advair Diskus)	DPI 1 inhalation Q12 hrs			+++	Use in horizontal position, have to slide lever to actuate dose. Rinse mouth after use
Vilanterol+Fluticasone (Breo Ellipta)	DPI 1 inhalation once daily			++	Rinse mouth after use
Other medications—*maintenance therapy*					
Roflumilast (Daliresp)	Oral tablets Take one 500 µg tablet once daily	Reduced exacerbations in chronic bronchitis and frequent exacerbators	Weight loss, decreased appetite, nausea, diarrhea, insomnia, headache, suicidal thoughts	+	N/A
Theophylline	Oral tablets, capsules, or solution; Aim for serum theophylline level of 8–12 mcg/mL	Third line bronchodilator: improve symptoms, exercise capacity, airflow obstruction, and quality of life	Headache, insomnia, nausea, diarrhea, seizure, arrhythmias	+	Take with water 1 h before meals or 2 h after meals. Monitor for drug interactions.
Azithromycin	Oral tablets Take one 250 mg tablet daily	Frequent exacerbators, not controlled by long-acting bronchodilators	QT-prolongation; macrolide-resistant organisms, hearing decrements of 5%	+	Avoid coadministration with calcium supplements
Triple-Inhaler Therapy: LAMA, LABA, and ICS via a common inhalation device (Ellipta)[d]—*maintenance therapy*					
Umeclidinium (Incruse Ellipta)			DPI 1 inhalation once daily		
Vilanterol+Fluticasone (Breo Ellipta)			DPI 1 inhalation once daily		

DPI, dry powder inhaler; HFA, hydrofluoroalkane; LABA, long-acting β_2-selective agonist; LAMA, long-acting muscarinic antagonist; pMDI, pressurized metered-dose inhaler; PIF, peak inspiratory fow; SABA, short acting β_2-agonist; SMI, soft-mist inhaler.
[a]Only medications FDA approved for use in COPD were included. Prescribing information obtained from package inserts.
[b]Limited to the most prominent and clinically-concerning side effects (list is not comprehensive). When considering side effects, note that risk is substantially increased by concurrent multimorbidity and polypharmacy, and that disease severity may itself be an important underlying mechanism (eg, comorbid cardiovascular disease in the setting of a severe COPD exacerbation).
[c]Scaled as 1 + to 4+, where 1+ = little to no effect and 4+ = highest effect.
[d]Ellipta allows triple-inhaler therapy to be administered using the same device platform.

The anticholinergic ipratropium is a short-acting inhaled bronchodilator, having little systemic absorption. It is

indicated as *maintenance therapy* (see **Table 84-9**), but adherence is problematic because it requires frequent dosing. Hence, ipratropium is often combined with albuterol as a nebulized solution, particularly in long-term care and hospital settings. Combined ipratropium and albuterol is also available as a soft-mist inhaler. Common side effects of short-acting anticholinergics are listed in **Table 84-9**, with concerns especially raised in COPD patients with cardiovascular disease, narrow-angle glaucoma, and benign prostatic hyperplasia.

Long-Acting Bronchodilators Long-acting β_2-selective adrenergic agonists (LABA—indacaterol, olodaterol, vilanterol) and long-acting anticholinergics (including the long-acting muscarinic antagonists [LAMA]—aclidinium, tiotropium, umeclidinium) are considered *maintenance therapy* (see **Table 84-9**) for persons whose symptoms are inadequately managed with one or both classes of short-acting bronchodilator(s), and for those who are frequent exacerbators or have moderate-to-severe airflow obstruction. Subsequent to initiating a long-acting bronchodilator, there is a continued role for a short-acting β_2-agonist (SABA) in the management of acute symptoms (rescue therapy).

Long-acting bronchodilators are currently limited to delivery by handheld inhalers. Treatment options for patients who require a longer-acting nebulized bronchodilator are limited to twice-daily β_2-selective adrenergic agonist (arformoterol, formoterol), whereas a nebulized anticholinergic is only available as a short-acting preparation (ipratropium 4 times daily).

Inhaled Corticosteroids Whereas oral corticosteroids are not indicated in stable COPD due to multiple side effects, long-term treatment with inhaled corticosteroids (ICS) have an important role in patients with more severe airflow obstruction or for frequent exacerbators not adequately managed by long-acting β_2-selective adrenergic agonist (LABA) or anticholinergic (LAMA). However, in contrast to asthma, the use of ICS as single therapy is not advised in stable COPD, since it is less effective than combined ICS+LABA. The latter improves respiratory symptoms, lung function, and health-related quality of life, as well as reduces exacerbations.

The adverse effects of ICS are dose and duration dependent, and influenced by patient-specific factors, namely inhaler technique. While ICS doses are lower than oral corticosteroids, the duration of therapy of ICS is often life long, leading to longer exposures. Significant localized deposition of ICSs occurs in the oropharynx (60%–90% of dose), and may lead to dysphonia, oropharyngeal candidiasis, and allergic contact dermatitis of the mouth, nostrils, and eyes. Poor inhaler technique may increase the risk for these localized adverse drug effects. For example, older adults who forget to rinse, gargle, and spit after using their ICS are more likely to develop dysphonia and/or candidiasis. Once swallowed, the remaining ICS is absorbed from the gastrointestinal tract, undergoes first-pass metabolism and the majority of the dose is inactivated. What is not inactivated is available systemically and contributes to potential adverse effects. Predicting the degree of systemic glucocorticoid activity from ICS is difficult. Factors that influence risk from systemic glucocorticoid activity include advanced age, sex, cigarette smoking, activity level, and dietary calcium and vitamin D intake.

The systemic adverse effects of ICS are well described. Several have unique implications in older COPD patients. In particular, ICS are associated with decreased bone mineral density and posterior subcapsular cataract development, both of which can increase the risk of injurious falls in older adults. While studies examining the impact of ICSs on the risk of osteoporosis are mixed, doses above 800 mcg/day of budesonide or equivalent appear to be associated with accelerated loss of bone mineral density, and increased risk of fracture. Hence, osteoporosis prevention therapy should be considered for any patient receiving long-term ICS. Though subcapsular cataracts are clearly linked to systemic glucocorticoids, causality with ICS is less clear (with advancing illness, patients are more likely to receive both oral and ICS). In addition to increasing the risk of falls, visual impairment due to cataracts can also contribute to medication errors and difficulty with proper inhaler technique.

Lastly, meta-analyses and a large case-control study have observed a mild increase (6%–9%) in the risk of pneumonia associated with ICS. Although prior work has shown that the use of ICS did not increase mortality in veterans hospitalized with COPD and pneumonia, it remains prudent to consider discontinuation of ICS among COPD patients who develop pneumonia. Otherwise, whether a specific ICS or delivery device poses greater risk has been inconclusive.

Combination Inhalers **Table 84-9** presents inhalers that combine (1) a β_2-selective adrenergic agonist and an anticholinergic, or (2) a β_2-selective adrenergic agonist and (inhaled) corticosteroid. Combination therapy provides additional benefit on lung function, symptoms, exercise capacity, and exacerbation risk as compared with its components, particularly in patients who have severe airflow obstruction.

Theophylline Theophylline is a nonselective phosphodiesterase inhibitor, available in multiple oral formulations. It is considered a third-line bronchodilator in the management of stable COPD, after inhaled β -agonists and

anticholinergics. Theophylline is otherwise NOT recommended for routine management of COPD exacerbations, given the lack of efficacy and high likelihood of side effects in this setting. Theophylline requires therapeutic drug monitoring with a goal serum level in older adults of 8 to 12 mcg/mL. Levels can increase significantly in the presence of cirrhosis, heart failure, hypothyroidism, and cimetidine. In older adults patients treated with theophylline, coadministration of ciprofloxacin (CYP1A2 inhibitor) is associated with a twofold increased risk of hospitalization. Conversely, theophylline levels decrease when hepatic enzymatic activity is increased as in hyperthyroidism, smoking, use of phenytoin, phenobarbital, and carbamezapine, or consumption of cruciferous vegetables and charbroiled meats.

Roflumilast Roflumilast is a once-daily oral phosphodiesterase-4 inhibitor, serving as maintenance therapy to prevent COPD exacerbations in patients with severe airflow obstruction, chronic bronchitis, and a history of exacerbations (despite standard therapy). Common side effects include nausea, diarrhea, and weight loss, occurring at higher rates in those aged greater than or equal to 65.

Macrolides Azithromycin (250 mg once daily) is a macrolide antibiotic that has been shown to decrease the frequency of COPD exacerbations when added to usual care. This effect is accompanied by an improved quality of life, but also an increased incidence of macrolide-resistant organisms and hearing decrements. Azithromycin should be considered maintenance therapy for frequent exacerbators who are maximized on triple-inhaler therapy and do not have a hearing impairment, resting tachycardia, or apparent risk of QTc prolongation.

Mucolytics Based on low efficacy and increased risk of adverse effects, there is little evidence to support mucolytics (eg, N-acetylcysteine) as routine care for stable COPD. Hence, mucolytic use is limited to tenacious sputum production that is refractory to standard therapy (smoking cessation, inhaled bronchodilator and corticosteroid, antibiotics, theophylline, and/or roflumilast).

Treatment barriers Medication nonadherence is reported in 50% to 60% of COPD patients. Nonadherence is associated with more frequent exacerbations, worsening of disease, and difficulty in reconciling medications. The causes of nonadherence include cognitive and physical impairments, cost, medication complexity, lack of perceived benefit, and adverse drug effects.

Cognitive Impairment A Mini-Mental Status Examination (MMSE) score less than 24, inability to perform intersecting pentagons, and/or an EXIT-25 cognitive test score greater than or equal to 15 is associated with impaired ability to learn inhaler techniques. Requiring patients to “teach-back” inhaler technique may further identify those with difficulty performing multistep commands. Cognitive impairment often leads to uncoordinated “press and breathe” use of inhalers, as well as nonadherence. Consequently, nebulizers often replace handheld inhalers in cognitively impaired patients.

Physical Impairment Many handheld inhalers require both fine-motor skills and adequate grip strength to actuate. This is especially problematic for certain pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and newer soft-mist inhalers (SMIs). Decreased hand strength, for example, is a predictor for incorrect use of a pMDI. The presence of arthritis, joint pain, or neuromuscular diseases may prevent proper use of handheld inhalers, by reducing grip strength or impairing dexterity. Impaired manual dexterity prevents patients from properly priming or preparing the inhaler/nebulizer, particularly if devices require removing capsules from foil packaging, mixing diluents with active agents, and puncturing capsules prior to inhalation.

Visual impairment can make distinguishing between products difficult (rescue inhaler versus maintenance inhaler) and negate the adherence feedback mechanisms built into certain devices (dosage counters). Individuals with impaired hearing may have difficulty understanding inhaler training, and several inhaler/valved-chamber devices (VCD) use auditory cues for proper inhalation technique, to which the hearing impaired older adult is unable to respond.

DPIs require a sufficient peak inspiratory flow (PIF) of greater than 45 L/min to disaggregate the dry powder from the container. Reduced respiratory muscle strength due to aging and progressive COPD may explain the variability in DPI drug-lung deposition in older adults. While DPIs result in higher drug-lung deposition (10%–40%) when compared to pMDIs (10%–20%), the increased PIF required to disaggregate the product also results in up to 80% oropharyngeal deposition. The use of pMDIs may be also adversely affected by a low PIF, since these require a slow, deep inhalation, preferably through a VCD, to allow for maximal drug-lung deposition. In contrast, soft-mist inhalers (SMI) require a gentle breathing maneuver, thus offering an advantage over DPIs and pMDIs for patients with reduced PIF or who struggle with “press and breathe” coordination. When performed correctly, SMIs can achieve 40% to 60% drug-lung deposition. Importantly, patients/caregivers should be reminded that inhalation technique varies with DPI,

pMDI, and SMI.

When functional impairments limit the use of handheld inhalers, a nebulizer is the easiest delivery device to use. Moreover, patients who have severe dyspnea, severe airflow obstruction, or frequent exacerbations may also find nebulizers more effective. Lastly, as discussed below, nebulizer therapy may be a cost-effective alternative in patients with high Medicare Part D health care costs. Unfortunately, nebulizers have disadvantages, requiring a power source, are not easily portable, must be carefully maintained/cleaned, and generally take longer to administer.

Cost Payers often seek lower cost therapies, potentially compromising efficacy, complexity, and patient adherence, or they require prior authorization for certain products (COPD prescription fill rates decline when patients perceive barriers to obtaining medications). In addition, because older adult patients regularly experience polypharmacy, they may have significant out-of-pocket expenses due to a coverage gap ("the donut hole") in their Medicare Part D annual provider and prescription expenses. This increased cost impacts handheld inhalers, as these are covered under Medicare Part D. However, nebulizers, compressors, and medications that are available as inhalation solutions are covered under Medicare Part B. Hence, any premiums, deductibles, and copayments for these items do not count toward Medicare Part D costs, potentially helping older patients avoid gaps in coverage.

Nonpharmacologic Therapies

Vaccination Annual influenza vaccination is a well-established safe and efficacious means of reducing complications related to the flu, including COPD exacerbations. Older adult patients can elect to receive either the regular dose influenza vaccine or newer high-dose influenza vaccine designed for persons aged 65 and older. Evidence supports recommending older adults receive the high-dose quadrivalent vaccine. This vaccine is associated with a higher immune response in older adults and was 24.2% more effective in preventing flu when compared to the standard-dose vaccine. The Center for Disease Control and its Advisory Committee on Immunization Practices have not expressed a preference for either vaccine.

Although pneumococcal vaccination has not been shown to directly impact COPD exacerbations or hospitalizations, it does have a demonstrable impact on pneumococcal pneumonia and bacteremia. Patients should therefore be vaccinated according to updated CDC guidelines, which now include use of both polysaccharide and conjugate vaccines in series.

Smoking cessation Abstinence from tobacco smoking is important for all persons with COPD, irrespective of age. Smoking status should be addressed at every office visit and during hospitalizations, including number of cigarettes per day, triggers for smoking, time to first cigarette use following morning awakening, details of prior quit attempts, and patient-identified barriers to quitting. Smoking cessation attenuates the rate of decline in lung function, and reduces the risk of COPD exacerbation, cardiovascular disease, cancer, and death.

Several methods are available to assist patients with smoking cessation. The combination of behavioral counseling and pharmacotherapy is most effective in achieving long-term abstinence. Importantly, available interventions for smoking cessation have comparable efficacy among older adults to that seen for younger persons. Therefore a nihilistic approach based on advanced patient age should not be taken. The "5 A's" algorithm (developed by the US Public Health Service): Ask, Advise, Assess, Assist, and Arrange—is an effective behavioral counseling strategy for use in the clinic setting. Referral to a smoking cessation program should be offered, and information regarding the US nationwide toll-free telephone counseling service (1-800-QUIT-NOW) should be provided. Mobile phone apps, text messaging, and computer-based interventions have been also developed. For patients ready to make a quit attempt, a quit date should be set, an action plan for managing cravings and triggers for smoking should be created, and a plan for follow-up with the health care provider must be arranged. The three pharmacologic treatments with the best efficacy include nicotine replacement (especially the combination of nicotine patch and a faster-acting agent such as gum or lozenges to address urges), varenicline, and bupropion. No single strategy has proven to be better than the other. Patient preference, comorbidities, and previous experience with quit attempts influences the choice of first line treatment. Nicotine replacement therapy is generally safe, even for persons with underlying cardiovascular disease. Bupropion may be the best first-line agent for persons with depression or schizophrenia, but nicotine replacement therapy may be preferable for persons with bipolar disorder, since antidepressant agents can trigger manic episodes. Patients taking bupropion or varenicline must also be monitored for development of neuropsychiatric symptoms, including suicidal ideation. Close partnering with patients' mental health care providers is important in choosing pharmacotherapy for smoking cessation. Combination therapy can be considered when single class pharmacotherapy has failed. Nicotine replacement should be provided as needed during hospitalizations, to prevent nicotine withdrawal

symptoms.

Long-term oxygen therapy Requirement for long-term oxygen therapy (LTOT) is a poor prognostic feature of COPD. The indications for LTOT are shown in **Table 84-10**. A formal oxygen prescription specifying the indications for treatment, conditions for use (rest, exercise, and/or sleep) and type of oxygen system(s) is required. LTOT worn more than 16 hours per day improves survival for hypoxemic patients ($PaO_2 \leq 60$ mm Hg) with COPD. Among persons with resting hypoxemia, LTOT can also improve exercise capacity, sleep quality, cognition, depression, cardiovascular comorbidity, and quality of life, as well as reduce the frequency of hospitalizations. Oxygen therapy also reduces dyspnea and improves exercise capacity when used during exertion for those who desaturate with ambulation.

TABLE 84-10 INDICATIONS FOR LONG-TERM OXYGEN THERAPY

Daily use (at least 16 h/d):
• Resting arterial PO_2 (PaO_2) ≤ 55 mm Hg, or pulse oxygen saturation (SpO_2) ≤ 88%
• $PaO_2 \leq 59$ mm Hg or $SpO_2 \leq 89\%$, concurrent with cor pulmonale, right heart failure, or erythrocytosis (hematocrit > 55%)
Nocturnal use:
• $PaO_2 \leq 55$ mm Hg or $SpO_2 \leq 88\%$ during sleep
• Decrease in $PaO_2 > 10$ mm Hg or in $SpO_2 > 5\%$ during sleep with symptoms or signs of nocturnal hypoxemia such as disrupted sleep, morning headaches, impaired cognitive function or insomnia
Use with exertion:
• Decrease in $PaO_2 \leq 55$ mm Hg or in $SpO_2 \leq 88\%$ during exercise

Practical issues and potential risks associated with providing LTOT must be considered, particularly among older adult persons. Long oxygen tubing attached to oxygen concentrators in the home can pose a fall risk. Cigarette smoking, cooking flames, and other heating systems can pose the risk of explosion or fire. Lightweight portable O_2 systems maximize the likelihood that the older adult patient will be physically capable of using their O_2 with exertion; rollator walkers with handbrakes, seat, and basket assist debilitated patients in carrying their O_2 systems and maintaining mobility. Patient cognition and home layout and safety should also be assessed.

Noninvasive positive pressure ventilation Noninvasive positive pressure ventilation (NPPV) is indicated for the management of some patients with COPD. First, obstructive sleep apnea (OSA) is a common comorbidity of COPD; persons with both conditions are considered as having COPD-OSA overlap syndrome. Individuals with COPD-OSA overlap syndrome have worse gas exchange disturbances, increased risk of pulmonary hypertension, and a higher mortality risk than those with either condition alone. Continuous positive airway pressure (CPAP) therapy is usually indicated for the management of OSA, when present. Second, NPPV (usually bilevel positive airway pressure [BPAP]) is indicated for persons with acute exacerbations of COPD associated with acute hypercarbia ($PaCO_2 > 45$ mm Hg) and respiratory acidosis (who lack contraindications as noted below). In this setting, NPPV improves gas exchange, improves breathing pattern, and provides support to the respiratory muscles, while allowing time for medical therapy such as bronchodilators, antibiotics, and corticosteroids to improve airflow and reduce the work of breathing. High-quality randomized controlled trials have shown that, as compared with medical therapy alone, NPPV for acute hypercarbia related to COPD exacerbations reduces intubation rates, shortens hospital length of stay, reduces the risk of ventilator-associated pneumonia, and improves survival.

The role of "chronic" NPPV for long-term management of COPD is less certain. Uncontrolled case series suggest that nocturnal NPPV can improve daytime gas exchange and daytime walking activity (postulated to be related to respiratory muscle rest and reduction in hyperinflation), but randomized trials have not consistently shown these effects. Chronic NPPV has not been demonstrated to reduce hospitalizations or long-term mortality rate. It has been shown in research settings to facilitate exercise training in pulmonary rehabilitation for some persons. However, patient intolerance and poor acceptance of NPPV commonly limits its long-term use. Chronic NPPV is considered for nocturnal use in persons with daytime hypercarbia ($PaCO_2 \geq 50$ mm Hg), in those with sustained alveolar hypoventilation for more than 5 continuous minutes during sleep despite supplemental oxygen therapy greater than or equal to 2 L/min, or in those who have episodes of hypercarbic respiratory failure requiring assisted ventilation. In these individuals, chronic NPPV may provide symptomatic relief, particularly if there is coexisting sleep disruption and

daytime fatigue.

Contraindications to NPPV include cardiorespiratory arrest, unstable vital signs, inability to tolerate the face mask (discomfort, skin breakdown, or claustrophobia), facial trauma, inability to protect the airway, combative behavior, severely impaired consciousness, need to clear purulent secretions, high aspiration risk, and recent gastric or esophageal surgery. Caution is also urged regarding NPPV in persons with giant bullae or very severe bullous emphysema, given the risk of inducing a pneumothorax with a nonhealing bronchopleural fistula.

Pulmonary rehabilitation COPD patients are less active than healthy age-matched persons. Exertional dyspnea, leg fatigue, anxiety, depression, impaired balance, and fear may all contribute to a low physical activity. Other contributory factors include skeletal muscle dysfunction (sarcopenia), which is common in COPD, and the increased dyspnea and gas exchange abnormalities that result from acute exacerbations. Importantly, because it can lead to deconditioning, including sarcopenia, decreased endurance, and exercise intolerance, physical inactivity is itself associated with an earlier onset of lactic acidosis at low work rates, yielding a greater ventilatory demand and dyspnea at any given activity level. Moreover, as physical inactivity progresses, there is increased physical disability, social isolation, anxiety, and depression, as well as risk of COPD exacerbation (hospitalization), obesity, diabetes, cardiovascular disease, and death.

Pulmonary rehabilitation is "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors." Pulmonary rehabilitation reduces dyspnea and leg fatigue, improves exercise tolerance and patient-reported quality of life, decreases the risk of hospitalizations and other urgent health care utilization, and reduces depression. It can also improve balance, reduce the risk of falls, and improve physical activity levels. The process of pulmonary rehabilitation includes patient assessment, supervised exercise training and reconditioning, patient education, and outcome assessment. Exercise training typically includes aerobic and strength training of the lower and upper extremities, using a treadmill or hallway walking, cycling, arm ergometry, stair climbing, and light weight lifting. Nordic walking and interval-type exercise, balance training, and Tai Chi are also effective. Walking aids such as rollator walkers can assist in improving tolerance of walking in severely disabled persons. The education component of pulmonary rehabilitation is geared toward helping patients understand and manage their condition (including early recognition of exacerbations), as well as promotion of a healthy and active lifestyle. Emphasis is also typically placed on training patients with pacing, energy conservation, and pursed lips breathing techniques, as well as strategies for management of anxiety and prevention of "dyspnea crisis."

Patients who remain symptomatic despite optimized pharmacologic therapy (including those with severely impaired lung function) should be referred for pulmonary rehabilitation. Persons over the age of 70, even those with severe lung function impairment and comorbidities, benefit to the same degree as younger persons. Close partnering between patients' health care providers and pulmonary rehabilitation staff is important to ensure patient safety.

Surgical therapies Surgical therapies for COPD include lung volume reduction surgery (LVRS) and lung transplantation. LVRS is a procedure wherein areas of lung that are virtually functionless (not contributing to ventilation or perfusion) are removed, thereby reducing hyperinflation and improving elastic recoil and diaphragm positioning and function. LVRS can be accomplished by surgical resection of regions of lung (typically upper lung zones), or bronchoscopic placement of coils or other devices that lead to atelectasis of targeted lung zones. When used in selected patients, LVRS can lead improvements in exercise tolerance, oxygenation, lung function, quality of life, and survival. LVRS can also serve as a bridge to lung transplantation for some patients. Ideal candidates for LVRS are those with emphysema-predominant COPD (heterogeneous distribution, upper lung zone predominant), who lack features of chronic bronchitis, are not at extremes of body weight, do not require regular treatment with systemic corticosteroids, and who remain symptomatic with low exercise tolerance despite optimized pharmacologic therapy and pulmonary rehabilitation. Those whose FEV_1 or diffusing capacity (D_{LCO}) is less than 20% of predicted have higher mortality following surgical LVRS and should not undergo the procedure.

Single or double lung transplantation may be considered for selected older adult persons with very severe COPD. Although lung transplantation can improve exercise tolerance, quality of life, and survival of some individuals, anticipated survival benefit should exceed the short-term and long-term risks of undergoing the procedure, including surgical and perioperative morbidity and mortality, and potential complications related to long-term immunosuppressive therapy. Since median survival following lung transplantation is 5 to 6 years, and since surgical risk is high among older adult persons with multi-morbidity, referral for lung transplantation should be undertaken only when anticipated survival related to the COPD is lower than that related to age and/or comorbidities. Given the

variable rate of progression of COPD over time, this is difficult to predict. Current guidelines suggest lung transplantation referral for COPD patients who have FEV_1 and diffusing capacity (D_{LCO}) less than 20% of predicted, pulmonary hypertension and/or cor pulmonale, BODE Index greater than 7, are worsening clinically despite optimized medical therapies, had at least one hospitalization for exacerbation with acute hypercapnia, and have demonstrated long-term complete abstinence from tobacco or other substance use. They must also lack other contraindications as indicated in the 2006 lung transplantation guidelines. Although age over 65 is a relative, rather than absolute contraindication to lung transplantation, recent studies have shown that those over age 70 have an increased risk of 30-day and 1-year mortality and are less likely to return to prior baseline functional status, as compared to younger persons.

ACUTE EXACERBATION

An acute exacerbation of COPD is defined as a change in sputum volume or purulence, and/or an increase in dyspnea beyond usual day-to-day variation that warrants a change in therapy. The frequency of exacerbations increases with severity of airflow obstruction, with older persons likely to have more severe disease. It is estimated that the average older person with COPD experiences two to three exacerbations per year, each lasting nearly 2 weeks. Each of these events presents a risk for respiratory failure, but more commonly results in tangible impacts on quality of life, increased airflow obstruction and related respiratory impairments, and disability. COPD exacerbations are responsible for up to 20% of hospitalizations in individuals 75 years of age or older, and are a source of expansive health care costs. Moreover, institutions are now financially penalized for all-cause readmissions following admissions for COPD exacerbations.

Risk Factors

Risk factors for acute exacerbations include advanced age, severe airflow obstruction, chronic bronchitis, comorbid diseases (particularly cardiovascular disease, diabetes mellitus, and gastroesophageal reflux), and prior exacerbations. In the aging patient, the weakening of thoracic muscles, degenerative changes of the spine, and impairment of mucociliary clearance make secretion clearance and cough less effective. Older adult patients are therefore less able to manage the increased secretions resulting from even a mild exacerbation. Age-related changes to both adaptive and innate immune systems make responses to infection less robust, and the inflammatory responses to acute illness more discordant. Protective immunity from prior immunization may be waning or frankly incompetent. The previously discussed changes to overall respiratory function with both age and COPD limit underlying pulmonary reserve. Comorbid conditions may make it more difficult to tolerate the stress of acute illnesses. For all these reasons, the presentations of and outcomes from acute exacerbations in older adults may be more severe than those in middle-aged individuals of similar spirometric severity.

Etiologies

Respiratory infection accounts for 70% of COPD exacerbations. Other triggers may include environmental irritants or changes in weather or air temperature.

Viruses, typically detected using direct fluorescent antibody (DFA) or polymerase chain reaction (PCR) based methods, can be found in up to two-thirds of individuals with acute exacerbations. Common viral pathogens, of which rhinoviruses are the most prevalent, are shown in **Table 84-11**. However, a positive PCR does not indicate causality, as positive results can also be found in asymptomatic, stable individuals with COPD. The exception to this is influenza, which should always be considered a causative pathogen and treated accordingly.

TABLE 84-11 COMMON INFECTIOUS PATHOGENS IN ACUTE EXACERBATIONS OF COPD

VIRAL	BACTERIAL
Rhinovirus	*H. influenzae*
Influenza	*M. catarrhalis*
Parainfluenza	*S. pneumoniae*
Adenovirus	*P. aeruginosa*

Coronavirus	*Enterobacteriaceae*
Respiratory syncytial virus	*M. pneumoniae*
Human metapneumovirus	*C. pneumoniae*
	Legionella spp.

Bacteria are responsible for half or more of COPD exacerbations, and may coinfect with viral pathogens. As shown in **Table 84-11**, *Haemophilus influenzae, Moraxella catarrhalis,* and *Streptococcus pneumoniae* are the most common, but *Pseudomonas aeruginosa* and enteric gram-negative bacteria are frequently isolated in more severe COPD and in residents of skilled nursing facilities; the contribution of atypical pathogens is more difficult to estimate accurately given the infrequency with which titers or accurate cultures are obtained. Acquisition of new strains of common pathogens plays a much more important role in acute exacerbations of COPD than changes in the load of colonizing bacteria. This is supported by observations that new bacterial strains are associated with more robust humoral immunity and inflammatory responses, and clearance of these strains correlates with resolution of acute illness.

Diagnostic and Therapeutic Approaches

COPD exacerbation is a clinical diagnosis. In many cases, sputum culture does not differentiate between colonizing flora and true infectious pathogen, and underestimates the most common bacterial culprits; therefore, sputum culture is not necessary in routine COPD exacerbations. However, sputum culture may be helpful in detecting worrisome pathogens or resistant strains, if an individual has failed empiric outpatient treatment strategies or has risk factors for *Pseudomonas aeruginosa* (hospitalization in the past 3 months, greater than or equal to 4 courses of antibiotics in the past year, or severe airflow obstruction). DFA, with or without PCR, is important during influenza season, as specific antiviral therapy may be initiated. Procalcitonin is a peptide precursor that increases in the serum in response to bacterial toxins, and is a potential biomarker to guide antibiotic use. Though further clinical validation is needed, a Cochrane meta-analysis demonstrated that procalcitonin guidance could reduce antibiotic exposure without increase in treatment failure or mortality.

Most exacerbations can be treated as an outpatient. Patients with more severe airflow obstruction, significant comorbidities, inadequate home support, new/worsening gas exchange abnormalities, or prior treatment failure should be admitted to the hospital for further evaluation (labs, chest x-ray, ECG, arterial blood gas); however, depending on home-based resources, a few such patients may still be candidates for intensive home care. Those with impending respiratory failure are admitted to the intensive care unit.

Escalation of inhaled medications Escalation of bronchodilator therapy is required for all COPD exacerbations and may be sufficient to treat mild cases. The preferred bronchodilator is a short-acting inhaled β_2-agonist with or without a short acting anticholinergic. Nebulized delivery may be more effective and comfortable than metered dose inhalers, particularly for patients with significant dyspnea, cognitive impairment, or severe airflow obstruction. Otherwise, usual maintenance therapies, such as long-acting bronchodilators and inhaled corticosteroids, should be temporarily withheld during an exacerbation. However, as recovery ensues, the patient is transitioned back to a maintenance regimen, but escalation may be warranted to reduce the risk of subsequent exacerbations. If clinical improvement is thereafter achieved, attention is given to streamlining the number of inhaled medication devices to improve self-efficacy and compliance.

Antibiotics General antibiotic recommendations for COPD exacerbations are presented in **Table 84-12**. Antibiotics should be used in moderate and severe exacerbations, but there is insufficient evidence to support its routine use in mild exacerbations. Choice of antibiotic is driven by a number of factors (history, tolerance, comorbidities, medication interactions, prior treatment failure, local patterns of resistance), and complicated by the fact that sputum culture data is unreliable in guiding decisions. Older adult residents of skilled nursing facilities, or those who have spent time in acute-care or subacute-rehab facilities within 90 days of exacerbation, and persons with severe airflow obstruction are more likely to be colonized with resistant organisms (methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and multi-drug resistant gram-negative organisms). These latter risk factors should guide choice of empiric therapy. The duration of antibiotic therapy, in the absence of complicating factors such as pneumonia, is typically 3 to 7 days.

TABLE 84-12 SUGGESTED ANTIBIOTIC REGIMENS FOR ACUTE EXACERBATION OF COPD

EXACERBATION SEVERITY	ANTIBIOTICS
Mild	None
Moderate[a,b]	Macrolide, doxycycline, cephalosporin, amoxicillin/clavulanate, bactrim, fluoroquinolone
Severe[c,d]	Fluoroquinolone, antipseudomonal penicillin, cephalosporin (third generation)

[a] Moderate exacerbations are accompanied by at least two of the following: increased dyspnea, sputum volume, and sputum purulence—in the absence of respiratory failure.

[b] Severe exacerbations are accompanied by at least two of the following: increased dyspnea, sputum volume, and sputum purulence—concurrent with respiratory failure.

[c] If risk factors for pseudomonas, use ciprofloxacin and obtain sputum culture.

[d] If risk factors for pseudomonas, use pipercillin-tazobactam or ceftazidime, and obtain sputum culture.

Corticosteroids The acute use of systemic corticosteroid is associated with improved symptoms, decreased treatment failure, improved lung function, and shorter duration of hospitalization, but can be complicated by side effects, particularly in the older persons with multimorbidity. The side effects include hyperglycemia, delirium, fluid retention, and myopathy. In addition, because older COPD patients often have atrial fibrillation requiring anticoagulation, and because systemic corticosteroids can cause skin thinning and purpura, this combination of medications may also lead to greater bruising and bleeding.

The adverse effects of systemic corticosteroid are dose and duration dependent. For example, delirium is more likely to occur with doses greater than 60 mg of prednisone per day. As such, dose and duration of therapy should be as conservative as possible. The optimal dose and duration of corticosteroids is unknown; however, a study of individuals hospitalized with COPD exacerbations (most of whom had severe disease) demonstrated that a 5-day course of oral prednisone was noninferior to a more conventional 7- to 14-day steroid taper in terms of event resolution and time to next exacerbation. In fact, those on the shorter course had a reduced length of stay, though reasons for this were unclear.

Invasive and noninvasive ventilation Many patients admitted to the hospital with impending respiratory failure in the setting of COPD exacerbation can be managed effectively with noninvasive ventilation, though less so in the case of concomitant pneumonia. Intubation and mechanical ventilation may be required in the case of severe respiratory failure, if consistent with an individual's goals of care.

Comorbidities Not all escalations of respiratory symptoms in an older COPD patient result from COPD exacerbations per se. Dyspnea, wheezing, cough, and sputum production may result from other causes such as heart failure, pneumonia, or pulmonary embolism. Increased rescue inhaler use in such settings is therefore usually associated with therapeutic failure. Moreover, treatments that are crucial to COPD exacerbations may exacerbate comorbidities or cause potentially dangerous drug interactions. These comorbidities may additionally complicate or prolong recovery from such events. Individuals with COPD are particularly vulnerable to cardiovascular morbidity and mortality both during exacerbations and in the recovery period. Hence, careful consideration should be given as to whether the escalation of symptoms is occurring as a result of a COPD exacerbation, as opposed to another cause.

Discharge planning Discharge planning should consider referral for pulmonary rehabilitation, the need for home oxygen, and a recalibration of maintenance therapy (see Management section). Because new treatment regimens increase the likelihood of medication nonadherence or errors, this may be addressed by a formal medication reconciliation and pharmacist-based review. Patient and caregiver education regarding the discharge treatment plan is likewise essential, as are interventions to support safe and prompt transition back to routine care by the primary care provider or specialist. Furthermore, advance care planning should be initiated or reviewed in the wake of hospitalization, as history of a severe exacerbation increases the risk of future events.

PALLIATIVE CARE

Average life expectancy for COPD from time of diagnosis is shorter compared with other chronic conditions such as heart disease or stroke (14.2 years for COPD compared with 21.2 years for heart disease). Typical health trajectories for aging persons with COPD are usually gradual, but include a progressive decline in lung function resulting in

increased disability, intermittent exacerbations requiring hospitalizations, and death. Respiratory symptoms of dyspnea, cough, and sputum production are frequently reported by patients with advanced COPD, affecting up to 98% of patients (**Table 84-13**). Dyspnea may be more pronounced in older persons with COPD due to coexisting respiratory muscle weakness and comorbidities. Chest tightness and wheezing are also commonly experienced. Older persons with advanced COPD may also suffer from non-respiratory symptoms. Fatigue and weakness are frequently experienced, likely secondary to shortness of breath and progression of underlying disease and comorbidities. Pain is also present in 20% to 70% of persons with advanced COPD. Finally, psychological and spiritual distress such as anxiety, depression, and spiritual worries are common in advanced COPD. These chronic physical, psychological and spiritual symptoms contribute to a poor quality of life.

TABLE 84-13 SYMPTOM BURDEN AND MANAGEMENT IN ADVANCED COPD

SYMPTOM	PREVALENCE	THERAPIES	NOTES
Physical			
Dyspnea	94%	Blowing fan/air	See Table 84-9, and text on pharmacologic and nonpharmacologic management sections
		Bronchodilators	
		Inhaled corticosteroids	
		Mucolytics (glycopyrrolate)	
		Pulmonary rehabilitation	
		Opioids	Monitor for respiratory depression, delirium, and constipation
		Benzodiazepines	Monitor for respiratory depression and delirium
Pain	54%	Acetaminophen, NSAIDs, opioids	Monitor for liver and renal dysfunction, delirium, and see above opioid note
Gastrointestinal			
Anorexia	67%	Dietary counseling, food fortification, mirtazapine (if depressed)	Monitor for underlying cause, particularly medication related adverse effects
Nausea/vomiting		Haloperidol	
Constipation	44%	Bowel regimen, increased mobility, careful hydration, dietary modification as tolerated	Routinely required when using opioids
Fatigue/weakness	68%	Dietary counseling, food fortification, pulmonary rehabilitation	Monitor for underlying cause, particularly medication related adverse effects
Psychological			
Depression	> 90%	Antidepressants, supportive counseling	Palliative care social worker and physicians discuss with patient and family future treatment and needs
Anxiety	> 90%	Benzodiazepines, behavioral interventions	
Delirium		Antipsychotics and behavioral interventions	Monitor for underlying cause, including medication related, infection, etc
Sleep disturbances			
	40%	• Symptom management (COPD-specific and psychological treatments), with judicious use of hypnotics (trazodone, Z-meds[a]) • Nocturnal supplemental oxygen • Continuous positive airway pressure (CPAP) • Cognitive-behavioral: reduce light and	• sleep efficiency and quality in COPD • COPD and obstructive sleep apnea (OSA) Overlap syndrome • Poor sleep contributes to fatigue and low quality of life

		noise, comfortably cool temperature in bedroom; may benefit from hospital bed and relaxation techniques (muscle relaxation, imagery, meditation)	

[a] Z-meds include eszopiclone, zaleplon, zolpidem (nonbenzodiazepine GABA receptor agonists).

Despite growing evidence of the substantial palliative care needs of patients with advanced COPD, optimal timing for referral to palliative care or hospice is difficult to predict, given the chronic nature of the disease. Very severe airway obstruction (FEV_1 < 30% predicted or FEV_1 Z-score < –2.55) can help identify patients at risk for uncontrolled symptoms from advanced COPD. However, COPD is a very heterogeneous disease and FEV_1 alone may not be sufficient to identify patients who would benefit from palliative care. Gas exchange impairments (hypoxemia or hypercarbia) also suggest advanced COPD. Weight loss is usually concerning for advanced disease. Health care utilization, including frequent emergency department visits, hospitalizations, or intensive care unit (ICU) admissions, may be a marker of advanced COPD that would benefit from palliative care involvement. Patients who face declining functional status as measured by their ability to complete activities of daily living, or have impaired mobility due to progressive dyspnea, have a considerably higher mortality rate than those with normal functional status.

Given the complexities of prognostication, some palliative care specialists suggest asking, “would you be surprised if this patient were to die in the next 12 months.” If the answer is “no,” this statement may help identify patients in need of palliative care. However, as with all serious life-limiting conditions, palliative treatment and support can be provided longitudinally to older patients with COPD. In addition, since the definition of palliative care has evolved to include patients and families facing serious and/or life-threatening diseases, as well as having physical, spiritual, or psychosocial sources of suffering, the population who might benefit from a palliative care team’s involvement has expanded significantly. Hence, rather than focusing on prognosis as the key criterion for referral to palliative care, medical providers could identify which COPD patients would benefit from an “extra layer of support” by an interdisciplinary team consisting of doctors, nurses, social workers, and chaplains.

The goal of palliative treatment for patients with advanced COPD is to improve overall quality of life. One important focus is physical symptom relief. To this end, supplemental oxygen should be provided to older persons with severe COPD who are chronically hypoxemic. Of note, in studies of patients with dyspnea and end stage disease, the level of measured peripheral oxygen saturation may not correlate with the level of perceived breathlessness. Therefore, a patient’s report of dyspnea is an important additional measure of oxygen effectiveness in end stage disease. For patients with more advanced disease and respiratory insufficiency resulting in gas exchange abnormalities and/or chronic respiratory failure, noninvasive positive pressure ventilation should be considered for nighttime support and as needed for uncontrolled symptoms (dyspnea). Noninvasive positive pressure ventilation is also a key tool to consider for patients presenting with acute respiratory failure, including those who have refused endotracheal ventilation. Palliative care and hospice teams recognize the value of noninvasive positive pressure ventilation in the end stage COPD population, and many programs are able to provide this treatment, although its availability in these settings is highly variable.

Inhaled bronchodilators, inhaled and systemic corticosteroids, and other adjuvant therapies that relieve symptoms should be continued during palliative treatment for patients with advanced COPD (see **Table 84-13**). However, it is important to consider deprescribing medications for COPD patients whose care is shifting toward palliation only. In addition, smoking cessation counseling and treatments should be offered, even during palliative-only stages of COPD treatment. Smoking cessation at any stage of disease can reduce exacerbation risk and improve quality of life. Nicotine replacement and non-nicotine-based therapies can usually be safely prescribed in older smokers with COPD. Symptoms of anxiety and depression are also important to treat for COPD patients with advanced disease. In addition to pharmacologic therapies, clinicians should also offer nonpharmacologic interventions, such as cognitive behavioral therapy and advanced relaxation techniques (eg, guided imagery training). Pulmonary rehabilitation can also improve symptom management for patients with advanced COPD through training in breathing techniques and improving exercise capacity. Finally, simple environmental changes may help decrease the sensation of dyspnea, including use of a fan or opening windows and doors to increase air movement, maintaining a relativity cool temperature, and providing humidified air.

For patients with uncontrolled symptoms despite maximal supportive and medical therapy, opioids may be considered for symptom relief. The American Thoracic Society guidelines support their use in refractory dyspnea at any stage of illness, chronic and end of life. Opioids are thought to be effective in relieving dyspnea by several mechanisms including decreasing respiratory drive through a direct effect on respiratory centers in the brain stem, by

altering the perception of dyspnea and anxiety (central effect), and by direct action on peripheral mu-receptors in the lung (bronchioles). Early studies of oral, sustained-release morphine in opioid naive patients with advanced COPD (doses 10–30 mg orally) suggest significant relief of dyspnea. Subsequent studies have not reported data to suggest the efficacy of one opioid (such as morphine) over another opioid (eg, oxycodone). As COPD progresses and patients near the end of life, swallowing may be impaired or the patient may experience episodes of worsening dyspnea. In this setting, intravenous or subcutaneous opioids are indicated. Studies of nebulized morphine have failed to prove efficacy compared to placebo, although case studies report improvement in dyspnea. Safety in the end stage COPD population is clearly a concern given the risk of CO_2 retention in this population. Recent data suggests, however, that carefully monitored patients who are given low-dose opioids in this setting are at low risk for opioid-induced respiratory failure. Opioids can be safely titrated to patient reported dyspnea. Importantly, the risk of respiratory failure does, however, increase with concurrent use of benzodiazepines and requires close monitoring, consistent with the overall goals of care. Constipation, cognitive impairment, somnolence and delirium are the most frequently experienced adverse drug events. The latter can be anticipated and managed prophylactically with close monitoring, careful use of low-dose antipsychotics, opioid dosage adjustment in response to adverse cognitive effects, and the prescription of a laxative regimen to prevent constipation in any patient who requires daily opioids.

Finally, data suggests that patients and families facing serious illnesses such as end stage COPD will value clear and honest communication about their disease process. The majority of patients want all information, both positive and negative, but also value statements of “hope” integrated into the shared information. Patients and families also desire the opportunity to discuss options for care, especially near the end of life. Several communication guidelines are available to assist medical providers in discussing distressing news, such as the results of medical tests that reveal progression of their disease. One widely shared framework is called SPIKES, created by Dr. Robert Buckman. In summary, these steps include:

S Setting: Ensuring that the setting is appropriate to provide patient comfort and privacy, and that adequate support is provided as needed/desired by the patient.

P Perception: Assessing the patient’s and/or family’s understanding of illness.

I Invitation: Obtaining the patient’s invitation or permission to discuss distressing news (and respecting their choice not to discuss such news).

K Knowledge: Giving knowledge and information to patient and family in a clear and concise manner, avoiding complex technical/medical terminology.

E Empathy: Address patient’s emotions with empathic responses.

S Strategy and Summary: Create a care plan for the next steps in treatment and follow-up, as well as provide contact information for future concerns.

Once information is shared, the medical provider can begin to discuss goals of care by asking patients what is most important to them. For example, a clinician may say to an end stage COPD patient: “we discussed that time may be short given this is your third admission to the ICU in 2 months and, each time you come to the hospital, your ability to care for yourself deteriorates significantly. Given this reality, what is most important to you? What do you hope for? What has been left undone?” Once the patient’s and/or family’s goals are elucidated, clinicians can help guide the medical decision making toward treatments that will likely achieve patient-centered goals, while refusing treatments that are unlikely to meet such stated goals. Ideally, these discussions occur in the outpatient setting, with medical providers that the patient knows well and trusts, when the patient is not in a crisis, and when time is not limited. Advance directive completion and identification of proxy decision maker are two key outcomes of these discussions, particularly in the ambulatory setting.

CONCLUSION

COPD presents a major public health challenge, projected worldwide to be a leading cause of disability (fifth) and death (third) by 2030. This is concurrent with a demographic shift toward an aging population, further amplifying the public health challenge. In particular, older persons are at high risk of developing COPD, given the age-related decline in respiratory physiology and the cumulative effect of frequent exposures to tobacco smoke, respiratory infections, air pollutants, and occupational dusts across the adult lifespan. Moreover, both advancing age and COPD are associated

with increasing multimorbidity, polypharmacy, and functional decline, as well as recurrent hospitalizations and end of life decisions. Hence, the management of COPD in older persons requires an approach that considers the interactions between aging and disease, and includes a multidisciplinary team of heath care providers.

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Chapter 85

Diffuse Parenchymal Lung Disease

Mary Beth Scholand, Robert Paine

Learning Objectives

- Understand the spectrum of diffuse parenchymal lung diseases (DPLDs), particularly those found more commonly in older adults.
- Describe the evaluation of patients with DPLD including exposure history, signs and symptoms, and results of diagnostic tests.
- Understand current treatment of the DPLDs with a focus on the treatment of idiopathic pulmonary fibrosis.
- Describe nonpharmacologic aspects of care of older adults with a DPLD.
- Discuss management of DPLD in patients approaching the end of life.

Key Clinical Points

1. **There are a large number of DPLDs many of which are more common in the older adult, specifically idiopathic pulmonary fibrosis.**
2. **A history focused on environmental and drug exposures, the clinical features, and high-resolution CT scan patterns help distinguish the types of DPLD.**
3. **Management of DPLD includes careful consideration of a pharmacologic approach with consideration of potential side effects associated with therapies.**
4. **Nonpharmacologic therapies, including lifestyle changes and multidisciplinary care interventions, play a fundamental role in optimizing care and outcomes for older patients with DPLD.**
5. **The overall prognosis of idiopathic pulmonary fibrosis, the most common DPLD in older adults, is poor. Therefore, it is critical to address goals of care and end-of-life planning as part of the clinical decision-making process.**

DEFINITION

Diffuse parenchymal lung disease (DPLD) refers to a large and heterogeneous group of pulmonary diseases that are characterized by replacement of extensive portions of the normal lung parenchyma with inflammation and/or fibrosis. The term DPLD is often used interchangeably with multiple others, including interstitial lung disease (ILD), restrictive lung disease, or fibrotic lung disease. The DPLDs share common features, including symptoms, radiographic characteristics, and physiologic derangement. However, despite these common clinical features, DPLD is a broad classification that refers to any one of more than 200 different clinical entities of highly variable etiology, clinical course, and prognosis (**Figure 85-1** and **Table 85-1**). These diseases can be associated with a known cause, but there is a large proportion of these processes that are idiopathic in nature and are grouped together as idiopathic interstitial pneumonias (IIP). In this chapter, we will describe common features shared by most DPLPs and discuss in detailed specific conditions most relevant for the geriatric population.

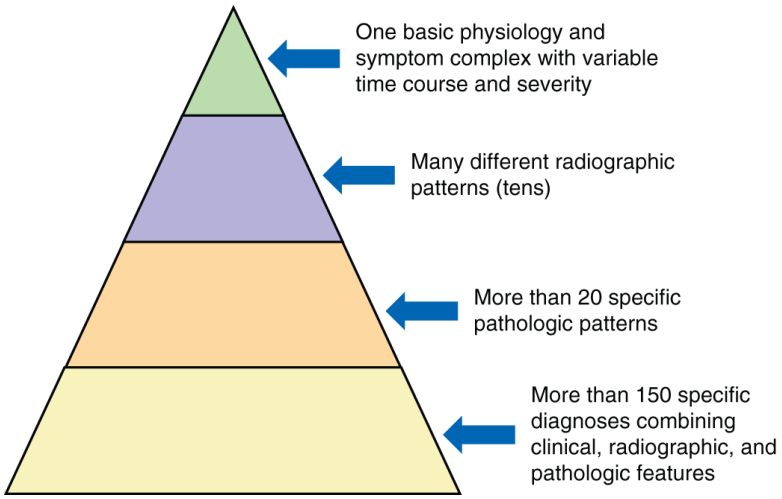


FIGURE 85-1. Hierarchy of diffuse parenchymal lung diseases.

TABLE 85-1 DIFFUSE PARENCHYMAL LUNG DISEASE CLASSIFICATION

Idiopathic Intersitial Pneumonias

Major idiopathic interstitial pneumonias

- Idiopathic pulmonary fibrosis (IPF)
- Idiopathic nonspecific interstitial pneumonia (NSIP)
- Respiratory bronchiolitis–interstitial lung disease (RBILD)
- Desquamative interstitial pneumonia (DIP)
- Acute interstitial pneumonia (AIP)
- Cryptogenic organizing pneumonia (COP)

Rare idiopathic interstitial pneumonias

- Idiopathic lymphoid interstitial pneumonia (LIP)
- Idiopathic pleuroparenchymal fibroelastosis

Unclassifiable idiopathic interstitial pneumonias

Other DPLD of Unknown Cause

Sarcoidosis

Pulmonary Langerhans histiocytosis (PLH)

Lymphangiomyomatosis (LAM)

DPLD Associated With Collagen Vascular Disease

Rheumatoid arthritis

Systemic sclerosis

Antisynthetase syndrome (polymyositis)

Systemic lupus erythematosis

Sjögren syndrome

Mixed connective tissue disease

Ankylosing spondylitis

DPLD Associated With Pulmonary Vasculitis

Wegener granulomatosis

Churg-Strauss syndrome

Hypersensitivity vasculitis

DPLD Associated With Drugs or Treatments (also refer to Table 85-2)

DPLD Associated With Drugs or Treatments (Continued)

Illicit drugs

Dietary supplements

Radiation

DPLD Associated With Environmental (Occupational) Exposures

Organic dusts/hypersensitivity pneumonitis (> 40 known agents)

- Hot tub lung
- Farmer's lung
- Air conditioner–humidifier lung
- Bird breeder's lung
- Baggasosis

Inorganic dusts

- Silicosis
- Asbestosis
- Coal worker's pneumoconiosis
- Berylliosis

Gases/fumes/vapors

- Oxides of nitrogen
- Sulfur dioxide
- Toluene diisocyanate
- Oxides of metals
- Hydrocarbons
- Thermosetting resins

Alveolar Filling DPLD

Diffuse alveolar hemorrhage

Goodpasture syndrome

- Idiopathic pulmonary hemosiderosis

Pulmonary alveolar proteinosis

Chronic eosinophilic pneumonia

Antibiotics Anti-inflammatory agents Cardiovascular drugs Antineoplastic drugs	Chronic aspiration syndrome Lipoid pneumonia Familial idiopathic pulmonary fibrosis Hermansky-Pudlak syndrome

EPIDEMIOLOGY

The overall prevalence of DPLD in the United States is estimated to be 20 to 80 per 100,000 persons. The incidence appears to be increasing. A major factor contributing to this increase is related to the increase in the older population. Increased exposure to agents, such as medications, associated with lung toxicity is likely an additional contributing factor.

The prevalence of the specific diseases varies in different portions of the population. Some specific DPLDs, such as those associated with collagen vascular diseases, are most common in younger individuals and in women. Conversely, idiopathic pulmonary fibrosis (IPF), the most common of the IIPs, is most prevalent in older individuals. The overall prevalence of IPF is estimated to range from 6 to 63 per 100,000 persons. Classically, this condition is most commonly diagnosed in individuals 50 to 70 years old. However, it is now clear that the prevalence of IPF increases markedly with advancing age and is estimated to be as high as 175 per 100,000 in individuals over the age of 75 years. These distinctive demographics combined with certain biological features of the syndrome, such as an association with decreased telomere length, indicate that IPF should be considered an aging-associated disease.

PATHOPHYSIOLOGY

The pathophysiology of the DPLDs is not completely understood but varies with the underlying processes. In general, it is postulated that these conditions share a common pathophysiologic pattern involving disordered repair following a lung insult that is often chronic and subtle. It is likely that a complex interplay of initial injury, host factors, and possibly repeated insults results in aberrant repair (**Figure 85-2**). This abnormal response may result in inflammation that is sometimes temporary but is often irreversible, and associated with disruption of tissue architecture and extensive fibrosis. The nature of the initial insult varies depending on the specific disease process. While it may involve immune and inflammatory pathways in many instances, it now appears that inflammation is less frequently a causal feature than had been previously suspected, especially for IPF.

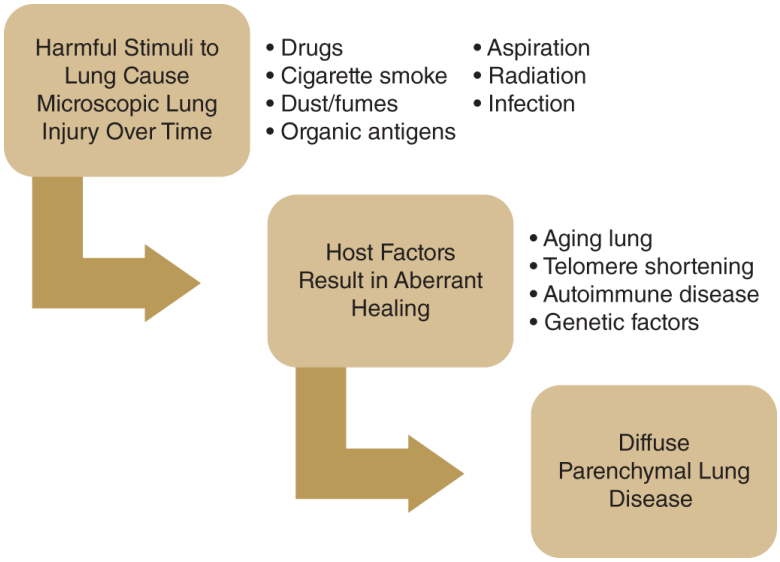


FIGURE 85-2. Diffuse parenchymal lung disease pathophysiology.

It is often useful to classify the DPLD into (1) those conditions with clearly identifiable etiologies, (2) those in which the lung disease is a manifestation of a known systemic illness, and (3) those conditions with unknown cause,

whose manifestations are restricted to the lungs.

Many of the conditions with clearly identifiable etiology involve exposures to agents that are either directly injurious to the lungs or that initiate an immune response resulting in lung injury and a fibrotic response. Occupational exposure to inorganic dusts such as asbestos or silica is a common cause of DPLD in which the etiology is well recognized. Similarly, hypersensitivity pneumonitis often results from the immune response to inhaled organic dusts, such as microbes contaminating hay (farmer's lung) or bird proteins (bird fancier's lung). A variety of drugs are also known causes of DPLD. The most common culprits among these drugs are listed in **Table 85-2**. Many systemic inflammatory conditions are associated with DPLD. Prominent examples include collagen vascular diseases, such as rheumatoid arthritis or scleroderma, and sarcoidosis. In these conditions, the underlying mechanisms of the systemic disease are expressed in the lung, resulting in DPLD.

TABLE 85-2 DRUGS COMMONLY ASSOCIATED WITH DIFFUSE PARENCHYMAL LUNG DISEASES

Cardiac Medications	**Chemotherapeutic Agents**
Amiodarone	Bleomycin
Flecainide	Carmustine
Statins	Vinblastine
Antibiotics	Nitrosoureas
Macrodantin	BCNU
Isoniazid	Cyclophosphamide
Sulfasalazine	Fludarabine
Amphotericin B	Melphalan
Anti-Inflammatories	Mitomycin C
Gold	Hydroxyurea
Methotrexate	Lomustine
Azathioprine	Paclitaxel
Penicillamine	
Biologics	
Tumor necrosis factor (TNF)-α blockers	
Rituximab	
Adalimumab	
Imatinib	
Infliximab	

However, quite commonly, the etiology of DPLD is unknown. This is particularly the case in the geriatric population, where IPF is common. IPF is the most common of the DPLD of unknown etiology overall and involves a distinctive collection of clinical and radiographic features. The specific triggers and pathways that result in IPF are unknown. In a subgroup of patients, it has been recognized that inherited abnormalities in telomerase resulting in premature telomere shortening lead to familial IPF. Even in the absence of mutations in telomere related genes, there is increased risk of IPF among those with a positive family history. Other known risk factors for IPF include cigarette smoking and chronic microaspiration. It was long assumed that inflammation played an important role in initiation and maintenance of IPF. This assumption led to extensive efforts to treat the condition with a range of immunosuppressive medications. Although this approach may be beneficial for immunologically mediated DPLD, such as hypersensitivity pneumonitis or sarcoidosis, recent multicenter trials have provided convincing data that immunosuppressive regimens per se are not beneficial for IPF.

Based on the histology of IPF, fibroblast biology has been an area of intense investigation of the pathophysiology underlying IPF. Interstitial fibroblasts are increased in number and activity, often assuming a contractile phenotype known as the myofibroblast. These distinctive cells are found organized in the collections known as "fibroblastic foci" that are an essential pathologic characteristic of IPF. A variety of growth factors support proliferation, mobility, and

collagen production by lung fibroblasts in IPF. Excess collagen is then deposited into the extracellular matrix, with adverse effects on gas exchange and work of breathing. However, the initiating events remain undefined. It is now recognized that a central feature of IPF is persistent alveolar epithelial cell injury, which in turn leads to pathologic signaling to interstitial cells contributing to the fibrotic response. Better understanding of these processes will inform future therapies. Possible reported mechanisms that may explain the onset of IPF later in life include accumulated stress to the endoplasmic reticulum, telomere dysfunction, epigenetic influences and even mechanical stress that accumulates over the years. It is likely that cumulative exposure to environmental stresses, such as air pollution, further contribute to oxidative stress.

PRESENTATION

The typical presentation of the DPLDs is nonspecific, with most patients reporting dyspnea on exertion or cough. Some patients may describe flu-like symptoms with a persistent cough and associated shortness of breath. The disease may also be detected during routine evaluations when crackles are heard on auscultation or interstitial markings are noted on chest imaging. The rate of onset is variable depending on the process, but is often subacute.

Dyspnea, a nonspecific complaint, is the most common presenting symptom. These patients often accommodate to their limitations and may not complain of pulmonary symptoms. Interestingly, when assessed with standardized questionnaires, older adults with chronic lung diseases tend to describe less impairment than younger patients and therefore may not feel as limited by their lung disease. It may be that competing comorbidities cause more significant limitations for geriatric patients or that older patients are less active or have a blunted perception of dyspnea.

In many instances, a nonproductive cough may be the most bothersome symptom. Many of the DPLDs, particularly IPF, are associated with an intractable cough that impacts life quality more significantly than the dyspnea of exertion, especially early in the disease course. Other signs and symptoms include fatigue, chest pain, hemoptysis, or pneumothorax.

EVALUATION

The evaluation of individuals with possible DPLD involves efforts to determine the specific disease pattern, to identify any specific etiology, and to determine the severity and morbid consequences of the illness. Key components of the evaluation should include history, physical examination, radiographic imaging, and physiologic assessment. History is particularly important for patients presenting with symptoms consistent with a possible DPLD. A careful history may elucidate the cause of the DPLD. In particular, patients should be queried as to environmental risks including exposures, prior medication use, aspiration symptoms, and symptoms consistent with a collagen vascular disease. Because agents such as asbestos or silica may result in symptoms many years later, it is important to obtain a detailed environmental exposure history over the course of the patient's entire life. Physical exam may identify extrapulmonary processes, such as inflammatory arthritis, which may suggest the presence of a systemic illness with manifestations in the lungs.

As noted above, an individual's age has important implications for the differential diagnosis in the setting of DPLD. With advanced age, conditions such as sarcoidosis or unsuspected collagen vascular disease become less likely. IPF is a major consideration, but care should be taken to identify drugs such as amiodarone or macrodantin to which older individuals are commonly exposed and that commonly cause lung disease.

Individuals with possible DPLD should undergo high-resolution CT scan of the chest with special attention to "lung windows." These scans will confirm the presence of DPLD and may provide evidence of the severity of the pulmonary disease. It may also provide information concerning the specific disease process in the individual patient. Common findings include increased linear shadows and evidence of scarring and destruction of lung parenchyma. In a smaller group of patients, there may be evidence of alveolar filling. Special attention should be paid to characteristics that strongly suggest a diagnosis of IPF. These include widespread peripheral increased linear shadows, predominant in the lower lung zones, and the presence of stacks of small subpleural cystic changes resembling honeycombs (**Figure 85-3**). These findings in an individual with an appropriate history are highly specific for the presence of IPF. Identification of this pattern has important implications for prognosis and potentially for treatment. Other radiographic patterns may lead one to consider other, less common, disease processes. For example, the presence of ground glass opacities with air trapping in a patient with a history of exposure to a potentially causative agent is highly suggestive

of a diagnosis of hypersensitivity pneumonia (**Figure 85-4**).

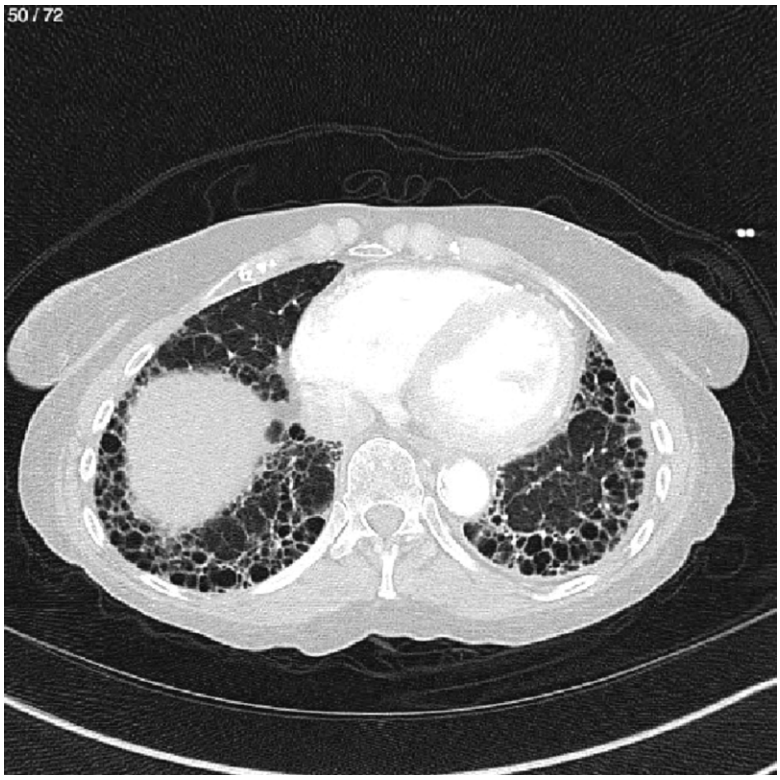


FIGURE 85-3. High-resolution CT scan displaying characteristic honeycomb pattern—stacks of subpleural small cysts—observed in idiopathic pulmonary fibrosis.

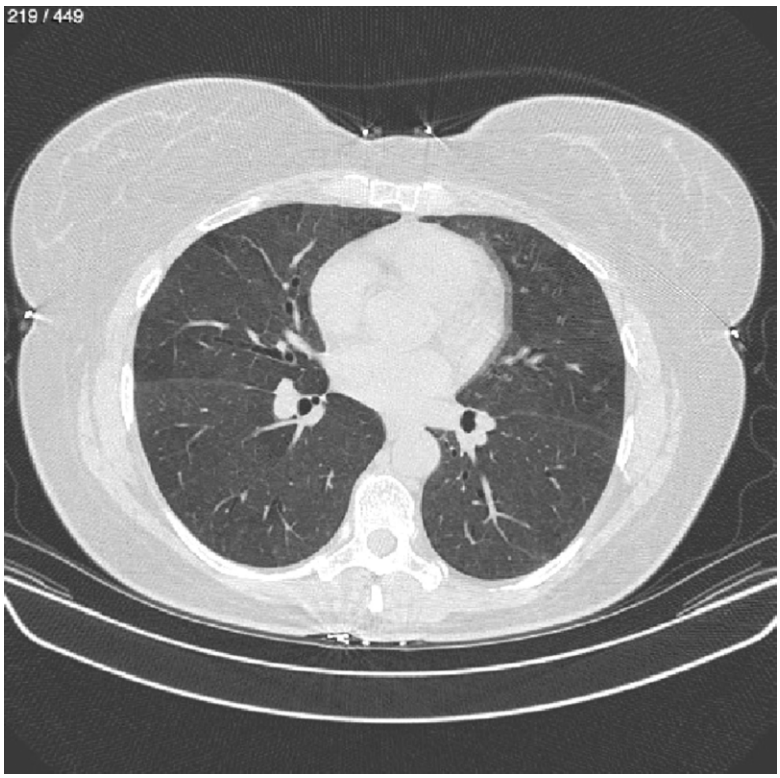


FIGURE 85-4. Ground glass opacities with air trapping CT scan pattern typically found in hypersensitivity pneumonia.

Pulmonary function tests are an important component in the evaluation of individuals with potential DPLD. These studies are helpful both to characterize the physiologic abnormality and to provide objective information concerning severity and progression. At a minimum, patients should undergo spirometry, measurement of diffusing capacity and

an assessment of oxygen saturation at rest and with ambulation by pulse oximetry. In selected instances, determination of absolute lung volumes by plethysmography or assessment of the response to inhaled bronchodilators may be indicated. Typically, individuals with DPLD will demonstrate a restrictive ventilatory defect, with reduced forced vital capacity (FVC) out of proportion to changes in the forced expiratory volume in 1 second (FEV_1). The result is a decreased FVC compared to predicted, in association with normal or increased FEV_1/FVC ratio. Normal aging is associated with a reduction in FVC as well as a reduction in the FEV_1/FVC ratio. However, the FVC is lower than age-predicted values in patients with DLPDs. Gas exchange is very commonly impaired in individuals with DPLD. Because the arterial oxygen tension (PaO_2) and thus the oxygen saturation typically decline as part of normal aging, older individuals with ILD may require oxygen supplementation with less severe lung disease than their younger counterparts.

Given that the patients with DPLDs present with dyspnea, careful cardiac evaluation is also warranted in order to exclude concomitant cardiac disease, a prevalent problem in the geriatric population. Coexisting coronary artery disease, left ventricular dysfunction and heart failure with preserved left ejection fraction are common entities in the older population and are frequent comorbidities with DPLDs. The net result is a combined etiology to patient's symptoms. Echocardiogram is an important evaluation tool. In addition, assessments for ischemia and cardiologic evaluation should be considered.

MANAGEMENT

Pharmacologic

The medical therapy depends largely on the type of DPLD. DPLDs that are related to environmental triggers such as hypersensitivity pneumonia or drug-induced DPLDs are treated by eliminating the offending agent. Prednisone can be an adjunctive therapy as well.

Immunosuppressive therapy is appropriate in the setting of collagen vascular mediated diseases. In addition, prednisone and steroid sparing agents are the mainstay of therapy in more severe hypersensitivity pneumonitis, sarcoidosis and in some idiopathic nonspecific interstitial pneumonitis.

IPF is a progressive disease with a dismal prognosis. In studies that include all age groups, mortality is estimated to be 30% in 5 years. Epidemiologic data suggest that increased age is associated with poorer prognosis in patients with IPF. In fact, age is incorporated into the prognostic risk assessment, known as the GAP (gender, age, and physiology) score, which provides an estimation of individual risk of mortality for patients with IPF.

There are two agents that recently have been demonstrated to be effective in slowing the progression of IPF—nintedanib, a tyrosine kinase inhibitor, and pirfenidone, an antifibrotic agent. Research to discover pharmaceutical agents that can stop or even reverse the fibrotic process is ongoing.

Oxygen therapy Most patients with DPLDs, particularly those with fibrotic disease, demonstrate a widened gradient between alveolar and arterial blood for oxygen and require oxygen therapy. Because the normal resting oxygen tension in the blood declines with advancing age, the requirement for supplemental oxygen is particularly common in older patients with ILD and may be present even in individuals with relatively mild disease assessed by other parameters. Oxygen therapy can improve breathlessness and exercise tolerance and decrease complications related to comorbid conditions such heart failure. Perhaps surprisingly, it is not known whether oxygen therapy has an impact on survival, other than through effects on comorbid illness such as cardiac disease. Oxygen prescriptions should be adjusted for exertional needs and sleep as well as for rest.

Management of cough Cough can be one of the most bothersome symptoms in IPF. Careful evaluation for secondary causes of cough, such as gastroesophageal reflux disease (GERD), use of ACE inhibitors, or postnasal drip, should be pursued and treated. If these are not a factor in the patient's cough, there are limited interventions for ILD-related cough. Benzonatate, guaifenesin, and low-dose opiates are all considerations.

Vaccinations It is critical to prevent secondary infections when possible. While recommended to the geriatric population in general, influenza and pneumococcal vaccines (including the recently available 13-valent pneumococcal vaccine) are particularly important in those with lung diseases as these infections can be major events leading to permanent deterioration in functional status or death.

Nonpharmacologic

Pulmonary rehabilitation is an important consideration for the treatment of DPLDs. Pulmonary rehabilitation has been studied in the treatment of DPLDs and is demonstrated to improve dyspnea, 6-minute walk distances, quality of life, and functional status in these patients. As the disease progresses, other modalities to support mobility, such as motorized scooters, may prove helpful.

PREVENTION

While the idiopathic entities have no known cause and thus appear to be nonpreventable, there are known causative agents. These include medications known to cause interstitial lung diseases such as amiodarone, nitrofurantoin, or methotrexate. In addition, occupational hazards such as asbestos and silica are known causes of the DPLDs and should be avoided. Removal of the offending agent, including drugs, is critical for individuals with hypersensitivity pneumonitis. As smoking is a known risk factor and exacerbates many aspects of the disease process, smoking cessation as well as avoiding exposure to air pollution should be very strongly encouraged.

There is growing evidence that untreated reflux and aspiration are contributing factors. Careful management of reflux with acid suppression and possibly fundoplication should be considered. Control of aspiration as soon as it is recognized is a critical intervention to prevent development and progression of aspiration-related ILD.

SPECIAL ISSUES

Patient Preferences

When a patient is diagnosed with a DPLD, there is often uncertainty about the exact etiology. A surgical lung biopsy may be considered to obtain a more precise diagnosis and inform further management. Diagnostic and management dilemmas are discussed with the patient to assess the degree to which they would like to pursue the biopsy and subsequent treatment. Combined assessment with history, pulmonary function, and CT scan under supervision of an expert in DPLD often allows one to avoid the need for lung biopsy. Consideration of diagnostic uncertainty and the potential information to be gained by lung biopsy are particularly relevant in light of some of the toxic therapies used in the treatment of the DPLDs.

Comorbidities

Patients with DPLDs have a high prevalence of a number of important comorbid conditions. More than 90% of patients with IPF have concomitant gastroesophageal reflux disease. Increasing evidence supports that control of GERD may slow progression of the underlying lung disease. Thus, GERD should be aggressively managed in these patients.

Other important and common comorbidities include cardiac disease and sleep apnea. Consideration of cardiac disease is important in the evaluation of individuals with DPLD. When DPLD and cardiac dysfunction are present together, treatment of the latter is important for symptom control and long-term outcome. Similarly, sleep apnea is typically underdiagnosed in these patients. Diagnosing and treating sleep apnea can improve quality of life by decreasing fatigue.

In this older population, screening for osteoporosis should be routine. However, the presence of an inflammatory disease, often treated with corticosteroids, increases the risk of developing osteoporosis.

Depression

Patients with IPF as well as other DPLDs that limit ability to function and remain independent have a high prevalence of depression. This comorbidity should be actively screened and treated.

Care Settings

With proper support, this disease is most frequently managed in the home setting. The majority of treatment regimens, even in the subgroup of patients for whom immunosuppressive agents are indicated, can be administered in the ambulatory setting. Laboratory monitoring is required for many of these agents. Supplemental oxygen therapy can be provided at home for most of the disease course. When oxygen demands become very high, supplying enough oxygen becomes a challenge. At this point, palliative measures and hospice care become relevant options. In addition, support

in the home to minimize energy expenditure and oxygen requirements, such as motorized wheelchairs or scooters, hospital beds, and bedside commodes, can all be helpful to allow the patient to remain at home. Alternatively, some patients may wish to reside in a care center to receive higher oxygen concentration and support with their ADLs.

Palliative Care

Many of these diseases, particularly IPF, have a poor prognosis. As described above, in IPF, current estimates are that only 30% of patients are alive 5 years from the time of initial diagnosis. Survival is further decreased with increasing age; median survival of those over age 70 years is less than 20 months. The current FDA-approved therapies may improve these statistics as they slow progression of the disease, but there are no therapies that prevent progression and ultimate death from IPF. Moreover, the physician is unable to provide accurate description of the rate of this inevitable decline as each person has an individual course. Consequently, patients diagnosed with IPF, as well as other DPLDs, have considerable anxiety surrounding the diagnosis and the inevitable dyspnea that ensues. These concerns should be addressed early in the course of the disease to avoid this anticipatory anxiety. In addition, palliation of symptoms should be offered to patients to relieve anxiety and breathlessness. Low-dose opioid therapy is an effective intervention.

Given that IPF is uniformly fatal, advance care planning discussions are imperative to allow patients and families to prepare for a personalized death. While lung transplant can be considered for some younger patients, given age implications for transplant outcomes, transplant is often not an option for the geriatric patient. Hospice choices can minimize suffering and allow for death at home with the necessary resources.

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Chapter 86

Aging of the Kidney

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Learning Objectives

- Understand normal kidney aging.
- Classify kidney disease using the estimated glomerular filtration rate (eGFR).
- Recognize environmental factors impact the rate of decline in kidney function.
- Recognize that genetic factors play a role in the age-related decline of kidney function.
- Understand the general guidelines for managing patients with CKD.

Key Clinical Points

1. **All older adults have some decline in renal function.**
2. **Older patients can typically maintain normal physiologic homeostasis, but are compromised in their ability respond to challenge.**
3. **Kidneys become more susceptible to injury with advancing age.**
4. **Rates of decline in renal function in aging are quite variable and impacted by both genetic and environmental factors.**
5. **Preventing people from reaching end-stage renal disease reduces cost of care and greatly improves quality of life.**

CLINICAL RELEVANCE

Kidney failure is a growing problem in the older population. Data on people reaching end-stage kidney disease (ESKD) is collected by the US Renal Data System (USRDS). All dialysis units that receive funding from Medicare are required to file data with the USRDS, so that national data are available on over 95% of people receiving renal replacement therapy. Information published in the 2014 USRDS annual data report shows that approximately 1.3 in 1000 persons aged 65 to 69 years are initiating treatment for ESKD each year. For the 70- to 75-year-old age group the incidence rate is 1.68 per 1000 persons, a growth rate of 7.1% per year. The peak incidence occurs in the 80 to 84 age group at 1.8 per 1000 population. Incidence rates over age 85 then fall to 1.36 per million population. Over the last 10 years, the number of older people enrolling for treatment has increased by 41% in the group of people aged 75 years or older and by 48% in the plus 80-year-old age group. Over 6 persons in 1000 are currently maintained on renal replacement therapy, with the plus 75-year-old age group growing at 10% per year. The peak incidence for ESKD is the 80- to 84-year-old age group. In contrast, the incidence of ESKD in the 20- to 44-year-old age group has remained

flat over the last 10 years, with only modest growth in the 45- to 64-year-old group. Although some of the increase in renal replacement therapy for the older population indicates a greater willingness to offer treatment to older individuals, much of the increase is owing to people surviving to experience the chronic changes that occur with aging. The kidney undergoes significant age-related change. Other common diseases such as hypertension and diabetes accelerate these changes.

THE AGING PROCESS

Aging in the kidney is characterized by changes of both structure and function. It must be emphasized that many of the aging studies have been performed on laboratory animals, particularly rodents, that demonstrate quite different patterns of aging from humans. For example, kidney weight increases throughout life in rats while kidney mass and size in humans peaks in the fourth decade and declines thereafter. Care should be taken when reading the literature to keep in mind that changes seen in animal models may not be reflected by parallel changes in humans. Historical data from human postmortems describing changes in the kidney made no effort to exclude patients with kidney disease or significant comorbidities. More recently data on aging have been developed from longitudinal studies, such as the Baltimore Longitudinal Aging Study, in which the medical histories of the study volunteers are well documented. There are also data accumulating from the kidney transplant population. Older living donors are increasingly being used and are put thorough a rigorous medical work-up for renal function and comorbid conditions before being accepted as donors. This has allowed acquisition of data on normal aging in the kidney, uncomplicated by the presence of medical comorbidities. Aging in the kidney is generally characterized by spontaneous progressive decline in renal function accompanied by thickening of the basement membrane, mesangial expansion, and focal glomerulosclerosis.

Functional Changes

Changes in renal function with age are well documented both in human and animal models. Although baseline homeostasis of fluids and electrolytes is maintained with normal aging, there is a progressive decline in renal reserve. This results in a compromise in the kidney's ability to respond to either a salt or water load or deficit. This manifests clinically in patients being vulnerable to superimposed renal complications during acute illnesses. Chronic conditions such as hypertension accelerate this age-related loss of renal reserve and increased vulnerability in these patients should be anticipated. Age-related changes in function will be considered by separate functional domain within the kidney.

Renal blood flow Average renal blood flow decreases about 10% per decade, dropping from 600 mL/min/1.73 m^2 to 300 mL/min/1.73 m^2 by the ninth decade. This is accompanied by increasing resistance in both afferent and efferent arterioles. These changes occur independent of a decline in cardiac output or reductions in renal mass. This decline in renal blood flow is thought to contribute to the decline in efficiency with which the aging kidney responds to fluid and electrolyte load and loss.

Glomerular filtration rate Newer data have shown a wide variation in the rate and extent of changes in the kidney within the older population. Approximately 30% of the population shows no measurable decline in renal function with normal aging. The bulk of the population loses about 10% of glomerular filtration rate (GFR) and 10% of renal plasma flow per decade after the fourth decade of life. Between 5% and 10% of the population shows accelerated loss, even in the absence of identifiable comorbidities. Since there is also a steady loss of muscle mass with age, with concomitant reduction in creatinine production, serum creatinine should remain constant. Elevations in serum creatinine should therefore be taken seriously and not dismissed as normal aging. As can be seen in **Figure 86-1**, serum creatinines at the upper limit of the "normal range" in an older individual represent significant functional decline, and thought should be given to renal dosing of medications. These curves were calculated using the Cockcroft-Gault equation for a 70-kg man:

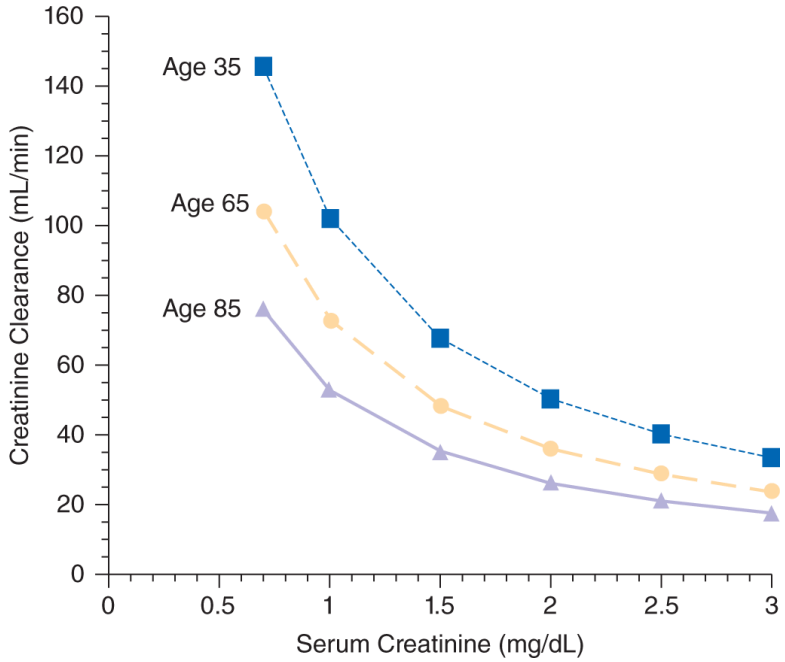


FIGURE 86-1. Relationship between serum creatinine and calculated creatinine clearance for men aged 35, 65, and 85 years. Calculations are based on a 70-kg man.

Results for women should be multiplied by 0.85, which shifts the curves downward. In frail older women with very little residual muscle mass, this equation probably overestimates GFRs. This steady decline in renal function with age manifests itself clinically as impaired ability to excrete a salt or water load. Extra care should be taken when replacing fluids in an older individual to prevent extracellular fluid overload.

In 1999, an improved formula for estimating GFR was developed known as the MDRD formula (because it was developed as part of the Modification of Diet in Renal Disease study). Many routine laboratories now automatically calculate an MDRD glomerular filtration estimate when a basic or a comprehensive metabolic panel is ordered. In some institutions, it is necessary to order a "renal panel" for the calculation to be done. It is important to understand that this formula was based on data from community-dwelling volunteers aged 18 to 70 years. It has never been validated in a very old or frail population. Several investigators have studied its performance in older patients and compared its efficacy with Cockcroft Gault, creatinine clearances based on 24-hour urines or iothalamate clearances, or a combination of these methods. All of the studies have shown large discrepancies between these methods in patients with advanced age and at both extremes of the weight spectrum. These limitations should be kept in mind when using the formula in clinical geriatric practice. Although iothalamate clearance is the gold standard, it is expensive and impractical for routine use. The most reliable results come from calculating creatinine clearances based on 24-hour urine collection. This will always be an overestimate of the GFR, since some creatinine is actively excreted into the urine from the proximal tubule, not all of the urinary creatinine is filtered. It is however more reliable than the formula estimations in the very old and frail people. In 2009, a new modification of MDRD—the CKD-EPI equation —was developed. This is more accurate than the original formula, but is used primarily for research and has not found its way into routine clinical practice. Using cystatin C as a measure of GFR circumvents the problem of the decline in creatinine production with age, but its current use is primarily limited to research studies, and is not routinely used in clinical medicine.

Classification of kidney disease The classification of kidney disorders has undergone a major revision over the past few years. A consensus committee, sponsored by the National Kidney Foundation, published new clinical practice guidelines in 2002. The traditional chronic renal insufficiency has become chronic kidney disease (CKD), and end-stage renal disease (ESRD) has become kidney failure. CKD is defined as either kidney damage or decreased kidney function for 3 or more months. Kidney failure is defined as a GFR of less than 15 mL/min or the need to start kidney replacement therapy. Along with renaming kidney disease, the committee also developed a system of staging. It was felt that having a structure would help with standardizing diagnosis and opportunities for preventative management. CKD is now classified into five stages, regardless of underlying diagnosis. The classification defines stage 1 as kidney damage (primarily proteinuria) with preserved GFR and progresses to stage 5 kidney failure (**Table 86-1**). Declines in GFR are accompanied by a broad range of complications (**Table 86-2**). In 2007, the classification was revised and

stage 3 CKD was subdivided into 3A and 3B. This was done because this is by far the largest category of patients and there was significant heterogeneity in complications that develop within this group. Early recognition of impaired kidney function allows the physician to screen for and manage these complications and thus prevent comorbidities and declines in quality of life. National Kidney Foundation guidelines recommend referral to a nephrologist when a patient reaches stage 4 CKD for management of the complications of impaired function such as acidosis, phosphorus retention, and anemia. Preparation for kidney replacement therapy should also begin during stage 4.

TABLE 86-1 NATIONAL KIDNEY FOUNDATION CLASSIFICATION OF CHRONIC KIDNEY DISEASE

STAGE	DESCRIPTION	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	> 90
2	Kidney damage with mild reduction in GFR	60–89
3	Moderate decrease in GFR	30–59 3A: 45–59 3B: 30–44
4	Severe decrease in GFR	15–29
5	Kidney failure	< 15 (or dialysis)

TABLE 86-2 COMPLICATIONS OF CHRONIC KIDNEY DISEASE

Hypertension
Anemia
Increased cardiovascular mortality and morbidity
Disorders of calcium and phosphorus metabolism
Compromised nutritional status
Metabolic bone disease
Neuropathy
Impaired functioning and well-being
Depression

Proteinuria Despite the significant decline in GFR that occurs with aging, proteinuria is not a normal feature of the aging process. Proteinuria is always a pathological finding and requires a full work-up. In contrast, in most rodent models, particularly in the rat, proteinuria is a normal feature of the aging kidney. This difference between humans and rodents should be kept in mind when reading the aging literature.

Tubular function Older individuals are well known to be more susceptible to acute renal failure. Much of the information on tubular function comes from animal studies, particularly rat models. Rats spontaneously develop proteinuria with aging, and this protein load is believed to be toxic to the tubule. Since proteinuria is not a feature of normal aging in humans, these animal studies may not paint an accurate picture of changes in tubular function in humans. There are also large numbers of studies in experimental animals looking at vasoconstrictive and vasodilatory responses in the older kidney. Impaired response to ANP, acetylcholine, and blunted responses of cAMP to β-adrenergic stimulus has all been implicated. Virtually none of these findings have been confirmed in humans. Functional magnetic resonance imaging (MRI) in older volunteers has demonstrated decreased ability to modulate renal medullary oxygenation. Whether this is caused by fixed vascular changes or changes in renal autocrine systems such as prostaglandins, dopamine, nitric oxide (NO), naturetic peptides, or endothelin is not clear. The clinical result is increased sensitivity to acute ischemic renal failure.

Animal and human studies have shown impaired concentrating ability in the older kidney. Whether this is caused by intrinsic defects in the tubular epithelium or impaired response to antidiuretic hormone (ADH) is not clear. Studies have also demonstrated impaired capacity to acidify urine manifested clinically as reduced excretion of an acid load. Whatever the underlying mechanism, older individuals are less likely to be able to maintain normal homeostasis when challenged. Although there is an age-related decline in tubular functions such as glucose and amino acid transport,

these declines closely parallel the decline in GFR and are believed to correlate with the loss of nephrons rather than age effects in the tubule. Age-related changes in sodium and potassium homeostasis and water handling are discussed in Chapter 89.

Older individuals are also more sensitive to nephrotoxic injury. Careful thought should be given to the choice and dosing of antibiotics and other nephrotoxic drugs. Increased age is a risk factor for the development of radiocontrast nephropathy. Special care should be exercised before tests requiring radiocontrast are ordered.

Donor organ viability Age also impacts the viability of kidneys for transplantation. With the steady increase in living related and unrelated donations, more organs have become available for use in the older population. Although people over age 65 account for 50% of people newly diagnosed with ESRD, they account for only 21% of those listed for kidney transplantation, presumably because they have multiple comorbidities. Many transplant programs are routinely offering transplantation to people in their late sixties and early seventies if they are otherwise in good health. Donated organs are commonly coming from a similar aged spouse or a family member. Age of the donated organ appears to be an independent risk factor for graft survival. This does not appear to be immune-mediated, as older recipients have lower risk of rejection. These organs typically show delayed graft function post-transplant, with chronic allograft nephropathy and result in higher baseline serum creatinines in the long term. It has been postulated that this is caused by impaired response to injury in the older kidney, but there is no real scientific evidence to support this at the current time. Newly published evidence suggests that older kidneys show more podocyte stress, and thus have a shortened graft survival.

Underlying Structural Changes

There are at least 100 years of meticulous research describing the anatomical changes that underlie the functional changes that are observed in patients as they age.

Gross anatomy Kidneys grow vigorously from birth through adolescence, reaching their maximum weight and volume during the third decade of life. In humans, although not in most laboratory animals, renal mass starts to decline after the fourth decade and continues its decline throughout the remaining life span. Most of the decline in weight and volume appears to happen in the cortex, with relative sparing of the medulla.

Glomerulus The young healthy human kidney contains roughly 1 million nephrons. There is no evidence for postnatal nephrogenesis. This underlies the hypothesis that low birth weight babies might have fewer initial nephrons and as a result are more susceptible to renal failure in later life. Although there is some observational data to support this hypothesis, no causal relationship has been proved. There is a steady decline in nephron number with age that starts around the fourth decade. This appears to be driven by podocyte loss. These specialized cells are postmitotic and if damaged in any way, cannot be replaced. This decline is believed to underlie the decline in GFR discussed above. Kidneys obtained at autopsy from patients with no known history of renal disease have been studied. Light microscopy showed the development of a focal sclerosing process, accompanied by thickening of the glomerular basement membrane. There was a steady progression with age in the percentage of glomeruli that were scared. By age 50 years, all subjects examined had some evidence of sclerosis, with the percentage of sclerotic glomeruli increasing steadily with age.

Age-related glomerulosclerosis Sclerotic glomeruli typically first appear in the fourth decade of life. This starts as a segmental process with one part of a glomerulus becoming acellular and the normal architecture being replaced by extra cellular matrix. The glomerular tuft becomes adherent to Bowman capsule (**Figure 86-2**). Gradually an entire glomerulus becomes sclerosed and shrivels down with resultant loss of that nephron and its filtration capacity. It is not known what triggers this pattern of focal sclerosis, which is apparently randomly scattered throughout the cortex. The glomerular tuft increases in size with age. Concomitant with this expansion is an increase in endothelial and mesangial cells, such that the ratio of cells to glomerular area remains constant. Podocytes, the specialized cells that form the filtration barrier in the glomerulus, are postmitotic. They are not able to multiply in response to the increase in tuft volume and become a progressively smaller percentage of the total cells making up the glomerular tuft. As the filtration area that they have to cover increases, it is believed that they may detach from the basement membrane, leaving a denuded area behind. It is this area of bare basement membrane that acts as the trigger for the sclerosing process. Many different experimental models of glomerulosclerosis have concluded that loss of the podocyte and its inability to be replaced is the sentinel event that triggers sclerosis. A transgenic rat model that expresses the diphtheria toxin receptor on the podocyte has been developed to deplete podocytes in a dose-dependent manner. This model has

shown that the loss of podocytes precedes the appearance of sclerosis, and podocytes markers can be detected in the urine prior to the development of global sclerosis.

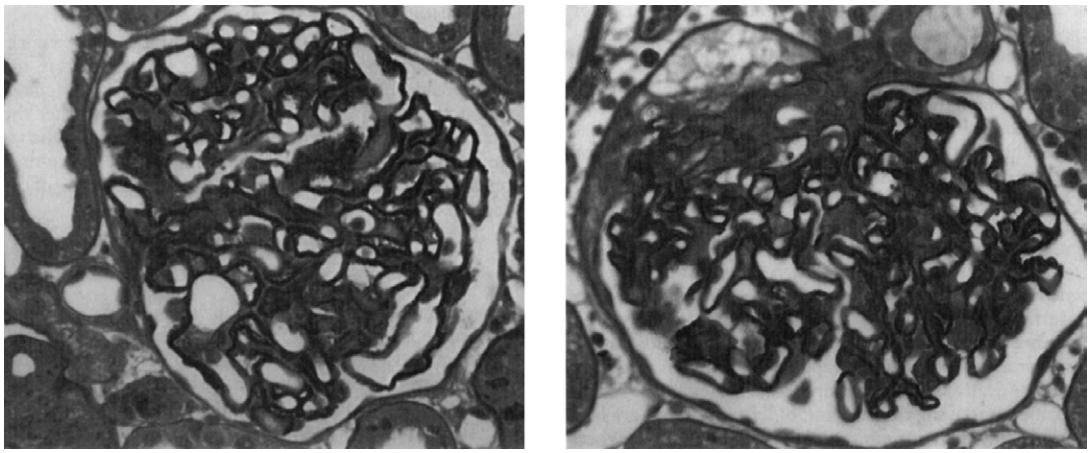


FIGURE 86-2. Renal glomeruli from a 24-month Fischer 344 rat stained with a podocyte marker, GLEPP1, and counterstained with PAS. Left panel: normal glomerulus showing normal architecture of the glomerular tuft. Right panel: age-related glomerulosclerosis showing normal cellular architecture replaced by extracellular matrix and adherence to Bowman's capsule.

Models of induced glomerular injury, of course, do not exist in humans. However, research has shown selective loss of podocytes in the kidneys of type 1 diabetics as diabetic nephropathy progresses. Podocyte number per glomerulus is the best predictor of progression of diabetic nephropathy in Pima Indians with type 2 diabetes. Studies of the aging process in rat kidneys noted that a decline in podocyte counts is accompanied by the appearance of glomerulosclerosis. Studies to address this in aging humans are currently being conducted.

Some authors have suggested a role for the mesangial cell in initiating the sclerosis process. Certainly with aging, there is an increase in mesangial matrix and in mesangial cell numbers. However, this increase is just as marked in strains of rat that do not develop age-related glomerulosclerosis, as it is in strains that do. Several investigators have studied mesangial cell activation in rat models of glomerulosclerosis and found little or none. This suggests that mesangial expansion is a benign manifestation of the aging process rather than a pathological one.

Tubule With the loss of the glomerulus, the tubular section of the nephron usually degenerates and is replaced by connective tissue. Tubular hypertrophy then occurs in the remaining nephrons, principally in the proximal convoluted tubule. This appears to result from both hypertrophy and hyperplasia. With thinning of the cortex, there is a decrease in tubule length and development of diverticuli in the distal convoluted tubule. As nephrons are lost, there is generalized tubular interstitial fibrosis. The structure of the distal tubule does not appear to change significantly with age.

Vasculature Renal arteries undergo age-related thickening, similar to that seen throughout the circulation. Smaller arteries may become tortuous and show luminal irregularities. When a glomerulus becomes sclerosed, there is frequent formation of an arteriovenous shunt as the afferent and efferent arterioles develop a direct connection when the glomerular capillary is lost. This shunt is very important in maintaining medullary blood flow. Physiologic studies in both animals and humans have documented a decline in renal blood flow and an increase in vascular resistance with age. Studies of renal perfusion in healthy older individuals from a pool of potential kidney donors have shown steady declines in renal perfusion with age that exceeded the reduction in renal mass, suggesting that declines in blood flow were a significant factor in the changes seen in renal function with age. These changes contribute to the susceptibility of older individuals to acute renal failure, volume overload, and electrolyte abnormalities.

Infarcts may occur in the kidney, just as they do in other tissues of the body. Since one-fifth of the circulating volume passes through the kidney each minute, the kidney is also particularly susceptible to embolization. If other signs of embolization are visible clinically, it is highly probable that the kidney is also undergoing embolization, and embolic disease should certainly be kept in mind in an older individual with widespread vascular disease who demonstrates accelerated loss of renal function.

MECHANISMS UNDERLYING THE DECLINE IN KIDNEY FUNCTION

There is no clear-cut consensus about what mechanisms may underlie the structural and functional changes occurring

in the kidney in the older population. It is fairly clear, however, that there are both predisposing genetic and environmental factors that play a role.

Genetic Predisposition

There are as yet no genes known to cause age-related glomerulosclerosis, although several podocyte genes have been identified as causative in childhood focal segmental glomerulosclerosis. Accumulating evidence from animals studies, combined with evidence of genetic predisposition in humans, has led to a concerted effort to seek genes that may increase susceptibility to renal failure. Many of the genes identified as playing a role in the aging process, such as IGF-1 and TOR (target of rapamycin) also seem to play a role in kidney aging. Rodent studies using rapamycin to slow the aging process are currently ongoing that are likely to produce information on renal aging.

Animal models Rats are particularly susceptible to kidney failure and much of the work with models of renal disease has been carried out in laboratory rat strains. There are very marked strain differences in susceptibility to age-related glomerulosclerosis. Since these rats are maintained in pathogen-free environments and are fed uniform scientifically developed diets, this strongly suggests a genetic basis for the development of age-related glomerulosclerosis. The appearance of glomerulosclerosis has been reported as early as 5 months in the Milan normotensive rat, with extensive disease by 10 months of age. This occurs in the total absence of hypertension and is not ameliorated by administration of ACE inhibitors. Wistar rats were used as controls in this study and showed no significant disease during the same time period. In Sprague-Dawley rats, spontaneous age-related glomerulosclerosis first becomes apparent around 9 months of age, and disease became widespread by 18 months of age. In studies of aging in Fischer 344 rats, little glomerulosclerosis is seen until almost 2 years of age with fairly rapid progression thereafter. Other rat strains appear remarkably resistant to renal disease. Brown Norway rats show minimal sclerosis, even at 32 months of age, an advanced age in rat lifespan.

Human studies Clearly, these kinds of studies cannot be duplicated in humans. However, there are observational data that would support a similar variation in genetic susceptibility in humans. Cross-sectional studies, donor organ data, and longitudinal studies clearly show a wide variation in kidney function with age. Around 5% to 10% of the population show accelerated loss of kidney function with age even in the absence of accelerating factors such as hypertension, while 30% show no measurable decline. In the presence of predisposing comorbidities, there is also wide variation in the development of kidney disease. Some diabetics may never develop nephropathy, while others develop rapidly progressive kidney disease early in the course of their diabetes, suggesting an underlying genetic susceptibility. Within the African-American population, rates of kidney disease are much higher than in the Caucasian population independent of the precipitating cause. Within an ethnic group, there are also distinct differences in vulnerability. An African-American who develops any predisposing disease, be it hypertension, diabetes, or lupus, who has a first-degree relative on renal replacement therapy has a ninefold increased risk of developing kidney disease compared to another African-American with the same disease burden who has no family history of kidney disease. Similarly human immunodeficiency virus (HIV)-associated glomerulosclerosis occurs almost exclusively in the African-American population, while HIV-associated mesangial hyperplasia and immune-complex glomerular nephritis occur equally in all ethnic groups. Thus, there is suggestive evidence for a genetic predisposition with respect to the development of glomerulosclerosis. Considerable effort and resources are currently being directed toward identifying genes that predispose to kidney disease.

Environmental Predisposing Factors

Several diseases predispose to kidney failure and accelerate the progress of age-related glomerulosclerosis. By far the most prevalent of these are hypertension and diabetes, both common disorders in the older population. There are, however, several other mechanisms that have been postulated to underlie the aging changes in the kidney.

Diet One of the most striking aspects of rodent models of age-related nephropathy is its complete reversal with caloric restriction. Both the anatomical and functional changes related to aging in the kidney are completely abolished in animals that are fed two-thirds of the calories given to their ad libitum-fed litter mates. Even though these animals live one-third longer than their ad libitum-fed littermates, they do not develop age-related glomerulosclerosis. Several explanations have been proffered to account for this observation.

Free radicals and lipid peroxides One possible explanation for the profound effects of caloric restriction is a reduction in the generation of free radicals and lipid peroxides. There is a wide body of literature discussing the

damaging effects of free radicals on cellular systems and the role that this plays in aging. It is not the scope of this chapter to review that literature. The main consequence of free radical production is lipid peroxidation, which results in damage to cellular proteins, lipids, and nucleic acids. Increased caloric intake is believed to fuel increased free radical production with accelerated aging damage. This hypothesis has generated interest in the role of antioxidants in slowing the aging process. The effects of supplementing the diets of Sprague-Dawley rats with vitamin E have been studied. Although there were reductions in markers of oxidative stress and the rate of decline in GFR slowed, glomerulosclerosis still developed. Vitamin E supplement studies in humans have also been disappointing.

Protein restriction The benefits of caloric restriction have been attributed to concomitant reductions in dietary protein. There is a large body of older literature on protein restriction in experimental animal models of kidney disease. In many of these studies, experimental and control animals were not fed isocaloric diets, and protein restriction also meant caloric restriction. Many of these studies have shown a slowing in the progression of established kidney disease; however, the results were not correct for total calorie content. Studies of spontaneous age-related glomerulosclerosis in Fischer 344 rats have shown that protein restriction was much less effective than caloric restriction in preventing age-related declines in kidney function. Modest benefits from protein restriction when rats were fed isocaloric diets have been demonstrated, as have some benefits when the type of protein in the diet was changed from casein to soy. In contrast, caloric-restricted animals had little or no decline in kidney function and they were not able to show significant glomerulosclerosis despite significantly increased longevity. Rats that were fed a high-protein diet, but restricted to 60% caloric intake compared to their ad libitum-fed litter mates, also showed dramatic reductions in age-related glomerulosclerosis. Clearly, protein restriction does have some benefit in the prevention of age-related nephropathy, but that advantage is small compared to that achieved with caloric restriction. Very few of the studies examined changes in sodium, phosphate, and calcium content of the experimental diets. Many of the results of protein restriction can be duplicated by phosphate restriction. The relevance of these studies in humans remains unclear. An observational study that included individuals up to 80 years of age compared healthy vegetarians who consume an average of 30 g/day of protein with nonvegetarians who consume an average of 100 g/day and showed no differences in kidney function between these groups. There is evidence to support protein restriction in patients with established renal disease to reduce symptoms of uremia, but none to support the role of protein restriction to prevent age-related changes in the human kidney.

Lipids There is a well-established link between lipids and cardiovascular disease, and restriction of fat intake accompanied by treatment of hyperlipidemia has been shown to be efficacious in preventing or slowing the progress of cardiovascular disease. Certainly protecting the integrity and function of the vascular supply to the kidney is important to maintaining normal function. Evidence for benefits from the manipulation of lipids in kidney disease comes mainly from animal models of diabetes. Animal studies using high-fat diets have shown accelerated progress of kidney disease, but in most cases, diets were not corrected for total caloric intake. Lipogenic diets fed to Sprague-Dawley rats resulted in earlier appearance of widespread glomerulosclerosis, compared to standard fed animals. Use of lipid-lowering agents in a variety of animal models of glomerulosclerosis has shown reductions in the incidence of glomerular damage. Patients with established renal disease with or without diabetes have more rapid deterioration of kidney function in the presence of hyperlipidemia. The relevance of lipids to the age-related decline in kidney function remains to be established, but it would certainly be reasonable to recommend a low-fat diet and lipid management in patients with declining renal function.

Hyperfiltration The term hyperfiltration is used to describe putative glomerular injury from long-term increases in intraglomerular pressure. Normal age-related loss of glomeruli causes intraglomerular hypertension with hypertrophy of remaining glomeruli. Persistent intraglomerular hypertension causes pressure-mediated renal injury. Most of the supporting evidence for this mechanism comes from animal models where one kidney and part of the remaining kidney are removed, leaving a partial kidney remnant. These animals develop a pattern of renal damage in the remnant indistinguishable from age-related glomerulosclerosis, but over an accelerated time course. Long-term follow-up in humans for over 20 years has not shown accelerated declines in renal function in people who have donated one of their kidneys for transplantation, even though the remaining kidney does undergo hypertrophy. Nutrition may also play a part in hyperfiltration. After a meal of protein, increases in both renal blood flow and GFR in animals as well as in humans have been demonstrated. Excessive intake, particularly of animal proteins, therefore could cause constant hyperperfusion in the kidney, leading to intraglomerular hypertension and accelerated glomerulosclerosis. This would certainly help to explain the benefits so clearly seen with caloric restriction in laboratory animals.

The efficacy of ACE inhibitors in preventing renal hyperperfusion damage early in the course of diabetes and

hypertension would also lend support to the hyperfiltration hypothesis. Angiotensin II appears to be important in maintaining glomerular filtration pressure by vasoconstricting the efferent arteriole. ACE inhibition is believed to preserve renal function by blocking the vasoconstriction of the efferent arteriole and reducing intraglomerular pressure. Long-term ACE inhibition dramatically reduces the incidence of age-related glomerulosclerosis in Munich-Wistar rats. However, a sufficient dose of ACE inhibitor to significantly lower systolic blood pressure was administered in the treatment group as compared to the control animals. Whether low doses of ACE inhibitors would help to maintain normal renal function in humans and prevent the appearance of age-related glomerulosclerosis is a matter for speculation. There is no doubt about their efficacy in preventing progressive decline in renal function when there is an underlying disease. It remains to be seen whether they have any role in modifying age-related changes.

CONSEQUENCES OF IMPAIRED KIDNEY FUNCTION

Patients who show signs of significantly diminished kidney function should be managed aggressively, regardless of their age. Individuals who reach dialysis have a mortality rate four to five times that of age-matched controls (**Table 86-3**) and are at 10 times the risk of a cardiovascular event. It costs more than $80,000 per year to maintain someone on dialysis, without including the cost of treatment for any other health problems. Transplantation is also expensive and requires patients to remain on toxic immunosuppressive regimens for the rest of their lives. Patients who show signs of impaired kidney function should be managed with the idea of preventing them from reaching end-stage disease. Aggressive measures should be taken to reduce blood pressure with a goal of 125/75 if tolerated. A regimen should be used that includes an ACE inhibitor or an angiotensin receptor blocker. However, it should be kept in mind that neither of these classes of drug will confer significant renal protection in the absence of good blood pressure control. Lipids should also be aggressively managed, as should blood sugar and other potential accelerators of renal decline. Overweight patients should be encouraged to lose weight. Great care should be taken to avoid potential renal toxins, such as aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and radiocontrast dyes. Medications excreted by the kidney should be appropriately dosed in amount and frequency. Maintaining residual renal function confers on the patient a greatly superior prognosis when compared to those on renal replacement therapies. Hopefully the current emphasis on finding genes that predispose to declines in kidney function and the development of age-related glomerulosclerosis will help us to identify those at greatest risk before major losses of function have occurred. As with recent gains in the prevention of cardiovascular disease through control of risk factors, we anticipate that similar guidelines will be available for the prevention of age-related declines in kidney function.

TABLE 86-3 LIFE EXPECTANCIES FOR SELECTED AGE GROUPS, COMPARING DIALYSIS PATIENTS WITH GENERAL POPULATION STATISTICS

AGE (y)	DIALYSIS POPULATION (y)	US POPULATION (y)
40–44	6.7–9.2	30.1–40.8
50–54	5.1–6.9	22.5–31.5
60–64	3.7–5.1	16.0–22.8
70–74	2.7–3.5	10.8–15.2
80–84	2.0–2.4	6.9–8.8

Numbers are shown as ranges to accommodate differences by gender and ethnic group.

In summary, kidney disease and failure are predominantly diseases of the older population. All older patients should have an estimate made of their GFR. If they have a deficit in their kidney function, they should be managed aggressively to prevent progression to kidney failure. As CKD progresses, special attention should be paid to choice of drugs and their dosing and to the use of contrast dyes for imaging.

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Chapter 87

Renal Disease

Markus Bitzer

Learning Objectives

- Kidney disease is common and increases morbidity and mortality.
- Signs of kidney injury include elevations of serum creatinine levels above baseline, proteinuria, and hematuria.
- Chronic kidney disease (CKD) is most often caused by common systemic diseases, including diabetes, hypertension, and peripheral vascular occlusive disease.
- Patients with nephrotic syndrome usually require a kidney biopsy to determine diagnosis, prognosis, and treatment options.
- Diabetic nephropathy is a chronic progressive kidney disease that requires treatment with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARBs) if tolerated, optimization of blood pressure and blood glucose levels, and management of comorbidities.
- Patients with acute kidney injury (AKI) need to be evaluated for pre-, post- and intrarenal causes. Even episodes of mild AKI can increase the risk for future CKD.
- Subacute rise in creatinine, proteinuria, and hematuria can be caused by glomerulonephritis (GN) (rapid progressive glomerulonephritis [RPGN]) and requires emergent diagnostic evaluation and treatment to prevent renal failure.
- Acute interstitial nephritis is most often caused by medications, in particular antibiotics and proton pump inhibitors.

Key Clinical Points

1. **In patients with CKD management of elevated blood pressure and avoidance of nephrotoxins, including nonsteroidal anti-inflammatory drugs (NSAIDs) and intravenous (IV) contrast dye, can delay progression to end-stage renal disease (ESRD).**
2. **Complications of CKD include iron-deficient anemia and secondary hyperparathyroidism.**
3. **Proteinuria in the absence of hematuria is a sign of intrarenal damage, is a risk factor for progression of CKD to ESRD, and requires a thorough evaluation.**
4. **Hematuria can indicate glomerular disease, but can also be associated with genitourinary malignancy, cystitis, or nephrolithiasis.**
5. **In patients with renovascular disease intervention is usually only indicated if conservative management failed.**

INTRODUCTION

The kidney is a complex organ structure comprised of several different cell types that serve many functions. Therefore, kidney injury and disease can present in many different ways depending on which part of the kidney is affected, and, in turn, the kidney can be affected by a large number of different diseases. The most widely used test to detect kidney dysfunction is loss of glomerular filtration rate (GFR), which can develop acutely with loss of renal function within days or chronically over years. If renal function decreases over the course of a few weeks it is called subacute kidney

injury. Damage to the renal parenchyma and ultrastructure leads to proteinuria or hematuria. In particular diseases affecting glomeruli and the renal artery can cause hypertension. Tubular cell dysfunction is responsible for abnormalities in electrolyte levels and intravascular volume.

These pathologic findings of kidney disease are caused by a variety of kidney-specific and systemic diseases. Establishing a specific etiology of the kidney disease has important implications for management and prognosis of the disease. Systemic diseases that affect metabolism including diabetes mellitus (DM) and hypertension are well known to cause CKD. Immune-mediated diseases including lupus erythematosus and vasculitis usually affect many organ systems and often the kidney.

KIDNEY AGING

With advancing age, the kidneys undergo anatomic and physiologic changes that are not only the consequences of normal organ senescence but also of specific diseases (such as atherosclerosis or diabetes) that occur with greater frequency in older individuals. Structural changes that are observed at increasing rate in older adults include glomerular hypertrophy and glomerulosclerosis, tubular atrophy, and interstitial fibrosis as well as arteriolosclerosis (**Figure 87-1**). Functionally, several longitudinal studies that measure serial GFR in subjects with and without CKD have shown that GFR declines in the vast majority of people with increasing age independent of other chronic diseases that can affect kidney function.

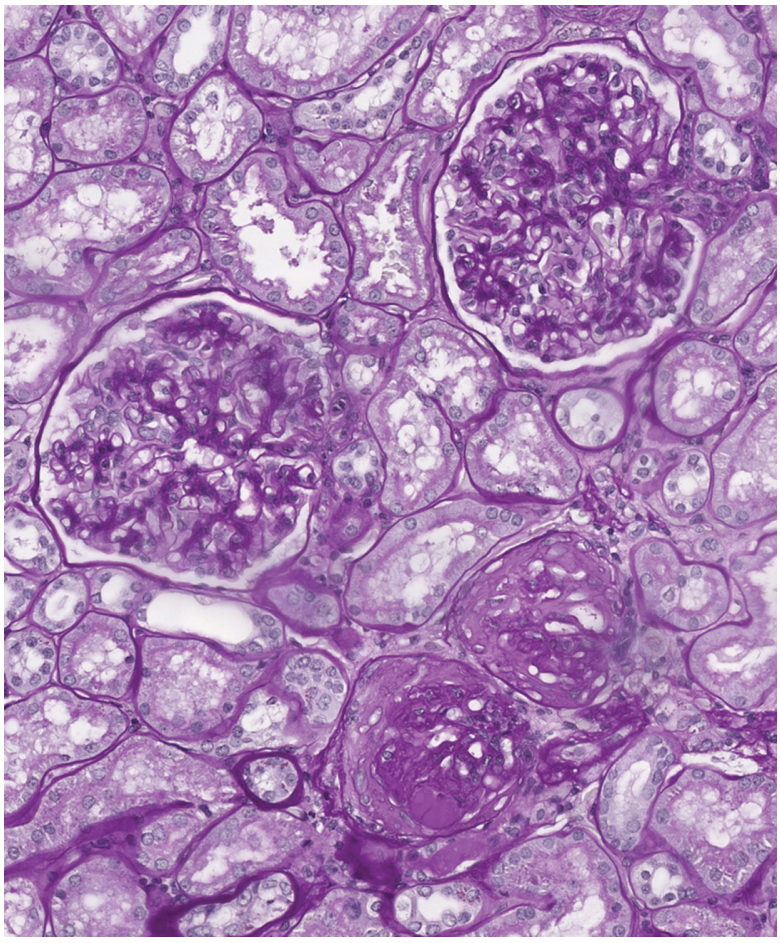


FIGURE 87-1. Human kidney tissue from an older adult person with two normal glomeruli (*left*) and two much smaller globally sclerosed glomeruli (*right upper corner*). The tubuli inbetween appear grossly normal and there is only minimally increased interstitial area between tubular segments.

One important mechanism that links CKD with aging includes the association of reduced levels of klotho—a receptor for FGF23 expressed almost exclusively in the kidney—with increased FGF23 levels resulting in systemic changes that are highly similar to changes associated with increased age, including vascular calcification. It can be speculated that FGF23/klotho signaling mediates accelerated atherosclerosis associated with decreased kidney function.

Other mechanisms include the glomerular hypertrophy and podocyte depletion hypothesis. Glomeruli, which are the network of capillaries, mesangial smooth muscle cells, and glomerular epithelial cells (podocytes), enlarge with age resulting in glomerular hypertrophy. Due to the limited capacity of podocytes to proliferate, podocyte hypertrophy ensues causing podocyte stress and thereby leads to decreased podocyte density (podocyte depletion hypothesis). The decline in podocyte density is also evident in other kidney diseases—in particular diabetic nephropathy—and has been shown to be sufficient to cause glomerulosclerosis and renal failure in laboratory animals. This could explain the well-established observation that the number of sclerotic glomeruli increases with age. Glomerulosclerosis leads to nephron loss and reduced capacity of the cells in the kidney to respond to acute stress during illness or exposure to nephrotoxins ("reduced renal reserve"). The underlying molecular mechanisms for these changes are not well understood and likely multifactorial and include proteasome dysfunction, epigenetic changes, accumulation of DNA damage, as well as telomere shortening. Disentangling these individual processes remains challenging and the timing of each process is highly variable.

CHRONIC KIDNEY DISEASE

Definition

CKD is a general term for heterogeneous disorders affecting kidney structure and function. CKD is now recognized as a worldwide public health problem and management in its early stages is mostly the task of general practitioners and geriatricians. The presentation of patients with CKD can vary, which is related partly to disease etiology, pathology, severity, and rate of progression. CKD is classified into stages of disease severity, which are based on GFR described in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines (**Table 87-1**). In general, the criteria for CKD include a GFR less than 60 mL/min/1.73 m^2 (normal GFR in young adults is about 125 mL/min/1·73 m^2; GFR < 15 mL/min/1·73 m^2 is defined as kidney failure), albuminuria (urinary albumin-to-creatinine ratio > 30 mg/g), hematuria (any degree on urine dipstick), presence of urinary casts in the urine sediment (seen by microscopy of urinary sediment), and abnormalities on kidney imaging for a duration of more than 3 months. This definition is based on the analyses of 45 cohorts that included over 1.5 million participants from general, high-risk, and kidney disease populations. It should be mentioned that some experts in the field have raised concerns that this classification overestimates the CKD burden in the older adult population when considering clinical outcomes. Nevertheless, a meta-analysis to evaluate whether age mitigates the clinical risk of decreased CKD determined that low estimated GFR (eGFR) and high albuminuria are independently associated with increased mortality and risk to develop ESRD regardless of age across a wide range of populations. In addition, even smaller decreases in eGFR (such as < 30% reduction over 2 years) were strongly and consistently associated with increased mortality and risk of ESRD. Thus, CKD contributes significantly to increased morbidity and mortality. However, patients with CKD are a very heterogeneous group of patients and eGFR and albuminuria alone may not be sufficient to predict outcome in particular in the older adult population. Therefore, care for older adults should be provided in context of the individual situation and needs.

TABLE 87-1 STAGES OF CHRONIC KIDNEY DISEASE

CKD stage GFR (mL/min/1.73 m^2) description	
Stage 1	> 90 kidney damage
Stage 2	60–89 kidney damage mild decrease GFR
Stage 3	30–59 kidney damage moderate decrease GFR
Stage 4	4 15–29 kidney damage severe decrease GFR
Stage 5	< 15 end stage (dialysis)

Modified from K/DOQI clinical practice guidelines from chronic kidney disease. Am J Kidney Dis. 2002;39:1.

Epidemiology

Even though the prevalence and incidence of kidney failure treated with dialysis and kidney transplantation is monitored closely in many countries, the estimation of the burden of early stages of kidney disease remains difficult.

Prevalence estimates might be biased by limitation of the markers and methods that are used to estimate GFR and to define kidney damage. In the United States, the prevalence of CKD based on estimated GFR and albuminuria was about 11·5% (4.8% in stages 1–2 and 6.7% in stages 3–5) in the general population during the period between 1999 and 2006, but was 47% in people over the age of 70. The prevalence continues to increase and the mortality risk and the risk to develop ESRD are significantly increased with decreased eGFR particularly the older adult population. Therefore, CKD constitutes a major health concern in particular in older adults.

Pathophysiology (Classification)

Many systemic diseases can result in CKD, in particular diabetes mellitus and hypertension. Diabetic nephropathy, and glomerular and tubule-interstitial diseases with defined etiologies and presentations will be discussed later. Hypertension can cause CKD (hypertensive nephropathy) but also can accelerate progression of CKD due to other etiologies. In addition, CKD can be caused by diseases that are due to specific genetic alterations. The most common monogenetic disease is polycystic kidney disease (PKD), characterized by the presence of fluid-filled cysts in the kidneys and other organs, leading to enlarged kidneys and renal insufficiency. PKD can be inherited as autosomal recessive (ARPKD) or autosomal dominant (ADPKD) traits. Whereas patients with ARPKD are almost always diagnosed as children, patients with ADPKD have a family history and are often middle-aged or even older adults when they develop CKD or ESRD. Mutations in either the *PKD1* or *PKD2* genes, which encode polycystin-1 and polycystin-2, respectively, are the underlying cause of ADPKD. Because mutations in *PKD1* are associated with more severe disease and therefore more rapid progression to CKD and ESRD, the patient's family history may be helpful to estimate the age when ESRD may be reached.

CKD can be easily detected in the kidney tissue by globally sclerosed glomeruli, atrophied tubuli, and interstitial fibrosis. These changes are independent of etiology and are considered as the common consequence of different types of kidney diseases. The earlier stages of CKD are characterized by podocyte and endothelial injury and inflammation of glomeruli and tubuli—specific etiologies are discussed later.

Presentation

CKD is usually asymptomatic until GFR falls below approximately 15 to 20 mL/min/1.73 m^2 when patients may report early signs of uremia. Initial symptoms are nonspecific and include decreased energy levels and appetite, metallic taste, and new onset or worsening of nocturia. Few patients notice bubbly or dark urine as a sign of proteinuria or hematuria, respectively. Patients who have conditions that increase the risk for CKD, including hypertension, diabetes mellitus, heart disease, peripheral vascular occlusive disease, or patients having autoimmune diseases and unexplained systemic symptoms should be evaluated for CKD.

Evaluation

In patients with risk factors for or suspected CKD, kidney function needs to be evaluated by measuring serum creatinine and blood urea nitrogen (BUN) levels, electrolytes, urinalysis, and urine protein-creatinine protein ratio (or quantitative albuminuria). If these tests are abnormal, further evaluation should include a kidney ultrasound with Doppler to determine kidney size (enlarged kidneys can be seen in patients with polycystic kidney disease, infiltrative processes, amyloidosis, and diabetic and HIV nephropathy; small kidneys can be congenital or due to long-standing CKD), echogenicity (increased in long-standing CKD and infiltrative processes), renal blood flow (decreased with long-standing CKD or with occlusion of renal arteries including after renal infarct), and renal pelvis dilatation (in ureteral or severe bladder outflow obstruction).

Previous blood, urine, and imaging test results should be obtained if available to determine duration and rate of change. A detailed medical and surgical history has to be obtained, including childhood diseases, in particular edema and proteinuria in the past, history of rheumatic fever or other severe conditions. The family history can point toward heritable kidney diseases (including PKD, and focal segmental glomerular sclerosis [FSGS]). Social history may identify exposure to toxins and herbal remedies. In addition to identifying specific disease etiologies and complications of CKD, the history can help to identify risk factors for progression of CKD to ESRD. A comprehensive physical examination can detect elevated blood pressure, obesity, signs of heart failure (including increased jugular venous distention (JVD), pulmonary and peripheral edema), liver disease, and vasculitis/autoimmune disease.

Management

Significant progress has been made in establishing disease-oriented approaches that target underlying specific disease mechanisms with the goal of improving disease-related outcomes. However, several features of geriatric populations may limit the utility of disease-oriented models of care. In older adults, complex comorbid conditions and geriatric syndromes are common; signs and symptoms often do not reflect a single underlying pathophysiologic process. There is substantial heterogeneity in life expectancy, functional status, and health priorities; and information about the safety and efficacy of recommended interventions often is lacking. Therefore, an individualized approach prioritizing patient preferences and embracing the notion that observed signs and symptoms often do not reflect a single unifying disease process and instead reflect the complex interplay between many different factors. This approach emphasizes modifiable outcomes that matter to the patient. Prognostic information related to these and other outcomes generally is used to shape rather than dictate treatment decisions. It can be argued that an individualized patient-centered approach to care may have more to offer than a traditional disease-based approach to CKD in many older adults.

Specific attention should be given to cardiovascular disease, which is not only a risk factor for CKD, but also for progression of CKD. Blood pressure control has been shown to limit the risk for cardiovascular complications as well as progression of CKD. The 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (JNC8) advised a blood pressure goal of less than 140/90 mm Hg in adults with CKD compared to less than 150/90 mm Hg in the general population greater than age 60. On the other hand, concern has been raised about too low blood pressure in patients with CKD. Additional studies are needed to better understand the association between hypertension, treatment goals, and clinical events in older patients with CKD.

Pharmacologic The choice of antihypertensive medications should be guided by their ability to control blood pressure, have additional benefits to delay CKD progression and control proteinuria, and have an acceptable side effect profile, in particular in older adults with multiple comorbidities. Blockade of the renin-angiotensin system (RAS) using ACEIs or ARB lowers blood pressure and also decreases proteinuria and is therefore the mainstay in patients with diabetes in whom diabetic nephropathy is suspected. Whether the use of ACEI or ARBs benefits older adults with CKD remains less clear, but if safe should be considered depending on patient-specific situations. Combination of ACEI and ARB is associated with increased therapy-related complications and is in general not advised. Direct renin inhibitors such as aliskiren have so far been mainly studied in patients with diabetic nephropathy monitoring secondary outcomes including albuminuria. It is not yet clear whether these medications are superior in preventing CKD progression, especially in older adults. Calcium channel blockers are considered second-line interventions if additional blood pressure control is needed. In addition, management of hyperlipidemia with statins or statins plus ezetimibe is recommended for older adults with eGFR less than 60 mL/min/1.73 m^2.

Nonpharmacologic Patients with CKD are more likely to experience AKI, and AKI is a risk factor for progression to ESRD. Thus, preventing AKI is an important measure to delay CKD progression. Avoidance of nephrotoxins is a mainstay of CKD management. In particular NSAIDs can have detrimental effects especially if patient is also taking ACEIs or ARBs by decreasing glomerular perfusion and filtration rate. Contrast dye can cause tubular cell damage and AKI possibly leading to CKD. Many antibiotics can have nephrotoxic effects and cause AKI. Weight gain is associated with compensatory glomerular hypertrophy, which causes podocyte hypertrophy that may progress to podocyte dysfunction, decreased podocyte density, and accelerated loss of kidney function. CKD is associated with salt retention and low-salt diet may slow progression of CKD independent of improving hypertension. Finally, although a low-protein diet has not been shown to delay CKD progression, a high-protein diet is not recommended.

Prevention

CKD prevention is the ideal approach to prevent ESRD and CKD-associated morbidity and mortality. It is predicted that about one in three residents of the United States will experience CKD during their lifetime with the vast majority of them during older adult life.

High-risk patient subgroups may particularly benefit from implementation of measures to detect and prevent CKD. Patients with diabetes mellitus should be screened regularly for albuminuria and elevations in serum creatinine levels. Similarly, patients with hypertension, peripheral vascular occlusive disease, reduced kidney mass (ie, after uninephrectomy), and a family history of kidney disease should be regularly evaluated.

Patients with risk factors for CKD should be monitored for optimal blood pressure control, avoidance of nephrotoxins, polypharmacy, and episodes of AKI. Patient should also be counseled about avoiding weight gain and obesity.

Special Issues

Patient preference Patient's preferences regarding goals of care, in particular dialysis should be explored sufficiently early to allow discussion of dialysis modalities and risks and benefits with patients and their family. Once the eGFR falls below approximately 20 mL/min/1.73 m^2 the risk to develop ESRD requiring dialysis support increases significantly and a discussion about patient preferences regarding dialysis should be initiated. In this context, the comorbidities and functional status of the patient should be considered, because quality of life and functional status may not improve after initiation of dialysis in patients with high comorbidity burden and low functional status. On the other hand chronological age may not be a sufficient guide in predicting outcomes.

Comorbidity Management of comorbidities is a central aspect in the care of patients with CKD. One of the most important comorbidity is hypertension and the optimal blood pressure goal is lower for patients with CKD compared to patients without CKD. With worsening kidney function secondary hyperparathyroidism can develop due to retention of phosphate and decreased activation of vitamin D causing parathyroid hormone (PTH) to increase. Therefore, serum phosphate, 25-OH-vitamin D, and PTH levels should be monitored. Hyperphosphatemia can usually be managed by low-phosphate diet, but oral phosphate binders, including calcium acetate or sevelamer, may have to be given if diet is not successful in maintaining normal phosphate levels. Decreased 25-OH-vitamin D levels should be treated with supplementation of cholecalciferol or ergocalciferol. Significantly elevated PTH levels unresponsive to vitamin D supplementation may require treatment with active vitamin D analogs, including calcitriol, but have to be used with great care due to the risk of hypercalcemia and hyperphosphatemia. Patients with PTH levels unresponsive to vitamin D supplementation should be evaluated for tertiary hyperparathyroidism.

Care settings CKD is managed as an outpatient, but patients with CKD are at increased risk for more and longer hospital admissions. Inpatient management of patients with CKD is focused on avoiding nephrotoxins, in particular IV contrast dye and nephrotoxic medications, and dose adjustments for medications. If interventions, in particular surgeries, are planned, the increased morbidity and mortality of patients with CKD, even at the moderate stage 3, should be taken into account and communicated with patients and health care providers.

ACUTE KIDNEY INJURY

Definition

Acute kidney Injury (AKI) is defined by an increase in creatinine (decrease in eGFR) within a few days or even hours, but it is important to understand that rising creatinine levels are likely not very sensitive. AKI is further subclassified into nonoliguric, oliguric, and anuric AKI, defined by urine output above 400 mL/day, 100 to 400 mL/day, and less than 100 mL/day, respectively, which has prognostic implications as nonoliguric AKI is associated with better outcomes. AKI can be further distinguished by etiology with the most widely used categories being prerenal, intrarenal, and postrenal.

Epidemiology

The incidence of AKI is overall increasing with age and the majority of patients who develop AKI are older than 65 years. When AKI does occur in older adults, it is associated with significant morbidity and mortality. The presence of multiple comorbidities as well as age-related changes in the kidney, systemic vasculature, and immunologic system render older patients more prone to renal injury. However, the epidemiology of AKI is difficult to determine consistently and detailed information about long-term outcomes is often lacking. Moreover, estimated incidence of AKI varies by how AKI is defined, the medical setting in which AKI occurs, and geographic region. Recent studies have shown that even mild increases (< 50%) of serum creatinine levels are associated with significantly higher risk of long-term CKD.

Pathophysiology (Classification)

Etiologies of AKI can be categorized into prerenal, postrenal (obstructive), and intrarenal (intrinsic) causes (summarized in **Table 87-2**). Prerenal etiologies include intravascular volume depletion due to fluid loss with decreased total body volume (ie, diarrhea, vomiting, active bleeding) or low intravascular oncotic pressure (hypoalbuminemia secondary to nephrotic syndrome, liver dysfunction, or malnutrition). Decreased cardiac output can

also lead to a prerenal state even if the patient has peripheral and pulmonary edema. Patients with preexisting renal vascular disease are also at increased risk for prerenal AKI even with milder degree of hypovolemia or hypotension.

TABLE 87-2 ■ ACUTE RENAL FAILURE IN OLDER ADULTS

PRERENAL (ACUTE REVERSIBLE RENAL HYPOPERFUSION)	RENAL OR INTRINSIC	OBSTRUCTIVE
Hypovolemia Fluid loss Gastrointestinal Diarrhea Fistulas Vomiting Renal Diuretic intake Salt wasting Redistribution of the extracellular Volume Shock (septic, cardiogenic), hypoalbuminemia, nephrotic syndrome, liver diseases **Malnutrition** **Hemorrhage** **Inappropriate fluid restriction** **Interference with renal autoregulatory mechanisms** ACEIs Cyclosporine NSAIDs **Cardiac failure** Acute Acute myocardial infarction Arrhythmias Cardiac tamponade Malignant hypertension Chronic: ischemic and hypertensive cardiomyopathies Valvulopathies	**Acute glomerulonephritis** Mesangiocapillary Postinfectious Rapidly progressive Goodpasture syndrome Idiopathic SLE **Vasculitis** Hypersensitivity angiitis Classic Hemolytic-uremic syndrome Henoch-Schönlein Mixed cryoglobulinemia Scleroderma Serum sickness Wegener granulomatosis Polyarteritis nodosa **Tubulointerstitial nephropathies** Drugs ACEIs Allopurinol Ampicillin Analgesics (including NSAIDs) Cimetidine Diphenylhydantoin Methicillin Thiazides **Infectious:** acute pyelonephritis **Infiltrative** Leukemia Lymphoma Sarcoidosis **Idiopathic** **Intratubular obstruction** Myeloma proteins Myoglobin Sulfonamides	**Ureteral and pelvic** Intrinsic obstruction Blood clots Fungus balls Sloughed papillae Diabetics Analgesic abusers Stones Extrinsic obstruction Fecal impaction Malignancy Retroperitoneal fibrosis **Bladder** Bladder carcinoma Blood clots Neuropathic Prostatic hypertrophy Stones **Urethra** Phimosis Strictures

	Urates	
	Hypercalcemia	
	Hepatorenal syndrome	
	Vascular obstruction	
	Arterial	
	Aneurysms	
	Atheroembolic disease	
	Venous: thrombosis of vena cava	
	Tubule cell damage	
	Nephrotoxin-related	
	Antibiotics (aminoglycosides)	
	Iodinated contrast media	
	IV immunoglobulin G	
	Metals (Hg, Ag, Pt, Bi)	
	Organic solvents	

ACEI, angiotensin-converting enzyme inhibitor; ARF, acute renal failure; NSAID, nonsteroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

Modified from Macias-Nunez JF, López-Novoa JM, Martínez-Maldonado M. Acute renal failure in the aged. Semin Nephrol. 1996;16:333–338.

Postrenal etiologies for AKI include bladder outflow or bilateral ureteral obstruction. Obstruction of one ureter usually does not cause elevated creatinine levels except in patients with some degree of preexisting CKD or only one functional kidney. In older adults, benign prostate hypertrophy and malignancies including prostate cancer, and cancer of cervix and uterus, have to be considered. In particular, bilateral ureteral obstruction without bladder retention is highly suspicious for a malignant mass in the lower abdomen. Retroperitoneal fibrosis is a rare cause of postrenal AKI caused by chronic inflammation of retroperitoneal tissue usually originating from around the aorta.

Intrarenal causes of AKI be caused by acute GN or tubule-interstitial nephropathies. Acute GN can be caused by rapidly progressive GN due to systemic vasculitis or autoimmune complex deposition in the kidney (see below). Tubulointerstitial nephropathies can be secondary to nephrotoxins, which cause acute tubular necrosis (ATN), intratubular obstruction, interstitial infiltration or inflammation. ATN can be caused by a large and diverse number of nephrotoxins, including IV contrast dye, chemotherapeutic agents, and antibiotics, which are taken up by tubular epithelial cells leading to acute tubular cell damage. Contrast-induced nephropathy (CIN) represents one of the most common forms of iatrogenic AKI. Major risk factors for CIN include old age, presence of CKD, diabetes, heart failure, volume depletion, and concomitant exposure to other nephrotoxins. The risk for CIN can be mitigated by pre- and postexposure intravenous isotonic fluids, avoidance of concomitant nephrotoxins, and use of low or iso-osmolar contrast agents. NSAIDs and ACEIs/ARBs on the other hand lead to constriction of vaso afferent or dilatation of the vasa efferent, respectively and thereby lead to decreased GFR and possible ATN due to hypoperfusion. In the setting of trauma or hemolysis free hemoglobin and myoglobin can cause ATN (pigment nephropathy). Tumor lysis syndrome is usually seen during treatment of cancer, in particular lymphomas and leukemias and is characterized by hyperkalemia, hyperphosphatemia, and hyperuricemia. Calcium phosphate and uric acid can precipitate in the tubuli, thereby causing AKI.

Polypharmacy and drug toxicity exacerbate the susceptibility of older adults to AKI. Drugs commonly associated with AKI include NSAIDs, diuretics, ACEIs, ARBs, and antibiotics. Many older adults take combinations of these medications, and age-related changes in renal function and pharmacokinetics increase the risk for toxicities. Moreover, long-term use of drugs such as NSAIDs, which attenuate prostaglandin function, might act synergistically in the setting of reduced arterial volume and perfusion pressure, increasing ischemia of proximal tubules. Not surprising, then, drug-related AKI is common among older adults, and AKI is a common adverse drug reaction that results in or prolongs hospitalization in the geriatric population. NSAID use doubles the risk for AKI in adults over the age of 65. Among patients hospitalized within the first 45 days of starting an NSAID prescription the average age is 78. Many cases of drug-related AKI result from inappropriate prescribing practices. Older adults are at increased risk for renal injury in particular due to hypovolemia, sepsis, and iatrogenic complications related to drug toxicity, contrast-induced

nephropathy, and perioperative complications.

Presentation

Patients with AKI can be asymptomatic and detectable solely by elevated creatinine levels or present with symptoms that result from various disturbances of kidney function. In patients with more advanced stages of AKI accumulation of substances cleared by the kidney can lead to uremic encephalopathy characterized by fatigue, loss of appetite, headache, nausea and vomiting, metallic taste, asterixis and lethargy on examination, and seizure. Some patients notice decreased urine output. Potassium level can increase and lead to cardiac arrhythmias, which can be severe and life threatening. Fluid retention can lead to peripheral and pulmonary edema, which can lead to respiratory failure.

Evaluation

Kidney function should be examined in every patient at risk for AKI based on presenting symptoms. If creatinine is found to be elevated, values from previous tests are helpful to determine duration of renal dysfunction. Urine output has to be monitored accurately and catheterization of the bladder should be considered, also to rule out bladder outflow obstruction. An ultrasound of the kidneys should be performed to evaluate for hydronephrosis and kidney size as well as echogenicity, which can be increased in both CKD and ATN. Doppler of the kidneys can determine blood flow (decreased or absent in renal artery or vein thrombosis) and resistive indices (increased in CKD and ATN). Prerenal volume depletion is suggested by clinical examination, including hypotension, tachycardia, decreased skin turgor, and dry oral mucosa.

Management

Although morbidity and mortality increase with advancing age, many older patients can survive AKI and do well. Thus, decision making should be thoughtful and individualized, and not dependent on age. Whenever possible, preventive approaches should be pursued to lessen the burden of AKI. The management of AKI is focused on treating the underlying cause and supportive care. AKI due to prerenal volume depletion is treated with volume repletion using isotonic solutions with careful monitoring of fluid status, respiratory function, and urine output. AKI due to postrenal causes requires placement of a bladder catheter for bladder outflow obstruction or placement of ureteral stents or nephrostomy for ureteral obstruction. The mainstay in the management of patients with intrarenal AKI is supportive care, which includes close monitoring of renal function, electrolytes, volume status, and urine output as well signs or symptoms of uremia in order to determine need for dialysis support. Diuretics can be used if needed to manage volume status and potentially avoid respiratory failure, but maintaining urine output above oliguric levels does not improve the outcome of AKI. Thus, diuretics should only be used to avoid complication from volume overload, in particular respiratory failure. Hyperkalemia can often be managed with low-potassium diet and Kayexalate. Lowering elevated phosphate levels requires low-phosphate diet and oral phosphate binders.

Dialysis support may be required in patients with AKI. Recent studies have shown that early dialysis initiation may be associated with greater mortality and hospitalizations, even after accounting for predialysis clinical factors. Thus, dialysis initiation is determined by the development of indications for dialysis, including, electrolyte, acid-base and fluid volume abnormalities that are life threatening and cannot be managed medically, and symptoms related to uremia.

Prevention

Older adults are at particular increased risk for AKI due to polypharmacy, high prevalence of preexisting CKD, and decreased oral intake (decreased thirst). Limiting the complications of polypharmacy is already a mainstay of geriatric care, but a particular focus should be on AKI prevention. The combination of diuretics, ACEIs or ARBs, and NSAIDs is relatively common, and can strongly increase AKI risk by combining prerenal intravascular volume depletion (diuretics, decreased oral intake, and/or vasodilatation in the setting of sepsis), decreased glomerular perfusion (NSAIDs), and a decrease in GFR (ACEI, ARB).

Special Issues

Patient preference AKI may require temporary dialysis support or lead to ESRD and permanent chronic dialysis dependence. It is important to discuss the patient’s preferences toward dialysis with sufficient time prior to initiation of

dialysis. In particular older adults who initiate dialysis in the intensive care (ICU) setting have a strongly decreased survival despite this intervention.

Comorbidity Almost half of Medicare beneficiaries age 65 years or older have three or more chronic conditions, and the number of preventable hospitalizations per 1000 beneficiaries increases with the number of chronic conditions. Comorbidities that increase the risk for AKI are common among older patients. Patients with both CKD and AKI tend to be older, have ischemic heart disease, and be less likely to recover kidney function than patients with AKI alone.

Care settings AKI is very common in the inpatient setting. Even though robust data are not available, it is likely that AKI is also very common in outpatients but remains largely undetected because creatinine levels are not checked as frequently and AKI is mostly asymptomatic. Therefore, patients who have changes in medications or systemic illnesses or unexplained symptoms or undergoing a procedure should be screened for AKI with serum creatinine levels and urinalysis, possible even repeatedly.

GLOMERULONEPHRITIS

Definition

The presence of a glomerular disease, is usually suspected from history, physical examination, and specific findings in the urine, in particular hematuria and proteinuria. Together with renal function tests two types of glomerular diseases can be distinguished—nephritic or nephrotic syndrome. Nephritic syndrome is characterized by hematuria and variable degree of proteinuria and renal failure. Nephrotic syndrome includes nephrotic range proteinuria (> 3.5 g/day), decreased serum albumin levels, peripheral edema, and dyslipidemia. Although the two syndromes are discussed as separate entities, overlap between the two is commonly encountered. For example, diabetic nephropathy presents most often as nephrotic syndrome, but some patients also have hematuria. Likewise, many patients with glomerulonephritis also have nephrotic range proteinuria or nephrotic syndrome. Nevertheless, these findings are distinct from those associated with tubulointerstitial disease and renovascular disease.

GN is characterized by inflammatory or vasculitic lesions in the glomerulus. If those lesions affect less than 50% of glomeruli on light microscopy it is called focal, otherwise it is referred to as diffuse GN. If less than 50% of the glomerular tuft is affected it is called segmental. In general, focal GN has a less severe presentation and often a better prognosis. Nephrotic syndrome and/or a significantly reduced glomerular filtration rate are more often seen with diffuse disease.

Epidemiology

Most glomerular diseases in older adults are caused by chronic systemic diseases, including arterial hypertension, diabetes, and atherosclerotic vascular diseases and do not present with nephritis or nephrotic syndrome. Furthermore, the incidence and prevalence of GN is likely underestimated in the older adult population since the mainstay of the diagnosis is pathologic evaluation of kidney tissue requiring an invasive biopsy. However, some GNs—notably small-vessel vasculitis, and postinfectious glomerulonephritis (PIGN)—have a second peak in the geriatric population and need to be considered in the differential diagnosis.

Pathophysiology (Classification)

GN can be classified into groups based on course, histopathologic findings, and disease etiology. RPGN can be associated with autoimmune processes, infectious diseases, and systemic diseases, in particular vasculitides, malignancies, and medications (**Table 87-3**). The most common primary GN worldwide is immunoglobulin A (IgA) nephropathy. It can have a highly variable course with some patients presenting with RPGN, approximately 30% to 40% of patients progressing to ESRD within 20 years and other patients only having persistent hematuria without proteinuria and changes in GFR. The incidence of ESRD in the older patients' IgA nephropathy (over the age of 50) is almost two times higher than that in younger patients. PIGN is considered primarily a childhood disease, but more recently its occurrence in older patients is becoming recognized. PIGN presents typically with hematuria and proteinuria 10 to 14 days after an infection. AKI may or may not be observed. A recent report of 109 cases of PIGN in patients greater than or equal to 65 years diagnosed by renal biopsy showed that 61% of patients had an immunocompromised background, most commonly diabetes or malignancy. Importantly, the most common site of infection was skin, followed by pneumonia and urinary tract infection—all infections that are very common in older

adults. The most common causative agent was *Staphylococcus* (46%) followed by *Streptococcus* (16%) and unusual gram-negative organisms. Hypocomplementemia was present in more than 70% and almost half of patients required acute dialysis. Only about 20% achieved complete recovery, half had persistent renal dysfunction, and about 30% progressed to ESRD. The factors that increase the risk for ESRD include presence of diabetes, higher creatinine at biopsy, dialysis at presentation, the presence of diabetic glomerulosclerosis, significant tubular atrophy, and interstitial fibrosis on biopsy. In summary, the epidemiology of PIGN is shifting as the population ages. Older men and patients with diabetes or malignancy are particularly at risk, and the sites of infection and causative organisms differ from the typical childhood disease. Prognosis for these older patients is often poor.

TABLE 87-3 CLASSIFICATION OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Primary diffuse crescentic glomerulonephritis
Type I: anti–GBM-mediated disease without pulmonary hemorrhage (with anti-GBM)
Type II: immune complex–associated disease (without anti-GMB or ANCA)
Type III: pauci-immune (with ANCA)
Type IV: mixed pattern (with anti-GBM and ANCA)
Type V: pauci-immune (without ANCA or anti-GBM)
Fibrillary and immunotactoid glomerulonephritis
Focal sclerosis (rare)
IgA nephropathy
Mesangiocapillary glomerulonephritis (especially type II)
Membranous glomerulonephritis (with or without anti-GBM)
Superimposed on another primary glomerular disease
Associated with infectious disease
Hepatitis B and C
Histoplasmosis
Infective endocarditis
Influenza (?)
Mycoplasma infection
Poststreptococcal glomerulonephritis
Visceral abscesses
Associated with multisystem disease
Carcinoma (lung, bladder, prostate)
Goodpasture disease (anti-GBM with pulmonary hemorrhage)
Lymphoma
Mixed (IgG/IgM) cryoimmunoglobulinemia (hepatitis C)
Relapsing polychondritis
Henoch-Schönlein purpura
Systemic lupus erythematosus
Systemic polyangiitis
Churg-Strauss syndrome
Microscopic polyangiitis (with ANCA)
Wegener granulomatosis (with ANCA)
Other variants

Associated with medications
Allopurinol
Bucillamine
D-Penicillamine
Hydralazine
Rifampin

ANCA, antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane.
Modified from Glassock RJ. Syndromes of glomerular diseases. In: Massry SG, Glassock RJ, eds. Textbook of Nephrology. 4th ed. Baltimore, MD: Williams and Wilkins; 2000:650.

Small-vessel vasculitis is rare and often presents with systemic symptoms, including fatigue, malaise, loss of appetite, fever, and weight loss. Occasionally hemoptysis, rash, and joint pain are noted. Some patients do not have any systemic symptoms, but rather develop hematuria, variable degree of proteinuria, and rising creatinine. In those patients, a kidney biopsy may show pauci-immune GN.

Presentation

Complex age-related changes and increased number of comorbidities and sensitivity to drug toxicity can render the diagnosis as challenging. The presence of glomerular disease is usually suspected by history, physical examination, and the presence of abnormal urinary findings—proteinuria (in particular if > 3 g/day), hematuria (in particular if dysmorphic erythrocytes are present), and red cell casts. On the other hand, many patients with GN do not exhibit these specific signs and symptoms but rather present with nephrotic syndrome or CKD and are diagnosed with GN only after a biopsy is performed. Furthermore, proteinuria (usually < 2.5 g/day) and hematuria (without dysmorphic erythrocytes) are commonly seen in patients without glomerular disease. Proteinuria can be due to tubulointerstitial disease and hematuria can be due to extrarenal sources, and is therefore difficult to diagnose, particularly in older adults.

Often patients with GN report constitutional symptoms, including decreased energy, general malaise, decreased appetite, fever and weight loss, and muscle aches. These symptoms are nonspecific and some patients attribute those symptoms to viral infections like upper respiratory infections (URIs). More specific symptoms include new onset of skin rash, joint pain and swelling in metacarpophalangeal joints (MCP) and proximal interphalangeal (PIP) joints, and/or pleuritic or cardiac chest pain secondary to serositis. Shortness of breath, cough, and hemoptysis seen in pulmonary renal syndromes represent an emergency. Any of those symptoms should prompt examination of kidney function and urine. The presence of hematuria and proteinuria should immediately raise concern for GN. Based on serum creatinine levels GN can be classified into acute or rapid progressive GN presenting with acutely rising creatinine, and chronic GN with stable and normal or slowly rising creatinine. RPGN constitutes an emergency as renal failure can develop within days unless appropriate treatment is initiated.

Evaluation

The evaluation of a patient with suspected glomerular disease depends primarily on the acuity of the presentation. If the patient presents with acute renal failure (ARF) and has hematuria and proteinuria, RPGN has to be suspected. This constitutes emergent further diagnostic testing which includes evaluation of urine sediment for dysmorphic erythrocytes and cellular (red cell) casts, quantification of C3 and C4 to determine complement activation and consumption, complete blood counts with differential to detect anemia, thrombocytopenia, leukocytosis, and testing of hemolysis (lactate dehydrogenase [LDH], haptoglobin), coagulation, and liver function. An ultrasound of the kidneys will determine the presence of nephrolithiasis, obstructive nephropathy, reflux nephropathy, nephrocalcinosis, cystic kidney diseases, and other conditions. Furthermore, small kidneys with increased echogenicity on ultrasound may suggest long-standing disease. Serologic evaluation includes markers for viral infections, in particular hepatitis B and C and HIV, and paraproteinemia (serum and urine protein electrophoresis, immunofixation for light chains). Testing for markers for autoimmune diseases should be considered in patients presenting with constitutional symptoms such as fever, chills, malaise, loss of energy, unexplained weight loss, and/or new onset of joint pain (in particular in small joints), skin rash, or pulmonary symptoms (cough, hemoptysis, or shortness of breath). A thorough physical examination is critical to detect signs of systemic diseases, including skin rash, Ehlers-Danlos spots suggestive of endocarditis, lower extremity edema, joint swelling or warmth, and wheezing or rales.

The decision whether and when to perform a kidney biopsy depends on the overall condition and status of each individual patient. Increased frailty and decreased functional status at baseline, preexisting baseline CKD with decreased eGFR and small echogenic kidneys on ultrasound, limited life expectancy as well as anemia, thrombocytopenia, and coagulopathy increase the risk for complications after kidney biopsy.

If the patient has stable renal function but a glomerular disease is suspected because of hematuria and proteinuria the patient should first undergo serologic evaluation. Depending on those results a kidney biopsy can be considered. If the creatinine is rising and pre- and postrenal causes of AKI have been excluded, an urgent kidney biopsy may be considered.

Management

The diagnosis of RPGN may justify empiric immunosuppressive therapy. Even with stable kidney function it is important to establish specific-disease etiologies to guide therapy.

Pharmacologic Corticosteroids are the mainstay in the treatment of acute and chronic GN. If an acute GN is suspected and either creatinine is rising or systemic potentially life-threatening symptoms are present pulse-dose corticosteroids (1 g methylprednisolone IV once daily × 3) followed by oral prednisone, usually 1 mg/kg body weight (up to 60 mg) once daily for up to 2 to 3 month followed by a slow taper over another 2 to 3 months is often used. Patients need to be monitored closely for any signs or symptoms of recurrence of disease in particular during tapering prednisone dose and after stopping it.

Cytotoxic therapy with agents such as cytoxan is considered in patients with crescentic and proliferative GN detected on biopsy or in the setting of other potentially life-threatening complications (ie, hemoptysis, severe hemolytic anemia, and thrombocytopenia). Whether to use IV or oral cytoxan and length of therapy depends on the specific disease, severity of initial presentation, and degree of response. Anti-CD20 antibodies (rituximab) can be considered with equivalent potency compared to cytoxan as suggested by recent studies.

Maintenance therapy is usually required to prevent disease recurrence. To minimize the dose of corticosteroids commonly used drugs include azathioprine (Imuran) or mycophenolate mofetil. The goal is to maintain the patient on the lowest dose of corticosteroids and steroid-sparing agents without flare of the disease or significant complications of therapy. Monitoring usually includes renal function, proteinuria, blood counts, liver function tests, and signs or symptoms of original disease or infections.

Supportive care is critical for patients with GN, in particular management of blood pressure (hyper- and hypotension), intravascular and total body fluid volume (hypervolemia with peripheral and pulmonary edema requires use of diuretics; hypovolemia requires isotonic fluid), electrolyte abnormalities. and unwanted effects and complications of therapy.

Nonpharmacologic Dietary restrictions include low-salt diet if patient has edema, hypertension, or nephrotic syndrome. High-protein diet should be avoided like in any patient with proteinuria, but low-protein diet has not been shown to benefit.

Prevention

Prevention of recurrence, flares, and complications of therapy remains a life-long aspect of care, even if patient has been tapered off immunosuppressive medication. Strategies to prevent long-term complications of corticosteroids like osteoporosis, obesity, and type 2 diabetes should be implemented at the beginning of therapy.

Special Issues

Patient preference Treatment of GN is associated with significant side effects and complications, which need to be balanced with side effects and complications of renal failure and ESRD. It is important to discuss the risks and benefits of all options with specific consideration of the underlying condition, renal and overall survival prognosis with and without treatment, comorbidities, functional status, and expectations. Furthermore, treatment with immunosuppressive medications often requires frequent office visits and laboratory tests, which may significantly impact quality of life or may even not be feasible depending on the specific situation of the patient.

Comorbidity The treatment options often include corticosteroid therapy, which can have significant side effects, in particular difficult-to-control blood glucose levels, hypertension, central obesity, fluid retention, osteoporosis, and accelerated atherosclerosis. Depending on preexisting comorbidities, those can significantly impact outcomes and

quality of life. Other treatment regimen include immunosuppressive medications that are also associated with significant comorbidities that need to be considered prior to initiation and patients need to be monitored closely and treated appropriately.

Care settings GN may require management as an inpatient to establish the diagnosis and initiate targeted therapy and continues in the outpatient setting, but requires close follow-up with frequent office visits and laboratory tests.

NEPHROTIC SYNDROME

Definition

Nephrotic syndrome (NS) is defined as the presence of nephrotic range proteinuria (> 3 g/day), hypoalbuminemia, edema, and dyslipidemia. It is caused by different diseases affecting primarily the glomerular structure, in particular podocytes and the slit diaphragm that spans between the foot processes of podocytes. Thus, patients with NS always have glomerular and podocyte damage detected on kidney biopsy.

Epidemiology

The incidence and prevalence of NS in older adults is not clear, but NS is likely to be missed in older adults who often have edema and low serum albumin caused by other etiologies. Patients in all age groups can develop NS, but the diseases causing NS varies depending on the age group. Minimal change disease is most common in children, but has a second peak in adults over the age of 50. Diabetic nephropathy may be the most common cause of NS in adults.

Pathophysiology (Classification)

Podocyte damage that causes podocyte foot process effacement leads to increased permeability of the glomerular filtration barrier for serum proteins, in particular albumin. The loss of massive amounts of albumin in the urine leads to hypoalbuminemia, which then results in edema formation and hyperlipidemia develops as a compensatory mechanism by the liver. In patients with multiple comorbidities the individual components of NS can be due to a combination of alternative common etiologies such as malnutrition, liver disease, heart failure, venous insufficiency, and hyperlipidemia.

Podocyte damage can be secondary to different diseases that require a kidney biopsy to establish the diagnosis and differ in response to therapy and risk of recurrence and progression to ESRD. Therefore, a significant number of patients with NS will undergo a kidney biopsy to elucidate the underlying etiology. The differential diagnosis in older adult patients aged greater than 65 presenting with NS includes most diseases that are detected in younger adults (**Table 87-4**). A kidney biopsy may be needed to delineate the various causes of NS and estimate the degree of irreversible fibrosis in this age group, and thereby may greatly aid in focusing the diagnostic evaluation in a cost-effective manner and in planning appropriate treatment. Many experienced clinicians recommend deferring additional laboratory or imaging procedures until the histopathologic diagnosis of NS has been made by renal biopsy.

TABLE 87-4 COMPARISON OF MODE OF PRESENTATION BETWEEN PATIENTS AGED OLDER THAN 65 YRS AND THOSE AGED 20 TO 65 YRS AT THE TIME OF BIOPSY AND REPORTED AS HAVING IDIOPATHIC GLOMERULONEPHRITIS

	AGE			
	> 65 YRS		20–65 YRS	
MODE OF PRESENTATION	(*N*)	(%)	(*N*)	(%)
Acute renal failure	37	14	240	11
Asymptomatic urinary abnormality	17	6	841	38
Chronic renal failure	54	20	168	7
Hypertension	4	1	40	2
Nephrotic syndrome	140	52	715	32

Unknown	19	7	226	10
Total number	271	100	2230	100

Modified from Davison AM, Johnston PA. Idiopathic glomerulonephritis in the elderly. Contrib Nephrol. 1993;105:41.

The most common diseases identified by kidney biopsy are membranous nephropathy (MN), minimal change disease (MCD), and amyloidosis, with approximately 60% of all cases accounted for by these three lesions. Less common lesions among older patients undergoing a biopsy for diagnosis of NS are FSGS, proliferative GN, and diabetic nephropathy. A membranoproliferative pattern of injury can be seen in association with a monoclonal deposition disease, such as light-chain deposition disease, which is more common in older adults. Diabetic nephropathy is less commonly encountered on biopsies, largely because patients with diabetes and NS seldom undergo renal biopsy unless “atypical” features are present such as onset of NS fewer than 5 years from discovery of diabetes, rapid progression of renal impairment, or absence of proliferative retinopathy and other microvascular complications of diabetes. Even though crescentic GN (eg, due to antineutrophil cytoplasmic or antiglomerular basement membrane autoantibodies) is relatively common in older adults, it seldom presents with isolated NS, rather nephritic syndrome. Autoimmune diseases such as lupus nephritis are distinctly uncommon in the older patient, particularly in men.

MCD is encountered in approximately 15% and MN in approximately 30% to 40% of renal biopsies in older adult with isolated NS. Both MN and MCD can be primary idiopathic glomerular diseases or secondary to extrarenal conditions such as neoplasia, drugs, or infection. Approximately 10% of renal biopsies in older patients believed to have primary idiopathic NS on clinical grounds will reveal amyloidosis. Amyloidosis in the older adult is most often of the primary variety, although secondary and hereditary amyloidosis have also been described in such participants.

Presentation

The most common symptom in patients with NS is lower extremity edema—sometimes patients also notice facial or upper extremity swelling or increased abdominal girth from ascites. Often, patients are asymptomatic and albuminuria is detected. Occasionally, patients are found to have hyperlipidemia as the first presenting abnormality. Rarely patients with NS present with an arterial or venous thrombotic event. Renal vein thrombosis should especially raise the concern for NS. Even though NS usually does not cause hypertension, in patients with new onset of hypertension, in particular if there is suspicion for secondary hypertension, NS should be ruled out.

Evaluation

New onset of lower extremity edema should always warrant a urinalysis, which is cheap, noninvasive, and can quickly guide further diagnostic interventions. If the urinalysis shows albuminuria, renal function, serum albumin, and lipid levels should be determined. A kidney ultrasound is used to evaluate for kidney size, which can be increased in patients with NS due to diabetic and HIV nephropathy, amyloidosis, and infiltrative diseases that can also cause membranous nephropathy. A kidney biopsy should be considered in all patients with new onset of NS.

Management

Pharmacologic Treatment of the underlying etiology of NS is usually divided into immunosuppressive and nonimmunosuppressive therapies. Immunosuppressive therapy usually includes induction and maintenance regimen. Which regimen is recommended depends on the specific disease etiology, risk for progression, presence of comorbidities, and risk of complications. Disease-specific immunesuppressive regimens usually include pulse-dose corticosteroids, followed by oral steroids very similar to patients with glomerulonephritis as described earlier. The rate of steroid taper often is guided by response to therapy. Additional therapeutic strategies may include B-cell depletion using anti-CD20 antibodies, calcineurin inhibitors, and mycophenolate mofetil.

Nonimmunosuppressive therapies target mainly proteinuria and edema. The mainstay of interventions to lower proteinuria is blockade of the renin-angiotensin system with either ACEI or ARB which lower intraglomerular pressure and also exhibit direct beneficial effects on podocytes. In addition, spironolactone can be considered but requires very close monitoring because of possible hyperkalemia and blood pressure–lowering effects. Peripheral edema and ascites require sodium restriction (< 2 g/day) and loop diuretics, but edema should be reversed slowly to avoid hypovolemia and AKI. Hyperlipidemia usually resolves with resolution of NS, but in patients who experience a thrombotic event due to hypercoagulopathy in NS, anticoagulation may have to be considered.

Nonpharmacologic It is unclear whether protein restriction should be recommended due to heavy protein loss. Low-salt diet is needed for management of edema. The same goals and issues as for patients with CKD have to be considered.

Prevention

The majority of etiologies of NS is not due to patient's actions, but some medications can cause NS (see **Table 87-5**). Patients who are started on any of these medications should be monitored for the development of NS and used with great caution or avoided in patients with history of NS or proteinuria.

TABLE 87-5 HISTOLOGY OF NEPHROTIC SYNDROME IN GERIATRIC PATIENTS

STUDY NO.	TOTAL (*N*)	MCD (%)	FSGS (%)	MN (%)	AMYLOID (%)	MPGN (%)	OTHER/PRO (%)	DN (%)	OTHERS (%)
1	63	21	16	33	14	5	5	5	1
2	164	21	3	38	12	5	14	4	3
3	107	2	15	48	10	5	4	5	11
4	317	11	4	37	11	6	13	4	13
5	50	4	4	32	22	4	34	—	—
6	31	6	—	52	—	16	—	—	22
7	35	6	3	43	3	3	23	—	—
8	92	14	0	35	20	11	15	1	2
9	33	27	—	39	9	6	6	—	13
10	87	8	0	34	10	8	15	0	—
11	59	3	6	21	7	4	5	8	5
12	76	25	4	41	13	—	13	—	8
Total	1114	11.2	7.4	37.7	11.1	6.6	13.3	3.7	9

Amyloid, amyloidosis; DN, diabetic nephropathy; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MCGN: membranoproliferative (or mesangiocapillary) glomerulonephritis; MN, membranous nephropathy; Other/Pro, other proliferative glomerulonephritis; Others, nonproliferative glomerulonephritis.

Adapted from Cameron JS. Nephrotic syndrome in the elderly. Semin Nephrol. 1996;16:319.

Special Issues

Patient preference NS, if left untreated, is a potentially life-threatening disease due to cardiovascular and infectious complications. In addition, nephrotic syndrome can lead to AKI, potentially requiring dialysis support, but is potentially reversible. Even after dialysis had to be initiated it is possible that renal function can recover with appropriate therapy to be able to stop dialysis. On the other hand, NS can lead to CKD and progression to ESRD even with treatment. Therefore, patients need to be educated about the overall prognosis and a discussion of goals of care should be initiated early during the course. Because some etiologies of NS including MCD and MN, are paraneoplastic syndromes, a malignancy work-up should be considered.

Comorbidity NS is associated with accelerated cardiovascular disease because of dyslipidemia and underlying disease process. In addition, patients are at risk for infectious complications in the setting of NS and immunosuppressive therapy. Patients are at increased risk for arterial and venous thrombotic events due to loss of coagulation factors. Systemic anticoagulation has to be considered after the first event, but comorbidities and overall status of the patient have to be carefully considered. Chronic lower extremity edema can lead to skin break down and decreased mobility. Underlying sodium retention can lead to hypertension. Some etiologies of NS in particular MCD and MN, are paraneoplastic syndromes of potentially undetected malignancies.

DIABETIC NEPHROPATHY

Definition

Diabetic kidney disease or diabetic nephropathy (formerly called Kimmelstiel-Wilson disease), is a progressive microvascular complication due to long-standing diabetes mellitus that can lead to ESRD.

Epidemiology

About 30% of patients with diabetes mellitus develop diabetic nephropathy (DN) during their lifetime. In the general adult population in the United States, DN is the most common cause of nephrotic syndrome and ESRD requiring dialysis. DN is more common in patients with other microvascular complications, neuropathy and retinopathy, and in patients with a family history of kidney disease, including DN.

Pathophysiology (Classification)

DN is a microvascular complication of patients with diabetes mellitus. DN has several distinct phases and complex molecular mechanisms are involved in the development of the disease and its outcomes. Patients with DN initially develop hyperfiltration with eGFR above 120 mL/min/1.73 m^2, and albuminuria, often below the detection limit of standard urinalysis tests. Over time, proteinuria increases up to nephrotic range and eGFR falls initially back to "normal" levels, but then into the more obvious CKD range. A significant proportion of patients exhibit accelerated loss of kidney function once eGFR is below 45 mL/min/1.73 m^2. Hyperglycemia appears to contribute significantly to development of DN because DN is a complication of both types 1 and 2 diabetes. Genetic studies have identified candidate genes that are associated with increased susceptibility to DN. Advanced glycation and oxidative stress alter the cellular physiology and the interaction of various cytokines with their signaling cascades. In particular, dysregulation of transforming growth factor β_1 and angiotensin II, two cytokines with fibrotic and hemodynamic functions, respectively, and their downstream signaling cascades appear to be affected.

Presentation

Most patients are diagnosed with DN because of routine screening tests for renal function and albuminuria, which is now the standard of care. Patients with earlier stages of DN can be found to hyperfiltrate with eGFR above 120 mL/min/1.73 m^2, and/or albuminuria, often below the detection limit of standard urinalysis tests requiring testing for "microalbuminuria." At later stages, patients may present with "macroalbuminuria" and nephrotic syndrome. In all patients with DM and eGFR below 60 mL/min/1.73 m^2 DN is the likely underlying etiology. Absence or less than nephrotic range proteinuria does not exclude DN. Even though a small proportion of patients with biopsy-proven DN also have microscopic hematuria, its presence should raise the concern for another underlying renal disease or a genitourinary malignancy.

Evaluation

All patients with DM should be regularly evaluated for development of albuminuria and changes in eGFR. A kidney ultrasound may show larger than expected kidney size, which can also be seen in patients with infiltrative disease, amyloidosis, cystic kidney disease, or HIV nephropathy. Serologic testing to rule out other etiologies has to include HIV, hepatitis, paraproteinemia/multiple myeloma, and other cancerous diseases depending on the specific presentation of each patient. Even though a kidney biopsy may not be necessary in many patients with suspected DN, it has to be seriously considered in the presence of any concern for other etiologies. Patients have to be evaluated for electrolyte abnormalities because type IV renal tubular acidosis (RTA) may lead to hyperkalemia, and serum albumin and lipid levels need to be determined to diagnose nephrotic syndrome and its associated complications.

Management

The main goals in patients with DN are optimization of blood glucose levels, blood pressure, and body weight. In addition, complications of CKD as well as timely preparation for dialysis have to be managed.

Pharmacologic Blockade of the renin-angiotensin system and tight glycemic control has shown to improve outcomes in patients with DN. The medications used to achieve these goals should be tailored specifically toward individual patient's comorbidities. ACEI and ARB are the only pharmacologic interventions that delay progression of CKD to ESRD and should be started in all patients with diabetes mellitus and any stage of CKD and/or hypertension if tolerated. Calcium channel blockers are the next choice for mild antiproteinuric effects in addition to control of blood

pressure. If sodium retention and edema are present diuretics may be used. The blood pressure goal for patient with diabetes and CKD is below 130/80 mm Hg. Optimization of lipid and glucose levels is a critical aspect of management of patients with DN. Pharmacologic lowering of uric acid levels in patients with hyperuricemia even in the absence of gout symptoms can potentially delay progression in DN.

Nonpharmacologic Obesity and weight gain can accelerate progression of kidney disease via worsening glomerular hypertrophy already present in DN and should be strongly avoided. Weight loss should be a high priority for its overall strong health benefits for patients with diabetes. Similarly, exercise improves control of blood glucose levels and blood pressure and may also improve outcome in patients with CKD. Similar effects have been proposed for treatment of sleep apnea.

Special Issues

Patient preference The natural course of DN is progression to ESRD and intervention can only delay this. Patients with diabetes who require dialysis have higher complication rate and mortality than other patients. Patient with DM should be educated about these significant adverse outcomes.

Comorbidities Many patients with DN suffer from other complications of DM, including neuropathy and retinopathy, hyperlipidemia, macrovascular disease (coronary artery disease [CAD]), and obesity. Management of these comorbidities can potentially delay progression of CKD to ESRD and improve quality of life. Diabetic patients with ESRD receiving dialysis have increased risk for cardiovascular and infectious complications, which need to be managed aggressively.

INTERSTITIAL NEPHRITIS

Definition

Interstitial nephritis is characterized by inflammation of the tubulointerstitial area of the kidney causing tubular dysfunction and thereby proteinuria and decrease in renal function.

Epidemiology

The number of patients with acute interstitial nephritis (AIN) is very difficult to assess with confidence as many episodes are likely undiagnosed and/or self-limited. However, it is reasonable to assume it is a common complication of drug therapy. In patients with acute kidney injury AIN is an important cause of AKI and its prevalence among older adults may be increasing. A recent study showed that older adults were found to have significantly more drug-induced AIN compared with younger patients (87% vs 64%), with proton pump inhibitor–induced AIN (18% vs 6%) being the most prominent. On the other hand, AIN due to autoimmune or systemic causes was significantly less common (7% vs 27%) among older patients. Compared with younger patients, older patients have a significantly higher prevalence of baseline CKD, higher peak creatinine, and more need for dialysis. About 86% of older patients showed partial or complete recovery within 6 months. Prompt initiation of steroids was correlated with recovery at 6 months. Lack of early recovery tended to correlate with progressive CKD.

Pathophysiology (Classification)

The most common cause of AIN is secondary to drug therapy, but autoimmune diseases or other systemic diseases (eg, systemic lupus erythematosus (SLE), Sjögren syndrome, sarcoidosis, IgG4-related diseases), infections (eg, *Legionella*, leptospirosis, and streptococcal organisms), and tubulointerstitial nephritis with uveitis (TINU) syndrome can also cause AIN. Even though virtually any drug can cause AIN, the most common culprits are antibiotics (in particular penicillins, cephalosporins, and ciprofloxacin), proton pump inhibitors, NSAIDs, and diuretics. In older adults the vast majority of AIN is due to drugs, primarily proton pump inhibitors and antibiotics, while AIN of autoimmune or systemic origin is uncommon. Nevertheless, a careful differential diagnosis with other entities that can also induce AIN is required.

Presentation

AIN usually presents with nonspecific signs and symptoms of AKI, including nausea, vomiting, and malaise, unless

the patient has systemic signs of an allergic drug reaction such as fever or rash. Hematuria is rare and proteinuria is usually not significant, with the exception of NSAID-induced AIN, which can be accompanied by nephrotic syndrome due to membranous nephropathy or minimal change disease. Presentations with minimal symptomatology that require a higher index of suspicion are increasingly recognized in older adults—NSAIDs and proton pump inhibitors are frequently the offending drugs in this setting.

Evaluation

In addition to the physical examination, serum creatinine levels have to be monitored. In the urine sediment white cells, red cells and white cell casts are typically seen. Eosinophilia may be present, but eosinophiluria lacks sensitivity and specificity to help in the diagnosis of AIN. Glucosuria, high fractional excretion of sodium (> 1%), and renal tubular acidosis may be present indicating renal tubular cell damage. A kidney biopsy can be considered in situations where the diagnosis of AIN would change the management. These include unclear etiology of AKI and consideration of treatment with corticosteroids if AIN is present. The patient's medication history needs to be carefully reviewed. If no culprit is identified, a search for other etiologies should be considered, including infection, SLE, sarcoidosis, Sjögren disease, TINU, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. The patient's history and physical examination findings can guide toward specific etiologies.

Management

The most important intervention if AIN is suspected is to stop the offending agent, if such can be identified. These are usually medications that have been recently initiated, but in the absence of a recent exposure to a new drug, medications that have been used for a longer period of time, in particular proton pump inhibitors, may have to be discontinued.

Drugs Corticosteroid therapy has been shown to improve outcomes if initiated within 14 days after first symptoms. Even though the recommended dose is equivalent to treatment of GN or vasculitis, lower doses used for allergic dermatitis should have the same effect in the kidney. Unfortunately, appropriate trials are not available.

Nonpharmacologic Discontinuation of the offending agent is the single most important intervention in AIN.

Prevention

To prevent AIN groups of medications to which the patient has a known allergy should be avoided. In addition, medications with known higher-than-average risk of AIN—in particular proton pump inhibitors—should only be prescribed if and as long as needed. If high-risk medications have to be given, renal function tests and a urinalysis should be ordered before and shortly after starting the medication.

Special Issues

Patient preference The use of corticosteroids in AIN can cause significant complications, in particular in patients with diabetes. Treatment regimen should be limited in length and lower-dose corticosteroids may be considered, even so the efficiency of lower doses remains uncertain.

Comorbidity AIN can present with systemic symptoms, in particular skin rash and peripheral eosinophilia. In rare cases, involvement of the airways in the allergic reaction can cause bronchospasm. The latter usually requires therapy with corticosteroids and usually no specific treatment of AIN is required.

Care settings AIN is often undetected because it is asymptomatic and requires blood and urine test to diagnose it. Therefore, it is very likely that many more episodes of AIN are occurring in the outpatient setting, when many new medications are prescribed without frequent monitoring of renal function.

RENOVASCULAR DISEASE

Definition

Renovascular disease is characterized by anatomic narrowing of a main renal artery (renal artery stenosis) or its

branches and can cause secondary hypertension and progressive renal insufficiency. Renal artery stenosis may be asymptomatic or cause hypertension and ischemic nephropathy. Renovascular hypertension is defined as the elevation of blood pressure secondary to compromised arterial circulation of the renal parenchyma causing chronic renal hypoperfusion. Ischemic nephropathy can be defined as a reduction in GFR resulting from a partial or complete luminal obstruction of the preglomerular renal arteries of any caliber.

Epidemiology

Renovascular hypertension is a common cause of potentially remediable secondary hypertension in older patients with an estimated prevalence of 2% to 3% in the general hypertensive population.

Pathophysiology

Atherosclerosis accounts for almost 90% of cases in the geriatric population, with fibrous dysplasia comprising the rest, but the spectrum of diseases that can cause renovascular disease includes many different disease entities (**Table 87-6**). It occurs in patients with hemodynamically significant stenosis in the renal artery of a solitary kidney or in both renal arteries if two kidneys are present. Atheroembolic renal disease falls into the category of renal insufficiency induced by preglomerular ischemia. This entity has been usually described in patients with clinical evidence of atheromatous occlusive disease following invasive intra-aortic diagnostic or therapeutic procedures, although spontaneous embolic episodes have been described.

TABLE 87-6 CATEGORIES OF RENAL ARTERY DISEASE

Aneurysms
Arteriovenous malformations
Atherosclerosis
Dissection of the aorta
Embolic disease
Fibrous dysplasia
Kawasaki disease
Neurofibromatosis
Other systemic necrotizing vasculitides
Polyarteritis nodosa
Takayasu arteritis
Thromboangiitis obliterans
Thrombotic diseases
Trauma
Vasculitis involving the renal artery

Modified from Greco BA, Breyer JA. Natural history of renal artery stenosis. Semin Nephrol. 1996;16:3.

Presentation

Clinical clues that might prompt the clinician to consider renal artery stenosis in older patients are onset of hypertension after the age of 50; accelerated or difficult-to-control hypertension; coexisting diffuse atherosclerotic vascular disease and decreased GFR; acute or subacute increase in serum creatinine levels after initiation of therapy with ACEIs or ARBs; recurrent pulmonary edema; grades III to IV hypertensive retinopathy; abdominal or flank bruit; hypokalemia in the absence of diuretic use; erythrocytosis; microangiopathic hemolytic anemia; and hyperuricemia.

Acute or subacute fall in GFR (rise in serum creatinine) can be precipitated by treatment of hypertension with ACEIs or ARBs during a period of days to weeks after initiating therapy. It is associated with hypoperfusion of the kidneys caused by inhibition of angiotensin II–dependent autoregulatory pathways in the glomerulus. Even so many patients with renovascular disease tolerate these agents and do not require additional noninvasive studies. Serum

creatinine and electrolyte levels need to be monitored in patients with risk factors for renovascular disease. Currently available clinical data estimate that 6% to 38% of patients with significant renal vascular disease will develop ARF following ACEI or ARB therapy. Other antihypertensive agents have been reported to cause reversible ARF in the setting of ischemic nephropathy. These cases should be distinguished from those hypertensive patients without ischemic nephropathy who develop ARF in the setting of renin-dependent decreases in renal perfusion such as intravascular volume depletion or low effective circulating volume states such as congestive heart failure or cirrhosis.

Patients with suspected or documented renovascular hypertension and poorly controlled hypertension may present with progressive azotemia or with recurrent pulmonary edema (23% prevalence in some series). Postulated mechanisms for the latter include angiotensin II–induced myocardial dysfunction, diastolic dysfunction secondary to left ventricular hypertrophy, and reduced pressure natriuresis in conjunction with subsequent volume expansion. Important clinical clues associated with atheroembolic renovascular disease are the presence of unexplained eosinophilia, purpuric-ischemic skin lesions, and the presence of heavy proteinuria, which can be in the nephrotic range.

Azotemia in an older patient that cannot be explained by other renal diseases—in particular in the setting of worsening renal failure, bland urinary sediment, proteinuria (< 1 g/day), hypertension, and evidence of peripheral vascular disease—should prompt an evaluation for renovascular disease. It is not clear what proportion of the dialysis population has renovascular disease as the underlying cause of ESRD. However, given that the prevalence of atherosclerotic disease and ESRD are both highest in the older age group, it is likely that renovascular disease is very common in older adults.

Evaluation

The diagnosis of renovascular hypertension is based on the demonstration of renal artery stenosis (usually by angiography or CT angiography), pathophysiologic significance of the stenotic lesion, and correction of the hypertension by an intervention that relieves the stenosis. In practice, the diagnosis of ischemic nephropathy is almost always made in the context of coexisting hypertension.

In the appropriate clinical setting such as those just described, the clinician should develop a high index of suspicion for the disease. According to the triage approach proposed by Mann and Pickering, the patient may be classified as having a low (< 1% prevalence), moderate (5%–15% prevalence), or high (> 25% prevalence) pretest probability for renovascular disease. Patients classified in the low-risk group should not undergo further work-up. The presence of azotemia in the high-risk group may impair the reliability of the noninvasive tests and may justify performing renal angiography regardless of the results of noninvasive tests. In patients with intermediate probability, noninvasive testing has the most important diagnostic role.

Duplex ultrasound scanning of the renal arteries is a screening tool with promising early results. Duplex ultrasound scanning also allows measurement of kidney size and is not affected by medications or the level of GFR. The reported sensitivity and specificity values are in the low- to mid-90% range. The main disadvantage of this test is that it is technically demanding and has a steep learning curve for each center that performs this test. Another caveat is that accessory renal arteries are difficult to detect and study.

Magnetic resonance angiography (MRA) has been effective in screening for the presence of renal artery stenosis with the advantage of being less exposed to contrast media and less invasive than the arteriogram. A publication from Italy reports overall accuracy of 97% for correct depiction of severe renal artery stenosis when compared head-to-head to conventional angiography. However, there have been recent case reports of patients with CKD developing nephrogenic systemic fibrosis (NSF) or nephrogenic fibrosing dermopathy (NFD) thought to be secondary to gadolinium exposure. Therefore, the future use of MRA for defining renal artery stenosis in patients with kidney disease needs to be determined. Another highly accurate noninvasive study for screening for renal artery stenosis is the spiral (helical) CT scan with CT angiography. However, there is a risk of contrast nephropathy with the spiral CT scan in patients with CKD.

ACEI radionuclide scintirenography is currently the most thoroughly evaluated noninvasive test for the diagnosis of renovascular hypertension. This study should be preceded by measurement of a random morning plasma renin activity (PRA). Evaluation of ACEI renography by using technetium-99m diethylenetriamine penta-acetic acid (^{99m}Tc-DTPA) has shown high sensitivity and specificity (91%–94%) for renovascular hypertension. Currently, renal scintigraphy with hippuran or Mag3 (renal plasma flow tracers) before and after ACEIs is the functional test of choice to diagnose ischemic nephropathy. Two limitations should be kept in mind: (1) these tests have not been evaluated in patients with azotemia, and (2) while a positive test predicts an improvement in blood pressure, it is not known

whether it also predicts an improvement in renal function.

The gold standard for diagnosing renal artery stenosis is selective renal angiography. Intra-arterial digital subtraction angiography (IADSA) or a CO_2 angiogram also provides excellent anatomic detail and requires less contrast than conventional angiography. The technique of intravenous DSA, although less invasive, does not provide comparable resolution to the aforementioned tests because of the high degree of bowel gas and motility artifacts, and usually requires a significantly larger amount of nephrotoxic contrast material.

The second step in making the diagnosis of renovascular hypertension is to determine the pathophysiologic significance of the lesion. Some of the diagnostic tests already mentioned are also used to assess this issue. Selective renal vein renin measurement is the gold standard for establishing the functional nature of the stenotic lesion and helps predict the blood pressure response to revascularization. In general, a renal vein renin ratio of greater than or equal to 1.5 between the two renal veins is predictive of a beneficial blood pressure response following surgery or angioplasty, but failure to lateralize does not predict a negative response. Overall, the blood pressure response to revascularization cannot be determined with confidence by using renal vein renin measurements. A positive ACEI renogram with ^{99m}Tc-DTPA has been reported to accurately predict the blood pressure response to revascularization. The predictive value of all of these tests in terms of the renal function outcome after revascularization is largely unknown and awaits further study.

Management

Renovascular disease can remain stable or worsen over time. Of patients with renal artery stenosis, up to 50% can expect their stenosis to worsen, with reported rates varying between 1.5% and 5% per year. In general, the rate of progression of renal insufficiency and the likelihood of deterioration of renal function correlates positively with the extent of stenosis at the time of diagnosis. Older adult patients who develop ESRD secondary to progressive atherosclerotic renal artery obstruction have the poorest overall survival, with a 27-month median survival rate and only a 12% 5-year survival rate.

There is no universally accepted treatment for renal artery stenosis. Therapy must be individualized and based on the general status of the patient, the presence of any concomitant disease, and the local surgical or angiographic experience of the center. Early studies have shown that surgical revascularization cures or improves over 80% of patients of all ages with renal artery stenosis with a mortality rate of approximately 1%. More recent larger and randomized studies have not confirmed those results and did not show improved outcomes, in particular rates of ESRD and survival. This may be particularly true in older patients with atherosclerotic renal artery stenosis in whom the prognosis is determined by the extent of atherosclerosis elsewhere.

In the presence of unilateral renal artery stenosis and at least moderately decreased GFR, the latter is usually not improved by intervention. In bilateral stenosis, there are two possible clinical presentations. The first is bilateral occlusion of the renal arteries. This situation does not necessarily imply irreversible damage because the viability of the kidneys may be maintained by a collateral blood supply. This is particularly true in patients who have a gradual onset of arterial occlusion. Clinical clues suggesting parenchymal salvageability include the following: angiographic demonstration of retrograde filling of the distal renal arterial system by collateral vessels; renal biopsy showing preserved glomerular architecture; kidney size greater than 9 cm by ultrasound; and function of the involved kidney on renal scintigraphy. Some centers perform kidney biopsies in surgical candidates if their serum creatinine is higher than 4 mg/dL. In patients with serum creatinine less than 3 mg/dL, improved renal function (defined as a reduction in serum creatinine of > 20% from the baseline value) can be expected post-revascularization in nearly half of patients undergoing this procedure.

The second scenario is bilateral stenosis without total occlusion or stenosis in a solitary kidney. Improvement in renal function is frequently seen after reconstructive surgery in 75% to 89% of these patients. Unlike cases with total renal occlusion, revascularization to preserve renal function is not worthwhile in patients with severe renal insufficiency (serum creatinine > 4 mg/dL) because they usually have advanced underlying renal parenchymal disease (nephrosclerosis and/or atheroembolic disease), which is not improved by revascularization. In older patients, severe atherosclerosis of the abdominal aorta may render an aortorenal bypass technically impossible. In such cases, alternate bypass techniques have been used, such as splenorenal bypass for left kidney revascularization and hepatorenal bypass for right kidney revascularization. Considering the significant risks of progressive renal occlusive disease and renal failure that are associated with medical management of this condition in older patients, the surgical results showing a favorable influence of revascularization on the natural history of untreated atherosclerotic renal artery disease are of interest and merit further study.

Initially percutaneous transluminal renal angioplasty (PTRA) had a limited role in older patients because of the concomitant presence of aortic atherosclerotic disease, making any endovascular procedure hazardous and technically difficult. Restenosis following dilatation of atheromatous lesions was quite common and a significant number of older patients present with ostial lesions, which are not amenable to PTRA. PTRA with the use of endovascular stenting devices have come into vogue with improved outcome of the revascularization of these ostial lesions. Surgical intervention is presently recommended for more complicated lesions, or angioplasty failures. One advantage of angioplasty over surgery is that it can be undertaken in patients who have prohibitively high surgical risks that are related to systemic atherosclerosis.

Prevention

Renovascular disease can be prevented by the same measures that prevent atherosclerosis, in particular smoking cessation, exercise, and control of hyperlipidemia.

Special Issues

Patient preference Even though interventions have not provided benefits in outcome, in specific patients an intervention may be considered if it improves quality of life to reduce side effects of antihypertensive medications.

Comorbidity Many patients who have renovascular disease also suffer from other complications of atherosclerosis, in particular peripheral vaso-occlusive disease, atherosclerosis of the aorta and CAD.

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Chapter 88

End-Stage Renal Disease

Mark L. Unruh, Pooja Singh

Learning Objectives

- Describe the indications for initiating dialysis among older adults with kidney failure.
- Understand the prognosis of older adults with kidney failure.
- Characterize the approaches to managing end-stage kidney disease among older adults.
- Describe the influence of multiple chronic health conditions on quality of life and functioning among older adults with kidney failure.
- Recognize the challenges in providing care to older patients with kidney failure due to increased cognitive impairment and frailty.
- Discuss the role of clinicians in advanced care planning for patients with end-stage renal disease (ESRD).

Key Clinical Points

1. **In addition to diabetes and hypertension, pauci-immune glomerulonephritis, renovascular disease, and acute kidney injury (AKI) contribute to the growing numbers of older patients with kidney failure.**
2. **Clinical guidelines suggest that patients with progressive chronic kidney disease (CKD) should be managed in a multidisciplinary setting. Nephrologist referral should be considered under the following circumstances: AKI, urinary red cell casts, CKD and refractory hypertension, persistent abnormalities of potassium, recurrent or extensive nephrolithiasis, hereditary kidney disease, CKD stages 4 and 5, and patients with severely increased albuminuria.**
3. **Older patients with kidney failure have a multitude of choices for kidney replacement therapy including hemodialysis, peritoneal dialysis, conservative management, palliative care, and kidney transplantation.**
4. **There are no age restrictions on access to kidney transplantation in the United States. Among older patients with kidney failure, it is important to consider kidney transplantation as an option. Older kidney transplant patients tend to have less kidney allograft rejection and a higher complication rate from infections.**
5. **Kidney failure is associated with a markedly high mortality rate among older patients initiating dialysis—average 1-year survival rate is 50% for octogenarians and nonagenarians who start dialysis.**
6. **There are major gaps in advanced care planning for patients with chronic kidney failure. Geriatricians and nephrologists should work together to establish goals of care for these high-risk patients.**

DEFINITION

End-stage renal disease (ESRD) or kidney failure, has been defined as having kidney function less than 15 mL/min/1.73 m^2. Kidney failure may be caused by progression of a chronic nephropathy or by acute kidney injury (AKI). Kidney failure is associated with the inability to excrete waste products, control serum electrolytes, handle the daily dietary and metabolic acid load, and maintain fluid balance. In addition, kidney failure causes inadequate production of erythropoietin, deranged calcium and phosphorous metabolism, high blood pressure, and accelerated progression of cardiovascular disease. Uremia is the term used to describe the symptoms or symptom complex attributable to advanced kidney failure or ESRD. Most chronic nephropathies demonstrate inexorable progression to kidney failure. While it is widely held that there is a straight line relationship between the decrement in kidney function over time when the kidney function is plotted longitudinally, there is variability in rate and trajectory of progression among individuals with kidney disease. This variability may be particularly important when caring for the older patient approaching ESRD. The rates of decline in kidney function vary by underlying nephropathy, by severity of hypertension and albuminuria, by modifying factors, and between individuals. Historically, the rate of decline could be estimated as 7 to 10 mL/min/year in those with untreated chronic nephropathies such as diabetic nephropathy. However, chronic nephropathies have similar effects on electrolyte homeostasis, causes of progressive decline in function, and manifestations of kidney failure so that classification by severity permits a better understanding of underlying routes to progression, symptoms, and hopefully, treatments of CKD. In parts of the world with access to dialysis and kidney transplantation, renal replacement therapy (RRT) has been thought to be necessary when the glomerular filtration rate (GFR) decreases to less than 15 mL/min. Albuminuria as a marker of kidney damage has been studied most thoroughly. CKD is the term used to describe patients with a chronic decrease in GFR. There are different levels of CKD, and these levels have underpinned an international classification system (**Figure 88-1**). The classification of CKD was revised to account for the impact of albuminuria on the rate of progression to kidney failure and other outcomes. The relationship of kidney function and albuminuria to the development of kidney failure and mortality was shown to be consistent across ages among diverse populations.

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (mL/min/1.73 m^2) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	< 15			

FIGURE 88-1. Prognosis of chronic kidney disease (CKD) by glomerular filtration rate (GFR) and albuminuria category. (From Kidney Disease: Improving Global Outcomes [KDIGO] CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Inter Suppl*. 2013;3:1–150.)

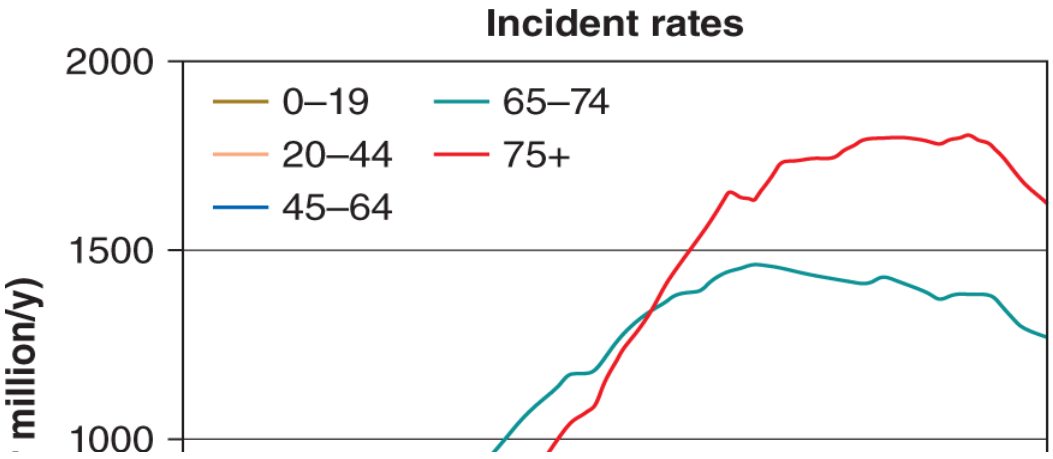
EPIDEMIOLOGY

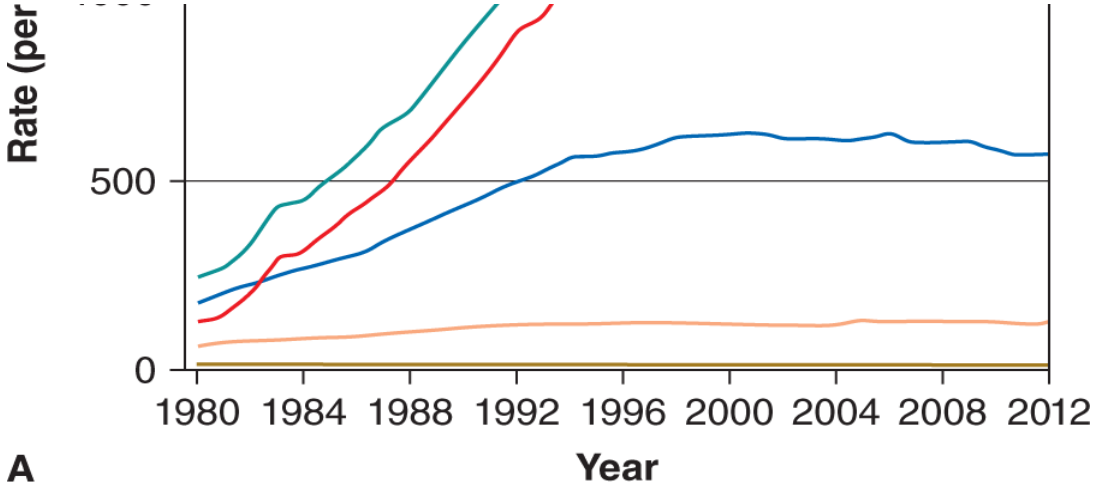
The prevalence of kidney failure is increasing rapidly worldwide; the projections are that the number of patients with kidney failure will double in the next 10 to 15 years. However, this is just the tip of the iceberg. Estimates are that there are 30 times as many people with CKD as compared to kidney failure. Approximately 10% to 15% of the adult population in North America, Europe, and Asia is thought to have some form of CKD. The majority of those with CKD stages 1 and 2 may not even be aware of their kidney disease. Nonmodifiable risk factors are important for risk stratification and for understanding the pathophysiology of CKD progression (**Table 88-1**). African-American patients with diabetes have a two- to threefold higher risk of developing kidney failure compared to white patients. Modifiable risk factors are important for both understanding disease progression and as a possible option for prevention or therapy. For example, the heavy consumption of analgesics has been associated with the development of kidney failure. The number of patients who develop kidney disease and at risk for developing kidney disease will increase with the increasing prevalence of diabetes and the aging of the population.

TABLE 88-1 CHRONIC KIDNEY DISEASE RISK FACTORS

NONMODIFIABLE RISK FACTORS	MODIFIABLE RISK FACTORS
Older age	Hypertension
Male gender	Obesity
Black race	Proteinuria
Genotype	Dyslipidemia Hyperuricemia Smoking

The burgeoning number of older people with kidney failure has been caused by an increased incidence of kidney failure, greater access to RRT, and improved survival of both dialysis patients and kidney transplant recipients. The majority of patients in the United States receiving hemodialysis are aged 65 and older and the prevalence of older patients undergoing hemodialysis is rapidly increasing (**Figure 88-2**). Hence, the growth of the ESRD population has largely been driven by those patients older than 65 years. This has been a worldwide phenomenon with a sevenfold increase in the rate of incident dialysis patients older than 75 years over the past two decades in Canada. Similar rates of increase of kidney failure in older adults have been noted in Europe and Japan with a 10-fold increase in octogenarian hemodialysis patients in Japan. Indeed, the very recent marked increase in incidence of end-stage kidney failure documented by renal registries suggests that this spike of disease has been driven by the increased access to RRT. Older and sicker patients have been referred for hemodialysis in Asia, Australia, Europe, and North America as a result of perceived improvements in quality of life on dialysis, as well as economic and cultural factors. Once referred for kidney failure, older patients have been surviving longer with RRT as dialysis treatment and kidney transplant outcomes have improved. As a result of improvements in technology and greater access to dialysis, the increased prevalence of older adults undergoing RRT generally mirrors the aging trend of the general population.





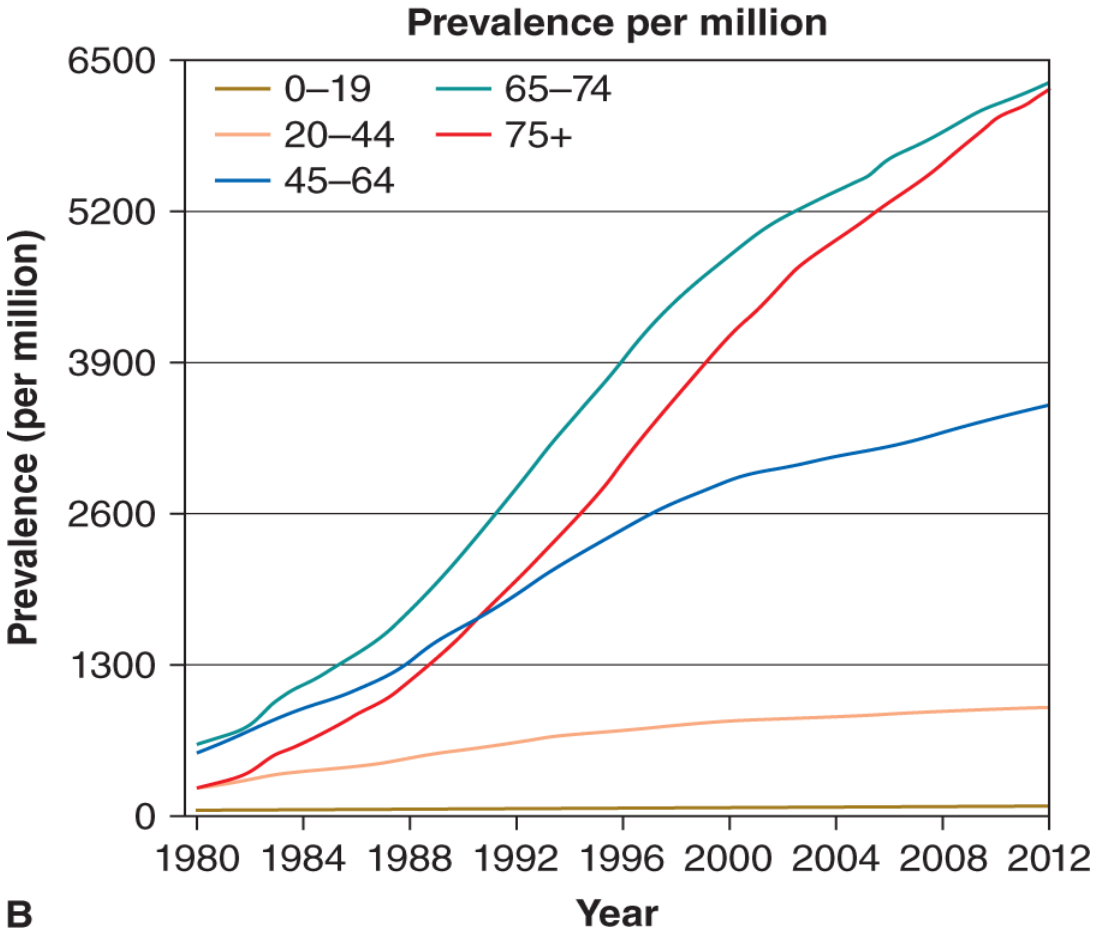


FIGURE 88-2. Trends in incident end-stage renal disease (ESRD) cases and the adjusted* prevalence of ESRD, per million, by age group, in the US population, 1980 to 2012. *Adjusted for sex and race. The standard population is the US population in 2011, point prevalence on December 31 of each year. (From US Renal Data System, USRDS. 2014 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014.)

Acute Kidney Injury in Older Adults

AKI has been defined as an abrupt decrease in kidney function. This decrement in kidney function is reflected by an increase of serum creatinine from baseline by 0.3 mg/dL, or an increase in serum creatinine by at least 50% over a week or markedly reduced urine output to less than 0.5 mL/kg/h for 6 hours. More than 50% of patients with AKI are older than 60 years. Older adults are thought to be predisposed to AKI owing to a reduced GFR, comorbid illness, and use of medications such as nonsteroidal anti-inflammatories and angiotensin-converting enzyme (ACE) inhibitors.

AKI may occur in older patients both in the outpatient or inpatient setting. Obstruction from prostatic hypertrophy, volume depletion, and medications are prominent causes of AKI among community-dwelling older adults. In the hospital setting, AKI may occur in up to 25% of critically ill patients and has been associated with a marked increase in mortality. Among hospitalized patients, AKI often arises from acute tubular necrosis or acute interstitial nephritis, although AKI merits a thorough evaluation for reversible causes. At present, the care of patients with AKI has been supportive care with acute dialysis and avoidance of further kidney injury from nephrotoxins. The indications for initiation of emergent or acute dialysis therapy in the geriatric population vary little from younger patients (**Table 88-2**). The prognosis for survivors of AKI depends on severity of illness, chronic health conditions, length of time requiring dialysis, and preexisting kidney disease. Patients who survive the initial insult of acute renal failure caused by acute tubular necrosis requiring dialysis may recover renal function and have adequate long-term kidney function. When older patients with CKD present with an acute increase in creatinine, they should be evaluated for reversible causes of their kidney failure such as obstruction or volume depletion.

TABLE 88-2 INDICATIONS FOR URGENT HEMODIALYSIS

Refractory
Progressive fluid overload
Hyperkalemia
Metabolic acidosis
Uremia
Nausea, vomiting, poor appetite
Altered mental status (encephalopathy)
Bleeding diathesis (uremic platelet dysfunction)
Pericarditis

PRESENTATION

Etiology of End-Stage Renal Disease in the Geriatric Population

The most common reported causes of ESRD in the geriatric population are diabetes and hypertension in the United States and worldwide. The high proportion of kidney failure diagnosed as nephropathy as a result of diabetes and hypertension may be in part because of a hesitance to perform a kidney biopsy in older patients in the face of usual indications such as nephrotic range proteinuria or unexplained renal failure. It may also be that age-related changes seen in many kidneys contribute to the disease-related changes of diabetes and hypertension to cause kidney failure in older adults. However, several disease processes including primary kidney and vascular diseases present in older patients with kidney failure. Minimal change disease, usually more associated with a pediatric population, has a second peak in incidence during the sixth decade of life. The declining immunity associated with aging may also play a role in the second peak in incidence of poststreptococcal glomerulonephritis seen in older adults. Pauci-immune necrotizing glomerulonephritis is also more common among those older than 65 years. In addition to immune-mediated kidney disease, renovascular disease, a term used to describe arterial sclerosis in the kidney, is more common in older individuals. The presence of a clinically significant narrowing of the renal artery may lead to marked hypertension and kidney failure. Diagnosis involves renal ultrasounds with Doppler, spiral computed tomography (CT) with CT angiography, or magnetic resonance angiography (MRA) which may be performed without gadolinium-based contrast agents. The treatment of renal artery stenosis depends on the severity of the lesion and the clinical presentation. Options for treatment include renal angioplasty and stenting, renal bypass surgery, or medical management. The best treatment of renal artery stenosis among older patients remains controversial with the current literature supporting conservative medical management, with some patients benefitting from revascularization.

REFERRAL OF PATIENTS TO NEPHROLOGY

The geriatrician can influence the outcome of kidney failure with the timing of referral for specialty nephrology care.

In the past, physicians would limit access to dialysis and transplantation simply by not sending a patient to a nephrologist. While this still happens and is common in certain practices and in parts of the world with more limited health care, many patients should be referred for kidney-targeted therapy. Older patients with kidney failure maybe referred late to nephrologists with resulting poor outcomes. These patients may lose the opportunity to consider conservative therapy and require delivery of emergent dialysis. The Kidney Disease: Improving Global Outcomes (K/DIGO) guidelines suggest that patients with progressive CKD should be managed in a multidisciplinary setting. These guidelines build on previous recommendations advising referral to a nephrologist after diagnosis under the following circumstances: AKI, GFR less than 30, consistent findings of significant albuminuria, progression of CKD, urinary red cell casts, CKD and refractory hypertension, persistent abnormalities of potassium, recurrent or extensive nephrolithiasis, and hereditary kidney disease. In general, patients with GFR less than 30 mL/min/1.73 m^2 (CKD stages 4 and 5) and patients with severely increased albuminuria should be referred to a nephrologist. The aim is to provide time for the nephrology team to provide individualized care plan consistent with the goals of the older patient with CKD. It is difficult to estimate the proportion of late referrals that have been caused by the failure to recognize kidney failure in older patients.

While most geriatricians may feel comfortable managing CKD and the concomitant metabolic and endocrine derangements, it is important to have nephrology involvement for patient education and preparation for dialysis. As outlined below, older patients with worsening CKD have a wide spectrum of choices for the treatment of kidney failure. It may take some time for the older patient to be educated and accept another chronic illness in the form of CKD, and then time to select a therapeutic approach to the kidney failure. Once therapy has been selected, some of the treatments require lead time prior to the development of an urgent indication for dialysis. For example, the placement of a vascular access may require a referral to a vascular surgeon, vein mapping, and months for fistula maturation and monitoring. Another example would be using a conservative management approach which provides maximal medical intervention to stave off the development of kidney failure. A large European Study has demonstrated that late referral was associated with poor outcomes and that outcomes among older patients referred late were significantly worse than younger patients referred late. In many studies of referral timeliness, the cut-points have been arbitrarily set at 3 to 4 months and up to 1 year. However, it is likely that less than a year is still too short of a time to optimize the care of the older patient with kidney failure.

Chronic Kidney Disease and Management of Chronic Health Conditions

Since liberalizing access to dialysis and kidney transplantation, there has been a steady shift for this population to include not only older patients, but also to those with multiple chronic conditions. In one cohort of adult patients treated with maintenance hemodialysis in the United Kingdom, 90% of patients older than 65 years had two or more chronic health conditions. These findings are underscored by data from the United States, which demonstrate that patients of age 65 to 74 have multiple chronic health conditions and that the number of comorbid illnesses has been steady or increased in this population. Cardiovascular, musculoskeletal, and neurologic problems predominate and adversely affect morbidity, hospitalizations' mortality, and quality of life. Given the complexity of managing older patients with a high burden of comorbid disease, the geriatric team has the opportunity to play a crucial role in the care of these patients. The role of the primary care provider for older patient on dialysis or following kidney transplantation varies by local practice patterns and resources. At times, the nephrologist may subsume the role of the geriatric team given the frequent interaction with the patient at the dialysis units or the complexities of immunosuppressant following kidney transplantation. In other instances, geriatricians retain the primary role and nephrologists administer the dialysis in more of a consulting role. Those with advanced CKD have been shown to have gaps in their primary care, diabetes care, and cardiovascular disease care. This has been illustrated by US Renal Data System (USRDS) data demonstrating worse diabetes care among CKD stage 4 to 5 patients compared to the general Medicare population as assessed by the performance of screening tests. There are also gaps in nutrition, fall prevention, management of depression, and frailty among older patients undergoing dialysis. It may be that nephrologists would benefit from targeted geriatric training, or as some propose, that there should be special geriatric dialysis units in order to address these gaps in care.

INDICATIONS FOR INITIATION OF DIALYSIS

The most common symptoms that present before initiation of maintenance dialysis in older patients tend to be anorexia, weight loss, fatigue, nausea, and vomiting. The recognition of uremia in the older patient, however, may prove more difficult than in the younger patient. Behavioral changes, unexplained impaired cognition, "adult failure to

thrive," unexplained worsening of congestive heart failure, or a change in sense of well-being may represent uremia in the geriatric patient.

The trend has been for earlier initiation of dialysis in older patients, perhaps because of the increased burden of comorbid disease. The trend for earlier initiation has attenuated somewhat due to observational studies demonstrating a higher risk of mortality among older patients with earlier initiation and a clinical trial demonstrating no significant benefit of early initiation of dialysis (GFR 10–15 mL/min/1.73 m^2) compared to later (GFR 5–7 mL/min/1.73 m^2).

Timely initiation of RRT (**Table 88-3**) not only avoids the need for urgent dialysis, but also is associated with decreased mortality. A strong correlation between "baseline" serum albumin just prior to initiation of dialysis and patient survival has been demonstrated. Although hypoalbuminemia itself does not necessarily indicate protein-energy malnutrition, it is believed to be a major contributing factor. Analysis of the Modification of Diet in Renal Disease (MDRD) study showed that patients tend to adapt to their declining GFR and associated uremic symptoms by reducing their protein intake. Nevertheless, approximately 60% of American ESRD patients experience nausea and vomiting at the time dialysis is initiated. NKF-K/DOQI guidelines (**Table 88-4**) recommend evaluating renal function by monitoring weekly urea clearance ($K_r t/V_{urea}$). Once the $K_r t/V_{urea}$ falls below 2 (equivalent to a creatinine clearance of 9–14 mL/min/1.73 m^2), there is increased risk for development of uremic anorexia leading to malnutrition, and RRT should be considered.

TABLE 88-3 ■ TIMELY INITIATION OF RENAL REPLACEMENT THERAPY

RRT should be initiated when:
GFR is approximately 10 mL/min/1.73 m^2
Protein-energy malnutrition develops or persists because of decreased nutrient intake without apparent cause for malnutrition
Unless there is:
Stable or increased edema-free body weight
Complete absence of clinical signs or symptoms of uremia
Serum albumin within normal range and stable or increasing

GFR, glomerular filtration rate; RRT, renal replacement therapy.

Data from The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline on Peritoneal Dialysis Adequacy, 1997 and modified using KDOQI Dialysis Adequacy 2006.

TABLE 88-4 ■ INDICATIONS FOR TRIAL OF DIALYSIS IN OLDER PATIENTS

- Uremia
- Potentially reversible acute renal failure
- Unexplained dementia
- Unexplained worsening of congestive heart failure
- Personality change (eg, irritability/irascibility or newly subdued demeanor)
- Adult failure to thrive
- Change in sense of well-being

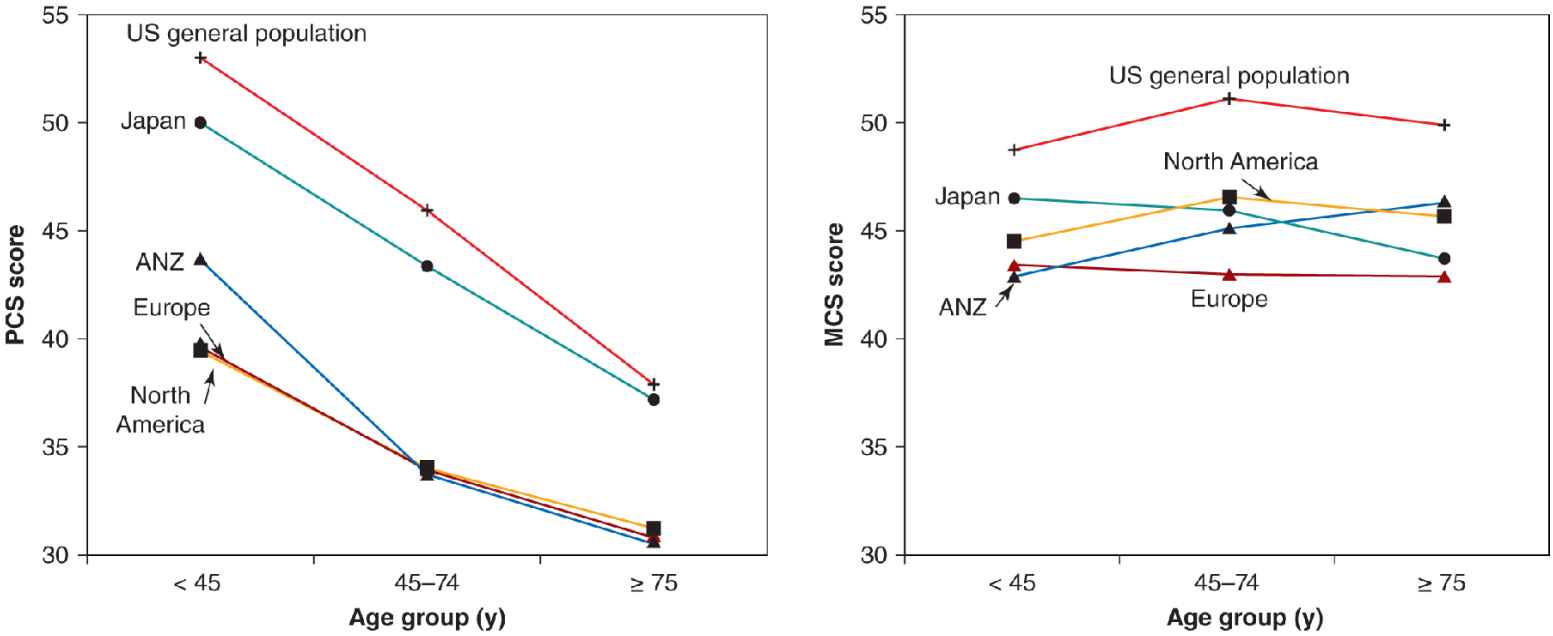
Contraindications to Renal Replacement Therapy

It may be reasonable not to start or to stop dialysis for older patients with a very poor prognosis or who cannot be dialyzed safely. Older patients with advanced CKD may choose to forgo dialysis or to stop dialysis. For the practitioner, there are few absolute medical contraindications to RRT. Some propose that advanced dementia, metastatic cancer, heart failure with marked hypotension, and advanced liver diseases are reasons for withholding RRT. However, progressive dementia can be confused with uremia-induced delirium in a patient with advanced kidney dysfunction, and a "trial" of dialysis may be justified. It may take as long as 3 to 4 weeks to clear uremic symptoms with dialysis. The patient's family should be aware that if the patient's mental status fails to improve, RRT may be inappropriate. Similarly, providing dialysis for a patient with metastatic cancer or end-stage liver disease may allow the patient to get their affairs in order and spend some important time with friends and family. Cognitive and

behavioral contraindications may play an even larger role in older patients than medical contraindications. Dialysis units are communities where a patient with inappropriate, unsafe, or violent behavior adversely impacts care provided to others at that unit. For example, most nephrologists would discourage the use of dialysis in a patient who is severely cognitively impaired and unable to understand the requirements for safe dialysis treatment.

Health-Related Quality of Life

Maintaining health-related quality of life (HRQOL) may be the most important role of health care in older patients with chronic illness. Studies of older patients undergoing dialysis have shown markedly lower functional status compared to older community-dwelling adults. However, hemodialysis has improved since these early studies and there have been advances in technology, treatment of comorbidities such as anemia and hyperparathyroidism, and quality improvement initiatives that have improved the HRQOL of patients on dialysis. While HRQOL was impaired in the hemodialysis population, the HRQOL scores at baseline reflect a preserved multidimensional quality of life among respondents in the HEMO Study greater than age 70 compared to younger hemodialysis patients. A large study in the Netherlands demonstrated decline in scores on physical domains over time in the age groups greater than 55 years. Stability of mental domains is consistent with a previous study of incident patients remaining on hemodialysis over 18 months. These authors also suggest that comorbid disease burden rather than age was associated with a composite outcome of hospitalization, decline in albumin, and a quality of life score of 2 standard deviations below the general population mean score. These longitudinal HRQOL data are also consistent with the North-of-Thames Study findings showing rather moderate use of resources and cross-sectional differences in quality of life among hemodialysis patients older than 65 years. In cross-sectional studies of HRQOL in the ESRD population, there have been larger differences in HRQOL for younger patients on hemodialysis compared to younger norms than for older patients on hemodialysis compared to older norms. As shown in **Figure 88-3**, there is evidence of both decrements in physical and mental well-being associated with dialysis compared to the general population across regions. While there is a marked decrement in physical well-being with older age, there are similar scores for physical well-being across age groups. These findings may be informative to older patients and health care providers and they also underline the need to improve HRQOL among all patients undergoing dialysis. Interventions aimed at preserving residual renal function, monitoring HRQOL, treatment of anemia, engaging the patient in physical therapy and rehabilitation, applying palliative care principles, and perhaps more frequent and longer hemodialysis treatments may preserve HRQOL among older patients undergoing hemodialysis.



Region	PCS Score			MCS Score		
	< 45 y	45–74 y	≥ 75 y	< 45 y	45–74 y	≥ 75 y
Europe	39.7	33.8	30.9	43.6	43.3	43.2
ANZ	43.7	33.8	30.6	43.2	45.5	46.7
Japan	50.0	43.3	37.1	46.9	46.4	44.0
North America	39.4	34.1	31.3	44.8	46.4	46.0
US general population	53.0	46.0	37.9	49.2	51.6	50.4

FIGURE 88-3. Kidney disease quality of life (KDQOL) physical component summary (PCS) and mental component summary (MCS) scores by age categories across Dialysis Outcomes and Practice Patterns Study (DOPPS) regions versus US population norm. Cross-section of participants in DOPPS III (2005–2007; *n* = 8161). Europe includes United Kingdom, France, Germany, Italy, Spain, Belgium, and Sweden; North America includes United States and Canada; ANZ represents Australia and New Zealand. (From Canaud B, Tong L, Tentori F, et al. Clinical practices and outcomes in elderly hemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol*. 2011;6:1651–1662.)

CHOICE OF RENAL REPLACEMENT THERAPY

When faced with kidney failure, the older patient has a number of choices to make regarding therapy consistent with their overall level of well-being and goals of care. The most common forms of kidney replacement are three-times weekly outpatient hemodialysis, peritoneal dialysis, and renal transplantation. There has also been a proliferation of home therapies and therapies tailored to older patients such as nursing home–based dialysis units. The older patient may also choose conservative management and thereby avoid dialysis or opt for palliative care. The patients should have time to develop a relationship with the nephrologist and team in order to have discussions of goals for care and how RRT may be tailored to meet those goals.

Hemodialysis

Hemodialysis removes excess fluids and solutes from the blood in order to maintain euvolemia and homeostasis. The conventional hemodialysis schedule requires three treatments per week for approximately 4 hours per treatment. In order to perform hemodialysis, the patient must have an access placed to circulate the blood through the hemodialysis filter. The three options for hemodialysis access include arteriovenous (AV) fistula, AV graft, and temporary hemodialysis catheters. Permanent hemodialysis access requires minor surgery in the arm or leg. The AV fistula, which creates a connection between the native artery and the AV fistula vein, matures and thickens to handle the higher blood flow rates and permit the use of a needle for access after approximately 3 months. The use of an AV fistula has been associated with better access survival, fewer infections, fewer hospitalizations, and longer patient survival. The AV graft uses a synthetic bridge between the artery and the vein. The graft has been used in a broader population than

the AV fistula but has the major limitations of shorter access survival as well as more infections and hospitalizations. For older patients who have been referred late or who have acute kidney failure, hemodialysis is performed using a dialysis catheter. This is a large-bore catheter placed in a major vessel such as the superior vena cava. In the outpatient setting, these catheters are usually tunneled under the skin and treated with sterile precautions by the dialysis unit when accessing the catheters for blood. They have been associated with high rates of bacteremia, catheter malfunction, venous stenosis, and increased costs.

By far, in-center hemodialysis remains the predominant form of RRT in the United States. Data derived from the USRDS for patients 75 years and older show the incident rate of dialysis or transplant (by first modality) in 2012 comprised 24% of that population initiating RRT. Only 5% of patients older than age 75 were initially treated with peritoneal dialysis, and less than 1% with renal transplantation.

Many older patients tolerate hemodialysis well. In addition, some studies demonstrate that older dialysis patients seem to enjoy the scheduled social interaction that in-center dialysis provides them. While most patients maintain a certain quality of life on hemodialysis, the drawbacks to in-center hemodialysis therapy include pain, fatigue, depression, loss of freedom, dietary and fluid restrictions, and concern about burden to caregivers.

Peritoneal Dialysis

Peritoneal dialysis (PD) permits older patients to maintain more control over their schedule and play a larger role in the management of their kidney failure. PD uses the peritoneal membrane as a dialysis membrane by drawing excess fluid and toxins from the blood and into the peritoneal cavity where the fluid will then be drained through a plastic catheter that has been placed into the abdomen. Depending on the dialysis prescription, the peritoneal cavity is filled with fluid and drained a number of times over the course of the day or night. The advantages to using PD include a less-restrictive diet and avoiding the need to travel to a dialysis unit for treatment. However, the disadvantages include back pain, peritonitis, hyperglycemia, obesity, and hernia formation. PD has been successfully used in older patients, but its use in patients with poor functional status depends on a caregiver willing to commit to performing the daily therapy. PD can also be performed safely and effectively in a long-term care facility by staff with specialized training and with assistance of medical staff or caregiver. The preferred mode of peritoneal dialysis in this setting is continuous cyclic peritoneal dialysis or nocturnal peritoneal dialysis, which requires less nursing time, allows patients to be more fully integrated into social activities, and allows interruption-free intensive rehabilitation.

Kidney Transplantation

Kidney transplantation is the optimal therapy for patients with ESRD, and the percentage of patients awaiting kidney transplantation has increased the most in those patients older than 65 compared to all other age groups. As shown in **Figure 88-4**, the trend for those older than 65 being wait-listed for a kidney transplant continues to increase, but the percentage still remains lower than the younger age groups. Overall life expectancy increases for older patients post kidney transplantation compared to those who are on dialysis and on the wait-list for a kidney transplant. Older patients with comorbidities such as diabetes and hypertension also have a survival advantage with kidney transplantation compared to those who remain on the wait-list on dialysis.

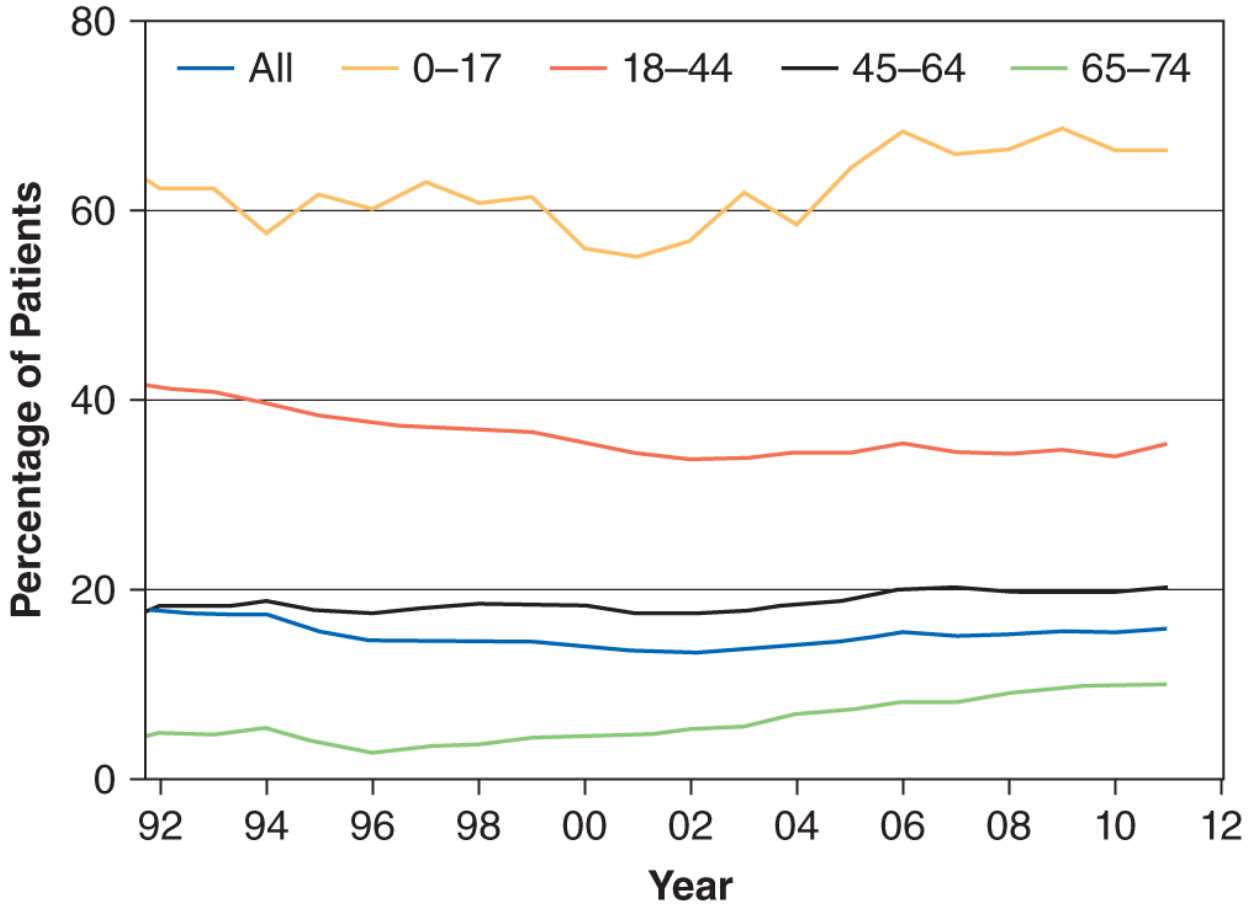


FIGURE 88-4. Percentage of incident patients being wait-listed or receiving a kidney transplant within 1 year of end-stage renal disease (ESRD) initiation, by age. The trend of patients above 65 being wait-listed or transplanted is increasing, although the percentage is still lower compared to the younger age groups. (US Renal Data System, USRDS. 2014 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2014.)

Health-related quality of life also improves for older patients after kidney transplant. The Short Form-36 (SF-36) is a quality-of-life questionnaire that encompasses eight scales: physical functioning, role limitation due to physical problems, bodily pain, social functioning, mental health, role limitation due to emotional problems, overall vitality, and general health perception. Transplant patients over the age of 65 have been shown to have significantly higher scores in the categories of physical functioning, general health perception, and mental health compared to hemodialysis patients. The older individual is not the only one to benefit from kidney transplant—health care systems also benefit, as the cost of care decreases in patients of all age groups who receive a kidney transplant compared to those maintained on dialysis. The reduction in cost is mostly secondary to decreased health care contact time and a decrease in transportation costs.

Older individuals may have less rejection after kidney transplantation secondary to changes in both adaptive and innate immunity. Cellular senescence, a less diverse T-cell response, and thymic involution occur with aging, which may dampen T-cell–mediated rejection. Defects in the function of CD4 T-helper cells, which are needed for B-cell–mediated antibody response also occurs with aging. As both T- and B-cell immunity are dampened with aging, transplantation is associated with a higher risk of infection in older adults. Prospective studies are needed to determine which immunosuppressive agents are best suited for older individuals as there are many factors to consider in this population of patients including long-term graft survival, increased risk of infections, medical comorbidities, and changes in drug pharmacokinetics.

For the older patient seeking a kidney transplant, screening for cognitive function and physical performance tests to better assess frailty are needed as part of the evaluation process. Physical performance tests can help screen older patients for the risk of falls, hospitalizations, and death posttransplantation. Cognitive assessment can help determine which older patients will need more social support and follow-up after kidney transplantation.

Deceased donor kidneys remain a scarce source; thus the pursuit of an organ allocation system that maximizes the life-year benefit of donor organs has generated strategies, which include matching kidneys with lower expected graft survival time to older patients with lower expected longevity. Expanded criteria donor (ECD) kidneys which are

associated with a decrease in the average number of years of graft survival are often offered to older patients seeking kidney transplant. ECD kidneys are either obtained from donors older than age 60 who are between the ages of 50 and 59 who have two out of the following three criteria at the time of death: (1) hypertension, (2) death from a cerebrovascular accident, and (3) serum creatinine greater than 1.5 mg/dL. Older patients who choose to accept an ECD kidney will decrease their time on the wait-list, and there is a survival benefit associated with ECD transplant compared to remaining on dialysis. However, graft and patient survival are worse with ECD transplant compared to standard criteria donor (SCD) transplant and living donation. An SCD transplant is a transplant from all other deceased donors who do not fall under the ECD criteria.

The implementation of a new kidney allocation system is currently under way. The new system will replace the SCD/ECD classification system for donors with the kidney donor profile index (KDPI) score. The KDPI score provides a more accurate estimate of kidney longevity. Donor variables such as age, height, history of diabetes or hypertension, etc are used to calculate a percentage score known as the KDPI score, which estimates how long the kidney is likely to function. A KDPI score of 10% suggests the kidney will likely function 90% longer than available kidneys. The new allocation system will also promote better longevity matching between donor and recipients to match the maximum amount of graft years with the estimated posttransplant survival (EPTS) score. The EPTS score will be based off of the recipient's age, diabetes status, history of prior transplant, and time on dialysis. With the new allocation system older recipients will likely get deceased donor kidneys with higher KDPI scores and therefore decreased graft survival.

The degree to which comorbidity influences graft and patient outcomes is significantly less in recipients of living donor kidneys compared to recipients of deceased donor kidneys. A living donor kidney may offset some of the risk of increased comorbidity in the older recipient and highlights living donor kidney transplantation as an important opportunity for older patients with kidney failure to receive optimal treatment. If the allocation of deceased donor kidneys in the future increasingly favors younger patients over older patients in the distribution of a scarce resource, living donor kidney transplantation may become the only realistic chance at successful kidney transplantation for older patients.

Time-Limited Trial of Dialysis

One of the options for older patients with ESRD would be to have a trial of hemodialysis to assess the extent to which the treatment is consistent with the life goals of the patient. The approach of a time-limited trial is reasonable when the patient, family, or physician is unsure about the prognosis or the impact that dialysis will have upon the patient's quality of life. If a trial of dialysis is to be conducted, it is important to predetermine a time period (usually 4–6 weeks) and to inform all the members of the dialysis team. Such measures will ease the appropriate withdrawal from dialysis and may also help to resolve conflicts when a consensus cannot be reached for the best approach to managing an older patient with ESRD.

Conservative Management and Palliative Care

The approach to managing older adults who chose to forgo renal replacement therapy is twofold. Comprehensive conservative therapy is focused on maximal medical management of CKD and the metabolic complications of advanced CKD. While comprehensive conservative care is focused on slowing the progression of kidney disease, palliative care or supportive care treats symptoms and addresses the psychological, spiritual, and social needs of the patient. It is difficult to assess the frequency of comprehensive conservative care or palliative therapy applied to management of patients with advanced CKD, but it is likely that the geriatrician plays a primary role in the decision-making process and management of these patients. In a study from the United Kingdom, 84% of patients with CKD stages 3 to 5 were not referred to nephrology. The proportion of referred patients declined dramatically with older age, with a maximum referral rate of 68% for those 40 to 49 years, and 4% of those older than 80 years. Another study presented 19% with palliative care as a recommended option based on age and comorbid disease burden; 76% of those recommended for palliative care followed through with management of kidney failure without dialysis. While it was somewhat difficult to provide accurate comparisons of survival times, these investigators reported no substantial difference in expected survival time for those undergoing palliative care compared to hemodialysis. Significantly fewer palliative care deaths (27%) took place in the hospital compared to the proportion of deaths among those patients undergoing hemodialysis (67%). In a study of octogenarians in a single center where older patients were advised not to undergo dialysis, 25% were conservatively managed. In this report, the median survival of those undergoing conservative management was 8.9 months compared to 28.9 months among those undergoing dialysis. In addition, the

cause of death of those managed without dialysis was uremia or pulmonary edema in approximately 60%. In a subsequent study of older patients with CKD in Australia, patients conservatively managed demonstrated a survival estimated 12 months beyond when dialysis would have been initiated and this report demonstrated a stable symptom burden and quality of life without dialysis.

Conservative management should aim to maintain quality of life while keeping in mind the shared decision to avoid dialysis therapy. In addition to continuing to manage fluid status, anemia, electrolytes, and bone metabolism, symptoms should be addressed by the geriatric, nephrology, and palliative care teams. Among both groups of patients undergoing dialysis and receiving palliative care, symptoms should be treated since pain, dry itchy skin, poor sleep, and fatigue impact mood and quality of life. A study has shown improvement in pain among ESRD patients managed using the World Health Organization (WHO) three-step analgesic ladder. A nutritional approach to avoiding dialysis therapy was assessed in nondiabetic patients older than 70 years. In this randomized study, patients with kidney failure were assigned a supplemented very low protein diet compared to usual care with dialysis. This study found that those patients assigned the dietary intervention spent an additional 10.7 months off dialysis without substantial differences in survival between groups. These findings suggest that nutrition and palliative care medicine approaches may play an important role in managing patients who elect to avoid dialysis.

MANAGEMENT OF END-STAGE RENAL DISEASE COMPLICATIONS

Anemia

Anemia is a common problem with CKD and kidney failure. The cause of anemia may be multifactorial and due to both CKD and other chronic conditions frequently observed among older patients. In addition to CKD, the geriatric medicine team should consider iron deficiency due to loss of blood from a lesion in the colon or hematologic etiologies. Among older patients with CKD, the fall in hematocrit correlates roughly with the severity of the renal disease, although individual variation is considerable. In general, anemia presents when the GFR is around 35 mL/min. The bone marrow is hypoproliferative while peripheral blood (red cell) indices are normal unless there is superimposed deficiency of iron or folic acid. Thus, the anemia seen with kidney failure is typically a normochromic, normocytic anemia. The lack of erythropoietin production, which occurs with CKD, is the primary cause of anemia with kidney failure. Since erythropoietin production occurs primarily in the kidney, erythropoietin levels are inadequate with CKD, thus depriving the bone marrow of the stimulus necessary for production of red blood cells. The isolation of human erythropoietin and subsequent production of recombinant erythropoietin has been a major advance in the care of those with CKD. Beginning in 1989, synthetic erythropoietin has been available and effectively treats the anemia of chronic renal failure (CRF). Darbepoetin permits less frequent dosing regimens and other agents are under investigation. Correction of anemia has been associated with improved quality of life, reduced the need for transfusions, improved cognitive performance, and decreased left ventricular hypertrophy. There are adverse effects of using erythropoietin in the CKD patient, including iron deficiency (the stimulation of red blood cell production outstrips iron stores), hypertension, cardiovascular events, and vascular thrombosis.

The optimal hemoglobin target for patients with anemia caused by CRF remains somewhat unclear. Recent data in the CKD population suggest untoward cardiovascular outcomes at higher hemoglobin levels. The current conservative target is a hemoglobin count near 11.5 mg/dL. In addition to close attention to erythropoietin dosing and hemoglobin levels, adequate anemia management requires routine analysis and treatment of iron deficiency. Iron levels tend to drop in patients on erythropoietin therapy because of increased iron utilization. All patients, however, should receive routine screening of stool for occult blood and periodic screening colonoscopy. Iron-deficient ESRD patients usually receive intravenous replacement iron at the end of their dialysis treatments. Because they absorb oral iron poorly, ESRD patients have “functional” iron deficiency when their ferritin falls below 500 ng/mL or their iron saturation is less than 30%.

Cardiovascular Disease

Many more patients have CKD compared to the numbers receiving RRT. The disparity between the number receiving RRT and the number with CKD is explained by the high mortality from cardiovascular disease prior to needing dialysis in the CKD population. Even on dialysis, the risk of death from cardiovascular disease remains 10 to 100 times higher than the risk of a person from the general population. While traditional risk factors account for only a portion of the increased risk associated with kidney disease, the etiology of the increased cardiovascular risk is unclear. There are

a number of potential factors that represent classical risk factors shared between atherosclerosis and kidney disease such as age, hypercholesterolemia, hypertension, smoking, and obesity. In addition, there are a number of factors specific to kidney failure such as anemia, hyperhomocysteinemia, hypervolemia, and hyperparathyroidism. These factors can act to promote both cardiomyopathy and ischemic heart disease. The current treatment recommendations focus on optimizing management of known cardiovascular risk factors and on recognizing harbingers of active cardiovascular disease. While guidelines recommend using statins among patients with CKD, whether these recommendation should extend to those with ESRD remains controversial given the negative results of several large trials examining the impact of statins on cardiovascular outcomes for patients with ESRD. A reasonable course would be to individualize cardiovascular disease care for older patients with ESRD. Those caring for patients with CKD should consider the cardiovascular disease management as an important part of their care.

Calcium, Phosphorous, Hyperparathyroidism, and Bone Disorders

Kidney failure is associated with abnormalities of divalent ions (Ca^{2+}, P) and of the hormones that regulate the concentration of these minerals in body fluids. One of the earliest detectable abnormalities in kidney failure is a rise in parathyroid hormone (PTH), which can occur at a GFR of 40 mL/min. Secondary hyperparathyroidism is a major cause of bone disease in patients with kidney failure. Two inhibitors of parathyroid hormone are ionized calcium (the active form of calcium) and 1,25-$(OH)_2D_3$, which has an independent inhibitory effect on parathyroid hormone release. No difference has been found in hyperphosphatemia or severity of renal osteodystrophy in older dialysis patients as compared with younger dialysis patients, and there is no correlation between plasma 1,25-dihydroxyvitamin D_3 levels and age in patients with kidney failure. Older female dialysis patients have significantly lower bone mineral content and bone width when compared with younger dialysis patients matched for duration of dialysis. There is a higher incidence of pathologic fracture, vascular or metastatic calcification, and bone pain in older patients on dialysis than in younger patients. The overall result of these disturbances is that patients with ESRD may develop a complex form of bone disease (renal osteodystrophy). Furthermore, there has been a strong association of disordered bone and mineral metabolism and risk of cardiovascular disease. This association between calcium and phosphate metabolism has been most striking when images of the heart demonstrating extensive calcification have been related to levels of both calcium and phosphate.

The management of bone disorders among older patients with ESRD is complicated by other bone diseases found among this age group. For example, osteoporosis and renal osteodystrophy may both present in the older patient with ESRD. Treatment of renal osteodystrophy and secondary hyperparathyroidism in the geriatric renal patient is similar to the younger patient. However, the optimal management of patients has been controversial. Hyperphosphatemia is treated with a low-phosphate diet and with various phosphate binders. Recent recommendations advise that daily calcium in the phosphate binder should be less than 2 g. Hypocalcemia can be treated with oral calcium, oral or intravenous calcitriol, or other vitamin D analog, or higher dialysate calcium. Refractory hyperparathyroidism can be treated with parathyroidectomy or with a trial of a calcimimetic. While the agents used to regulate calcium and phosphate levels remain controversial, the goals of normalizing calcium and phosphate levels and improving bone health are widely accepted as important in the management of CKD patients.

Cognitive Impairment

Cognitive impairment has been shown to be widely prevalent among patients with ESRD, particularly among older patients. The potential causes of cognitive impairment in patients with CKD might be explained by two hypotheses. The vascular hypothesis states that the brain and the kidneys are low-resistance end organs exposed to high-volume blood flow which is exacerbated by CKD and thus are susceptible to microvascular damage that contributes to the cognitive impairment in CKD patients. The neurodegenerative hypothesis states that the accumulation of uremic toxins in ESRD patients impairs the functions of the central nervous system in this population. Many studies have linked ESRD with cognitive impairment in the geriatric population. Cognitive impairment in ESRD is associated with decreased quality of life, suboptimal medical care, decreased adherence to medication regimens and dietary modifications, more frequent and prolonged hospitalizations, and decreased decision-making capacity, especially in making very important health-related decisions, such as making the decision to obtain a kidney transplant. Diagnosing and treating cognitive impairment in older ESRD patients is important especially since we know that the annual conversion rate from mild cognitive impairment (MCI) to dementia among older patients in the general population ranges from 5% to 20%. This underlines the need for close follow-up and periodic screening to accurately identify ESRD patients with cognitive impairment in order to improve their clinical care. Thus, we believe that older ESRD

patients should be screened regularly for cognitive impairment and dementia. There are several screening tools that are currently being widely used to assess cognitive impairment. The Mini-Mental State Examination (MMSE) has been used frequently as a screening tool for cognitive impairment. However, it focuses on memory and neglects other cognitive domains such as executive function. This may lead to an underestimation of the prevalence of cognitive impairment in ESRD patients. The Montreal Cognitive Assessment (MoCA) is a widely used brief cognitive screening test for detection of MCI with a sensitivity of (90%) and specificity of (87%) for detecting MCI in the general geriatric population and distinguishing them from individuals with normal cognition. It is considered a better screening instrument compared to the MMSE since it not only assesses executive functions that are particularly important in ESRD patients, but it also demonstrates a higher sensitivity for MCI. Moreover, the MoCA was also shown to be an adequate screening tool for the evaluation of cognitive function in ESRD patients on hemodialysis and has been recommended as a standardized approach to cognitive assessment in this patient population. Recognizing and treating cognitive impairment in ESRD may lead to improved adherence to treatment, increased ability to make informed medical decisions, decreased rate and length of hospitalization, decreased morbidity and mortality, and improved HRQOL.

Metabolic Acidosis

The acidosis associated with renal disease is not more severe in the older patient despite the decreased ability to handle an acid load seen with normal aging. Acidemia caused by metabolic acidosis is associated with increased oxidation of branched-chain amino acids, increased protein degradation, and decreased albumin synthesis. Because of the adverse metabolic effects of chronic acidosis, such as accelerated bone loss and muscle wasting, goals of therapy should be directed at achieving predialysis serum bicarbonate levels of at least 22 mmol/L. If predialysis levels routinely fall below 22 mmol/L, acidemia may be treated by supplementation with oral sodium bicarbonate tablets. The role of increasing dialysis bicarbonate to treatment academia among older patients with ESRD remains unclear.

Malnutrition

Nutrition plays an important role in the health and well-being of patients with kidney failure. Older patients with ESRD face multiple challenges to maintain adequate nutrition since they may have a low-sodium, low-potassium, low-phosphorus, diabetic diet. Poor nutrition in older patients may be linked to symptoms and dietary restrictions for ESRD patients together with shared challenges among all older adults of access to foods, difficulty with food preparation, medication side effects, and decrements in appetite. Patients with kidney failure are thought to benefit from intensive monitoring of nutritional status. The recommended assessments include body weight, dietary interviews and diaries, serum albumin, and total nitrogen appearance. A renal dietician may offer alternative foods and recommendations to patients that feel limited by fluid, sodium, potassium, and phosphate restrictions. Weight loss and inability to maintain nutritional status are indications for initiating hemodialysis and adequacy of dialysis therapy should be evaluated to avoid anorexia and nausea. Dietary supplements and vitamin and mineral supplements, such as zinc or oral pyridoxine (50 mg/day), might be helpful. It is unclear whether intradialytic parenteral nutrition offers real benefit. There are only limited studies available in ESRD, and these studies have not focused on older patients. Rather than adhering to a very regimented diet, clinicians should avoid dietary restrictions in the older patient undergoing dialysis in order to encourage adequate protein and calorie intake.

Physical Functioning and Frailty

Most older individuals with ESRD have some degree of functional decline or frailty which are associated with high risk for falls, disability, hospitalization, and mortality. Among patients initiating dialysis, frailty has been associated with increased risk of death and shorter time to first hospitalization. Several potential mechanisms have been suggested to explain the association of ESRD with poor functional status and frailty. Elevated inflammatory markers, poor nutritional status, weight loss, and sarcopenia as well as complications related to ESRD such as electrolyte and acid-base disturbances, hyperphosphatemia, bone and mineral disorders are also linked to frailty in ESRD population. Management includes evaluation and treatment of reversible conditions attributable to frailty such as neglect, alcohol abuse, and depression. High-intensity resistance exercise training, improvement in nutritional status, and treatment of complications of CKD such as anemia are also suggested to address frailty.

Pruritus

Itching has been reported in up to 40% of patients with kidney failure and can adversely affect sleep and quality of life. The causes of itching in older patients with kidney failure include xerosis, uremic itching, medication sensitivity, and other chronic health conditions such as diabetes. Pruritus is also common in the older dialysis patient, possibly because of skin changes seen with aging. As a part of an approach to managing uremic pruritis, it has been recommended to optimize dialysis treatment by increasing dialysis dose, treating anemia and iron deficiency, and maintaining a low serum phosphate. Treatment of itching caused by xerosis or uremia has been largely symptomatic local treatment consisting of keeping the skin moist with emollients, bathing less frequently and with tepid rather than hot water, education to reduce scratching, and increasing ambient humidity with vaporizers or humidifiers. In addition to these symptomatic approaches, topical capsaicin and pramoxine lotions may also be effective. Gabapentin has been shown to reduce uremic pruritus among patients with advanced CKD on hemodialysis. However this improvement in uremic pruritis should be balanced against a high rate of side effects. A promising systemic approach to managing uremic pruritus has been opioid receptor modulators. The studies of these agents among patients with severe uremic itching demonstrated improvement in itching intensity and sleep disturbances compared to placebo. Finally, antihistamines such as diphenhydramine or hydroxyzine may be used, but may cause sedation and cognitive impairment in older patients.

SPECIAL ISSUES

Prognosis and Survival

Kidney failure is associated with a decrease in life expectancy for all age groups when compared to age-matched patients. The need for dialysis impacts the risk of death in the patient older than age 75 to a lesser degree than it impacts patients age 45, with a threefold versus 20-fold increased risk as compared to nondialysis patients, respectively. The survival of older patients undergoing dialysis has been recently assessed. Overall, the 1-year survival rate for octogenarians and nonagenarians after dialysis initiation was 54%. The characteristics strongly associated with death were older age, nonambulatory status, comorbid conditions, and frailty. In addition to survival, it is important to convey the impact of dialysis on HRQOL. In the HEMO Study, a randomized clinical trial of dialysis dose and membrane flux, patients were assessed for HRQOL at baseline and annually. Among those with HRQOL data at the first three annual assessments, there were no substantial mean declines in physical or mental well-being over the 3-year period. However, there were high rates of adverse HRQOL events in all age groups and significantly higher adverse event rates of either death or clinically significant decline in HRQOL over 3 years among those older than 70 years. The composite outcomes of clinically significant decline in HRQOL or death of those older than 70 years over 3 years was approximately 70%. These findings underline the importance of conveying the limited life expectancy of those patients who are not transplant candidates, and particularly those with limited functional status and comorbidity. While lifespan is limited, it remains up to the individual whether to pursue dialysis or palliative therapy.

There have been increasingly successful attempts to develop and test predictive survival models for outcomes of older patients with ESRD that could be used for shared decision making. As one example, residing in a nursing home conveys a high risk of death in the first year of dialysis. As shown in **Figure 88-5**, 87% of nursing home residents died or experienced decreased functional status within one year of starting HD. In addition to place of residence, clinicians can use functional status, other chronic health conditions, and frailty to improve their estimate of prognosis. Integrated prognostic models can provide additional precision by taking into account laboratory values, comorbidities, changes in clinical factors over time, functional status, frailty, quality of life, and either the patient's or clinician's prediction of survival. The "surprise question"—Would you be surprised if your patient died within the next 6 months?—is a strong indicator of mortality, and when combined with serum albumin, age, and two comorbid factors (dementia and peripheral vascular disease) results in an instrument with clinically adequate sensitivity and specificity. This practical and reliable predictive instrument is available online (http://touchcalc.com/calculators/sq). Other prediction scores have been developed using administrative data and show adequate performance to be used as a clinical tool. The application of new prediction tools will help to overcome practitioner uncertainty about prognosis and increase the likelihood of meaningful dialogues between clinicians, older patients, and their families. However, there remains a critical gap among the existing predictive instruments since they uniformly assess only survival. Other issues such as quality of life, functional status, and independence are critical factors for older patients when deciding whether to proceed with renal replacement therapy.

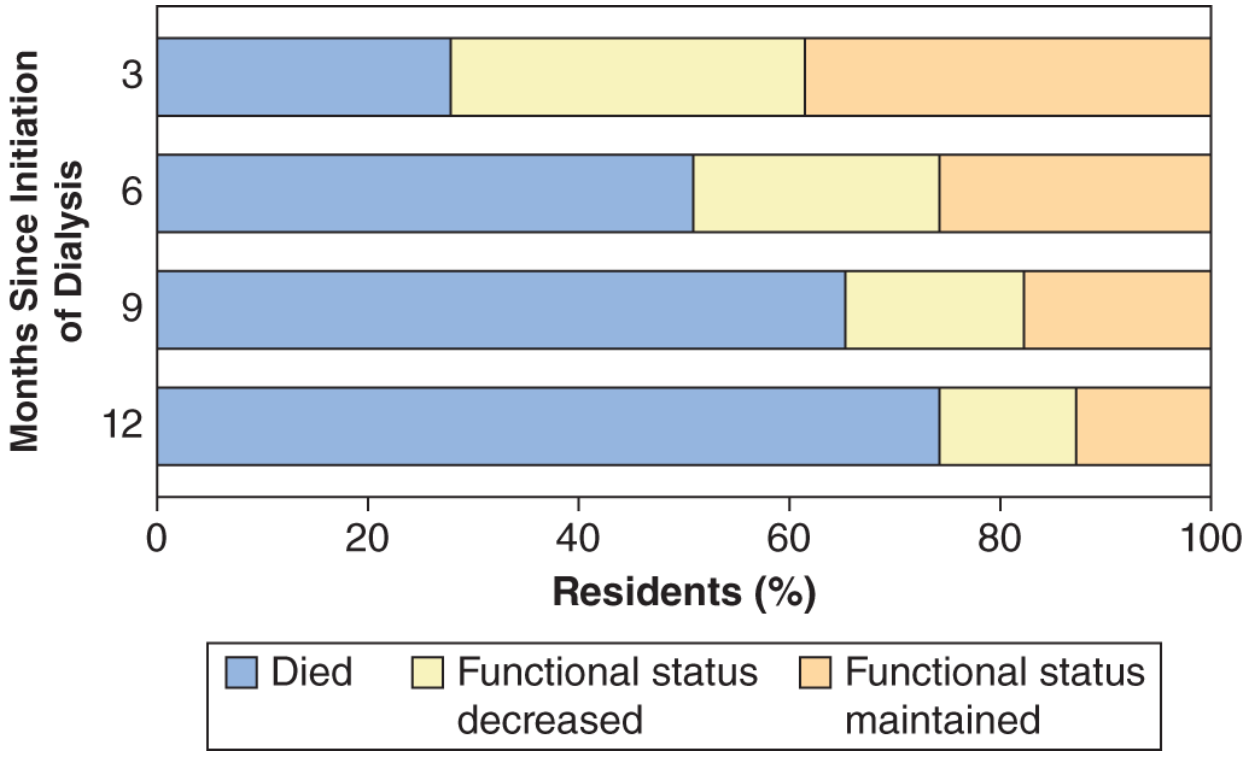


FIGURE 88-5. Change in functional status after initiation of dialysis. (From Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE. Functional status of elderly adults before and after initiation of dialysis. *N Engl J Med*. 2009;361:1539–1547.)

Withdrawal From Dialysis

Stopping dialysis has been a common reason for death in the dialysis population, especially for older patients. Up to one-third of patients are withdrawn or voluntarily withdraw from dialysis therapy annually. The factors associated with dialysis discontinuation in the United States include white race, diabetes, female sex, symptoms, and older age. The reasons cited for withdrawal for dialysis include failure to thrive and medical complications. While dialysis patients should understand that they have the right to stop treatment, the health care team should ensure that the patient is not withdrawing because of an underlying depression or "burdens" that can be ameliorated. It is important to document the decisional capacity of the older adult on dialysis wishing to withdraw and involve family and friends. One prospective observational study of 131 adult (average age 70) maintenance dialysis patients examined the quality of dying following dialysis termination. Quality of death was evaluated by the use of a quality-of-dying tool that quantified the duration (length of time it took to die), pain and suffering, and psychosocial factors. Death occurred on average 8 days after the last dialysis treatment. Thirty-eight percent of the patients on dialysis had a "very good" death, 47% had "good" deaths, and only 15% had "bad" deaths. However, during the last day of life, 42% of the patients had some pain (5% severe), reiterating the importance of end-of-life palliation once the decision to withdraw therapy is made. While the end-of-life issues in renal failure have received increasing attention, there remain many barriers to management of these issues, as underscored by the fivefold lower use of hospice among patients undergoing hemodialysis compared to those older patients not using dialysis. In order to overcome the barriers to a good death for those on dialysis, it is important to have a multidisciplinary approach to advanced care planning and an awareness of local hospice services.

Advance Directives

Recent guidelines underscore that a complete review of treatment options, prognosis, and quality of life should be included when discussing advanced directives of a patient with CKD stages 4 and 5. Having the patient's wishes expressed prior to starting dialysis makes the burden of decision making much easier for the families and physicians should the patient become critically ill. It is crucial to involve the family and surrogates in the advanced directives process and to fully document the directives in order to avoid a change in direction with an unplanned hospitalization. Patients who decide not to undergo dialysis should have clear documentation in their medical records. There should be similar documentation of do-not-resuscitate orders, wishes regarding artificial nutrition and other measures, and

identification of their health care surrogate.

SUMMARY

As the population ages, there will be increasing numbers of older patients with advanced CKD and kidney failure. The older patient with kidney failure now has a multitude of choices for RRT including hemodialysis, peritoneal dialysis, conservative management, palliative care, and kidney transplantation. Primary care physicians and geriatricians should identify CKD in older patients who have risk factors and refer them kidney disease management. After referral, the geriatric team remains in the key role of addressing advanced directives and planning long-term care, since they may have a long-standing relationship with the patient and have the best insight into the patient's goals and values. In addition, the geriatric team may choose to continue managing the many other health issues in the kidney failure patient so that it remains clear who will manage comorbid illnesses. Older patients with CKD will remain an economic and medical challenge, but a multidisciplinary approach to care of these patients will provide the best long-term outcomes.

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Chapter 89

Disorders of Fluid and Electrolyte Balance

Eleanor Lederer, Vibha Nayak

Learning Objectives

- Understand the effects of normal aging on body composition, and how these changes may contribute to the development of fluid and electrolyte imbalance.
- Describe the clinical features—including symptoms, signs, and results of diagnostic tests—that accompany common fluid and electrolyte disorders.
- Describe unique clinical situations that place older individuals at risk for fluid and electrolyte disturbances.
- Understand current treatment of common fluid and electrolyte abnormalities tailored to the geriatric population.

Key Clinical Points

1. **Aging is associated with extensive changes in body composition that alter water and electrolyte distribution and predispose older adults to the development of fluid and electrolyte abnormalities.**
2. **The aging kidney and chronic kidney disease are not synonymous.**
3. **The causes of fluid and electrolyte disturbances in older adults may differ from those in younger individuals.**
4. **Medications and comorbidities contribute substantially to the greater frequency of fluid and electrolyte abnormalities in older adults.**
5. **Fluid and electrolyte management follows the same principles in older and younger patients, but in older patients must be tailored to account for diminished kidney function, a smaller volume of distribution of water and electrolytes, and altered hormonal function.**

INTRODUCTION

The kidney is the primary organ responsible for salt, water, and mineral homeostasis through selective reabsorption and secretion of these substances. Under physiologic conditions, normal kidney function makes it possible for a person to ingest a wide variety and quantity of nutrients and fluids yet remain in water and electrolyte balance. This remarkable capacity of the kidneys to maintain fluid and electrolyte homeostasis in the face of widely divergent intake is generally taken for granted, until kidney failure develops or some other process prevents the kidney from functioning optimally. Abnormalities of fluid and electrolyte balance are generally recognized through physical examination and routine laboratory work. This chapter will review changes in kidney function or in the regulators of kidney function that occur with aging that have an impact on fluid and electrolyte handling followed by a more in-depth discussion of specific disorders of fluid and electrolyte balance in older adults.

Effect of Aging on Body Composition

An examination of the changes that occur in fluid and electrolyte balance in older adults has to take into account how the composition of the human body changes with aging (**Table 89-1** and Chapter 34). The percentage of body weight occupied by “water” progressively decreases. Whereas the water weight of a young person with a relatively normal

body habitus is approximately 60% of the total body weight, this percent declines to 50% in older adults as muscle mass decreases and fat mass increases. The implications of this dramatic change are tremendous. Loss or gain of mathematically the same amount of body water will have a much greater effect on blood pressure, cardiovascular status, and osmolality in the older individual than in the younger individual. The loss of muscle mass decreases the total body pool of potassium; thus, the older individual will require lesser amounts of potassium to replete potassium stores and will be unable to handle a large potassium load as efficiently as a young person.

TABLE 89-1 AGING AND CHANGES IN BODY COMPOSITION

BODY COMPOSITION CHANGE	EFFECT ON BODY FLUID/ELECTROLYTE DISTRIBUTION	EFFECT ON ELECTROLYTE CONCENTRATION	IMPLICATIONS FOR THERAPY
Increased adipose tissue/muscle ratio	Decreased total body water	None under physiologic conditions. More prone to hypernatremia with water deprivation. More prone to hyponatremia with excess water intake.	Less water needed for replacement therapy but greater tendency to become dehydrated.
Decreased muscle mass	Decreased total body potassium stores	None under physiologic conditions.	Less potassium needed for replacement. Lesser ability to translocate potassium to intracellular space by insulin/β-agonists when treating hyperkalemia.
Poor nutritional status	Decreased serum albumin Decreased gastrointestinal nutrient absorption	Low calcium due to low albumin binding. Hyponatremia due to low solute ingestion and inability to excrete water load. Normal serum levels of potassium, phosphorus, and magnesium despite diminished total body stores.	Need to recognize the contribution of albumin binding when interpreting total serum calcium. Need to ensure adequate sodium and protein intake to facilitate water excretion. Need to recognize high-risk situations for sudden drop in potassium, phosphorus, magnesium.
Decreased bone mass	Decreased calcium and phosphate stores	Calcium level does not change with age. Phosphorus level decreases progressively with age.	Recognize that serum phosphorus 2.4–2.8 is normal in an older individual. Does not need replacement.

Effect of Aging on Kidney Function

At least two-thirds of adults undergo a significant reduction in kidney function as defined by the glomerular filtration rate (GFR) as they age; however, one-third of the population exhibits stable or even improved kidney function with age. While the determinants for decline are only now becoming understood, clinicians caring for older adults generally will be dealing with individuals who have reduced kidney function. In the absence of overt structural or urinary abnormalities, an estimated glomerular filtration rate (eGFR) of less than 60 mL/min has been defined as the cutoff for declaring a state of chronic kidney disease (CKD). Significant controversy surrounds the definition of CKD relative to normal age-related events in older adults, the best methods for determining kidney function in older adults, and the clinical significance of reduced kidney function in this population as discussed at length in Chapter 86. For the purposes of this chapter, only changes affecting renal handling of water and electrolytes will be reviewed.

A decline in GFR automatically limits the capacity of the kidney to filter and excrete virtually any substance. Clinically this manifests as a lesser ability to handle an excessive water or solute load. So, for example, while a young individual may be able to excrete a 20 mL/kg water load easily within 2 hours, an older individual may take

considerably longer. Development of glomerulosclerosis or interstitial fibrosis, both commonly seen in aging kidneys, leads to proteinuria and distortion of the architecture required for normal homeostatic functions of the kidney such as tubuloglomerular feedback, urinary concentration, and dilution. The singular arrangement of tubules and vasculature permits the rapid movement of water and solutes between the compartments. This creates the graded corticomedullary progressively hypertonic interstitium composed of sodium chloride and urea, and ensures the horizontal transfer of urea, potassium, and ammonium from one tubular segment to another that facilitates urinary concentration, sodium reabsorption, and net acid excretion. Vascular changes associated with accompanying chronic diseases such as hypertension will exacerbate the development of glomerulosclerosis and interstitial fibrosis, intensifying the effects of aging on the architecture.

Effect of Aging on Regulators of Kidney Function

Alterations in kidney responsiveness to specific hormonal stimuli occur which can also have an impact on fluid and electrolyte handling. For example, age-related changes in the function of dopamine and angiotensin II receptors in the proximal renal tubule may impair the ability of the proximal tubule to regulate a sodium load resulting in a tendency to develop salt-sensitive hypertension. Vasopressin levels tend to be higher in older individuals but have a lesser effect on urinary concentration than in younger individuals. Likewise, natriuretic peptide levels are higher in older adults; however, most data suggest that the responsiveness to changes in sodium homeostasis and the effect on the renal tubule remain intact.

DISORDERS OF WATER BALANCE

Physiologic Regulation of Water Balance

Water balance determines body fluid osmolality—the solute to water ratio—and is approximated by the serum sodium concentration. Serum sodium remains relatively stable for the individual but there is significant interindividual variability. While the determinants of this variability are not fully understood, studies suggest a strong genetic component. Serum osmolality is sensed primarily by central nervous system osmoreceptors that express neural connections with the posterior pituitary, the site of antidiuretic hormone (ADH) production and secretion. An increase in osmolality will stimulate ADH production and secretion that circulates to the collecting tubule of the nephron, stimulating the expression of aquaporin water channels and urea transporters geared toward production of a concentrated urine. Maximal urine concentration capability in the human is approximately 1200 mOsm/kg. Alternatively, a decrease in serum osmolality leads to a decrease in ADH release, allowing the excretion of a dilute urine. The minimal urine concentration in the human is 40 to 50 mOsm/kg. As ADH is a small peptide hormone with a short half-life, serum osmolality is sensed and regulated on a minute-to-minute basis.

Aging is accompanied by curtailment of all steps in the process of regulation of water homeostasis. Osmoreception is impaired. ADH release is more sluggish, though the effect of ADH on the collecting tubule is more sustained. The end result is a compromised ability to regulate water homeostasis to the same degree as a younger person, often resulting in either hyponatremia or hypernatremia.

Hyponatremia Hyponatremia is the most common electrolyte abnormality in clinical medicine, resulting primarily from the inability to excrete a water load due to excessive ADH presence or due to lack of sufficient solute excretion. Hyponatremia affects approximately 10% of ambulatory older individuals, and is even more common in hospitalized or institutionalized patients with estimates ranging from 25% to 50%. Hyponatremia frequently accompanies common medical conditions that affect older adults such as congestive heart failure, cirrhosis, many cancers, and chronic kidney disease. Hyponatremia is also seen with chronic central nervous system disorders and chronic pulmonary disease and is a side effect of a number of medications such as thiazide diuretics, chemotherapeutic agents, pain medications, and antipsychotics. The most common cause of hyponatremia in older individuals is the syndrome of inappropriate ADH secretion (SIADH).

Symptoms of hyponatremia vary depending on severity and underlying clinical conditions. Many patients are apparently completely asymptomatic, especially if the serum sodium is greater than 130 mEq/L, and the condition is discovered serendipitously on routine laboratory evaluation. However, even mild degrees of hyponatremia may produce symptoms—commonly fatigue, inanition, weakness, and nausea. As the hyponatremia worsens, more significant signs and symptoms become apparent including a clouded sensorium, inability to concentrate on tasks, falls,

seizures, and coma. When evaluating symptomatic status, it is important to ascertain the individual's baseline mental function. As a general rule, the more chronically and gradually that the hyponatremia has developed, the fewer the overt symptoms even with serum sodium concentrations as low as 120 to 125 mEq/L. However, serum sodium less than 115 mEq/L is virtually always accompanied by symptoms, even if chronic.

The approach to hyponatremia in older adults is dependent on clinical context, severity, and chronicity. A relatively straightforward approach to hyponatremia includes the following steps. First, determine if the individual has true hypo-osmolar hyponatremia or pseudohyponatremia (**Table 89-2**). Pseudohyponatremia can be seen with significant hyperglycemia, where the osmotically active glucose obligates egress of water from the intracellular space, thus diluting the serum sodium. In these cases, the serum osmolality will be high, while the serum sodium is low. Several equations to estimate the "true" serum sodium in the setting of hyperglycemia have been developed. One simple one is the following:

$$[(\text{Measured glucose} - 100)/100] \times 1.5 + \text{measured serum Na} = \text{corrected serum Na}$$

TABLE 89-2 CATEGORIZATION OF HYPONATREMIA BY OSMOLALITY STATUS

HYPERTONIC OR NORMOTONIC HYPONATREMIA		HYPOTONIC OR HYPO-OSMOLAR HYPONATREMIA(SEE FIGURE 89-1)
TRANSLOCATIONAL	PSEUDOHYPONATREMIA	
Hyperglycemia	Severe hyperlipidemia, especially hypertriglyceridemia	Hypervolemic
Post TURP in older men due to absorption of irrigant solutions like glycine, mannitol, and sorbitol	Paraproteinemia, like multiple myeloma	Euvolemic
Intravenous immune globulin (IVIg) due to maltose infusion	Cholestatic and obstructive jaundice	Hypovolemic

TURP, transurethral resection of prostate.

If the corrected serum sodium falls within the normal range, then the patient has pseudohyponatremia. Serum sodium may also be low with severe hyperlipidemia, particularly hypertriglyceridemia, or hyperproteinemia as may be seen with multiple myeloma or other paraproteinemias. In these instances, a measured serum osmolality will be normal. Further testing and therapy then should be directed toward determining the cause of the underlying hyperlipidemia (eg, pancreatitis or uncontrolled diabetes mellitus) or hyperproteinemia (eg, multiple myeloma).

The second step is determining whether the individual's kidneys are responding appropriately to the hyponatremia by diluting the urine. While this is best assessed by measurement of the urine osmolality, the specific gravity of the urine can also give insight. A specific gravity of 1.010 is isosthenuric with normal serum, that is, osmolality is approximately 300 mOsm/kg. A very high specific gravity in the absence of severe glycosuria suggests urinary concentration, while a very low specific gravity, less than 1.006, suggests urinary dilution. As indicated previously, the minimum urine osmolality attainable by human beings is 40 to 50 mOsm/kg. Older individuals may not be able to achieve this degree of dilution, but certainly an expected normal response to a hypo-osmolar condition would be a urine osmolality less than 100 to 150 mOsm/kg. Failure to dilute the urine appropriately suggests that excessive ADH is present. The vast majority of cases of hyponatremia are associated with an inappropriately high urine osmolality, that is, an inability to excrete a free water load.

At this point, an assessment of volume status can help in developing the differential diagnosis for the hyponatremia (**Table 89-3**). Hypovolemia is suggested by a low blood pressure, orthostatic hypotension, weight loss, and a low urine sodium (< 20–40 mEq/L). Hypervolemic hyponatremia is suggested by the presence of hypertension and/or peripheral or pulmonary edema. The three classic edema forming conditions—congestive heart failure, cirrhosis, and nephrotic syndrome—may be accompanied by hyponatremia, particularly in the late states. Euvolemic hyponatremia can be seen with thiazide diuretics, mild adrenal insufficiency, hypothyroidism, and SIADH. SIADH is not an end diagnosis, but a sign of another underlying disorder. SIADH is commonly seen with head trauma or central nervous system disorders, pulmonary diseases, cancers, many medications, or as an idiopathic finding. The diagnosis of SIADH is one of exclusion. At times, the volume status may be difficult to assess. Some additional laboratory work that may be useful in distinguishing hypovolemia from euvolemia are the urine sodium, fractional excretion of sodium, and uric acid. The urine sodium tends to be lower with hypovolemia, as does the fractional excretion of sodium (**Table 89-4**). The serum

uric acid tends to be higher with hypovolemia or with thiazide diuretics than in the euvolemic condition, especially SIADH. An elevated aldosterone level may suggest hypovolemia as well and is frequently suppressed with SIADH. However, no laboratory test or physical examination finding is definitive for establishing volume status and this assessment remains a clinical one. Two additional causes of hyponatremia that may occur in older adults warrant discussion here—cerebral salt wasting and renal salt wasting. As suggested by the names, both of these syndromes present with hyponatremia and high urine sodium, generally greater than 40 mEq/L (see **Table 89-4**). Cerebral salt wasting presents most frequently in the neurosurgical setting. Renal salt wasting most commonly follows the use of drugs such as cisplatin for the treatment of cancer. Both conditions are characterized by hyponatremia, high urine sodium, and relative hypovolemia which can be quite severe with renal salt wasting. Both conditions are also generally self-limited, but may present significant challenges in diagnosis and treatment. Despite the degree of hypovolemia, uric acid may be low in both conditions and so they may be mistaken for SIADH. Making the correct diagnosis is critical as the treatments are very different.

TABLE 89-3 APPROACH TO DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA BY EVALUATION OF VOLUME STATUS

HYPOVOLEMIC	EUVOLEMIC	HYPERVOLEMIC
GI losses; nausea, vomiting, diarrhea	Age-related excess release or lack of suppression of ADH causing idiopathic hyponatremia	Liver cirrhosis
Sweating	SIADH from pulmonary diseases, malignancies such as small cell cancer of the lung, lymphomas, strokes, head trauma, subdural hematoma, medications, HIV	Congestive heart failure
Diuretics, especially thiazides	Hypothyroidism	Nephrotic syndrome
Cerebral salt wasting	Primary adrenal insufficiency	
Salt-losing nephropathy	Drugs such as NSAIDs, Haldol, SSRIs, antidepressants	
	Postoperative hyponatremia due to infusion of hypotonic solutions, anesthesia	

ADH, antidiuretic hormone; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate ADH secretion; SSRI, selective serotonin reuptake inhibitor.

TABLE 89-4 DIFFERENTIAL DIAGNOSIS OF HYPONATREMIA WITH HIGH URINE SODIUM

	SYNDROME OF INAPPROPRIATE ADH (SIADH)	CEREBRAL SALT WASTING (CSW)	RENAL SALT WASTING (RSW)
Extracellular fluid volume			
Serum albumin	Normal		
Serum uric acid			
BUN/creatinine			
Hematocrit	Normal		
Treatment	Fluid restriction	Normal saline	Normal saline

If the urine osmolality is low in the setting of hyponatremia, less than 100 mOsm/kg, then the individual most likely is suffering from a low solute ingestion state, either subsistence on the so-called tea and toast diet or beer potomania (**Figure 89-1**). Because it is not possible to excrete water in the absence of any solute, failure to ingest salts or proteins will limit water excretion by limiting solute delivery in the nephron. Predisposing conditions are common in the older population and include poor functional status where cooked meals cannot be prepared, difficulties with chewing or swallowing, excessive intake of solute-free liquids such as beer. Very rarely, an individual may be hyponatremic with true psychogenic polydipsia, and these individuals will also excrete a very dilute urine as with the

low solute ingesters, but generally with a high volume. Psychogenic polydipsia generally accompanies an established severe psychiatric disorder.

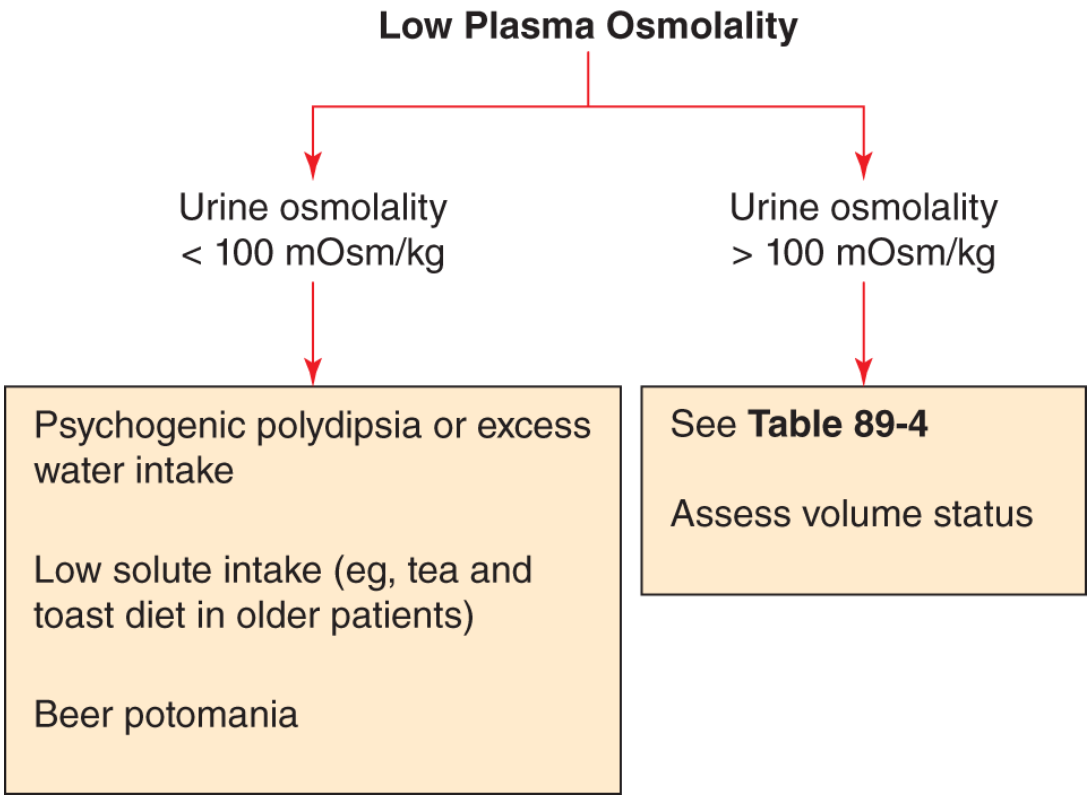


FIGURE 89-1. Causes of hypo-osmolar hyponatremia.

Most instances of hyponatremia are mild and asymptomatic with serum sodium ranging between 130 and 135 mEq/L. Interestingly, however, even mild degrees of hyponatremia have been associated with falls, bone loss, and cognitive impairment in older adults. Whether correction of the hyponatremia will improve these outcomes has yet to be shown. If correction is thought to be desirable, then addressing easily correctable causes such as medications, poor diet, or forced fluid ingestion, and institution of mild fluid restriction would be appropriate steps. More severe hyponatremia can be accompanied by symptoms ranging from fatigue and slowed mentation to frank altered mental status, seizures, and respiratory arrest. Severe symptomatic hyponatremia is a medical emergency warranting immediate treatment, no matter what the underlying cause is. The goal for treatment is to raise the serum sodium to a level where the life-threatening symptoms abate, generally aiming for an increase of no more than 8 mEq/L within the first 24 hours. The rate at which this is most safely accomplished remains an area of intense study with some advocating a rapid increase followed by stabilization while others recommend a steady gradual increase over the 24-hour period. The mechanism for achieving this increase will very much depend on the underlying cause. Patients afflicted with SIADH, with a high urine osmolality, respond most effectively to hypertonic saline with or without the use of a loop diuretic to enhance free water excretion. Hypovolemic individuals will respond to 0.9% saline with correction of the hyponatremia. Hypervolemic individuals such as those with heart failure will respond to a combination of high-dose loop diuretic and water restriction. In contrast, individuals who are already excreting a dilute urine, may be able to correct themselves without specific intervention. In all circumstances, frequent monitoring of serum sodium is critical to ensure adequate but not excessive correction of the serum sodium within the critical first 24-hour period.

Hypernatremia Hypernatremia occurs far less frequently than hyponatremia and tends to occur at the extremes of ages —neonates and the very old. This hyperosmolar condition generally results from a loss of water through renal or extrarenal mechanisms and/or inability to sense or respond to thirst by increasing fluid intake (**Table 89-5**). Older individuals show a reduced thirst sensation, and therefore lose a critical mechanism to prevent the development of hypernatremia. Moreover, they are frequently unable to concentrate the urine maximally, thus obligating more water losses through renal excretion. Common clinical scenarios in the older population associated with the development of hypernatremia include individuals debilitated by stroke or other significant limitation to mobility rendering them

unable to obtain fluids, development of severe diarrhea leading to profound intestinal fluid losses, advanced chronic kidney disease, or uncontrolled diabetes mellitus with severe polyuria. More rarely, development of partial or complete central diabetes insipidus will develop in the setting of head trauma after a fall or surgery. Severe hypernatremia carries a high mortality that is attributable more to the underlying causes leading to the hypernatremia than the hypernatremia itself. Thirst is a powerful mechanism to guard against hypernatremia. Thus, the appearance of hypernatremia signifies a profound aberration in the regulation of body fluid.

TABLE 89-5 CAUSES OF HYPERNATREMIA CHARACTERIZED BY LOSS OF WATER VERSUS GAIN OF SODIUM

DECREASED EXTRACELLULAR FLUID (ECF) VOLUME (LOSS OF FLUID AND ELECTROLYTES)			
RENAL LOSSES (POLYURIA, > 2 L URINE/d)	**NONRENAL LOSSES (OLIGURIA, < 1 L URINE/d)**	**NORMAL ECF VOLUME (PURE WATER DEFICITS)**	**HIGH ECF VOLUME (SODIUM GAIN)**
Diuretics, especially loop diuretics	Nausea, vomiting, diarrhea	Defects in thirst mechanism, especially in older patients after stroke, post fall trauma, etc	Hypertonic sodium chloride or sodium bicarbonate fluids during resuscitative efforts
Osmotic diuresis from hyperglycemia, urea, mannitol	Nasogastric suction	Lack of water access in immobilized, restrained older patients	Hypertonic hyperalimentation in TPN solutions
Recovery phase or diuretic phase of ATN, postobstructive diuresis	Sweating	Altered mental status due to infections, dementia, medications, etc	NACL tablets
		Diabetes insipidus—neurogenic and nephrogenic	Hypertonic dialysis
		Mechanical ventilation	Cushing syndrome
			Primary hyperaldosteronism

ATN, acute tubular necrosis; TPN, total parenteral nutrition.

As with hyponatremia, assessment of the renal response to hypernatremia is critical to determine cause and treatment. Assessment of acute hypernatremia can be relatively straightforward. The normal renal response to hypernatremia will be elaboration of a low-volume, highly concentrated urine, generally with a urine output of less than 20 mL/h and a urine osmolality of greater than 600 mOsm/kg. If the hypernatremic person exhibits this response, then the cause of the hypernatremia is extrarenal water losses such as diarrhea or inability to obtain water to drink due to immobility. Diagnostic and therapeutic efforts should be directed toward determination of the cause of the failure to obtain adequate fluid or the cause of the extrarenal fluid loss. If the hypernatremic person shows polyuria with a urine output greater than 50 to 100 mL/h and/or a urine osmolality of 300 mOsm/kg or less, then this suggests renal losses of water due to an osmotic diuresis as is seen commonly with uncontrolled diabetes mellitus or nephrogenic or central diabetes insipidus. Distinguishing between partial central diabetes insipidus and nephrogenic diabetes insipidus as a cause for polyuria can be very difficult, particularly if the hypernatremia is chronic. While the gold standard for diagnosing the cause of polyuria/polydipsia syndromes has been 18- to 24-hour water deprivation with measurement of serum and urine osmolality and serum ADH levels followed by an assessment of the response to exogenous ADH, this approach may be impractical in an older debilitated person and probably unnecessary in the acute situation. The interpretation of polyuria/polydipsia syndromes is also complicated by the fact that any high urine volume state may result in medullary “washout” of the interstitial solute required for urinary concentration and downregulation of aquaporin channels required for water reabsorption from the tubule. Consequently, the response to exogenous or endogenous ADH may be impaired, leading to the mistaken diagnosis of nephrogenic diabetes insipidus. Newer modalities for evaluation such as measurement of serum copeptin, a small peptide secreted along with ADH, hold promise as more sensitive and specific diagnostic tools, particularly for chronic hypernatremia. Nephrogenic diabetes insipidus is relatively common, seen with a variety of chronic kidney diseases, chronic urinary tract obstruction as occurs with prostatic hypertrophy, and some medications such as lithium. The polyuria in these conditions may be extreme—6 to 7 L/day—but more commonly is closer to 3 to 4 L/day and can be managed conservatively. The addition of a thiazide diuretic can be a useful adjunct. If true ADH deficiency is suspected, then a trial of oral

vasopressin beginning with 0.1 mg daily can be tried, working up to 0.4 mg daily.

Aside from treating any underlying cause of water loss or water deprivation, the cornerstone of therapy for hypernatremia is water replacement. As for hyponatremia, correction of hypernatremia should be judicious in rate, limiting the decrease serum sodium to approximately 8 to 10 mEq/L/24 h, although some have suggested that 50% of the water deficit can be safely corrected in the first 24 hours. The water deficit can be estimated by the following equation:



If the water deficit is less than 3 L and the patient is able to drink safely, then oral water repletion is reasonable. If not, then the deficit will need to be addressed with intravenous administration of 5% dextrose in water. Frequently, patients with hypernatremia are also intravascularly volume depleted and may be frankly hypotensive. If the cardiovascular status is in jeopardy, then the initial fluid of choice is 0.9% saline to ensure adequate intravascular volume. Once the volume status is established, switching to more hypotonic fluid is reasonable. If the degree of volume depletion is felt to be moderate, then initial therapy with 5% dextrose in 0.45% saline would be a reasonable choice, taking into account that twice as many liters would be required to deliver the volume of free water equivalent to that delivered using 5% dextrose in water. Serum sodium should be carefully monitored throughout the therapy as the above calculation is based on several assumptions that may not apply to the individual person such as the estimated percentage of body weight that is comprised of body water, the projected volume of distribution of the fluid, and ongoing salt and water losses.

DISORDERS OF SODIUM HOMEOSTASIS

Physiologic Regulation of Sodium Balance

From a clinical standpoint, regulation of sodium balance is equivalent to regulation of extracellular fluid volume. Loss of sodium from the body results in volume depletion; gain of sodium results in volume overload. Volume status is maintained through the combined actions of the central nervous system, cardiovascular system, and kidney. Extracellular fluid volume status is sensed by a variety of pressure and volume receptors located in the heart, blood vessels, interstitium, and kidney. Pressure receptors in the carotid arteries, volume receptors in the cardiac atria, and sodium chloride receptors in the macula densa of the kidney have all been identified as major contributors to the volume sensing machinery, though other receptors undoubtedly exist. The output from these sensors results in alterations in the release of several modulators of renal sodium handling including sympathetic neurotransmitters, components of the renin-angiotensin-aldosterone system, intrarenal endothelin and prostanoids, the atrial natriuretic peptides, and cardiac glycosides. At any given time, vasoconstrictive and antinatriurietic forces such as epinephrine and norepinephrine, angiotensin II, aldosterone, endogenous ouabain, and thromboxanes compete with vasodilatory and natriuretic forces such as endothelin, prostacyclins, and the atrial natriuretic peptides to determine the extent of renal sodium retention or excretion in the effort to maintain adequate circulatory volume.

Aging has several notable effects on these systems, with consequences for sodium homeostasis that parallel the discussion of water homeostasis. Concisely put, older individuals have more difficulty in excreting a sodium load due to age-related decrease in GFR as well as concomitant medical conditions such as heart failure, and have more difficulty adjusting to an abrupt decrease in sodium ingestion or frank sodium loss. The former defect predisposes the older person to significant volume overload and exacerbation of hypertension, while the latter defect potentiates the development of volume depletion. Interestingly, despite the overall tendency for older individuals to retain sodium, atrial natriuretic peptide (ANP) levels are higher in older individuals, the ANP response to a sodium load is more pronounced, as is the renal natriuretic response to ANP. In contrast, renin response to the upright position is dampened in older adults and the levels of aldosterone tend to be lower. These alterations in hormone balance would be predicted to result in renal salt wasting, yet older individuals are more likely to exhibit salt-sensitive hypertension, being either more susceptible to sodium retention or perhaps more sensitive to the effects of sodium on blood pressure. The explanation for these apparent discrepancies has not been fully established.

Sodium Depletion

Older individuals are more prone to extracellular fluid volume depletion—total body sodium depletion—than younger individuals. Volume depletion is a common reason for admission to the hospital for older patients. A major

consequence of aging is a slowed ability of the kidney to increase sodium reabsorption in response to volume depletion, thus potentiating sodium losses. Furthermore, when faced with a salt-losing condition such as food deprivation, aged animals ingest less sodium than younger animals, suggesting defects in the sensing mechanisms for sodium loss in addition to intrinsic defects in the renal response to volume depletion. The consequence is an increase in the susceptibility to volume depletion.

Assessment of volume status relies heavily on physical examination and selected laboratory findings. Physical examination findings of volume depletion in older adults are similar to those in younger patients, but may not be as obvious. Also complicating the evaluation of volume status in older adults are the changes in body composition that occur with aging, including loss of muscle mass and increase in fat mass, resulting in an overall reduction in total body water. Hypotension with tachycardia and orthostatic hypotension are commonly used parameters to detect volume depletion. These findings may not be as reliable in older individuals due to peripheral neuropathy, medications, or deconditioning, all of which may result in orthostatic hypotension even in the absence of volume depletion. In addition, examination of the cardiovascular response to volume depletion in older women has demonstrated that older women manifest a lesser increase in heart rate than do younger women. Laboratory findings suggestive of volume depletion may also be less reliable in older adults than in the young. A blood urea nitrogen (BUN)/creatinine ratio of greater than 20:1 is consistent with volume depletion, but in older adults could be due to a decrease in muscle mass and not volume depletion. Conversely, poor protein intake could result in a lower BUN/creatinine ratio, masking the presence of underlying volume depletion. A low urine sodium concentration of 20 mEq/L or less or a low fractional excretion of sodium less than 1% are commonly used parameters to help determine volume status; however, in older individuals, the ability to decrease urine sodium concentration may be impaired or delayed. Thus this usually valuable clue to volume depletion may be lost. Additional laboratory studies such as assessments of brain natriuretic peptide, cortisol, and aldosterone levels have limited value due to changes in the levels of these hormones with aging as well as the time required to obtain the results.

Treatment of volume depletion in older adults centers around the cause and the status of other underlying conditions. Common causes of volume depletion include gastrointestinal fluid losses, bleeding, anorexia associated with infection or chronic disease, diuretic use, and adrenal insufficiency. In particular, mineralocorticoid insufficiency due either to primary pituitary failure, involution of the adrenal gland or isolated aldosterone deficiency can present with repeated episodes of fatigue and hypotension that responds to parenteral saline administration. Frank hyperkalemia may be present, but often is not, and urine studies will show a relatively high urine sodium. Thus, the diagnosis of mineralocorticoid deficiency may not be initially suspected. The treatment of volume depletion is administration of sodium either orally, parenterally, or both. Diuretics should be discontinued and their ongoing use reevaluated once the sodium deficit is replenished. If the index of suspicion is sufficiently high, measurement of fasting morning cortisol, renin, and aldosterone may also be considered. If frank adrenal insufficiency is diagnosed, then treatment with both glucocorticoid and mineralocorticoid replacement is indicated. If isolated mineralocorticoid deficiency is diagnosed, then initiation of therapy with a mineralocorticoid-specific replacement such as fludrocortisone 0.1 mg daily should be initiated.

Sodium Excess

Peripheral and pulmonary edema are the hallmarks of volume overload or sodium excess. Lower extremity edema is common and can be attributed to local or systemic factors. It is important to determine if a patient has a systemic cause of edema, as treatment of the edema will center around the treatment of the systemic disorder. In contrast, local causes of edema such as venous insufficiency are addressed through local measures such as compression stockings. Likewise, pulmonary edema may be due to decompensated congestive heart failure, chronic kidney disease, or excessive sodium chloride administration, but it may also occur in the setting of severe lung injury due to sepsis or a toxin. The former would be addressed by a diuretic among other therapies, while the latter would be treated with supplemental oxygen and measures to address the primary lung injury.

Volume overload is common in older adults, predominantly related to the high incidence of congestive heart failure in this population. In fact, heart failure is the most common cause of admission to the hospital in individuals older than 65 years (see Chapter 79). Common causes of heart failure decompensation include intrinsic issues such as acute myocardial infarction and extrinsic issues such as excessive dietary salt intake, inadequate medical therapy, or even the use of medications that cause salt retention. Medications that may contribute to volume overload include nonsteroidal anti-inflammatory drugs, thiazolidinediones, direct vasodilators, calcineurin inhibitors, and steroid hormones that contain mineralocorticoids such as prednisone. Even in the absence of heart failure, these drugs may

cause sodium retention and subsequent edema. Additional causes of volume overload include kidney failure and liver failure. Individuals with acute or chronic kidney disease frequently have impaired ability to excrete a large sodium load. This is especially true if the individual has a kidney disease with proteinuria in the nephrotic range. Chronic glomerular diseases such as diabetic nephropathy or membranous glomerulopathy are frequently accompanied by significant and refractory edema. Acute glomerular disease associated with acute vasculitis syndromes such as granulomatosis with polyangiitis (formerly known as Wegener granulomatosis) or chronic infections such as osteomyelitis or cellulitis are also characterized by edema. Interestingly, edema may also be seen with chronic urinary tract obstruction. Finally, liver failure with portal hypertension of any cause frequently produces edema.

Common presenting symptoms of volume overload or sodium excess are shortness of breath and lower extremity edema. Physical examination may show hypertension, crackles on lung examination, dilated jugular veins, an S_3 gallop with tachycardia, and edema. Depending on the cause of the volume overload, additional pertinent physical examination findings to elicit include a displaced cardiac impulse, rash, frank arthritis, spider angiomata, caput medusa, jaundice, or ascites. Notably, it is very common for older individuals to have some combination of heart, liver, and/or kidney failure; thus, they may exhibit edema seemingly out of proportion to the degree of organ failure. Chest radiograph may show engorged lung vasculature, Kerley B lines, visible fissures, pleural effusions, or cardiomegaly. Most common laboratory work is not helpful in supporting a diagnosis of volume overload, but a high serum level of brain natriuretic peptide is consistent with volume overload. A low level should prompt reevaluation of the impression of volume overload.

The treatment of volume overload includes three principles: treatment of the underlying cause, restriction of sodium ingestion, and enhancing urinary excretion of sodium. The treatment of heart failure, kidney failure, and hepatic failure are covered elsewhere and so will not be recapitulated here. Certainly, review of the medication list for the identification and discontinuation of any medications that may promote sodium retention or worsen cardiac and renal function is warranted, bearing in mind that some medications such as nonsteroidal anti-inflammatory can be obtained over the counter and therefore may not appear on a medication list. Initiation of a 2-g sodium-restricted diet is generally sufficient for limiting further fluid retention. The choice of diuretic will depend in large part on the cause of the volume overload. Thiazide diuretics have the advantage of a long half-life and a generally mild diuretic effect, thus the chance of diuretic-induced volume depletion is low. On the other hand, as many older patients have depressed kidney function, they may require the more potent loop diuretics, which are more effective in removing excess sodium and preventing sodium retention, but are shorter acting and more likely to result in volume depletion. Another undesirable side effect of diuretics, especially loop diuretics, is urinary urgency which can lead to incontinence in older patients or which can exacerbate nocturia. When querying patients about their adherence to diuretic therapy, asking about these particular side effects may yield insights into drug nonadherence. Alterations in the scheduling of these drugs may help with the ability of older patients to adhere with medical therapy. For example, instructing the older patient to make sure that he/she is within easy range of a toilet for 2 hours after taking a loop diuretic and not taking the medication beyond late afternoon are simple adjustments that can prevent future episodes of volume overload. Another commonly used tool is daily weight, especially when coupled with telehealth connections, which can allow patient and provider to monitor volume status.

DISORDERS OF POTASSIUM HOMEOSTASIS

Physiologic Regulation of Potassium Balance

As the major determinant of transmembrane potential, and therefore neural, muscular, and neuromuscular currents, both total body potassium homeostasis and the extracellular-to-intracellular potassium gradient are strongly defended. Potassium is the major intracellular cation and the vast majority of body potassium stores are located in the skeletal muscle cells. Thus, serum potassium concentration reflects total body stores imperfectly, especially under stress conditions. Serum potassium is influenced by two separate sets of factors: those related to kidney function and those related to the transmembrane movement of potassium in and out of cells. In the setting of relatively well-preserved kidney function, older individuals have a normal serum potassium under unstressed conditions, but as the GFR declines, the fractional excretion of potassium does not rise as much as in young individuals. Additionally, the kaliuretic response to furosemide is blunted in older adults relative to younger individuals. These changes have been attributed at least in part to lower aldosterone levels and/or aldosterone resistance in older adults. Several factors will regulate the movement of potassium in and out of cells including the glucoregulatory hormones insulin and glucagon,

adrenergic stimulation of either α- or β-receptors, acid-base balance, and alterations in serum osmolality. The effect of aging on the transmembrane movement of potassium has not been studied systematically. However, it has been established that the sodium-potassium ATPase in muscle cells of older adults differs in pattern of isoform expression and phosphorylation status. These changes may alter the ability of skeletal muscle to take up and sequester potassium after a significant load, thus predisposing older individuals to hyperkalemia; however, this has not been well studied.

Hypokalemia

Hypokalemia, defined as a serum potassium less than 3.5 mEq/L, occurs rarely in healthy adults (**Table 89-6**). However, because older individuals frequently are taking medications that alter potassium homeostasis such as diuretics or have a poor diet, the frequency of hypokalemia can be as high as 5%. Hypokalemia associated with medications, underlying disease processes, or diet, has been reported in 21% of hospitalized patients, of which older adults comprise a preponderance. Although many individuals with hypokalemia are clinically asymptomatic, hypokalemia is associated with a wide variety of clinical manifestations including muscle weakness including proximal muscle weakness and intestinal ileus, cardiac arrhythmias—especially atrial tachyarrhythmias—polyuria, and fatigue. Rarely, muscle weakness will proceed to frank paralysis. Hypokalemia is frequently accompanied by multiple electrolyte abnormalities including hyper- or hyponatremia, metabolic acidosis or alkalosis, and hypomagnesemia. Individuals with very poor diets such as those with alcoholism or eating disorders may present with normal or minimally decreased potassium that belies the extent of their potassium deficiency. The potassium level may plummet with refeeding, leading to potentially catastrophic cardiac events, especially if this has occurred in the setting of underlying organic heart disease. A similar dramatic fall in potassium can occur with aggressive insulin therapy or aggressive bicarbonate replacement. For these reasons, it is recommended that potassium replacement, parenteral, enteral, or both, be initiated immediately when these therapies are anticipated. Avoidance of dextrose containing parenteral fluids should be considered in the setting of severe hypokalemia, until it can be at least partially corrected.

TABLE 89-6 DIFFERENTIAL DIAGNOSIS OF HYPOKALEMIA BY PATHOGENESIS

	INCREASED EXCRETION		
DECREASED INTAKE	**URINARY LOSSES**	**GI LOSSES**	**SHIFT INTO THE CELLS**
Edentulous older patients	Diuretics of the carbonic anhydrase inhibitor, loop, and thiazide classes	Gastric acid losses such as with nasogastric suction in patients with bowel obstruction	Insulin either exogenous or endogenous release after a carbohydrate load as in refeeding syndrome
Inadequate access to food due to poverty	Osmotic diuresis from mannitol, hyperglycemia	Severe diarrhea of infectious etiology, laxative abuse	β-Agonists such as albuterol in treatment of asthma or COPD, terbutaline in preterm labor, dobutamine in heart failure, pseudoephedrine in OTC decongestants
Lack of appetite in older patients (tea and toast diet)	Mineralocorticoid activity both endogenous as in adrenal adenoma and exogenous as in steroid therapy, glycyrrhizic acid in licorice and Chinese herbs	Bowel cleansing for colonoscopy in older patients	Metabolic and respiratory alkalosis
Eating disorders such as anorexia nervosa and bulimia	Drugs such as penicillins, gentamicin, amphotericin, cisplatin	Acute colonic pseudo-obstruction (Ogilvie syndrome) especially in older patients after surgery, infections, trauma, cardiac events	Hypokalemic periodic paralysis
K poor parenteral nutrition formulas	Hypomagnesemia	Malabsorption syndromes	Some antipsychotics like risperidone and quetiapine
	RTA, both proximal and distal	Enteric fistulas	Hypothermia

	RTA		
	Postobstructive diuresis, diuretic phase of ATN		

ATN, acute tubular necrosis; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; OTC, over the counter; RTA, renal tubular acidosis.

Hypokalemia can result from poor intake (eating disorders, alcoholism), increased losses (diuretics, mineralocorticoid excess, diarrhea), or shift of potassium from the extracellular to the intracellular compartment (insulin therapy). Often, the history alone will alert the clinician to the most likely cause of hypokalemia, but additional testing of the urine for potassium, creatinine, and osmolality can effectively narrow the differential diagnosis by establishing whether there are excessive urinary potassium losses. An isolated urine potassium of greater than 40 mEq/L suggests excessive renal losses, but a more accurate assessment is accomplished by calculating the transtubular potassium gradient (TTKG) through the following equation with values obtained at a time when the patient is present with hypokalemia:

$$TTKG = (K_{urine} \times osmolality_{serum})/(K_{serum} \times osmolality_{urine})$$

This equation is only applicable when urine osmolality is equal to or greater than the serum osmolality. Recent studies have identified additional caveats that may affect the interpretation of this result; nonetheless, the calculation does offer an additional data point that may be useful in evaluating an individual with hypokalemia. TTKG greater than 7 suggests urinary loss as a major mechanism for hypokalemia, while TTKG less than 3 suggests that urine losses are not a major contributor.

The safest method for potassium replacement is orally, through potassium-rich foods or potassium supplements, as overdose is unlikely. For severe hypokalemia or hypokalemia associated with acute cardiac arrhythmias, however, parenteral potassium may be required. Determining the amount of potassium needed to replace losses is inexact at best due to confounding factors such as ongoing losses, acid-base status, differences in muscle mass, and underlying medical conditions. Administration of relatively small doses such as 10 or 20 mEq at a time with frequent repeat measures is the safest approach, and this is particularly true in patients who have some degree of kidney disease, who are on potassium-sparing medications, or who are very emaciated. For patients who require continuous diuretic therapy, addition of a potassium-sparing diuretic in low dose may blunt potassium losses. However, these agents need to be used carefully in the individuals with chronic kidney disease or those who are already taking a medication that blunts renal potassium excretion such as trimethoprim-sulfamethoxazole, a calcineurin inhibitor (cyclosporine or tacrolimus), an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker.

Hyperkalemia

Hyperkalemia rarely occurs in the setting of normal kidney function because of the tremendous capacity of the kidneys to excrete the daily potassium load. Older patients are more susceptible to hyperkalemia because of the loss of kidney function, the loss of muscle mass, the changes in regulation of muscle ion content described earlier, lower levels of renin and aldosterone, and the use of many medications for chronic conditions which are associated with hyperkalemia such as ACE inhibitors, angiotensin receptor blockers, and potassium-sparing diuretics (**Table 89-7**). Older individuals also are more likely to have glucose intolerance which may blunt the ability of potassium to be translocated to the intracellular compartment and type IV renal tubular acidosis which will diminish renal potassium excretion even in the presence of relatively normal kidney function. The exact incidence of hyperkalemia in older patients is not known. Hyperkalemia is seen in up to 10% of hospitalized patients. Despite the theoretical predisposition to hyperkalemia, it has been difficult to show that older patients using inhibitors of the renin-angiotensin-aldosterone system, singly or in combination, have a higher incidence of hyperkalemia than do younger patients.

TABLE 89-7 DIFFERENTIAL DIAGNOSIS OF HYPERKALEMIA BY PATHOGENESIS

INCREASED INTAKE (URINE K > 20 mEq/L)	DECREASED RENAL EXCRETION (URINE K < 20 mEq/L)	SHIFT OUT OF THE CELLS (URINE K > 20 mEq/L)	PSEUDOHYPERKALEMIA
High K foods especially in older patients with underlying CKD	Medications more likely to be taken by older patients such as K-sparing diuretics like	Metabolic acidosis mostly due to inorganic acids Stored cells in PRBC	Prolonged tourniquet or repeated fist clenching during phlebotomy

	spironolactone, ACEI, ARBs, NSAIDs, and heparin, other medications such as trimethoprim-sulfamethoxazole, calcineurin inhibitors such as cyclosporine and tacrolimus		
Salt substitutes labeled “no salt” or “low salt”	Type 4 renal tubular acidosis, seen in the setting of type 2 diabetes, sickle cell disease, adrenal insufficiency, lower urinary tract obstruction, for example, BPH or neurogenic bladder	Meds like β-blockers, methotrexate, digitalis, fluoride toxicity	Severe leukocytosis and thrombocytosis
Potassium supplements prescribed routinely with diuretics	Chronic kidney disease	Succinylcholine use in anesthesia	Traumatic venipuncture
K-rich parenteral nutrition formulas		Insulin deficiency and hyperglycemia	Delay in processing the blood sample in laboratory
		Rhabdomyolysis, tumor lysis syndrome	
		Neuroleptic malignant syndrome following haloperidol Malignant hyperthermia after certain anesthetic agents	

ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; BPH, benign prostatic hyperplasia; CKD, chronic kidney disease; K, potassium; NSAIDs, nonsteroidal anti-inflammatory drugs; PRBC, packed red blood cell.

The definition of hyperkalemia varies from laboratory to laboratory and from clinical report to clinical report. Generally, a potassium of greater than 5.3 mEq/L is accepted as hyperkalemia, though may not be considered significant enough to document. Spurious hyperkalemia, where the measured potassium is elevated but the ambient serum potassium is normal, can occur in the setting of hemolysis of the blood sample associated with difficult phlebotomy or deterioration of the sample, severe thrombocytosis, severe leukocytosis, or red cell disorders. If this is suspected, obtaining a plasma potassium would be the next appropriate step. Hyperkalemia is frequently asymptomatic. Muscle weakness and fatigue are the most common symptoms. The heart is the major target of significant hyperkalemia as increasingly greater potassium concentrations result in varying degrees of heart block progressing to cardiac arrest. Unfortunately, the electrocardiographic manifestations of hyperkalemia may be subtle and missed; conversely, the same level of hyperkalemia may produce vastly different effects on the electrocardiogram (ECG). Numerous case reports document the varied ECG findings of even quite severe hyperkalemia, potassium greater than 7 mEq/L, including sinus bradycardia, complete heart block, wide QRS tachycardia, or the classic sine wave pattern. The widely taught progression of the ECG manifestations of hyperkalemia such as peaked T waves, prolonged PR interval, absence of P wave, and QRS prolongation is seldom seen. Thus, the absence of ECG findings in the presence of a high potassium level should not lead the clinician to conclude that the hyperkalemia is erroneous or insignificant. The physical examination may show muscle weakness, a reduction in deep tendon reflexes, and bradycardia. However, generally the physical examination is not helpful in making the diagnosis of hyperkalemia.

The causes of hyperkalemia are numerous. As indicated earlier, older patients are generally more prone to hyperkalemia primarily due to the reduction in kidney function. Most cases of significant hyperkalemia are multifactorial due to a reduction of kidney function coupled with excessive potassium intake, use of medications that reduce potassium excretion or movement into cells, or occurrence of acute kidney injury superimposed on chronic kidney disease. A complete history can generally identify these factors. Recent studies have identified particularly high-risk situations for severe hyperkalemia in older adults including the use of trimethoprim/sulfamethoxazole in patients on spironolactone, the use of two inhibitors of the renin-angiotensin-aldosterone axis, the use of nonsteroidal anti-inflammatory drugs, and the presence of type 2 diabetes. Notably, the highest risk appears to be within the first month of the use of the hyperkalemia-inducing medications, suggesting that early laboratory monitoring could help to

avoid later, more severe complications. One additional diagnosis to consider when an older patient presents with unexpected hyperkalemia is adrenal insufficiency. Modest adrenal insufficiency in the geriatric population may present episodically with recurrent volume depletion and acute kidney injury with varying degrees of hyponatremia and hyperkalemia which correct easily with the administration of parenteral sodium chloride. Often, the only symptom is fatigue or failure to thrive.

The treatment of hyperkalemia is determined by the severity and the presence or absence of significant cardiac effects. Asymptomatic, non–life-threatening hyperkalemia can be approached in the outpatient setting through elimination of medications that cause hyperkalemia, improving hydration status, and addressing any reversible causes of reduction in kidney function such as medications and volume depletion. Severe hyperkalemia manifested as advanced degrees of conduction delays or bradycardia will require, in addition to the above measures, more immediate interventions. Intravenous calcium gluconate will stabilize the myocardial cell membrane, decreasing the potential for cardiac arrest. This effect is essentially immediate, but transient, and does not lower potassium levels. Intravenous insulin, inhaled β-agonists, and, if the individual also has a metabolic acidosis, intravenous bicarbonate, will enhance potassium entry into the cells, thus lowering serum potassium and diminishing the risk of a fatal cardiac event. Insulin works fastest, within 15 minutes, but is more transient than the β-agonists. All of these interventions are transient, and ultimately treatment is directed toward removal of excessive potassium from the body. The three options listed in order of aggressiveness are forced diuresis with loop diuretics, the use of exchange resins such as sodium polystyrene sulfonate, or dialysis. The choice of which modality or modalities to employ is dependent on the severity of hyperkalemia, the level of kidney function, the presence or absence of any intestinal disease, and patient/physician preference. Without doubt, the least invasive approach, forced diuresis, is highly effective in the presence of preserved kidney function, requiring only peripheral intravenous access for high-volume administration with parenteral diuretic, and can be combined with the immediate measures listed previously to achieve the desired acute and sustained reduction in serum potassium. When kidney function is impaired, exchange resins and/or dialysis can be considered. Studies identifying severe complications of exchange resins such as bowel perforation or obstruction have forced a reexamination of the use of this therapy. A recent study demonstrated good efficacy and safety, especially with higher potassium levels in hospitalized patients. Notably nearly all of the patients received oral therapy and thus the decline in potassium was somewhat delayed. For severe hyperkalemia, the immediate therapies as well as oral exchange resins would be required.

DISORDERS OF MINERAL METABOLISM

Physiology and Pathophysiology of Calcium

The majority of calcium is found in the bone. Serum calcium is maintained within a tightly regulated range by the ability of the calcium-sensing receptor located on parathyroid cells to adjust the secretion of parathyroid hormone, the major physiologic regulator of ionized serum calcium. A limited number of foods contain a significant amount of calcium. Intestinal absorption of calcium is enhanced by vitamin D. Thus, since vitamin D deficiency occurs in as many as 70% of older individuals, many older individuals may be in negative calcium balance. Poor gut absorption of calcium will result in secondary hyperparathyroidism, and subsequent bone losses of calcium, an important factor contributing toward bone fragility in the older population. The ability of the parathyroid gland to maintain a stable ionized calcium level can mask significant calcium losses. Considerable debate exists over the ideal calcium intake for the older population. The most recent recommendations are in the range of 800 to 1000 mg/day.

The most common cause of hypocalcemia is a low albumin (**Table 89-8**). Calcium exists in the circulation in three forms and the total serum calcium is what is reported from the laboratory. When the total serum calcium is within the normal range, the ionized free calcium which is the active component constitutes approximately 50%, albumin bound calcium approximately 40%, and that complexed to anions approximately 10%. Therefore, if the serum albumin level decreases, the fraction of the total falls. To determine if the fall in total serum calcium can be attributed to a decrease in albumin alone, the clinician can "correct" the serum calcium by the following equation:

$$\text{Calculated total [Ca]} = \text{measured [Ca]} + ([4 - \text{measured albumin}] \times 0.8)$$

TABLE 89-8 DIFFERENTIAL DIAGNOSIS OF HYPOCALCEMIA BY ETIOLOGY

LOW PTH (HYPOPARATHYROIDISM)	HIGH PTH (SECONDARY TO HYPOCALCEMIA)	DRUGS	OTHER

Inadvertent surgical removal as in radical neck dissection	Vitamin D deficiency from malabsorption, vitamin D–poor diet, lack of sun exposure	AEDs like phenytoin, barbiturates, and carbamazepine	Severe hypomagnesemia
Postirradiation or radioiodine therapy	Acute pancreatitis	Bisphosphonates, particularly zoledronic acid, calcitonin, denosumab, cinacalcet	Severe sepsis
Postparathyroidectomy in dialysis patients	Renal failure	Isoniazid	Acute respiratory alkalosis
Infiltrative diseases of the parathyroid such as granulomatous diseases like sarcoid, metastatic malignancies, iron overload	Laxatives with sodium phosphate causing hyperphosphatemia	Rifampin	Hungry bone syndrome
	Liver disease	Foscarnet	
	Rhabdomyolysis, tumor lysis syndrome	Chelators like citrate, EDTA	
	Osteoblastic metastatic disease from breast, prostate cancers	Alcohol	

AEDs, antiepileptic drugs; EDTA, ethylenediaminetetraacetic acid.

If the calculated total calcium falls within normal parameters, the clinician can generally make the assumption that the ionized calcium fraction is also normal. Low calcium levels can be seen at times with severe malnutrition, malabsorption, vitamin D deficiency, or small bowel disease, but not commonly. Alternative causes of low calcium include hypoparathyroidism, which can be acquired surgically or by autoimmune disease, infusion of blood products that are suspended in a citrate solution, or infusion of an anion that can complex calcium such as phosphate, pancreatitis, or rhabdomyolysis. The clinical situation generally makes the differential diagnosis fairly obvious. Evaluation would include measurement of total and ionized calcium, serum phosphate, magnesium, and intact parathyroid hormone (PTH). Symptoms of hypocalcemia can range from nonspecific weakness to fasciculations, carpopedal spasm, periorbital numbness, or seizures when severe. ECG findings may show prolongation of the QT interval, predisposing to ventricular arrhythmias. In addition to addressing the cause of the hypocalcemia, calcium replacement is best accomplished orally through a combination of active vitamin D (calcitriol) and calcium. Under emergent conditions, calcium infusions are required—the preferred form being calcium gluconate which has fewer irritative effects on the vasculature than calcium chloride. For unexplained or persistent hypocalcemia, checking the serum magnesium is also useful as prolonged hypomagnesemia can impair PTH release.

Hypercalcemia is common in the older population. The two most common causes are malignancy and primary hyperparathyroidism (**Table 89-9**). However, several other fairly common causes include mild alkali syndrome due to excessive calcium carbonate plus vitamin D ingestion, immobilization, hyperthyroidism, thiazide diuretics, lithium, and theophyllines. The symptoms of hypercalcemia range from none to anorexia, nausea and vomiting, lethargy, and coma. The ECG will show a short QT interval. The first step in evaluation, if the cause is not immediately apparent, is to obtain a serum intact PTH level. A high PTH in the setting of hypercalcemia will almost always signify primary hyperparathyroidism, whereas a suppressed PTH in the same setting will point toward one of the alternative diagnoses. The relationship between PTH and serum calcium changes in advanced age such that a higher PTH is required to sustain calcium and this change in the relationship may at times complicate the interpretation of the PTH level. However, the expectation is still that a frankly elevated calcium will suppress the PTH level if the cause of hypercalcemia is not PTH related.

TABLE 89-9 ■ DIFFERENTIAL DIAGNOSIS OF HYPERCALCEMIA BY ETIOLOGY

PARATHYROID MEDIATED	MALIGNANCY MEDIATED	DRUGS	OTHERS
Primary hyperparathyroidism: adenoma, hyperplasia, MEN syndromes	Hematologic malignancies such as leukemias, lymphoma	Estrogen administration	Immobilization, especially in older nursing home patients

Tertiary hyperparathyroidism: CKD, ESRD	Solid tumors—breast, lung	Retinoic acid or hypervitaminosis A	Endocrine: thyrotoxicosis Adrenal insufficiency Pheochromocytoma
	Bone metastasis from breast cancer and multiple myeloma	Thiazide diuretics	Granulomatous diseases such as sarcoid, TB, fungal infections
		Lithium	Paget disease
		Calcium-containing antacids, milk-alkali syndrome hypervitaminosis D	

CKD, chronic kidney disease; ESRD, end-stage renal disease; MEN, multiple endocrine neoplasia; TB, tuberculosis.

Hyperparathyroidism may be treated by either surgery or a calcium-sensing receptor agonist such as cinacalcet which will lower PTH by enhancing the effect of calcium on PTH. Long-term studies suggest that nonsurgical treatment of asymptomatic or minimally symptomatic hyperparathyroidism is safe and does not result in excessive bone loss. If the hypercalcemia is not mediated by PTH, then a search for a malignancy or another secondary cause is warranted. Malignancies that commonly cause hypercalcemia include multiple myeloma, lung cancer, prostate cancer, and renal cell carcinoma. Asymptomatic, mild elevations in calcium can be managed conservatively with adequate hydration and avoidance of aggravating factors. Treatment of severe elevations in calcium (> 1 mg/dL above normal) or symptomatic hypercalcemia accompanying malignancy or other cause of hypercalcemia can range from aggressive hydration with saline to bisphosphonates or denosumab depending on setting and severity along with treatment of the underlying disorder.

Physiology and Pathophysiology of Phosphorus

Phosphorus is a major component of bone, but plays critical roles in a variety of processes including protein regulation, acid-base balance, and DNA and RNA structure. Abnormalities of serum phosphorus are uncommon. It is important to recognize that serum phosphorus varies with age, being highest in the neonatal period and lowest in the later stages of life. Therefore, seeing an older individual with a serum phosphorus of 2.2 to 2.8 mg/dL is not abnormal and does not require treatment. Furthermore, phosphorus is predominantly an intracellular ion—thus, the serum level may not accurately reflect total body stores.

Phosphorus is present in most nutrients. Intestinal absorption of phosphorus greatly exceeds daily needs so phosphate balance is accomplished by renal excretion of the excess daily load. Phosphorus depletion due to poor intake is very rare, but the older population is one of the populations at risk for this complication (**Table 89-10**). Other populations at risk within the older age group include alcoholics, individuals with short gut syndrome or extensive intestinal surgery, chronic diarrhea, or very severe vitamin D deficiency. Oftentimes, even with a large phosphorus deficit, the serum phosphorus level may be normal or low-normal. These malnourished individuals are at high risk for refeeding syndrome on admission to the hospital and may develop dangerously low levels of phosphorus (< 1.5 mg/dL) only after administration of nutrition. Profound decrease in phosphorus may result in the hypophosphatemia syndrome complicated by altered mental status, cardiac failure, and hemolysis. Because serum phosphorus is not routinely measured, dangerous hypophosphatemia may be overlooked in this setting. The treatment is oral phosphorus replacement in the form of dairy products or sodium phosphorus powder in mild conditions, whereas parenteral phosphate in the form of sodium or potassium phosphate may be required in the rare emergency situations.

TABLE 89-10 DIFFERENTIAL DIAGNOSIS OF HYPOPHOSPHATEMIA BY PATHOGENESIS

INADEQUATE INTAKE	INCREASED EXCRETION	SHIFT INTO THE CELLS
Starvation, neglect	Acquired Fanconi syndrome as a result of paraproteinemias such as MM in older patients, heavy metal toxicity	Refeeding syndrome
Concurrent vitamin D deficiency especially in older patients with	Alcoholism	Recovery from hypothermia

reduced sun exposure		
Concurrent use of antacids containing either calcium, magnesium, or aluminum	Posttransplant renal tubular disorders	Severe sepsis, burns
Malabsorption, chronic diarrhea	Primary and secondary hyperparathyroidism	Hungry bone syndrome after parathyroidectomy
Parenteral nutrition formulas	Continuous renal replacement therapies	Acute respiratory alkalosis
Phosphate binders	Diuretic use in older patients—especially acetazolamide and thiazides such as metolazone	DKA recovery
	Other drugs: glucocorticoids, IV iron formulations, some bisphosphonates	
	Hypokalemia, hypomagnesemia	
	Postobstructive diuresis, diuretic phase of ATN	

ATN, acute tubular necrosis; DKA, diabetic ketoacidosis; MM, multiple myeloma.

Phosphorus overload occurs almost exclusively in the setting of kidney failure (**Table 89-11**). Rarely, severe hyperphosphatemia may be seen with massive intoxication such as the use of phosphosoda for colonoscopy preparation. Hyperphosphatemia accompanying kidney failure is best treated by the addition of phosphate binders to the medication regimen. Notably, however, studies have shown that even in advanced kidney failure, many older patients do not develop hyperphosphatemia, possibly as a result of poor dietary intake.

TABLE 89-11 DIFFERENTIAL DIAGNOSIS OF HYPERPHOSPHATEMIA BY PATHOGENESIS

INCREASED INTAKE	DECREASED EXCRETION	SHIFT OUT OF CELLS	PSEUDOHYPERPHOSPHATEMIA
Use of phosphate-based laxatives or enemas, especially in older patients with mild renal insufficiency and constipation	Kidney disease, both chronic and acute	Rhabdomyolysis	Hemolysis in vitro
Excess use as IV replacement	Hypoparathyroidism	Tumor lysis syndrome, particularly lymphoproliferative disorders seen in older patients	Hyperbilirubinemia
Parenteral nutritional formulas	Bisphosphonates	Acute hemolysis	Hypertriglyceridemia
Vitamin D intoxication	Severe hypomagnesemia	Acute respiratory or metabolic acidosis	Multiple myeloma and other paraproteins
Milk-alkali syndrome	Tumoral calcinosis		

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Chapter 90

Aging of the Gastrointestinal System

Karen E. Hall

Learning Objectives

- Understand the effects of aging on various parts of the gastrointestinal tract.
- Recognize common presentations of gastrointestinal dysfunction in older adults.
- Understand the effects of aging on hepatic, biliary, and pancreatic function.

Key Clinical Points

1. **Dysmotility in the esophagus, stomach, and colon is common in older adults and is often due to a combination of effects of aging and superimposed disease.**
2. **Older patients with serious gastrointestinal (GI) disease, such as intestinal ischemia or perforation, may present with more subtle symptoms due to visceral hyposensitivity, and the severity of the condition may be underestimated.**
3. **The aging process per se has clinically significant effects on GI immunity and GI drug metabolism.**

Gastrointestinal symptoms are common in patients aged 65 and older (geriatric aged) and can range from mild self-limited episodes of constipation or acid reflux to life-threatening episodes of infectious colitis or bowel ischemia. According to data from the US Census Bureau in 2005, 45 to 50 million people over age 65 had at least one GI complaint that impacted their daily life and that might result in a medical visit. Common comorbidities such as pain with nonsteroidal anti-inflammatory drug use or atrial fibrillation requiring use of anticoagulants increase the risk of gastrointestinal ulceration or bleeding. Older patients have increased prevalence of diseases such as diverticulitis and colon cancer. Geriatric-aged patients may present with unusual or subtle symptoms of serious GI disease due to alterations in physiology with aging. For example, a patient with a GI perforation or colitis may not have guarding or significant abdominal tenderness due to decreased visceral sensitivity.

The aging process has clinically significant effects on oropharyngeal and upper esophageal motility, colonic function, GI immunity, and GI drug metabolism (**Figure 90-1**). On the other hand, because the GI tract exhibits considerable reserve capacity, many aspects of GI function, such as intestinal secretion, are preserved with aging. Superimposed effects of chronic diseases and environmental/lifestyle exposures (medications, alcohol, tobacco) on aging-related changes can impair GI function in older patients. A modest decline in gastric mucosal cytoprotection or esophageal acid clearance may become significant when superimposed side effects of certain medications or concurrent disease are also present. Common age-related changes in GI function, such as constipation, are viewed as dysfunctional by patients and health care providers. Research areas that have been identified as important in aging include the pathophysiology of swallowing disorders, esophageal reflux, dysmotility syndromes, GI immunobiology,

and the cellular mechanisms of neoplasia in the GI tract. Animal studies provide important insights into the cellular physiology of aging, despite the issue of species variation.

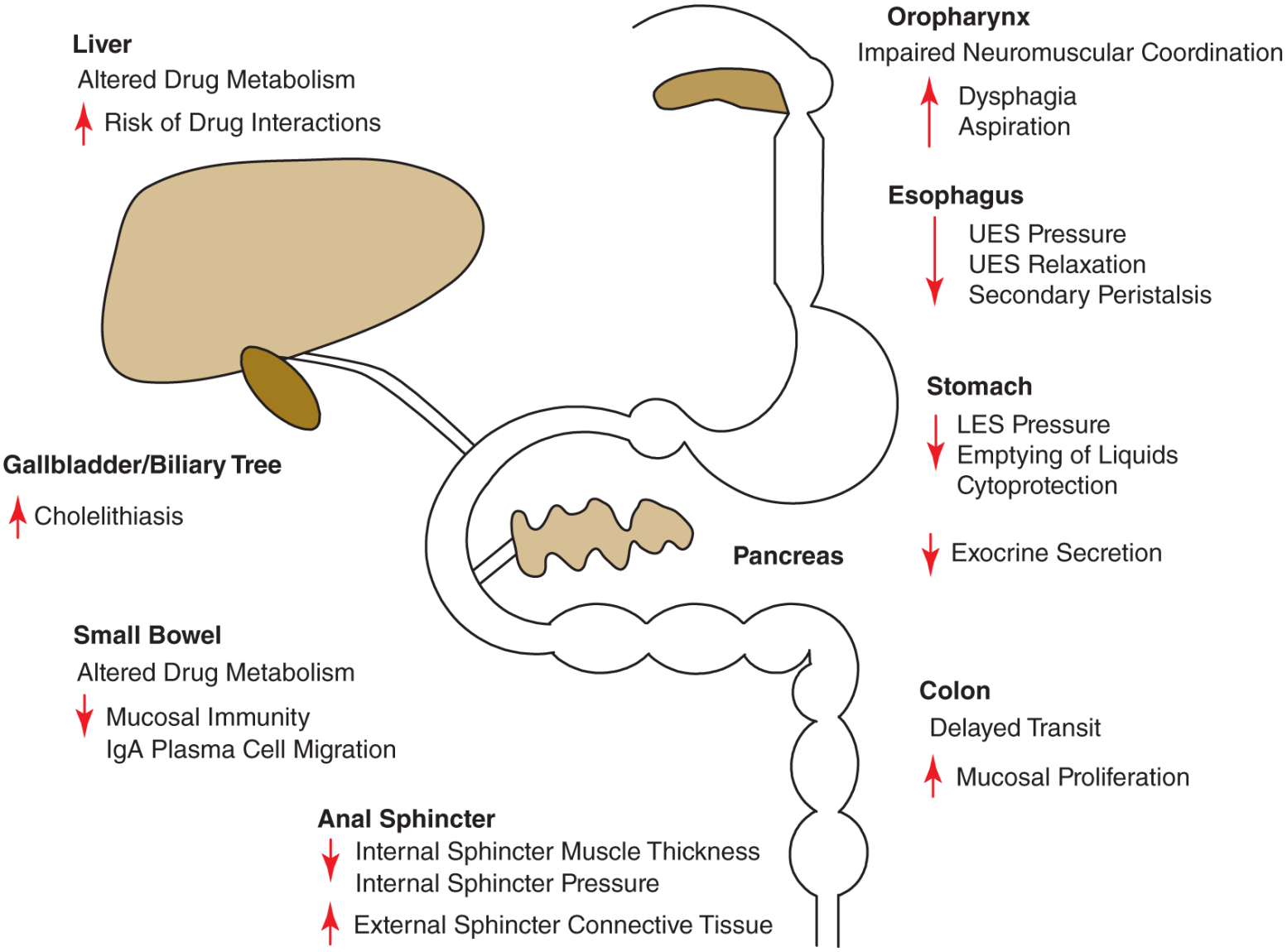


FIGURE 90-1. Effects of physiologic aging on the gastrointestinal tract. This schematic diagram summarizes significant effects of aging on various divisions of the gastrointestinal tract. *Key*: *up arrow*, increased; *down arrow*, decreased.

OROPHARYNGEAL FUNCTION

Dysphagia, or difficulty swallowing, is a common complaint in older individuals. Dysphagia is usually classified as oropharyngeal (transfer) or esophageal (transit). **Figure 90-2** illustrates how various risk factors may interact with aging effects to lead to clinical swallowing problems, and is a model that may apply to how aging contributes to other GI tract disorders as well.

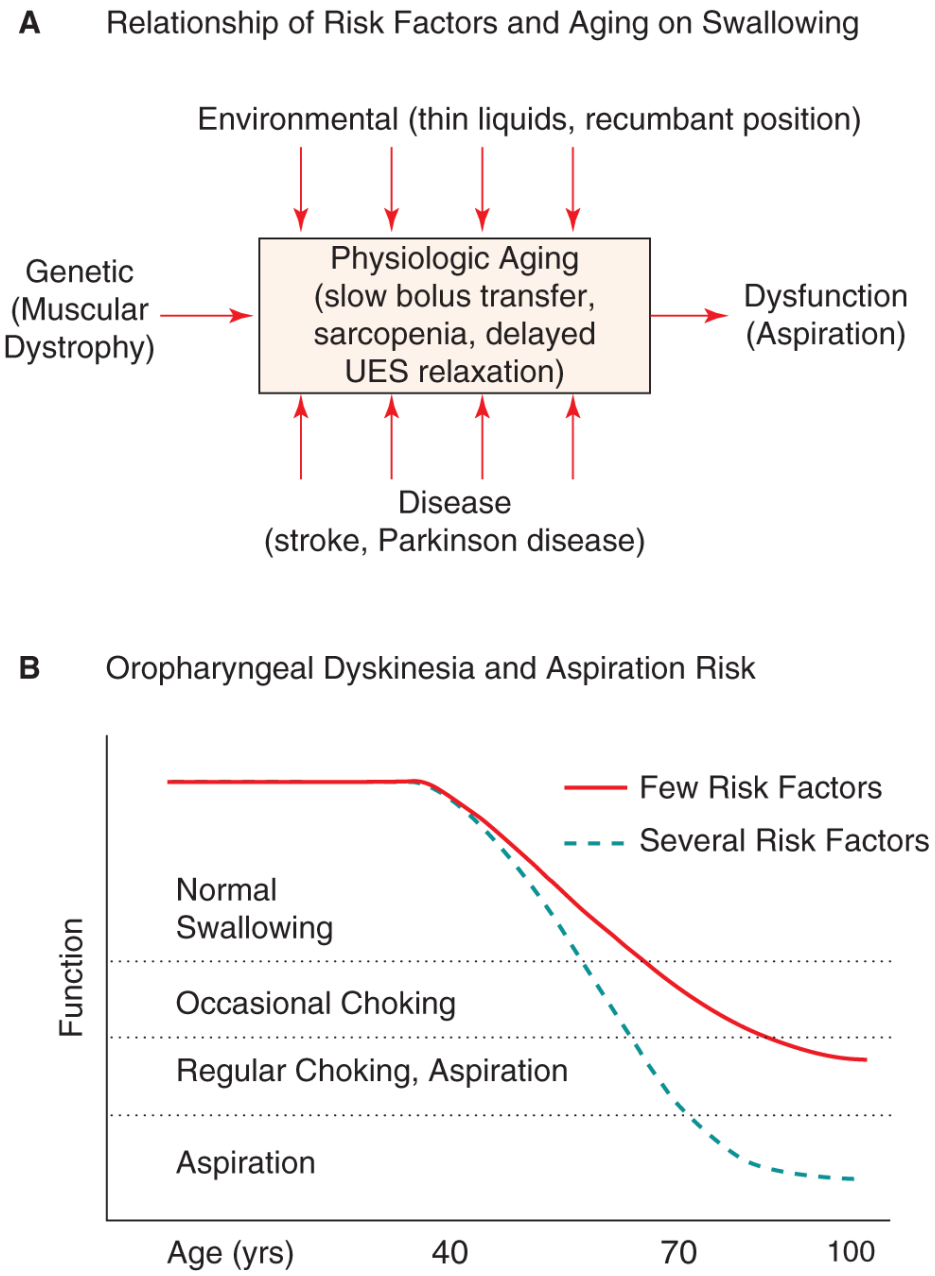


FIGURE 90-2. **A.** Physiologic aging may be thought of as a baseline state upon which can be superimposed the effects of risk factors such as genetic predisposition, environmental exposure, and superimposed disease. The net result is symptomatic dysfunction in senescence that results in impairment. An example of this kind of synergy is dysphagia, which can manifest as a result of a combination of superimposed risks such as neurodegenerative disease and drug-induced damage on age-related oropharyngeal dyskinesia. UES, upper esophageal sphincter. **B.** Graph illustrating how risk factors may affect swallowing function at various ages. Horizontal lines indicate three theoretical thresholds for clinically significant dysphagia (mild, moderate, severe symptom). Physiological aging of the gastrointestinal tract in individuals with few risk factors for dysphagia (solid red line) results in minimal alterations in swallowing in middle age through the sixth decade. Superimposed risk factors such as neuromuscular disease (dashed line) can lead to earlier onset of dysphagia, and increased risk of moderate or severe dysphagia.

Oropharyngeal dysphagia refers to impaired movement of liquids or solids from the oral cavity to the upper esophagus. Changes with aging affecting the ability to chew and swallow food include painful or diseased teeth, xerostomia (dry mouth), poorly fitting dentures, and loss of mandibular bone density. Xerostomia affects roughly 25% of older patients, while as many as 50% have subjective complaints of dry mouth. Medication side effects are a common cause of xerostomia, while a minority is caused by specific diseases affecting the salivary glands, such as Sjögren syndrome. A mild loss of saliva production appears to occur with normal aging.

After food is broken up in the mouth by mastication, the act of swallowing moves the food bolus from the oral cavity into the pharynx and esophagus (also see Chapter 36). The oral and pharyngeal stages of swallowing are regulated by cortical input to medullary swallowing centers, which innervate skeletal muscle groups in the pharynx. The proximal esophagus contains skeletal muscle controlled by nerves from the medullary swallowing centers, whereas

the mid and distal esophagus consists of smooth muscle regulated by intrinsic enteric innervation and extrinsic innervation by the vagus nerve.

Normal aging, however, is associated with alterations that predispose older individuals to dysphagia. Oropharyngeal muscle function slows with aging and there is delayed relaxation of the upper esophageal sphincter, both resulting in slower transfer of food into the pharynx. The resultant inability to move food into the esophagus can cause penetration of food into the area above the vocal cords, and possibly aspiration into the trachea. Approximately 10% of healthy adults over age 85 have silent aspiration documented on barium cinefluoroscopy. Video fluoroscopy demonstrates abnormal transfer of a food bolus from the oral cavity to the pharynx in up to 60% of older adult patients without dysphagia. Other anatomic changes in esophageal neuromuscular anatomy occur in the aged oropharynx, such as cricopharyngeal bars caused by osteoarthritic spine disease. The pathophysiologic significance of these are not clear; however, as they are seen in older patients with normal deglutition. Upper esophageal sphincter pressure gradually decreases with age and is associated with a delay in relaxation after deglutition.

Aspiration risk is increased in older subjects by delayed elevation of the larynx and decreased ability to clear food from the pharynx compared to younger subjects. However, clinically significant aspiration usually does not occur unless there are superimposed risk factors such as neurodegenerative diseases affecting the tongue, soft palate, oropharynx, and upper esophageal sphincter, or medication side effects on oropharyngeal function. Neurodegenerative diseases that affect swallowing include cerebrovascular disease, Parkinson disease, multiple sclerosis, Alzheimer disease, upper motor neuron diseases, and muscular disorders such as myasthenia gravis, polymyositis, and amyloidosis. Dementia is associated with impaired oropharyngeal coordination. Finally, patients with a history of surgery or radiation to the oral cavity or neck are at risk for transfer dysphagia. This can occur many years later due to structuring or fibrosis in the irradiated muscles. In this group, recurrence of cancer should be checked for as well.

ESOPHAGEAL FUNCTION

Complaints of dysphagia, regurgitation, chest pain, and heartburn are fairly common in the geriatric population, with a prevalence of 35% reported in the general population aged 50 to 79 years (see Chapter 93). However, it is difficult to demonstrate a consistent relationship between symptoms and underlying pathophysiology, as demonstrable esophageal abnormalities are found in only 20% to 30% of symptomatic patients. The term “presbyesophagus” describes age-related changes in esophageal function observed in barium x-ray studies and manometric measurements of esophageal contractions. This includes decreased number of myenteric neurons in the esophagus and contractile amplitude, polyphasic waves in the esophageal body, incomplete relaxation of the lower esophageal sphincter, and esophageal dilation. The most common alteration in motility observed in older subjects is an increase in rapidity of propagation of the peristaltic wave, together with increased simultaneous contractions.

These changes likely contribute to symptoms of transit dysphagia, as they increase acid reflux and impair clearing of acid in the esophagus with subsequent mucosal damage. In a primary care setting, the most common diagnoses of patients presenting with dysphagia were esophageal reflux (44%), benign strictures (36%), esophageal motility disorder (11%), neoplasm (6%), infectious esophagitis (2%), and achalasia (1%). Common causes of odynophagia (painful swallowing) in older patients are listed in **Table 90-1**.

TABLE 90-1 CAUSES OF ODYNOPHAGIA

1. Medications
Tetracycline
Quinidine
Doxycycline
Alendronate
Iron
NSAIDs
ASA
Vitamin C
Potassium chloride

2. Infections
Viral (HSV, CMV, HIV, VZV)
Bacterial (*Mycobacteria*)
Fungal (*Candida, Asperigillus*)
3. Acid reflux disease
4. Miscellaneous
Ischemia
Chemotherapy
Radiation
Crohn disease
Sarcoid

ASA, acetylsalicylic acid; CMV, cytomegalovirus; HSV, herpes simplex virus; NSAIDs, nonsteroidal anti-inflammatory drugs; VZV, varicella zoster virus.

A particular concern in an older adult patient is that symptoms of dysphagia are more likely to have a serious underlying etiology, such as malignancy. Older patients also appear to be more susceptible to complications of inadequately treated chronic esophageal disease, such as aspiration, malnutrition, and Barrett metaplasia.

Achalasia, although uncommon, is the most well recognized motility disorder of the aging esophagus. Its prevalence increases with age; 7 to 12 in 100,000 older adult patients are affected, and most geriatricians or generalists who treat patients aged 70+ will encounter this disorder. Patients often present with weeks or months of difficulty swallowing and substantial weight loss. Treatment options include pneumatic dilatation, botulinum toxin injection of the lower esophageal sphincter, and surgery. Medical therapy (eg, nitrates, calcium channel blockers) is rarely effective in achalasia, although these can be helpful in treatment of other motility disorders that cause dysphagia.

GASTRIC FUNCTION

Dyspepsia is defined as chronic or recurrent pain or discomfort in the upper abdomen, which is thought to arise in the upper GI tract. It is exceedingly common in clinical practice, affecting an estimated 20% to 30% of older adults. It can sometimes be difficult to distinguish abdominal pain due to gastric or esophageal irritation from a colonic source, but the latter is usually “spasmodic” in that it waxes and wanes within minutes, whereas dyspepsia lasts for a longer time (hours). There is overlap with the symptoms of cholecystitis, and patients often end up being evaluated for gallbladder disease as well.

Aging-associated changes in gastric function are summarized in **Table 90-2**. They include decreased clearance of liquids from the stomach, which can be markedly exacerbated by anticholinergic medications. Aging is also associated with decreased perception of gastric distension as measured by subjective fullness during inflation of a gastric barostat balloon. Delayed emptying may prolong the gastric contact time of noxious agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs). This may have serious consequences, as significant age-related changes do occur in gastric mucosal defense mechanisms (**Table 90-2**). These may predispose aged people to gastric mucosal injury and the subsequent complication of ulceration. Increased risk of gastric injury does not appear to be to the result of excessive secretion of agents that promote mucosal injury, as most healthy older individuals have decreased, not increased, acid and pepsin output. A small minority has severe acid hyposecretion (achlorhydria) associated with atrophic gastritis. Animal studies have shown a small age-related reduction in gastric acid secretion. Gastrin levels tend to rise with age in humans, possibly as a compensatory response to decreased acid production as a result of increased gastric autoantibodies and *Helicobacter pylori* colonization. The increased prevalence of *H pylori* carriage in the older adult population does not appear to result in increased rates of duodenal ulceration, but is associated with increased risk of gastric ulceration, pernicious anemia, and gastric lymphoma. Increased susceptibility to gastric mucosal injury from NSAIDs in older people appears to be caused by a reduction in gastric mucosal cytoprotective factors such as mucosal prostaglandins. Human and animal aging is associated with decreased gastric bicarbonate, sodium ion and nonparietal fluid secretion, and thinning of the mucus gel layer, particularly in *H pylori*–positive individuals. Aging in rats is associated with a decrease in the basal and injury-induced rate of proliferation of stem cells in the neck of gastric glands. In vivo expression and activity of several intestinal growth factors, such as transforming growth factor alpha (TGF-α) and epithelial growth factor (EGF), are decreased in animal models of

aging. However, activation of EGF receptors by membrane-bound TGF-α in vitro is actually increased in gastric and colonic mucosa of aged rats, suggesting that the relative lack of activity may not be caused by intrinsic inactivation.

TABLE 90-2 AGING-RELATED CHANGES IN GASTRIC FUNCTION PREDISPOSING TO DAMAGE AND BLEEDING

DECREASED	INCREASED
Clearance of liquids from stomach	Contact time with NSAIDs/other noxious agents
Perception of gastric distension	Prevalence of *H pylori*
Cytoprotective factors (prostacyclins)	Pernicious anemia
Mucosal blood flow	Gastric adenocarcinoma
Sensory neuron function	Lymphoma
Pepsin, sodium, fluid secretion	
Acid secretion	

Mucosal blood flow plays an essential role in maintaining gastric mucosal integrity. In rats, aging is associated with a decrease in basal gastric blood flow associated with impaired healing of acid-induced mucosal lesions. Impaired healing of gastric ulcers has also been associated with underlying impairment in sensory neuron function in several aging models.

Gastric secretion of intrinsic factor is necessary for vitamin B_{12} absorption in the small bowel. Decreased secretion of intrinsic factor in aging is invariably caused by atrophic gastritis, not aging per se.

Gastric Cancer

The highest incidence of gastric cancer is in China, Japan, Korea, and Eastern Europe, most of which occurs in patients older than 60. The incidence of gastric cancer is increasing in older people worldwide, while it is decreasing in younger cohorts. The overall 5-year survival rate is estimated at 16%. Nearly 95% of gastric cancers are adenocarcinomas, followed by lymphoma at 4%. Gastrointestinal stromal tumors, carcinoids, and sarcomas make up the remaining 1%. Risk factors for gastric cancer include chronic atrophic gastritis, *H pylori*, pernicious anemia, family history of gastric cancer, partial gastrectomy, tobacco use, alcohol use, and possibly consumption of large quantities of salted or smoked foods containing nitrites and nitrates.

SMALL INTESTINAL FUNCTION

Much of the data concerning the effect of aging on small bowel function is from animal studies, but small bowel function appears to be relatively preserved in normal human aging. The small intestine has a large functional reserve capacity, because of the substantial mucosal surface area available for secretion and absorption. Intestinal surface area does not change after 6 weeks of age in rats. It is unclear whether the specific activity of intestinal disaccharidases and aminopeptidases is affected by aging, as both higher and lower activity has been reported in aged animals compared to youthful controls. Delayed maturation and expression of brush-border enzymes in small intestinal villous epithelial cells during crypt-to-villous migration appears to be the underlying cause. However, absorption of lactose, mannitol, and lipid in individuals greater than 60 years of age is unaffected, suggesting that any effects of changes in mucosal surface area or enzyme activity with aging on macronutrient absorption are minor. There is little evidence that older individuals are at risk for impaired absorption of most macronutrients in the absence of superimposed disease or surgical resection of small bowel. Limited data suggest that absorption of raw and heat-treated soybeans is impaired in old rats compared to youthful animals, while casein, skimmed milk powder, and autoclaved soybean powder were absorbed equally well. This may have implications for older individuals who follow a macrobiotic diet. Studies of protein turnover indicate that rapidly absorbed proteins such as whey protein resulted in greater net protein gain in older subjects compared to younger individuals, although the effect disappeared if fat and carbohydrate were added to the test meal. It is not clear whether this indicates a true impairment in protein absorption, or effects of fat and carbohydrate on small bowel motility.

Micronutrient absorption does appear to be affected by aging. Vitamin D absorption is significantly impaired in aged rats. This is also a concern in older humans, who have decreased uptake of vitamin D, folic acid, vitamin B_{12},

calcium, copper, zinc, fatty acids, and cholesterol. Current recommendations by the US Department of Agriculture to increase calcium, vitamin B_{12}, and vitamin D supplementation in persons older than 70 years of age reflect these findings. Iron is one nutrient that is usually present in overabundance in the diet for older individuals, often negating any impairment in absorption. Older patients may be at risk of diseases such as hepatic iron overload (particularly in individuals who are monozygotic for hemochromatosis), and iron overload has been implicated in some models of oxidative stress. Older men and postmenopausal women do not require additional iron unless there is evidence of low serum iron levels, superimposed blood loss, or bone marrow impairment.

Aging may alter visceral chemosensitivity or hormone responsiveness, as an enhanced satiating effect of carbohydrates delivered into the small intestine by infusion has been reported in older men. Mucosal regeneration is actually increased in aging. Crypt cell proliferation rates in all segments of the small intestine were found to be greater in aged versus younger rats. Minor effects of aging on small bowel motility have been described despite reports that several neuronal subtypes (substance P-, VIP-, somatostatin-, and nitric oxide–containing neurons) are decreased in aged animal models. Studies in cats do not demonstrate effects of age on small bowel transit of radiolabeled lipids. In human studies, small bowel transit time measured by breath hydrogen was shorter in older men, but not women. Caloric restriction to 70% of normal intake prevents ileal myenteric neuronal loss in rats up to 30 months of age, similar to beneficial effects of calorie restriction on other changes in aging.

COLONIC FUNCTION

Unlike the small bowel, aging is associated with diverse effects on the large intestine including alterations in mucosal cell growth, differentiation, metabolism, and immunity. Disorders commonly observed in older patients include colon cancer, diverticulosis, and altered bowel habits, leading to constipation or diarrhea (see Chapters 94 and 95). While constipation is a common complaint in older people, age-associated alterations in colonic transit have been difficult to demonstrate and are variable across studies. Inclusion of chronic laxative users in investigations of colonic function in aging should be interpreted cautiously, as chronic use of phenolphthalein results in loss of interneurons. Other cathartic laxatives, such as senna, do not cause significant anatomic damage in animal studies when used for up to 5 months.

Age-associated reduction in the nitric oxide–containing neurons in the myenteric plexus involved in receptive relaxation has been reported. The remaining myenteric neurons may be functionally impaired. Release of the excitatory neurotransmitter acetylcholine was diminished in the colon of aged rats, an effect that may be caused by decreased calcium influx. Neurotransmitter release from myenteric neurons in the aged colon could be restored to youthful levels by use of calcium ionophores that bypass membrane calcium channels. Similar impairment of calcium signaling with aging has also been demonstrated in peripheral sensory neurons and muscle. These findings may explain why constipation becomes increasingly prevalent with age.

Diarrhea, while less common than constipation, causes significant morbidity in older adults. The etiology of acute diarrhea (lasting < 2 weeks) is similar in older versus younger adults, with a few exceptions. Most cases of acute diarrhea are related to viral or bacterial infection, but it can also be caused by medications, medication interactions, or dietary supplements. *Clostridium difficile* colitis is more prevalent in older adults because of more frequent hospitalizations, increased antibiotic use, and increased time in institutional settings. *C difficile* colonization in long-term care facilities has been estimated to be at least 50% in the United States.

Chronic diarrhea, lasting > 2 weeks, may result from fecal impaction, medications, irritable bowel syndrome, microscopic or lymphocytic colitis, inflammatory bowel disease, obstruction from colon cancer, malabsorption, small bowel bacterial overgrowth, thyrotoxicosis, or lymphoma. Many of these conditions are not due to changes with aging per se, but due to superimposed disease. Older patients may present with new-onset fecal urgency and frequency that is similar to diarrhea-predominant irritable bowel syndrome. The onset may coincide with an acute diarrheal illness caused by viral or bacterial infection. However, many patients continue to have distressing fecal urgency for weeks or months, resulting in considerable lifestyle impairment. Many curtail their travel and social activities outside the home for fear of fecal incontinence. The etiology is often multifactorial. Side effects of medications that increase small bowel and colonic motility should always be considered. Decreased rectal compliance occurs with aging, and may contribute to sensations of fecal urgency in these patients. Screening for fecal impaction resulting in constipation is always warranted in older patients, as it is often overlooked. Diarrhea and fecal urgency should not be attributed simply to aging as it is often due to superimposed disease or other potentially treatable causes.

Colonic Neoplasia

Colon cancer is a common disorder in older patients, primarily because most colon cancers occur sporadically and are associated with polyp formation rates that increase with age. The observation that crypt cell production rate is higher in colonic tissue from aged rats raises the question of whether normal aging predisposes the colon to malignant transformation. The aged colon may be sensitive to the oncogenic effects of growth factors and carcinogens. Methylazoxymethanol, the active metabolite of the colonic carcinogen azoxymethane, induces a greater stimulation of ornithine decarboxylase activity and tyrosine kinase activity in aged versus younger rats. Similar results have been reported with TGF-α and insulin-like growth factor-1 (IGF-1), both potent mitogens for a variety of tissues in the GI tract including the colon. It is not yet clear whether changes in the expression and/or affinity of TGF-α receptors or altered postreceptor events contribute to this process. There is some evidence that use of calcium supplements and NSAIDs may decrease polyp formation rates in older patients. These agents have also been shown to decrease polyp formation in younger patients with polyposis syndromes. The mechanism of action of calcium is not clear. NSAIDs have been proposed to decrease formation of PGE2 and other prostaglandins involved in tumor promotion and growth.

HEPATIC AND BILIARY FUNCTION

There is very little effect of age on conventional liver function tests, such as serum concentrations of aminotransferases, hepatic alkaline phosphatase, and bilirubin. However, dynamic assessments of liver function do show a decrease with aging. In healthy subjects, liver size, blood flow, and perfusion decrease by 30% to 40% between the third and tenth decade. Aminopyrine demethylation, galactose elimination, and caffeine clearance decrease in parallel with the reduction in liver volume and blood flow. Studies in isolated perfused livers from young adult and senescent Sprague-Dawley rats indicated age-associated reductions of approximately 50% in bile acid-dependent and -independent bile flow as well as hepatocellular uptake of taurocholate and rates of bile acid secretion. Tight junction permeability and transcellular transport were decreased modestly in senescent rats. Animal studies suggest that hepatic damage may also be related to accumulation of oxidative metabolites with age, resulting in increased apoptosis of liver parenchymal cells. Based on studies of hepatic impairment, including subtotal resection and diseases such as hepatitis or cirrhosis, it is likely that a decrease of greater than 70% of the total functional hepatic reserve would result in clinically relevant impairment of hepatic function in aging. In general, physiologic aging does not result in this degree of diminution in hepatic function.

However, the senescent liver may be more susceptible to stress insult from diet, alcohol consumption, tobacco use, nutritional status, coexistent diseases, and genetic factors. Liver injury is associated with a regenerative response characterized by increased hepatocyte mitogen-activated protein (MAP) kinase activity. Aged animals have an age-associated decline in MAP kinase activity and epidermal growth factor–stimulated hepatocytes. Specific impairment of intracellular transcription factors that are involved in transducuction of growth hormone receptor activation has been reported in senescent mice. However, the ability of the liver to recover from injury in older age appears to be preserved. Mitogenic stimulation of these pathways in aged mice results in hepatic regeneration following partial hepatectomy that is equivalent to that seen in younger animals. This has potential implications for management of hepatic resection in older patients, such as that used in treatment of solitary hepatoma. A major area of research that is likely to grow in future years is the effect of chronic viral hepatitis (B and C) on liver function as patients age with these diseases. It is well known that long-term chronic viral hepatitis predisposes patients to development of primary hepatic cancer, likely due to genetic mutations acquired during chronic cellular damage and repair. It is not clear whether patients of advanced age will benefit from new antiviral therapies; however, with new screening guidelines many more patients in the geriatric age range will be identified as having chronic viral hepatitis.

The prevalence of cholelithiasis increases with age. Age-related increases in cholesterol secretion in bile, combined with decreased bile acid secretion, leads to increased cholesterol saturation and, therefore, increased bile lithogenicity. Cholelithiasis is twice as common in women as in men and is often asymptomatic and discovered during radiological studies of the abdomen performed for unrelated reasons. Cholelithiasis can cause obstruction or may contribute to cholecystitis. Much of the available human data have been obtained from subjects younger than age 65 years. Therefore, it is unclear whether gallbladder function is altered in old age. Some studies have demonstrated impaired gallbladder function in older subjects. Fasting and postprandial gallbladder volumes are increased in subjects older than 35 years of age, with less complete emptying following a meal observed in older individuals. Increased gallbladder volumes correlate with cholelithiasis; however, no difference in fat-induced gallbladder emptying is observed in either male or female subjects older than 50 years of age, compared to younger individuals. However, aged females may have impaired gallbladder contractility, with decreased contractile response to acetylcholine in

postmenopausal females compared to aged males. Animal studies in aged guinea pigs suggest that deceased density of receptors for hormones such as cholecystokinin (CCK) and galanin may underlie the decreased gallbladder contractility and increased gallstone formation in this model. Impairment in intracellular calcium mobilization and decreased muscle compliance correlate with decreased CCK responsiveness. The functional significance of these animal studies to humans is unclear, as decreased CCK responsiveness in older human subjects may be compensated by increased CCK release, with no net change in gallbladder kinetics in aging. Aging does not appear to significantly increase the risk of cholecystitis; however, the morbidity and mortality are increased in older patients likely due to the prevalence of other comorbidities.

PANCREATIC STRUCTURE AND FUNCTION

The exocrine pancreas possesses adequate reserve to maintain normal digestive capacity with aging. While there are some contradictory reports, there is little evidence for clinically significant decreases in pancreatic exocrine function in older humans. Age-related changes in pancreatic anatomy and histology include decreased pancreatic weight after the seventh decade in humans, with ductal epithelial hyperplasia, interlobular fibrosis, and acinar cell degranulation. A modest decrease in bicarbonate and enzyme output in response to secretin and caerulein in older compared to younger subjects has been reported. However, secretin and caerulin (CCK receptor agonist)–mediated stimulation of sphincter of Oddi motor function, pancreatic bicarbonate, enzyme, and volume output are not changed in individuals older than 60 years of age. In contradistinction to human studies, animal models of pancreatic function do show effects of aging on trophic responses to hormonal stimulation. Caerulin and secretin administration increased pancreatic weight, protein content, mRNA expression, enzyme, and polyamine concentrations in young and aged rats, but the magnitude of the responses were greater in young rats. The pancreas of aged animals demonstrates a diminished capacity to increase pancreatic lipase and amylase content in response to a high fat or high carbohydrate diet. Given the significant reserve capacity of the exocrine pancreas, the clinical significance of these observations to healthy aged individuals is questionable.

Pancreatitis in older patients is usually due to either gallstone obstruction (80%) or other obstructive causes (benign and malignant tumors, intrapancreatic stones, sphincter of Oddi spasm); therefore, obstruction should always be screened for. Aging does appear to be associated with the potential for increased risk of drug-induced pancreatitis due to azathioprine, 6-mercaptopurine, estrogen, mesalamine, furosemide, and angiotensin-converting enzyme inhibitors. The mechanism of drug-induced pancreatitis is thought to be premature activation of trypsin within the acinar cells and subsequent intra- and extrapancreatic inflammation due to tissue digestion. It is not clear whether aging predisposes to increased activation, or increased inflammation and impaired recovery. Aging is associated with increased production of autoimmune antibodies which have been implicated in other inflammatory conditions; therefore an overexuberant inflammatory response could be a factor in risk of drug-induced pancreatitis.

GASTROINTESTINAL IMMUNITY

The GI tract is the largest immunological system in mammals. Older people are susceptible to infections that enter the body via the GI tract. This observation suggests that aging may impair mucosal immunity. The GI mucosal immune response in the small intestine is a complex process that involves a series of events: antigen uptake and presentation of antigen at the mucosal surface by specialized epithelial cells (M cells) overlying Peyer patches in the small intestine; differentiation and migration of immunologically competent lymphocytes to the lamina propria; regulation of local antibody production in the intestinal wall; and mucosal epithelial cell receptor–mediated transport of antibodies to the intestinal lumen. The effect of aging on antigen uptake and presentation in animal studies is unclear. In rats, there was no change in the number of Peyer patches or the yield of lymphocytes per patch in the small bowel. Increased T suppressor/cytotoxic lymphocytes could explain the observed decrease in lamina propria IgA plasma cells because of decreased cytokine-mediated differentiation of B-lymphocytes by helper T cells. Animal studies also confirm that IgA plasma cell recruitment into the lamina propria is decreased in rats and macaque monkeys. Human studies have demonstrated a decrease in T lymphocytes and mast cells in the rectal mucosa in normal individuals aged 55 years or older, which was not reflected in other muscosal cell populations, such as neuroendocrine cells. Thus, differentiation and migration of lymphocytic immunoblasts into the lamina propria appears to be decreased with aging. IL-2 production in lamina propria lymphocytes and intestinal IgA production is decreased in aged subjects. A tissue-

specific, age-associated reduction in transport of polymeric IgA across rat hepatocytes may be the result of decreased synthesis of polymeric immunoglobulin receptors or diminished microtubule-dependent translocation of the receptor–ligand complex.

GASTROINTESTINAL DRUG METABOLISM

An evolving area of interest to clinicians and investigators is the field of age-associated changes in drug metabolism (see Chapter 24). Older patients are at increased risk for drug interactions and adverse drug reactions, primarily because of known side effects of the large number of drugs prescribed in this age group. The cytochrome P450 system plays an essential role in drug metabolism in humans. The CYP3A subfamily expressed in the GI tract and liver is the most abundant form of hepatic cytochrome P450. It oxidizes a wide variety of clinically and toxicologically important agents, including endogenous and exogenous steroids, and activates procarcinogens such as aflatoxins. CYP3A metabolizes numerous drugs including calcium channel antagonists, immunosuppressant agents, cholesterol-lowering agents, benzodiazepenes, nonsedating antihistamines, and macrolide antibiotics. The divergent structures of the drugs metabolized by CYP3A indicate a broad substrate specificity of these enzymes, which contributes to adverse effects reported with the concomitant use of antihistamines, macrolide antibiotics, and prokinetic drugs.

High levels of CYP3A activity present in both the intestinal epithelium and the liver result in significant first-past metabolism of oral medications. For example, CYP3A-mediated metabolism of cyclosporin results in bioavailability of only 18% of the ingested dose. CYP3A activity is reduced by 25% to 50% in aged individuals, explaining some of the risk for adverse drug effects.

SUMMARY

As understanding of how the aging process affects GI function evolves, it is evident that many essential aspects of GI function are preserved with aging. Much of the GI dysfunction in older patients can be attributed to the superimposed effects of chronic diseases and environmental/lifestyle exposures (medications, alcohol, tobacco). A modest decline in function with aging, such as decreased gastric mucosal cytoprotection or decreased esophageal acid clearance, may be significant when superimposed on the side effects of certain medications or concurrent disease. The aging process per se has clinically significant effects on oropharyngeal and upper esophageal motility, colonic function, GI immunity, and GI drug metabolism. Age-related changes in GI function will have increasing importance for health care delivery, as the number of older individuals increases over the next two to three decades.

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Chapter 91

Hepatic Disease

Sean G. Kelly, Courtney Barancin, Michael R. Lucey

Learning Objectives

- Learn aging-associated changes in hepatic function, epidemiology, genetics, pathogenesis, and pathology of common hepatic diseases in older adults.
- Understand the prevalence, common clinical presentations, diagnosis, and treatment of hepatotropic viruses, autoimmune hepatitis, and drug-induced injury in older patients.
- Learn the appropriate indications and limitations of liver transplantation in older adults.

Key Clinical Points

1. **Older adults are more prone to hepatic injury due to aging-associated changes, including a reduction in regenerative capacity, functional hepatocyte volume, and hepatic blood flow.**
2. **Patients with metabolic syndrome are at high risk for developing nonalcoholic fatty liver disease (NAFLD).**
3. **Administration of chemotherapy or immunosuppressive drugs can lead to reactivation of hepatitis B and rarely to acute liver failure.**
4. **Drug induced liver injury occurs more frequently in older patients and tends to be more severe.**
5. **Alcohol-related liver disease and chronic hepatitis C are the two most common causes of end-stage liver disease in older patients.**

INTRODUCTION

The liver is remarkable in its ability to preserve its function despite advanced age. Older patients are at an increased risk of more severe hepatic injury when exposed to hepatic insults. This increased risk is likely related to the liver's age-related decrease in regenerative capacity. We will review the hepatic changes that are known to occur with aging and their pathologic consequences of liver disease in older patients (**Table 91-1**).

TABLE 91-1 EFFECTS OF AGE ON THE LIVER

Liver chemistry tests and coagulation factors: unaffected by age
Serum albumin: slightly decreased but within the normal range
Serum cholesterol and triglycerides: increase with age
Phase I drug metabolism: significantly decreased with age
Phase II metabolism: unaffected by age
Hepatic proliferation after surgical resection: diminished by age
Hepatotoxicity: (hepatitis viruses, drug reactions) more severe in the elderly

As will be discussed multiple times in this chapter, most of the therapies available for younger patients are safe and appropriate for use in the geriatric population. However, older patients with advanced pancreatic, liver, or biliary disease may not be eligible for curative treatments in some circumstances. For example, due to comorbid disease, few patients over 70 years of age meet entry criteria for liver transplantation. Similarly, geriatric patients with newly diagnosed neoplasms of the pancreas or hepatobiliary system may not tolerate the extensive surgery that may be appropriate in a younger patient. Palliative care for patients with advanced pancreatic and hepatobiliary disease has become a well-recognized subspecialty and provides valuable therapies and counseling to alleviate suffering near the end of life.

LIVER MORPHOLOGY

For a number of years, liver volume was thought to decrease with age. More recently, it was determined that liver volume remains unchanged over time when adjusting for body surface area. Tagged albumin scans have shown that while corrected liver volume remains constant with age, functional hepatocyte volume decreases significantly. There is also a contemporaneous decrease in hepatic blood flow by approximately 35% to 40%. The cause of decreased blood flow is likely multifactorial—as a result of changes in cardiovascular output, diminished splanchnic blood flow, reduced portal vein blood flow, and increased resistance to portal flow. On the cellular level, both hepatocytes and the mitochondria of hepatocytes become hypertrophied, but decrease in overall number with age. Hepatocytes accumulate lipofuscin with age while undergoing a decrease in the concentration of smooth endoplasmic reticulum (SER), telomere length, and the activity of several liver microsomal enzymes.

LIVER FUNCTION

Despite the observed changes in functional hepatocyte volume and blood flow, age-related changes to hepatic function are less evident in clinical practice (see **Table 91-1**). The capacity to sustain liver function during aging is reflected in the ability to successfully transplant livers from older deceased donors. Traditional liver chemistry tests, including serum aminotransferases, bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase, do not change with age. Likewise, there are no significant changes in coagulation factors. Serum albumin slightly decreases with age, but typically remains within the normal range. Serum cholesterol and triglycerides increase with age as there is a gradual decline in the metabolism of low-density lipoprotein (LDL) cholesterol.

There are age-related changes in the hepatic metabolism of certain medications, which is important since more than 30% of prescription drugs are prescribed to older men and women. The incidence of adverse drug reactions significantly increases with increasing age. Phase I drug metabolism relies on microsomal enzymes and results in metabolism by oxidation, reduction, demethylation, and hydrolysis. Phase II drug metabolism relies on cytosolic enzymes and results in metabolism by conjugation with several different polar ligands. Phase I reactions are usually catalyzed by the cytochrome P450 system in the hepatocyte SER. There is a significant decrease in the phase I metabolism of several medications by as much as 50% with increasing age. Interestingly, medications that undergo phase II metabolism remain unaffected by aging. The activity of phase I metabolism is dependent on oxygen delivery. Thus, some of the age-related decreases in phase I metabolism could be explained by decreased hepatic blood flow as well as by decreased SER concentration. Medications with known phase I metabolism should be started at a low dose and titrated slowly in order to circumvent the problems associated with adverse drug reactions in older patients (**Table 91-2**).

TABLE 91-2 ■ DRUGS WITH EXTENSIVE PHASE I METABOLISM

Alprazolam, diazepam, midazolam, triazolam
Amitriptyline, imipramine
Atorvastatin, lovastatin, simvastatin
Carbamazepine, phenytoin
Clozapine, olanzapine
Corticosteroids
Cyclosporine, tacrolimus

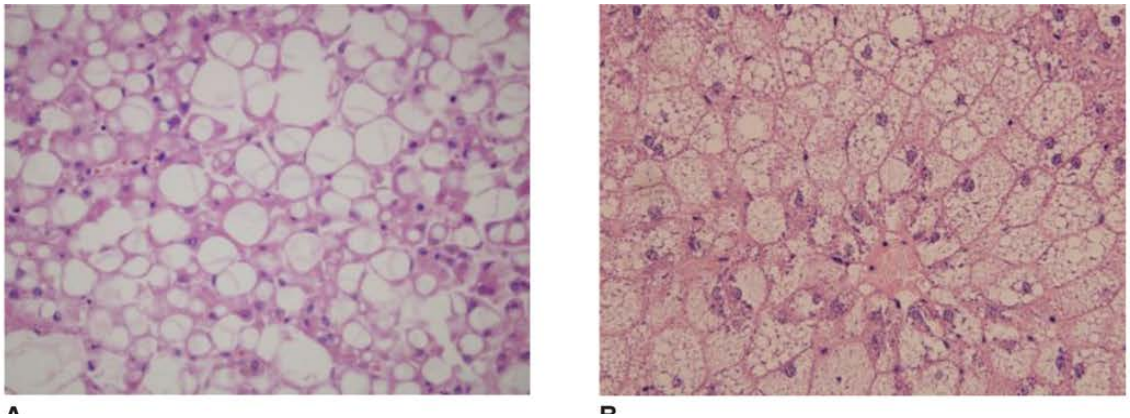
HIV protease inhibitors
Sildenafil, tadalafil, vardenafil
Theophylline
Warfarin

Another important aspect of the effects of aging on hepatic function is the diminished ability of the liver to recover and regenerate in response to injury. There is an age-related proliferative decline in the rate at which partial living donor livers regenerate. Also, there is a higher mortality in older patients after partial hepatic resection. Lastly, the hepatotoxic effects of hepatitis viruses and medications like acetaminophen and amoxicillin-clavulanate are more pronounced in older adults. Drug-induced liver injury will be discussed later. Refer to **Table 91-3** and **Figure 91-1** for information on patterns of drug injury and pathology findings, respectively.

TABLE 91-3 DRUG-INDUCED LIVER INJURY

DRUG	TYPE OF LIVER INJURY	UNIQUE FEATURES
Acetaminophen	Marked hepatocellular necrosis	Dose-dependent injury; fatal doses 15–25 g; thiol therapy within 12 h often prevents significant toxicity
Amoxicillin-clavulanic acid	Cholestasis	Small percentage affected, but common cause of liver injury since medication is used so frequently
Isoniazid	Hepatocellular necrosis	Hepatitis in 21 of 1000, 5%–10% of cases are fatal; increased ALT in 10%–36% in first 10 wk; second only to acetaminophen as indication for LT for DILI
Methotrexate	Macrovesicular steatosis, periportal fibrosis	Patients on methotrexate require regular monitoring of LFTs and avoidance of alcohol
Amiodarone	Phospholipidosis (similar to steatosis)	Widespread effects, liver damage among most serious, abnormal LFTs in 15%–80%; progression may occur despite discontinuation
Tetracyclines	Mixed; necrosis and microvesicular steatosis	Toxicity is rare with newer forms of oral tetracyclnes
Tamoxifen	Mixed; cholestasis, peliosis hepatis, necrosis, steatosis	Steatosis occurs in 30% of women
Phenytoin	Histiocytic granulomas, cholestasis, multifocal necrosis	Pathology also shows lymphocyte beading in sinusoids (similar to mononucleosis)
Nitrofurantoin	Mixed; eosinophils seen in 1/3	8:1 female predominance for chronic hepatitis; mortality rate for chronic hepatitis is 20% vs 5%–10% for acute hepatitis
TMP-sulfa, griseofulvin, terbinafine, ketoconazole	Cholestasis	Hepatic toxicity of antifungal drugs is enhanced by alcohol

ALT, alanine aminotransferase; DILI, drug-induced liver injury; LFT, liver function test; TMP, trimethoprim.



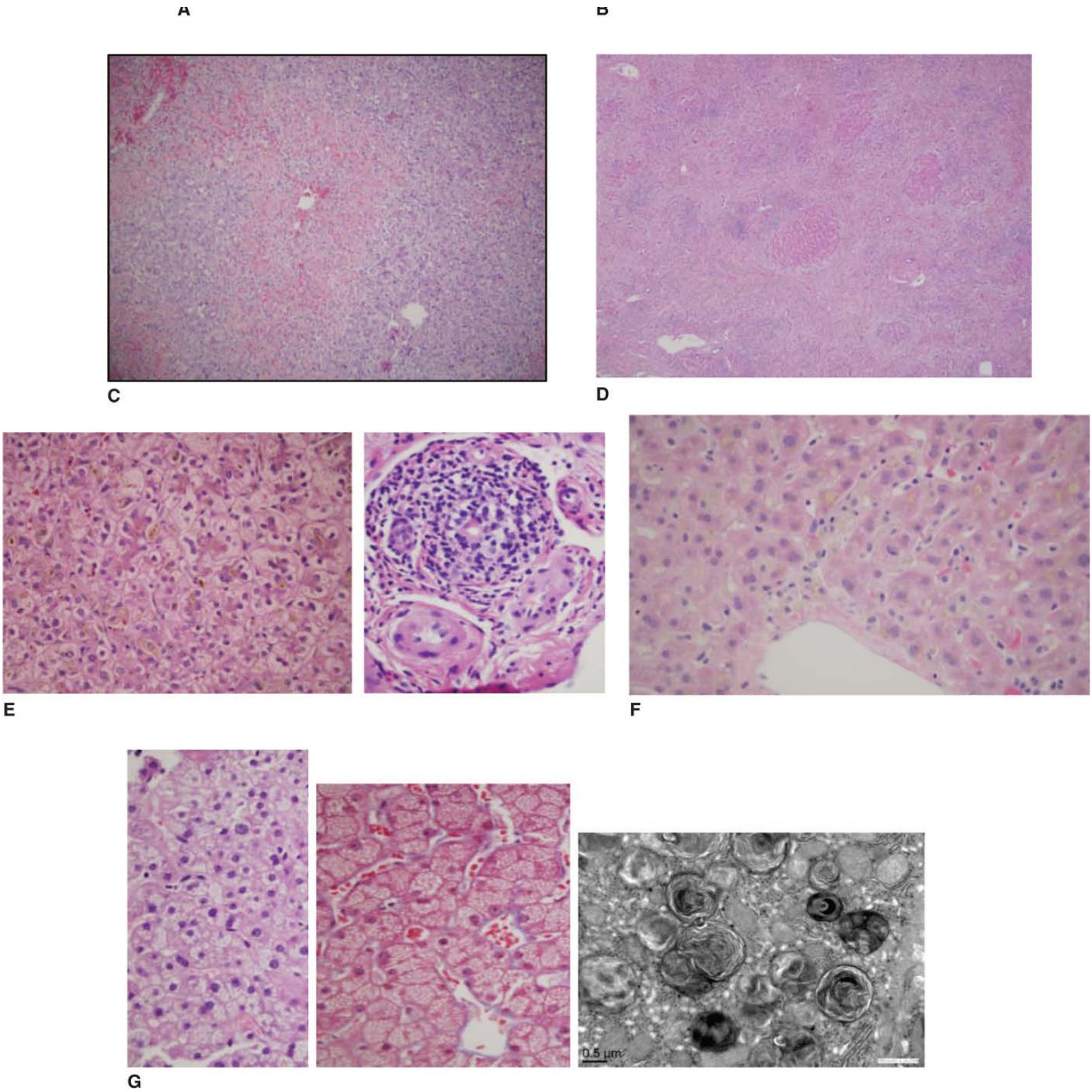


FIGURE 91-1. Examples of drug-induced liver injury. **A.** Macrovesicular steatosis—methotrexate. **B.** Microvesicular steatosis indicating mitochondrial injury: valproate, tamoxifen, tetracyclines. **C.** Hepatocellular necrosis in acetaminophen toxicity in zone 3. **D.** Necrosis due to isoniazid. **E.** Cholestasis, duct damage, and portal inflammation due to amoxicillin-clavulanate "Augmentin." **F.** Bland cholestasis (anabolic steroids, erythromycin, and chlorpromazine). **G.** Phospholipidosis due to amiodarone toxicity; electron micrograph showing lamellar inclusions. (Images courtesy of Rashmi Agni, MD, University of Wisconsin, Madison, WI.)

LIVER DISEASES

Nonalcoholic Fatty Liver Disease

The obesity pandemic affecting Western countries and now spreading to other parts of the world has not spared the geriatric population. Patients with the metabolic syndrome comprised of hypertension, insulin resistance, central obesity, and dyslipidemia are at high risk for developing NAFLD. Fatty liver infiltration may be seen on imaging studies, and liver biopsy demonstrates fatty infiltration with associated inflammation called steatohepatitis. Long-standing steatohepatitis may lead to cirrhosis over a period of years to decades. In many circumstances, histologic findings of NAFLD are indistinguishable from inflammation caused by alcohol. Despite many attempts at medical therapies, the most effective treatment for this condition is weight loss, which may be accomplished through diet, exercise and risk factor modification, or in selected patients by bariatric surgery. Loss of 10% of body mass has been shown to result in significant improvement in liver chemistries and histologic findings on liver biopsy. Weight loss and risk factor modification also decrease the risk of progressing to cirrhosis. In a recent randomized controlled trial, the use of obeticholic acid resulted in a significant improvement in the NAFLD activity score at 72 weeks. The medication acts on the farnesoid X receptor to regulate bile acid production. Pharmaceutical trials and FDA approval are needed prior to use. It may have beneficial effects in patients with primary biliary cirrhosis (PBC) as well, which will be discussed later.

Hepatotropic Viruses

Acute hepatitis related to hepatitis A, B, C, D, and E is clinically indistinguishable. Most adults present with fatigue, malaise, nausea, vomiting, and anorexia. Right upper quadrant discomfort, jaundice, and fever may be present as well. Relative to younger patients, acute viral hepatitis in older adults has a longer duration, higher rate of complications, and higher mortality rate, owing to an increased incidence of acute liver failure. **Table 91-4** summarizes the hepatotropic viruses.

TABLE 91-4 HEPATOTROPIC VIRAL DISEASE

	GENOME	ROUTE OF TRANSMISSION	OUTCOME	SEROLOGIES	SEROLOGY INTERPRETATION	PREVENTION; TREATMENT
HAV	RNA	Fecal-oral	Acute only	HAV IgG and IgM	(+) IgM = acute infection (+) IgG = prior exposure or vaccination and immunity	HAV vaccine; supportive
HBV	DNA	Parenteral	Acute and chronic	HBV core Ab, surface Ag, surface Ab, quantitative DNA	(+) core Ab only = prior exposure (+) surface Ab only = immunity (+) core Ab and surface = prior exposure and immunity (+) surface Ag = infection	HBV vaccine; entecavir, adefovir, tenofovir, telbivudine
HCV	RNA	Parenteral	Acute and chronic	HCV Ab, quantitative RNA	(+) Ab = infection; check RNA with negative Ab and high suspicion for HCV	No vaccine; sofosbuvir and other new agents
HDV	RNA	Parenteral	Acute and chronic	HDV Ag, IgM Ab, IgG Ab, quant. RNA	(+) Ag = infection	HBV vaccine; PEG-IFN-α +/- HBV meds
HEV	RNA	Fecal-oral	Acute and chronic	HEV IgM Ab, IgG Ab, quant. RNA	HEV RNA most reliable marker of infection	Supportive; PEG-IFN-α and ribavirin with chronic HEV

Hepatitis A virus Hepatitis A virus (HAV) is an RNA virus spread via fecal-oral transmission. Acute HAV infection is diagnosed by the demonstration of HAV IgM antibodies within the serum in symptomatic patients. As the acute illness resolves, anti-HAV IgG antibodies develop conferring life-long immunity. With the development of improved sanitation, the proportion of adults lacking immunity to HAV has increased. However, the incidence of HAV infection in the United States has drastically decreased over the past 20 years due to the widespread acceptance of vaccination. Current transmission of HAV among patients in the United States occurs with consumption of contaminated food and travel to endemic areas. There is a safe and effective vaccine for HAV. Providers should screen and vaccinate older patients traveling to endemic areas. No outbreaks of hepatitis A have been reported at nursing facilities to date. While

HAV vaccination is not required for most geriatric patients, it is safe and simple, and providers should have a low threshold for vaccinating susceptible patients of any age.

Hepatitis B virus Hepatitis B virus (HBV) is a DNA virus and blood-borne pathogen. Nearly 350 million people are infected with chronic hepatitis B worldwide. Less than 5% of acute HBV infections arising de novo in adults living in the United States will lead to chronic infections. Acute HBV infection is relatively rare in older adults, as the primary risk factors associated with transmission are intravenous drug use and high-risk sexual behavior. There is an increased risk of becoming a chronic HBV carrier with increasing age at acquisition, which is possibly related to an age-related decline in cellular immunity. Chronic HBV infection is a risk factor for hepatocellular carcinoma, and this risk increases with age. With regards to therapy, antiviral agents such as entecavir, adefovir, and telbivudine are safe to use irrespective of age. Lastly, there is a significant age-related decreased antibody response rate after immunization with the HBV vaccine. The HBV vaccine is delivered in a series of three injections. Older patients might require a fourth injection in order to improve immunogenic HBV vaccine response. Hepatitis B infectious status must be known prior to initiation of chemotherapy and immune modulation therapy such as antitumor necrosis factor inhibitors for rheumatoid arthritis and inflammatory bowel disease. Use of chemotherapy or immune modulation therapy can lead to reactivation of hepatitis B in chronic carriers and, in rare cases, can lead to acute liver failure.

Hepatitis C virus Hepatitis C virus (HCV) is an RNA virus and blood-borne pathogen. Approximately 170 million people are infected with chronic hepatitis C worldwide. HCV is the most common cause of viral-induced acute hepatitis in older patients. Intravenous drug use is the major risk factor associated with disease transmission. Patients without a history of intravenous drug use may have acquired the infection with exposure to unscreened blood products prior to 1992. Acute HCV infection in a person not abusing illicit drugs should prompt a search for a source such as an infected medical professional involved in phlebotomy, surgery, or dental care. Chronic HCV infection develops in 50% to 80% of infected individuals with the subsequent development of cirrhosis in a significant proportion of these patients. The prevalence of chronic HCV infection is increasing in the older population. Chronic HCV-related cirrhosis is associated with the development of hepatocellular carcinoma, and this risk is increased significantly with age. Also, the severity of liver disease among patients with chronic HCV infection is worse with increasing age. Similarly, the progression to cirrhosis is faster in older patients, and the serum HCV viral load is significantly higher when compared to younger adults. The geriatric population should be screened for HCV, especially patients who used intravenous or intranasal drugs or received blood products prior to 1992. New antiviral therapies have dramatically changed HCV management and geriatric patients will be eligible for treatment. Cost of therapy relative to comorbidities and overall life expectancy is an important consideration at this time.

Hepatitis D Hepatitis delta virus (HDV) is a RNA virus that requires the hepatitis B virus for transmission and life cycle. Approximately 5% of chronic HBV patients worldwide are coinfected with hepatitis D, which leads to an accelerated disease course. Patients with chronic hepatitis B should be tested for hepatitis D as well.

Hepatitis E Hepatitis E virus (HEV) is a RNA virus and very common infection worldwide, but is mainly a zoonosis in the United States. It is usually a mild transient infection, but may cause acute liver failure in pregnant or immunosuppressed patients. In endemic regions, which include several parts of Africa and Asia, HEV is the most common cause of acute hepatitis. Outbreaks relate to contamination of drinking water supplies with human feces containing HEV. Small, food-borne outbreaks have occurred, but person-to-person transmission is negligible. In the United States, there is zoonotic transmission through pigs or other animal reservoirs.

Drug-induced liver injury Older patients consume the largest portion of both prescription and over-the-counter medications. Both age and polypharmacy are risk factors for drug-induced hepatotoxicity. Older patients often have altered pharmacokinetics and pharmacodynamics caused by changes in renal, hepatic, cardiovascular, and pulmonary function and decreased body mass. Drug-induced liver toxicity occurs more frequently in older patients and tends to be more severe. Clinically, drug-induced hepatotoxicity presents with nonspecific symptoms or subclinically, reflected only in serum laboratory abnormalities. Some medications have a well-recognized increased risk of liver toxicity with age. For example, isoniazid frequently causes some evidence of liver toxicity in patients older than 50 years, yet, rarely causes liver damage in patients younger than 20 years. Health care providers taking care of older patients should be aware of this increased risk of drug-induced hepatotoxicity and should be vigilant in assessing for hepatic inflammation. Medications that are heavily metabolized by the liver, some of which are listed in **Table 91-2**, should be initiated at a dose 30% to 40% lower than average doses used in middle-aged adults. LiverTox is a very helpful website sponsored by the National Institutes of Health for drug-specific information (http://livertox.nih.gov/). Refer to

Table 91-4 and **Figure 91-1** for information on patterns of drug injury and pathology findings, respectively.

Primary biliary cirrhosis Primary biliary cirrhosis (PBC) is a disease characterized by an immune-mediated destruction of the intralobular biliary system. It is predominantly regarded as a disease affecting middle aged women; however, greater than one-third of patients with PBC are older than 65 years. Many patients remain asymptomatic and are diagnosed on the basis of an elevated alkaline phosphatase level, though pruritus may present as an early symptom. Patients with PBC have a higher incidence of other autoimmune conditions such as thyroiditis or Sjögren syndrome. They are also at increased risk for developing osteoporosis. The antimitochondrial M2 antibody is a highly sensitive and specific serologic test for PBC. Older patients diagnosed with PBC likely have long-standing and slowly progressive disease. Compared to younger adults, the liver-related mortality is greater in patients diagnosed with PBC who are older than 65 years. Symptomatic older patients with PBC are associated with a poor prognosis. Treatment should be focused on symptom management of pruritus and malabsorption. Ursodeoxycholic acid slows the progression of the disease and obeticholic acid is emerging as a potential additive treatment. Pruritis is the main side effect of obeticholic acid. Liver transplantation remains the ultimate therapy and should be considered in well-selected geriatric patients.

Autoimmune hepatitis Autoimmune hepatitis is a condition of unknown etiology leading to chronic hepatic inflammation and destruction, with resultant cirrhosis in untreated patients. It has a bimodal onset, with a second peak of presentation in persons in their sixth decade or older. Older patients may present with clinically less aggressive disease. Initial serologic workup should include IgG antibody level, antinuclear antibody and antismooth muscle antibody. Liver biopsy is essential for making the diagnosis. Autoimmune hepatitis generally responds well to immunosuppressive therapy. For years, prednisone and azathioprine have been the cornerstones of treatment. More recently, budesonide has replaced prednisone in many cases for both initiation and maintenance therapy. Budesonide effectively reduces hepatic inflammation without causing systemic side effects that are seen with prednisone. Despite this, budesonide is often avoided or used in reduced doses for patients with cirrhosis since it is metabolized by the liver and there is a concern for significant side effects. Older patients receiving chronic therapy with corticosteroids need to be monitored closely for serious side effects such as osteoporosis, glucose intolerance, and cataract formation. Prognosis is likely similar between older patients and younger adults.

HEPATOCELLULAR CARCINOMA

In western Europe and North America, hepatocellular carcinoma (HCC) usually occurs in older patients. HCC may occur at a much younger age in patients with hepatitis B infection acquired at time of delivery or during childhood. Major risk factors for the development of HCC include chronic hepatic inflammation and cirrhosis. Presentation and diagnosis of HCC in older patients are associated with a significantly worse prognosis when compared to younger adults. This is likely related to the advanced stage of liver disease and tumor within this patient population. Treatment of carefully selected geriatric patients by surgical resection, liver transplantation, or by anticancer therapies such as radiofrequency ablation, chemoembolization (TACE), radioembolization (yttrium-90) or chemotherapy (sorafenib) appear to have a similar morbidity and mortality as compared to younger patients. Thus, age should not be a contraindication for therapy for HCC in the appropriate older patient.

Patients with cirrhosis have a 3% to 8% of developing HCC each year and one-third will develop HCC at some point. Screening may be performed with abdominal ultrasounds every 6 months or with biphasic CT or abdominal MRI yearly. AFP levels may be monitored as well, though the relatively low sensitivity and specificity of AFP levels prohibit their use as a singular screening method. As discussed above, hepatitis B confers a risk of developing HCC prior to the onset of cirrhosis and more specific screening guidelines are established for that population. Given the complexity of HCC management, patients with HCC should be referred to a tertiary care center so their treatment regimen can be determined by a multidisciplinary tumor board.

TRANSPLANTATION

Liver transplantation is the ultimate therapy for patients with end-stage liver disease. The number of transplants completed in the United States continues to increase. Alcohol-related liver disease and chronic hepatitis C are the two most common reasons for end-stage liver disease within the older population. Unfortunately, there is a growing

discrepancy between the patients waiting for a liver transplantation and available donors. This discrepancy will continue to worsen as the population of older patients with cirrhosis continues to grow. As a result of this disparity, patients are forced to wait longer periods of time on the transplant recipient list prior to transplantation. Pretransplant evaluation of older patients should take into account age-related comorbidities, specifically, cardiovascular disease, osteoporosis, and malignancy. Despite the need for a thorough pretransplant evaluation, advanced age is not a contraindication for liver transplantation. Unfortunately, age is an independent risk factor for perioperative mortality, largely because of nonhepatic causes and few patients over age 70 are candidates for transplant. Similarly, older adults receiving transplants have a worse postoperative long-term survival. Owing to the risks associated with liver transplantation, geriatric patients should be carefully selected by a multidisciplinary team noting significant comorbid conditions. Post-transplant care should entail continued management of cardiovascular risk factors, assessment and treatment for osteoporosis, and vigilant surveillance for malignancy.

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Chapter 92

Biliary and Pancreatic Disease

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Learning Objectives

- Learn the epidemiology, genetics, etiology, and pathogenesis of common biliary and pancreatic diseases in older adults.
- Understand the common and atypical manifestations, and tests to diagnose common gallbladder and pancreatic diseases in older patients.
- Learn state-of-the-art and emerging treatments for biliary and pancreatic disorders in older population.
- Acquire knowledge about the symptoms, diagnosis, and treatment of gallbladder and pancreatic cancers in older adults.

Key Clinical Points

1. **Age is a major risk factor for gallstones, which are more common among older adults, especially women.**
2. **Acute cholecystitis may present atypically in older patients without fever, nausea, vomiting, or severe abdominal pain.**
3. **Ultrasound is the initial diagnostic test of choice, and incidental discovery of gallstones is not an indication for treatment. When appropriate, early laparoscopic cholecystectomy is the treatment of choice in older patients.**
4. **In the absence of gallstones and alcohol abuse, the most common cause of acute pancreatitis in older adults is malignancy.**
5. **Alcohol abuse is the most common cause of chronic pancreatitis in older patients.**

BILIARY DISEASE

Cholelithiasis

Table 92-1 outlines the risk factors associated with gallstone formation. Age is a major factor, although the reasons for this are unclear. By the ninth decade of life, the prevalence of gallstones is 38% in women and 22% in men. In men older than 90 years, the incidence increases to 31%. The prevalence of gallstones in the US population increases by 1% per year in women and by 0.5% per year in men after age 15. Native Americans are predisposed to gallstone formation at an earlier age. At age 50, the prevalence of gallstones in Native Americans is 80% in women and 70% in men. The increase in risk in women is related to increased biliary cholesterol excretion by estrogen. Approximately 500,000 people in the United States develop symptomatic gallstones each year.

TABLE 92-1 RISK FACTORS FOR GALLSTONE FORMATION

Increasing age
Female sex

Obesity
Dyslipidemia
Rapid weight loss
Medications
Ethnicity—Caucasian, Native American and Hispanic

The great majority of patients with gallstones remain asymptomatic. Gallstones are frequently found incidentally when a patient undergoes abdominal imaging. It is often a challenge to the medical practitioner to determine whether the symptoms that led to the discovery of gallstones, such as mildly abnormal liver tests, or chronic nonsevere abdominal pain are causally related to the newly discovered gallstones. Serious complications that may arise from cholelithiasis include severe abdominal pain ("biliary colic"), sepsis, pancreatitis, or cancer of the gallbladder.

Approximately 80% of gallstones in the United States contain cholesterol as their major constituent and are termed cholesterol stones. Cholesterol crystals tend to precipitate and form stones or sludge when an excess of cholesterol is present in bile relative to the concentrations of bile acids and phospholipids. Pigment stones develop in the setting of excess bilirubin in bile. In conditions such as hemolysis or cirrhosis with high heme turnover, unconjugated bilirubin in the form of calcium bilirubinate crystallizes forming black pigment stones. These account for 10% to 20% of gallstones in the United States. Bacterial colonization of normally sterile bile may lead to an increase in unconjugated bilirubin and in turn calcium bilirubinate. Gallstones arising from this process are brown pigment stones. Black pigment stones are found primarily in the gallbladder, whereas brown pigment stones may be found not only in the gallbladder but also in the intrahepatic or extrahepatic bile ducts.

Choledocholithiasis

With gallbladder contraction, gallstones can enter and potentially obstruct the common bile duct. Such obstruction can lead to jaundice, ascending cholangitis, liver abscess, and pancreatitis. Stones are present in the common bile duct in approximately 15% of patients undergoing cholecystectomy for chronic cholecystitis with gallstones. The prevalence of stones in the common bile duct increases with age. Although dilatation of the common bile duct correlates with choledocholithiasis, the common bile duct may become dilated as a result of the normal aging process or following cholecystectomy. In general, 6 mm is considered the upper limit of normal for the common bile duct measured by ultrasound. Perhaps a more useful tool, especially in older adults, is a common bile duct measurement of 1 mm per decade of life. For example, a patient who is 70 years old may have a common bile duct measurement of 7 mm in the absence of choledocholithiasis. Comparison to previous imaging studies for interval change is important as well.

The classical signs and symptoms of biliary obstruction are called biliary colic and include epigastric or right upper quadrant pain, nausea, vomiting, and pruritus. Patients may develop dark urine and acholic stools. Tender hepatomegaly may develop because of the increased pressure in the biliary tree. The presence of fever and jaundice is concerning for ascending cholangitis. The constellation of abdominal pain, jaundice, and fever, known as Charcot triad, is helpful in making the diagnosis of ascending cholangitis.

Acute Cholecystitis

Approximately 50% to 70% of cases of acute cholecystitis occur in the geriatric population. This condition in characterized by prolonged obstruction of the cystic duct by one or more gallstones. This leads to inflammation and possibly infection of the gallbladder. Acalculous cholecystitis refers to inflammation of the gallbladder in the absence of gallstones. It is usually idiopathic, but tends to occur in debilitated and or vasculopathic patients. Acalculous cholecystitis accounts for 5% to 10% of cases of cholecystitis. The severity of cholecystitis varies from mild edema to severe inflammation and, at its most catastrophic, necrosis, or perforation of the gallbladder.

Acute cholecystitis has several classic clinical manifestations. The usual symptoms include abdominal pain, especially in the right upper quadrant or epigastrium. This pain may radiate to the back or shoulder. It is typically continuous and severe. Patients may notice the onset of such pain after eating a fatty meal. Fevers, chills, nausea, and vomiting are common as well.

Physical examination often shows a patient who appears ill and uncomfortable. Pain is usually elicited by palpating the right upper quadrant and/or epigastrium of the abdomen. A Murphy sign is characterized by cessation of inspiration while palpating the area of the gallbladder because of extreme discomfort.

Acute cholecystitis may present atypically in older adults and with delayed recognition results in a greater risk of

complications. Older patients usually have right upper quadrant or epigastric pain and tenderness, but other signs and symptoms may be lacking. Older patients may present without fever, nausea, or vomiting in more than 50% of acute cases. These signs may not be present in 33% even in the setting of gallbladder gangrene or perforation. Acalculous cholecystitis is more common in older adults, and diagnosis of such cases may be more difficult because of the lack of stones on imaging studies.

Chronic Cholecystitis

Chronic cholecystitis refers to biliary pain caused by recurrent episodes of cystic duct obstruction leading to a chronic inflammatory response. Ultimately this may lead to scarring and gallbladder dysfunction. On ultrasound, chronic cholecystitis has a more subtle appearance than acute cholecystitis. A review of 412 patients with histologically proven acute or chronic cholecystitis showed gallbladder wall thickening in 80% of those with acute cholecystitis as opposed to 18% of those with chronic cholecystitis. Dilated gallbladder was seen in 60% of acute versus 12% of chronic. Thus, preoperatively, chronic cholecystitis may be difficult to distinguish from noninflammatory symptomatic gallstone disease. As with acute cholecystitis, elective cholecystectomy is the treatment of choice.

Investigations

In acute cholecystitis, ultrasound typically shows gallstones and pericholecystic fluid and/or edema. A sonographic Murphy sign is helpful in establishing the diagnosis. Ultrasonography will demonstrate the presence of stones with an accuracy of 90%. A HIDA (^{99m}technetium-N-substituted hepatoiminodiacetic acid) scan will show opacification of the bile ducts, but not of the gallbladder, in cholecystitis.

Ultrasound is the usual initial diagnostic test of choice for choledocholithiasis with a sensitivity of 20% to 38% and specificity of 80% to 100% (**Table 92-2**). It has the advantage of being noninvasive, easily tolerated by the patient, widely available, and inexpensive. Abdominal CT has higher sensitivity than ultrasound (50%–88%), but often fails to identify stones less than 5 mm. Magnetic resonance cholangiopancreatography (MRCP) allows for visualization of biliary anatomy as well as stones and has sensitivity of 57% to 100% and specificity of 73% to 100% for common bile duct stones. It also has the advantage of being noninvasive, but its disadvantages include cost and potential patient discomfort from claustrophobia.

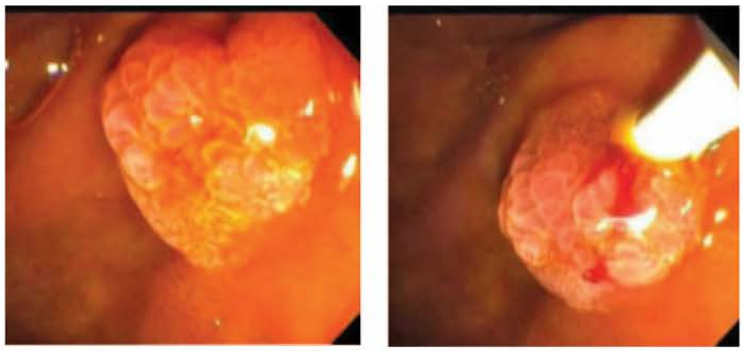
TABLE 92-2 IMAGING AND THERAPIES FOR CHOLEDOCHOLITHIASIS

TEST	SENSITIVITY	SPECIFICITY	ADVANTAGES	DISADVANTAGES
Ultrasound	20%–38%	80%–100%	Noninvasive, low cost	Low sensitivity, nontherapeutic
CT	50%–88%	84%–98%	Ease for patient	Expensive, nontherapeutic
MRCP	57%–100%	93%–97%	Highly sensitive	Expensive, nontherapeutic, may cause claustrophobia
EUS	94%	95%	High precision	Expensive, nontherapeutic, sedation
ERCP	57%–100%	73%–100%	Therapeutic	Expensive, may cause pancreatitis
PTC			Therapeutic	Bleeding, pain (especially in the absence of dilated bile ducts)

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; PTC, percutaneous transhepatic cholangiography.

Endoscopic ultrasound (EUS) has become a useful imaging modality in cases where the presence of stones in the common bile duct is suspected, but remains uncertain. EUS has sensitivity and specificity of 94% and 95%, respectively, and sedation needs are similar to an upper endoscopy. Endoscopic retrograde cholangiopancreatography (ERCP) is both a diagnostic and therapeutic modality for choledocholithiasis. Though there are varying estimates of precision with ERCP, multiple studies report a sensitivity and specificity of greater than 95%. The injection of contrast material into the biliary tree allows visualization of all but very small stones. A sphincterotomy is often performed to prevent recurrent obstruction. In the case of cholangitis, a stent is often left in the common bile duct to drain purulent material, stones, and sludge. The disadvantages of ERCP include the potential for acute pancreatitis, technical and infrastructural requirements, and cost. However, ERCP poses no greater risk in older adults than in the younger

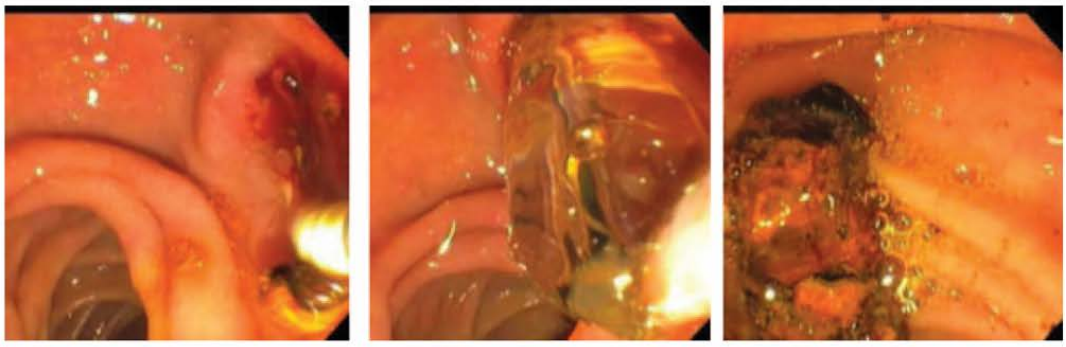
population. One study of ERCP in the geriatric population showed no difference in the rate of therapeutic ERCP complications in patients older than 80 years (6.8%) versus those younger than 80 years (5.1%). In a retrospective cohort between 2002 and 2005, there were no significant differences in successful biliary drainage, complications or mortality in a group of 178 patients over 75 years of age compared to 159 patients less than 75 years. Another study evaluated the safety of ERCP in patients older than 90 years, and the complication rate in this age group was 6.3% compared to 8.4% in patients 70 to 89 years of age. Therefore, ERCP is a safe procedure even in those with very advanced age. The rate of recurrence of symptomatic CBD stones after ERCP was higher in patients older than 80 years (20%) versus 4% in patients 50 years old or younger. Thus, older adults are at higher risk for needing a repeat ERCP. A study of 206 patients from 2006 to 2010 demonstrated that combined EUS/ERCP in one session is safe in the geriatric population with no increased risk of adverse events compared to younger patients. Refer to **Figure 92-1** for review of multiple ERCP images.



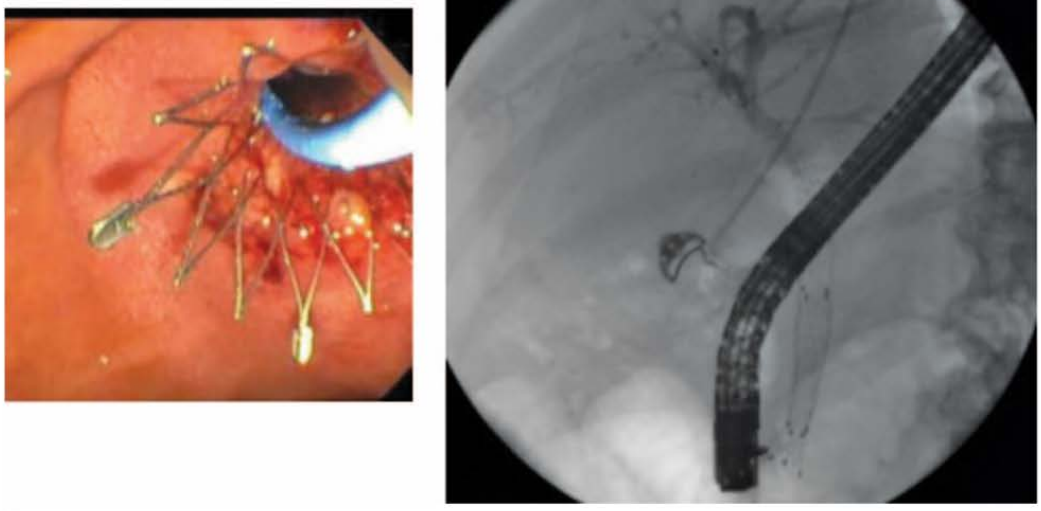
A



B



C



D

FIGURE 92-1 **A–D.** Multiple ERCP images. **A.** Normal ampulla with cannulation. **B.** Bulging, ulcerated ampulla found to be adenocarcinoma s/p sphincterotomy and plastic biliary stent placement. **C.** Common bile duct stone removed with balloon **D.** Common hepatic duct stricture due to cholangiocarcinoma. Endoscopic and fluoroscopic images s/p metal biliary stent placement. (Images courtesy of Deepak Gopal, MD, University of Wisconsin, Madison, WI.)

Treatment

Incidental discovery of gallstones is not an indication for therapy. In a study of 123 subjects with silent gallstones, biliary pain occurred in only 16 persons in the follow-up period of up to 24 years. Of those 16 subjects, only three had significant complications: one with acute pancreatitis and two with acute cholecystitis. The cumulative probability of developing biliary pain in this population was 10% at 5 years, 15% at 10 years, and 18% at 15 and 20 years. None of these subjects died as a consequence of gallstone disease. Because asymptomatic gallstones tend to follow a benign course, cholecystectomy should be considered primarily in those with symptoms or complications.

Prompt treatment of acute cholecystitis is warranted to prevent deterioration, complications, and progression to chronic cholecystitis. In addition to intravenous fluids, antibiotics, and pain control, surgery is the mainstay of treatment. Each patient's clinical status and comorbidities must be considered in the decision to proceed with general anesthesia and surgery. Laparoscopic cholecystectomy has several advantages over open cholecystectomy including less discomfort, shorter hospital stay, and lower cost. Complications from this procedure often involve biliary trauma. Agrusa and colleagues performed a retrospective study involving 1227 patients who underwent cholecystectomy at their institution between 2010 and 2014. Among this cohort, 351 patients were 65 to 79 years of age and 65 patients were 80 years of age or older. There was no significant difference in the conversion rate from laparoscopic to open cholecystectomy between those under 65 years of age and those over 80 years of age, 0.7% versus 1.5%, respectively. Most of the procedures done for those under 65 years were done on an elective basis (89.7%), whereas a much higher percentage of procedures done in those older than 80 years were done emergently (43.1%). There were two deaths in the older population. Age and comorbidities are predictors of surgical outcomes. Timing of intervention is also important with better outcomes in patients who undergo early laparoscopic cholecystectomy for acute cholecystitis. Whenever possible, this should be performed within the same hospital stay for definitive treatment of gallstone disease.

As discussed above, in older patients with acute cholecystitis who are felt to be suitable surgical candidates, laparoscopic cholecystectomy is a reasonable option. However, for older patients who are very ill or have significant comorbidities, gallbladder drainage prior to surgery may be a viable alternative. This was evaluated in a case series of 84 patients with acute cholecystitis older than 70 years with severe cholecystitis or an American Society of Anesthesiologist score of II to IV. In 83 of these patients, a percutaneous cholecystostomy drain was placed. A transcatheter cholangiogram was done and those with common bile duct stones underwent endoscopic sphincterotomy. Elective cholecystectomy was then performed in 70 patients with no deaths and a 24% morbidity rate. Percutaneous cholecystostomy drainage is an effective and often definitive treatment for acalculous cholecystitis as well. In a study of 15 patients with acute acalculous cholecystitis, prompt improvement was seen in 14 patients after placement of a pigtail catheter into the gallbladder. Morbidity rate after this procedure was 13%, and no deaths were seen.

Patients with symptomatic gallstone who cannot or do not wish to undergo invasive procedures may benefit from dissolution of gallstones with ursodiol. This medication is only useful in the setting of cholesterol gallstones. A meta-analysis of randomized trials using ursodiol for treatment of gallstones found a dissolution rate of 37% after 6 months with doses of at least 7 mg/kg or greater than 500 mg/day. However, at least 50% of patients treated with ursodiol for gallstones will have recurrent stone formation.

Carcinoma

Gallbladder cancer Cancer of the gallbladder is uncommon in the United States and carries a poor prognosis. Often, this diagnosis is not made until late in its course. The 5-year survival for local disease is 42%, but drops to 0.7% with distant spread of disease. SEER data show that gallbladder cancer occurs primarily in older adults. Approximately 75% of cases occur in patients older than 65 years. Ninety percent of all gallbladder cancers are carcinomas and occur in approximately 3:1 female-to-male ratio. Ethnic background and geographic distribution appear to influence the development of gallbladder cancer, as the highest incidence rates are found in those of Native American and Mexican descent and those living in the region of the Andes. It has been noted that 80% of patients with gallbladder cancer have a history of cholelithiasis. Chronic inflammation from gallstones is thought to induce metaplasia of the gallbladder. Size and duration of gallstones appear to be important in carcinogenesis. Prophylactic cholecystectomy in certain higher risk groups is controversial. Among those who may benefit from this procedure include patients with a

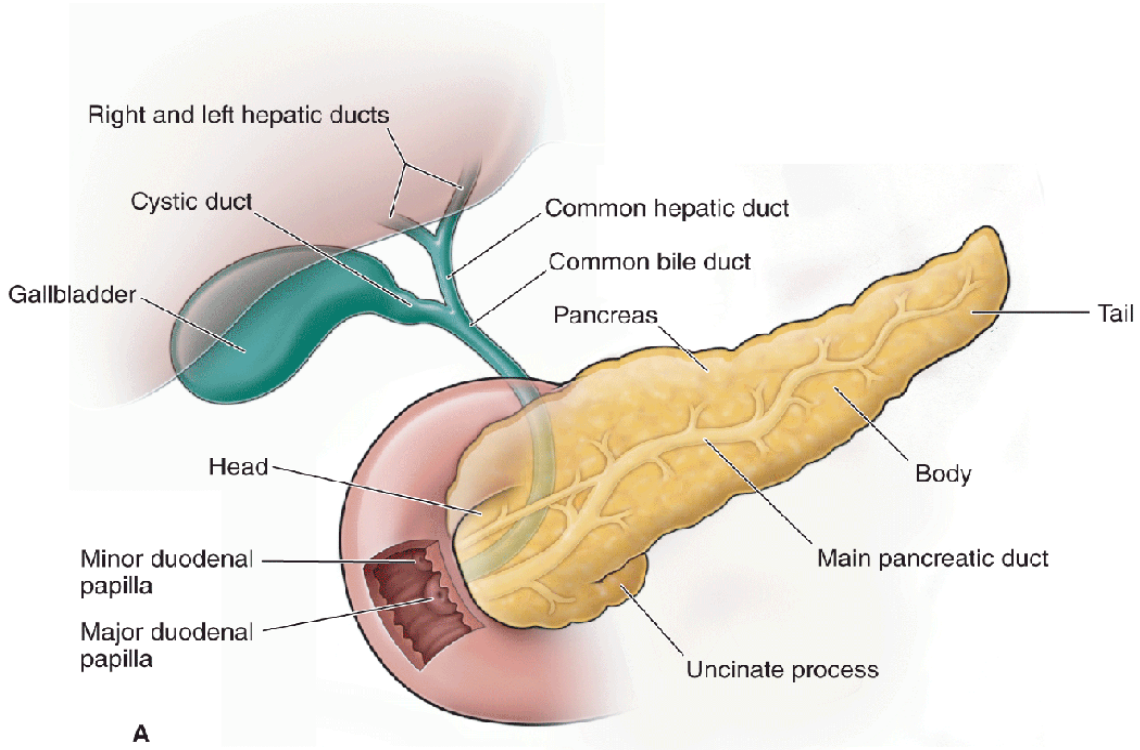
porcelain gallbladder and patients with a congenital defect in the junction of the pancreatobiliary duct.

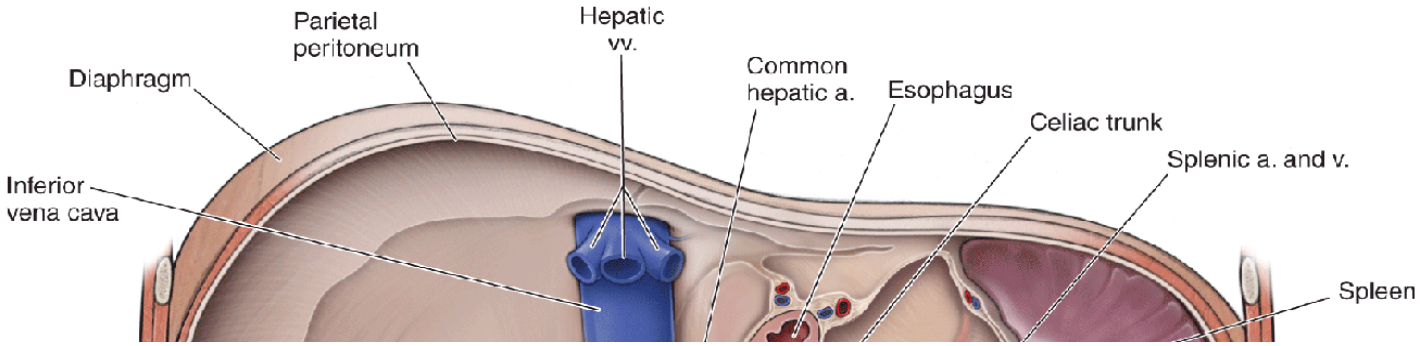
Cholangiocarcinoma—cancer of the bile ducts Primary bile duct cancers account for less than 3% of all cancers diagnosed in the United States. Cancer of the extrahepatic bile ducts is more common in older adults, as 65% of cases are found in those older than 65 years and 69 is the median age. Ninety-nine percent of these are carcinomas. The 5-year survival rate ranges from 26.5% with localized disease to 1.3% with distant spread. The incidence is 1.2 per 100,000 in males and 0.8 per 100,000 in females. The tumors tend to infiltrate along the wall of the bile duct and may be difficult to differentiate from benign strictures. Patients present with signs and symptoms of biliary obstruction with jaundice, pruritus, and weight loss. Treatment is primarily surgical, most commonly with a Whipple procedure. Rare patients may be suitable for liver transplantation. For those who are not surgical candidates, biliary decompression by stent placement is a reasonable option for palliation to maintain patency of biliary drainage.

PANCREATIC DISEASE

Anatomy

Figure 92-2 shows the gross anatomy of the pancreas. The pancreas can be divided into the endocrine and the exocrine pancreas. Four different types of islet cells comprising the endocrine pancreas produce hormones such as insulin, glucagon, pancreatic polypeptide, and somatostatin. The exocrine pancreas is the focus of this chapter. The exocrine pancreas is composed primarily of acinar cells and duct cells. The acinar cells produce the digestive enzymes. The key enzyme is trypsinogen. The duct cells produce the bicarbonate-rich fluid for secretion.





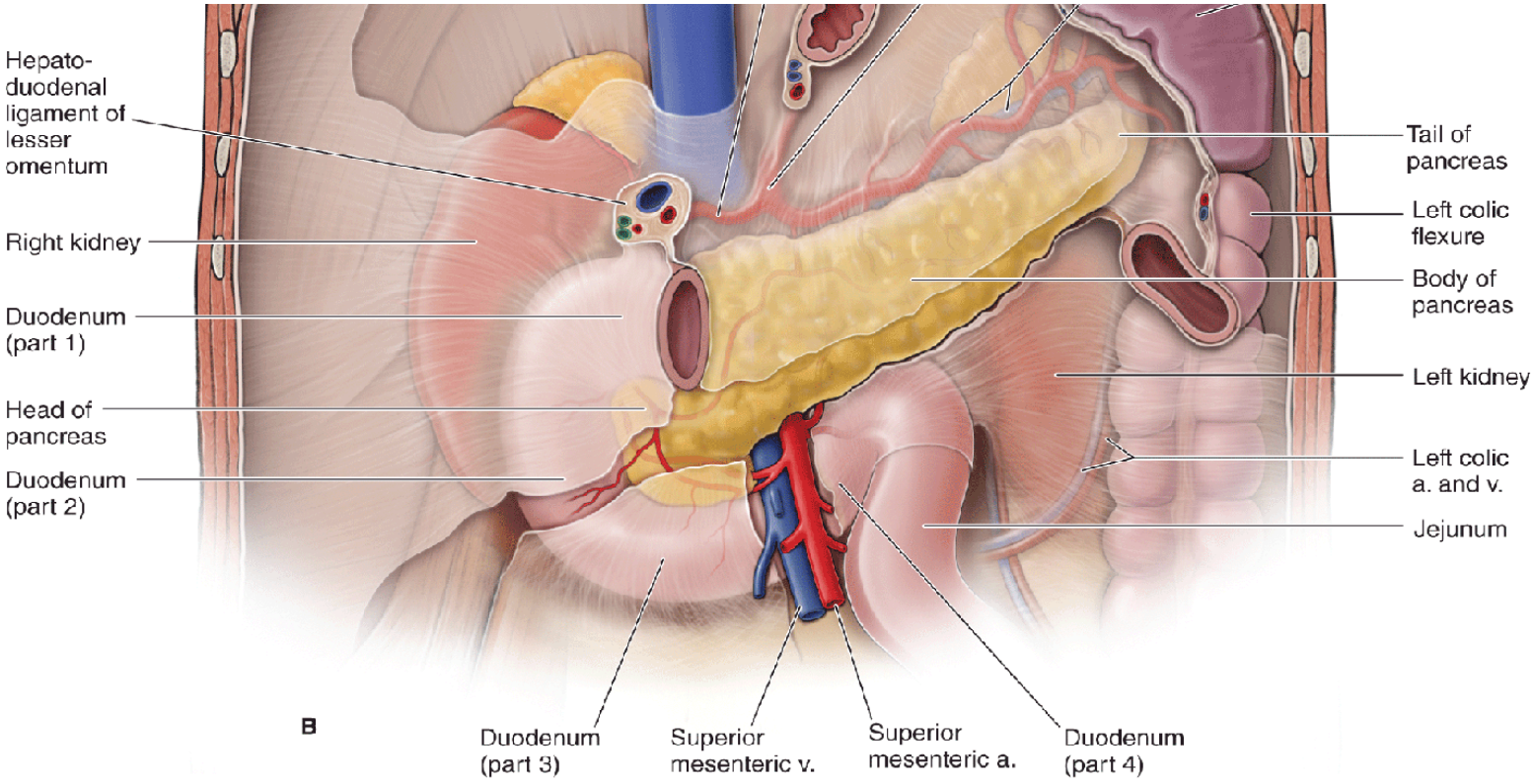


FIGURE 92-2. Normal anatomy of the pancreas. (From Morton DA, Foreman KB, Albertine KH. *The Big Picture: Gross Anatomy*. New York: McGraw-Hill, 2011.)

Physiology

The exocrine pancreas has proteases, lipases, glycosidases (amylase), and nucleases. The proteases and the nucleases are stored in an inactive form. The proteases constitute greater than 75% of the pancreas by weight. Trypsinogen is the primary protease. Trypsinogen is activated to trypsin in the duodenum by enterokinase—the only physiologic function of this enzyme. Trypsin subsequently activates the other digestive enzymes and in the presence of calcium activates trypsinogen to trypsin. In the absence of calcium, trypsin has negative feedback by degrading other trypsin molecules. Trypsin's primary site of action is on arginine and lysine amino acids. The most common genetic defect that facilitates the development of hereditary pancreatitis is called R122 H, in which arginine at position 122 of trypsin molecule (an important regulatory site) is substituted for by histidine. This defect negates the negative feedback safety mechanism for trypsin regulation.

There are two additional important mechanisms regulating pancreatic function. First, acid in the duodenum stimulates secretion of the hormone secretin and through vagal mediation leads to the duct cells of the pancreas to secrete bicarbonate. The second regulatory mechanism involves the cholecystokinin (CCK) feedback loop. Human pancreatic acini lack CCK receptors. The presence of protein in the duodenum effectively increases cholecystokinin releasing factor (CCK RF), which stimulates CCK release. The elevated CCK level is recognized by the brain, leading to vagal stimulation of the acinar cells of the pancreas to secrete more digestive enzymes.

Aging and the Pancreas

Table 92-3 outlines the age-related changes of the pancreas. The maximal volume of pancreatic juice excreted in response to secretin and CCK stimulation increases until the fifth decade and thereafter decreases steadily. Bicarbonate decreases steadily after the fourth decade of life. Also, in ERCP studies, a slight increase in size of the pancreatic duct in the head and body but not the tail has been noted with aging. Despite these anatomic and physiologic changes, only rare cases of pancreatic exocrine deficiency are clinically apparent in healthy older adults.

TABLE 92-3 AGING AND THE PANCREAS

Fat, fibrosis, and reduced weight after seventh decade

Bicarbonate decreases steadily after the fourth decade of life
Pancreatic exocrine deficiency: rare in the elderly without underlying pathology
Alcoholic pancreatitis: a disease of the middle age
Gallstone prevalence, and therefore gallstone pancreatitis, increases with age
Increased incidence of malignancy, particularly adenocarcinoma

Over and above the normal changes of aging, advanced age poses other threats to pancreatic structure and function. Pancreatitis secondary to alcohol tends to be a disease of the middle age, while gallstone disease continues to have a relatively high incidence in older cohorts. The biggest risk in the older population is an increased incidence of malignancy, particularly adenocarcinoma. In addition, during imaging studies of the abdomen, incidental small cystic and solid lesions of the pancreas are now frequently found.

Acute Pancreatitis

Acute pancreatitis has a variety of etiologies, but all eventually lead to activation of the digestive enzymes particularly trypsin in the pancreatic acinar cells. The most common etiologies for acute pancreatitis are gallstones and alcohol. However, in an older patient without gallstones or a history of chronic excessive use of alcohol, the suspicion for underlying malignancy needs to be especially high. Inherited defects in the trypsinogen to trypsin pathway may lead to rare forms of acute pancreatitis, termed “hereditary pancreatitis.” Obstruction of the pancreatic duct by a gallstone is an important mechanism of initiating pancreatic injury. Alcohol, on the other hand, causes mitochondrial dysfunction, which allows for increased levels of intracellular calcium and subsequent activation of trypsin. Hypertriglyceridemia is often overlooked as a cause of acute pancreatitis. Triglycerides should be measured on admission to hospital because levels will often quickly decrease with bowel rest and fluids. Many medications may cause acute pancreatitis or elevate levels of triglycerides. See **Table 92-4** for etiologies of acute pancreatitis.

TABLE 92-4 ETIOLOGIES FOR PANCREATITIS

Gallstones
Alcohol
Hypertriglyceridemia
Medications/toxins
Hereditary pancreatitis
Cystic fibrosis gene mutation
Autoimmune pancreatitis
Pancreatic divisum
Trauma
Post-ERCP
Tumors
Elevated calcium
Idiopathic

The predominant symptom of acute pancreatitis is epigastric pain, commonly with radiation into the back. Nausea and vomiting are also frequently present. Acute pancreatitis is a clinical diagnosis with support from elevated serum amylase and lipase. Levels at least 3 times the upper limit of normal are typical of acute pancreatitis. Many other conditions cause minor elevations in amylase or lipase. Radiographic studies have little role in diagnosis, but do play important roles in evaluating etiology (gallstones, neoplasia, pancreatic calcification indicating chronic pancreatitis) and complications such as necrosis, and pseudocysts. Care needs to be taken in the acute setting not to add intravenous contrast load to a patient that is extremely intravascularly depleted already. Acute pancreatitis can be divided into mild and severe pancreatitis. The range of disease is from self-limited disease to multiorgan failure and death. A variety of grading systems including Ranson criteria, Apache score, Glasgow score, and the Baltazar CT grade ± necrosis do correlate with morbidity and mortality.

Treatment of mild pancreatitis is accomplished with bowel rest, with or without parenteral feeding, intravenous

fluids, and pain control. Gallstone pancreatitis is treated with ERCP, sphincterotomy, and stone extraction if cholangitis or evidence of biliary obstruction is present. Severe pancreatitis often becomes management of multiorgan failure. Early placement of nasojejunal tubes with subsequent enteral feedings is the standard of care. Evidence of necrosis on CT scan warrants intravenous antibiotics with good pancreatic penetration such as imipenem. Patients who develop sepsis in the setting of pancreatic necrosis should be surveyed by interventional radiology for biopsy, gram stain, and culture. Evidence of infection may require temporary drain placement or surgical debridement.

Pseudocyst formation is an important complication of acute pancreatitis. Approximately 10% of patients with acute pancreatitis proceed to formation of these fluid collections. Most pseudocysts resolve with time; however, if symptoms are present (early satiety, pain, infection, bleeding), then drainage via interventional radiology, endoscopic cystgastrostomy, or surgery may be necessary.

Chronic Pancreatitis

Alcohol abuse accounts for approximately 70% of chronic pancreatitis. Idiopathic causes are the second most common cause of chronic pancreatitis. Cystic fibrosis gene mutations are now frequently being identified as an etiology in approximately a third of idiopathic pancreatitis diagnosis. Hereditary pancreatitis frequently leads to chronic pancreatitis at a young age. In older adults, it is important to evaluate for tumors compressing the pancreatic duct as the etiology.

The diagnosis of chronic pancreatitis can be a challenging diagnosis to make. Amylase and lipase can be mildly elevated or normal. Evidence of calcifications by x-ray or by CT scan is found in 30% to 40% of cases and can give a diagnosis. Often, more advanced imaging studies such as ERCP, MRCP, or EUS are used to evaluate the anatomy of the pancreas and give a diagnosis. The major features of chronic pancreatitis include pain, malabsorption, and frequently diabetes.

Treatment is based on resolving malabsorption with pancreatic enzyme replacement, which also downregulates the CCK feedback loop, decreasing pancreatic stimulation. Narcotic pain medication is often needed. If a dilated main pancreatic duct is present, a pancreaticojejunostomy (Puestow procedure) can be helpful. In some cases, near total pancreatectomy is needed with or without islet cell transplantation.

Pancreatic Cancer

Approximately 34,000 new cases of pancreatic cancer will be diagnosed, and 33,000 patients will die secondary to pancreatic cancer each year. Approximately 87% of patients will be older than age 55 at diagnosis with the median age being 72. The overall 5-year survival is 5%. Unfortunately, little progress has been made to change the mortality from this disease over the last several decades. The genetics have now been further elucidated showing that 85% of adenocarcinomas of the pancreas have an activating point mutation in the K-ras oncogene. In addition, 95% have an inactivated p16 tumor-suppressor gene. Genetic changes and new knowledge about the cytokine milieu are current areas of active research.

More than 70% of adenocarcinomas arise in the head of the pancreas, which leads to common presentations including jaundice, gastric outlet obstruction, and pain. Approximately 15% of lesions do not have vasculature invasion or metastatic disease on presentation making surgical resection possible, with curative intent. The 5-year survival in this population is approximately 20%. Staging with CT scans and EUS to evaluate for metastatic disease and vascular invasion is thus important. In addition, tissue diagnosis can be made with EUS and fine needle aspiration (FNA). Autoimmune pancreatitis (sclerosing pancreatitis) can present as a pancreatic head mass and obstructive jaundice, making this diagnosis important to consider prior to surgical or medical therapy for presumed pancreatic cancer. Autoimmune pancreatitis has elevated ANA as well as IgG4 autoantibodies in the majority of cases and responds to prednisone.

Other tumors exist in the pancreas including neuroendocrine tumors and many types of cystic lesions of the pancreas. Neuroendocrine tumors of the pancreas are typically solid tumors. Evaluation by EUS with or without FNA and surgical resection are often performed except in multiple endocrine neoplasia (MEN) 1, where the pancreatic lesions are often multifocal in nature.

Pancreatic Cysts

Cystic lesions of the pancreas are becoming increasingly recognized because of more widespread abdominal imaging (**Table 92-5**). Incidental pancreatic cysts are noted on 1% of abdominal CT scans obtained for any reason. These

lesions include pseudocysts, congenital cysts (also known as simple cysts), and cystic neoplasms including serous cystadenomas (SCN), mucinous cystadenomas (MCN), cystadenocarcinomas, and intraductal papillary mucinous neoplasm (IPMN). According to guidelines from the American Society of Gastrointestinal Endoscopy, cystic lesions of the pancreas, even when found incidentally, may represent malignant or premalignant neoplasms and require diagnostic evaluation regardless of size. Pancreatic pseudocysts and congenital cysts have no malignant potential. Serous cystadenomas represent nearly 30% of pancreatic cystic neoplasms and are most commonly found in women over 70 years of age. Malignant transformation is extremely rare and serous cystadenomas are often managed nonoperatively. Over 95% of mucinous cystic neoplasms occur in women with a peak incidence in the fifth decade of life. MCNs account for 10% to 45% of all cystic pancreatic neoplasms and have risk of malignant transformation near 20%. Intraductal papillary mucinous neoplasms occur most commonly in males with peak incidence in the seventh decade. Unlike MCNs, IPMNs communicate with the main pancreatic duct (main duct IPMN) or side branches of pancreatic duct (branch duct IPMN). The distinction between main duct and branch duct IPMN is significant since carcinoma is a feature of approximately 50% of main duct IPMN lesions and about 10% of branch duct IPMNs. After a lesion is identified on imaging studies, EUS with FNA is used to obtain fluid for cytologic evaluation and for tumor markers and amylase in order to classify pancreatic cystic lesions (see **Table 92-5** and **Figure 92-3**). Given the high malignant potential, MCNs and main duct IPMNs are managed with surgical resection in geriatric patients who are healthy enough to tolerate surgery. Branch duct IPMNs may be surgically resected as well, though serial imaging is often appropriate based on current guidelines.

TABLE 92-5 IMAGING FEATURES OF PANCREATIC CYSTS AND CYST FLUID ANALYSIS

	PSEUDOCYST	SCN	MCN	IPMN
Imaging features	Often occurs in setting of pancreatitis	Hypodense cysts with central scar	Peripheral calcification, no communication with pancreatic duct	Irregular, polycystic, communicates with pancreatic duct
Malignancy risk	None	Extremely low	Up to 20%	Main duct IPMN 50%; branch duct IPMN 10%
Cystic fluid characteristics	Inflammatory cells	Glycogen-containing cells	Mucin-producing cells, possible dysplasia	Mucin-producing cells, possible dysplasia
Cyst amylase	> 250 U/L	< 250 U/L	< 250 U/L	< 250 U/L
Cyst CEA	< 192 ng/mL	< 10 ng/mL	> 192 ng/mL	> 192 ng/mL

CEA, carcinoembryonic antigen.

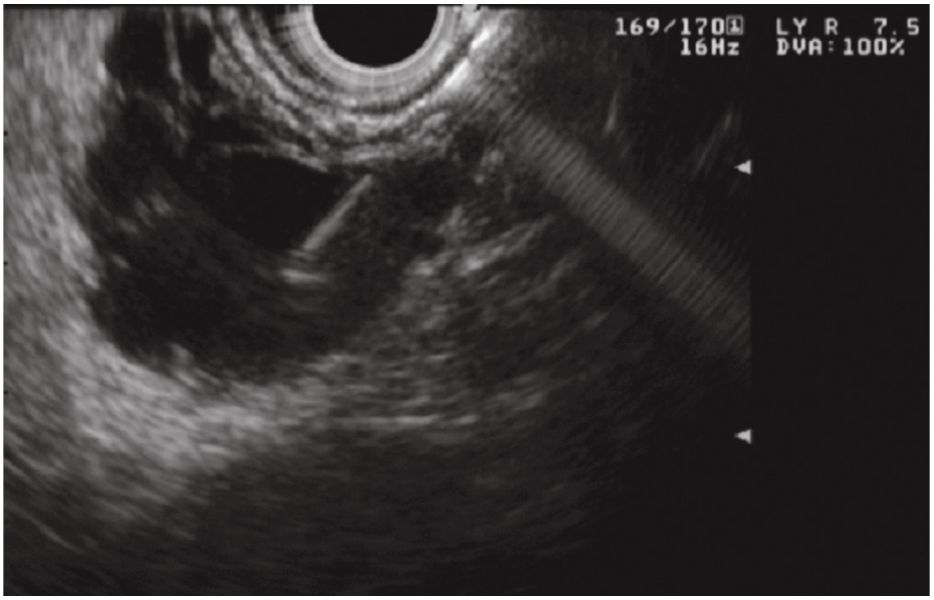


FIGURE 92-3. Endoscopic ultrasound with FNA needle in pancreatic cyst. This cyst proved to be a serous cystadenoma. (Image courtesy of Deepak Gopal, MD, University of Wisconsin, Madison, WI.)

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Chapter 93

Upper Gastrointestinal Disorders

Alberto Pilotto, Marilisa Franceschi

Learning Objectives

- Identify the presentation of gastroesophageal reflux disease (GERD) in older adults and select the most appropriate therapeutic strategies.
- Employ management strategies that reduce the risk of peptic ulcer disease (PUD) in older adults including: limiting the use of nonsteroidal anti-inflammatory drugs, and eradicating *Helicobacter pylori* when indicated.
- Recognize the risk factors for upper GI cancers in older adults and initiate evaluation in those at risk, particularly those at risk for Barrett esophagus.

Key Clinical Points

1. **GERD is common in older adults with a incidence of 5 per 1000 person years in the United Kingdom and United States. Symptoms are less likely to correlate with the severity of esophageal findings on endoscopy so a trial of proton pump inhibitors (PPIs) should rarely be done without endoscopy for suspected GERD in older adults. PPIs are more effective than H_2-blockers, but prokinetic agents have not been shown to be superior to placebo.**
2. **Peptic ulcer disease (PUD) increases with age, likely due to *H pylori* infection, use of mucosa-damaging drugs, and an imbalance between mucosal erosive and protective factors. Despite clear data that treatment of *H pylori* reduces relapse of peptic ulcer disease, many older adults with PUD go untested for *H pylori* and only 1/2 to 3/4 of those who test positive are treated. *H pylori* cure after treatment should be documented with a breath test or stool antigen.**
3. **Upper GI bleeding (UGIB) occurs in older adults due to the same pathologies as seen in young adults, but may present with exacerbation of underlying disease (eg, cardiac disease) or non-GI symptoms such as syncope.**
4. **The types of upper GI cancers have changed markedly in recent decades with adenocarcinoma increasing in frequency in the esophagus. Older white men represent a very high risk group due to Barrett esophagus, and those with GERD symptoms or high suspicion of GERD should undergo screening endoscopy. Gastric cancer remains very common in developing nations. The risk of both esophageal and gastric cancer increases with age.**
5. **PPIs interact with many drugs prescribed in older adults and long-term PPI use has been associated with B_{12} deficiency, an increased risk of fractures (hip, wrist, or spine), and bacterial diarrhea (including *Clostridium difficile*), and some studies suggest pneumonia, functional decline, and mortality in frail older adults. Thus, long-term PPI use should be contemplated only in those with clear indications to do so.**

GASTROESOPHAGEAL REFLUX DISEASE IN OLDER ADULTS

Definition

Gastroesophageal reflux disease (GERD) is defined by symptoms and/or histopathologic alterations (esophagitis) caused by reflux of gastric contents into the esophagus. Manifestations of GERD range from mild episodes of heartburn and acid regurgitation without esophagitis, to chronic mucosal inflammation with erosive esophagitis and ulceration, complicated in severe cases by stricture and bleeding.

Epidemiology

GERD is a frequent condition with worldwide distribution. The prevalence of GERD is estimated to be 11.6% in Australia, 7.8% in East Asia, 8.8% to 25.9% in Europe, 8.7% to 33.1% in the Middle East, 18.1% to 27.8% in North America, and 23.0% in South America. There is evidence of an increasing burden in GERD prevalence since 1995, particularly in North America and East Asia; in the UK and US general populations, the incidence is approximately 5 per 1000 person years.

While it is still unclear whether the incidence and prevalence of GERD symptoms increase with advancing age, several studies suggest that the frequency of esophagitis is significantly higher in older vs. younger adults. Indeed, older age was found to be a significant risk factor in the development of severe forms of GERD in both epidemiologic and clinical studies from the United States, Japan, and Europe. Consistently, GERD was the sixth most common disorder in a retrospective cross sectional study of almost 20,000 long-term care residents of nursing homes aged more than 65 years, with an overall prevalence of 23%.

In summary, GERD is a highly prevalent disorder in older adults, and associated with more severe and advanced disease than in young adults.

Pathophysiology

Pathophysiologic changes in esophageal function that occur with aging may be responsible, at least in part, for the high prevalence of GERD in old age. These include (1) a shorter intra-abdominal segment of the lower esophageal sphincter (LES), (2) a reduction of secondary peristalsis, (3) an increase in the prevalence of tertiary contractions, (4) alterations in salivary secretion, (5) a reduction in gastric emptying, (6) a decreased esophageal mucosal resistance resulting from impaired epithelial cell regeneration, and (7) duodenogastroesophageal reflux of bile salts (**Table 93-1**). Older patients have a high prevalence of other risk factors that predispose the aging esophagus to lesions (see **Table 93-1**): (1) difficulty in maintaining an upright position after meals; (2) hiatus hernia associated with both repeated episodes of acid reflux and with more severe diseases such as Barrett esophagus; (3) increased drug use, including those that may have a directly damaging effect on esophageal mucosa or an indirect effect on reducing LES pressure; and (4) delayed esophageal transit time of many drugs, creating a potentially dangerous situation when it coexists with acid reflux, as reported for alendronate and nonsteroidal anti-inflammatory drugs (NSAIDs) (**Table 93-2**).

TABLE 93-1 PATHOPHYSIOLOGIC CHANGES IN ESOPHAGEAL FUNCTION THAT OCCUR WITH AGING

FUNCTIONAL CAUSES	ANATOMICAL CAUSES
Impaired motility of the esophagus	Hiatus hernia
Reduced LES pressure and length	Difficulty in maintaining an upright position
Normal gastric acid secretion	
Delayed gastric emptying transit time	
Reduced salivary secretion	
Decreased tissue resistance as a result of impaired epithelial cell regeneration	
Duodenogastroesophageal reflux of bile salts	

TABLE 93-2 DRUGS THAT MAY INCREASE THE RISK OF SEVERE GERD

DIRECT EFFECT ON ESOPHAGEAL MUCOSA	REDUCTION IN LES PRESSURE
Aspirin	Theophylline
NSAIDs	Nitroderivates

Potassium salts	Calcium channel blockers
Ferrous sulfate	Benzodiazepines
Corticosteroids	Dopaminergics
Alendronate	Tricyclic antidepressants
	Anticholinergics

Presentation

Particular attention has been given to the clinical presentation of GERD in older adults since important differences have been reported when compared to younger individuals. Indeed, with advancing age, a significantly lower prevalence of typical symptoms, that is, heartburn, acid regurgitation, and epigastric pain has been reported by patients (**Figure 93-1**). Atypical symptoms also are relatively rare in older adults (**Table 93-3**). In contrast, the prevalence of nonspecific symptoms, that is, vomiting, anorexia, weight loss, and anemia significantly increase with age (**Figure 93-2**). Reflux esophagitis in older adults may thus be missed, and a substantial number of patients may suffer subclinical relapses of the disease. The cause of such a different clinical expression of the disease in older adults is not clear, but a diminished sensitivity to visceral pain has been documented in older adults. Moreover, 24-hour esophageal pH monitoring and endoscopy examinations demonstrated an age-related reduction in acid chemosensitivity and a reduced symptom severity despite a tendency toward increased severity of esophageal mucosal injury.

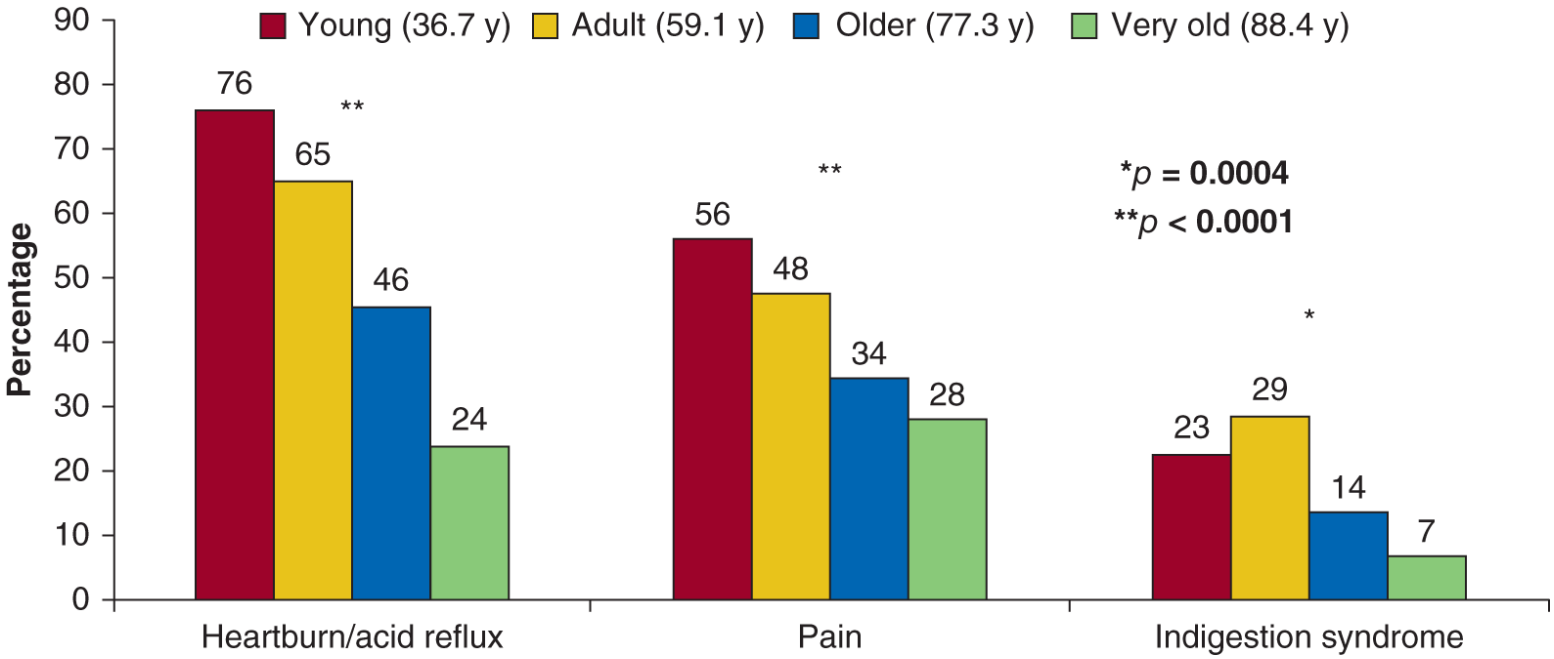


FIGURE 93-1. Prevalence of typical symptoms in 840 subjects with reflux esophagitis divided according to age. (Adapted from Pilotto A, Franceschi M, Leandro G, et al. Clinical features of reflux esophagitis in older people: a study of 840 consecutive patients. *J Am Geriatr Soc*. 2006;54:1537–1542.)

TABLE 93-3 TYPICAL AND ATYPICAL SYMPTOMS OF GASTROESOPHAGEAL REFLUX DISEASE

TYPICAL SYMPTOMS	ATYPICAL SYMPTOMS
Heartburn	Pulmonary symptoms:
Acid regurgitation	Bronchial asthma
Epigastric pain	Bronchiectasis
	Chronic bronchitis
	Chronic cough
	Otorhinolaryngeal symptoms:
	Hoarseness

	Chronic laryngitis Odynophagia Noncardiac chest pain

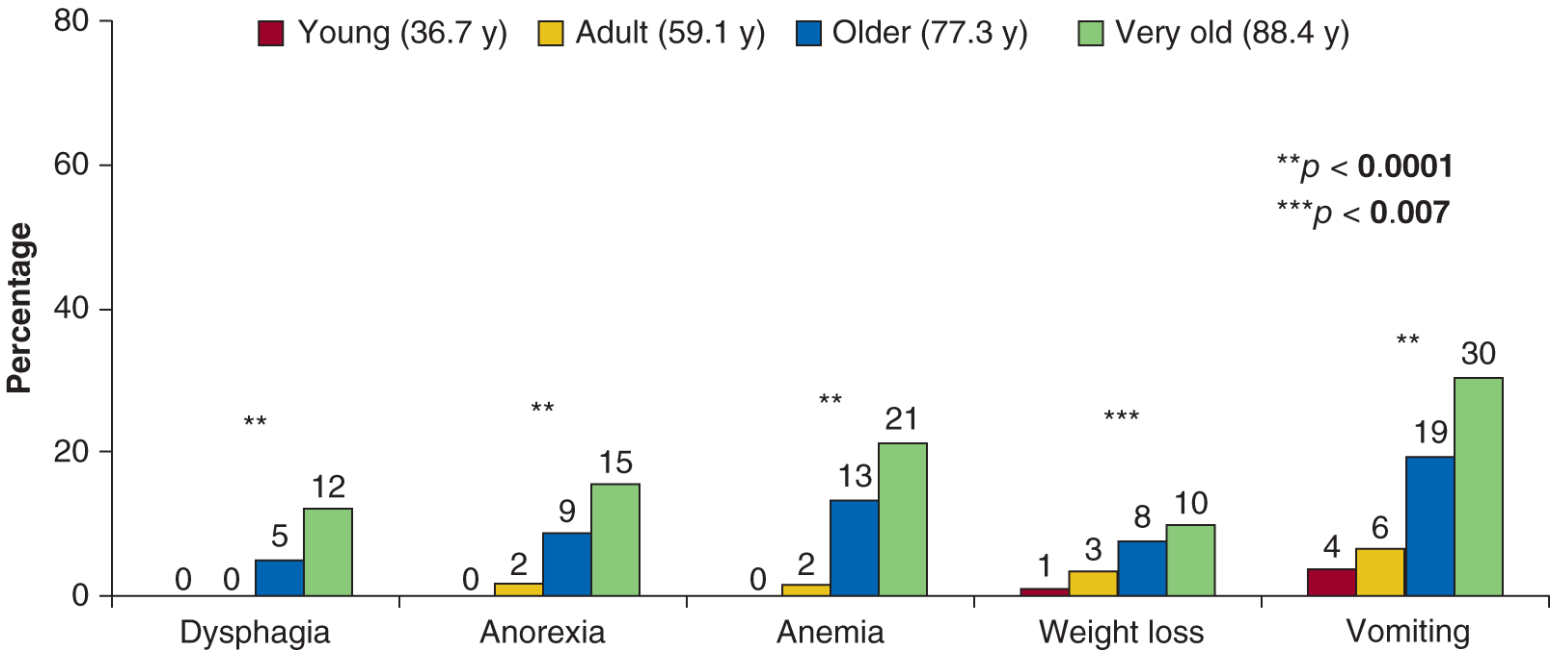


FIGURE 93-2. Prevalence of nonspecific symptoms in 840 subjects with reflux esophagitis divided according to age. (Adapted from Pilotto A, Franceschi M, Leandro G, et al. Clinical features of reflux esophagitis in older people: a study of 840 consecutive patients. *J Am Geriatr Soc*. 2006;54:1537–1542.)

Evaluation

Since the presentation of GERD is often nonspecific in older adults, *endoscopy* should be undertaken early as the initial diagnostic test in all older patients suspected of having GERD. Early endoscopy is very useful in diagnosing the presence and the grade of severity of esophagitis (**Table 93-4**) and/or hiatus hernia, which are important prognostic factors to be considered in long-term treatment. Endoscopy will also identify GERD complications, especially esophageal stricture and Barrett esophagus, and concomitant gastroduodenal diseases, that is, gastric or duodenal ulcers and/or *H pylori* infection. *Barium radiography* of the esophagus is a useful test to establish the presence of a hiatus hernia and is indicated as part of the evaluation of the patient with suspected motility abnormalities or peptic stricture. A barium study may also identify rings and webs or other obstructive lesions. The barium swallow test is also a key test in studying older patients with dysphagia, and it should be performed in conjunction with endoscopy in all older patients with this symptomatology. Barium studies are widely available and usually well tolerated by older people. *Esophageal 24-hour pH testing* is helpful before antireflux surgery and in those patients not responsive to medical treatment. In the patient with persistent symptoms and a negative endoscopy, an abnormal esophageal pH test may suggest the need for more aggressive drug therapy, whereas a normal test may indicate the presence of a functional disorder. In the patient with persistent esophagitis, a normal test could differentiate pathophysiological mechanisms, that is, a drug-induced esophagitis from acid reflux disease. *Esophageal manometry* is useful in identifying abnormalities of LES pressure or esophageal motility. In older patients, its major use is reserved for the localization of LES before pH testing and for obtaining preoperative information on esophageal peristalsis.

TABLE 93-4 ENDOSCOPIC CLASSIFICATION OF ESOPHAGITIS (ACCORDING TO THE LOS ANGELES GRADING SYSTEM)

GRADE	DESCRIPTION
Grade A	One or more mucosal breaks no longer than 5 mm, none of which extends between the tops of two mucosal folds

Grade B	One or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds
Grade C	Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference
Grade D	Mucosal breaks that involve at least 75% of the esophageal circumference

From Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45:172–180.

A therapeutic trial with PPI test has been suggested as a useful diagnostic test in patients with GERD. Meta-analyses of clinical studies demonstrated that an empiric PPI trial has 78% sensitivity and 54% specificity in confirming the diagnosis of GERD when compared with endoscopy or 24-hour esophageal pH monitoring. In patients with noncardiac chest pain, sensitivity and specificity are reported to be 80% and 74%, respectively. Since typical (heartburn, acid regurgitation) and extraesophageal symptoms (asthma, chronic cough, noncardiac chest pain) of GERD are often absent in older patients, the patient's history is less reliable and the high prevalence of severe esophagitis despite mild symptoms suggests a trial of PPIs should be used with great caution in older patients, possibly only after endoscopy as a first diagnostic test.

Management

The objectives of GERD treatment are (1) relief of symptoms, (2) healing of the esophagitis, (3) prevention of the relapse, and (4) prevention of the complications.

Nonpharmacological Recommendations for lifestyle modifications are based on the presumption that certain foods, body position, tobacco, alcohol, and obesity contribute to a dysfunction in the body's antireflux defense system. Although there is clinical and physiologic evidence that smoking, alcohol, chocolate, peppermint, coffee, fatty, or citrus intake may adversely affect symptoms or esophageal pH, there is little evidence that cessation of these agents will improve GERD variables. Elevation of the head of the bed and weight loss, however, has been associated with improvement in GERD variables in case-control studies. Medications that decrease LES pressure and promote gastroesophageal reflux as well as drugs that may cause direct esophageal injury (see **Table 93-2**) should be avoided when possible or used with caution in older patients with GERD. In any case, these drugs must be taken while maintaining an upright position and with a full glass of water.

Drugs

Short-Term Therapy Antacids and alginic acid provide symptomatic relief in mild nonerosive esophagitis. Possible side effects of antacids include salt overload, constipation, hypercalcemia, and interference with absorption of other drugs, particularly antibiotics such as tetracycline, azithromycin, and quinolones.

Prokinetic drugs, either alone or in combination with antisecretory drugs, are only moderately effective in GERD. Currently, prokinetic drugs include metoclopramide, clebopride, domperidone, and partially levosulpiride. Unfortunately, no controlled clinical trials have evaluated the role of these drugs specifically in the treatment of GERD in older adults. Antireflux therapy is focused largely on suppressing gastric acid secretion with H_2-blockers and PPIs.

A series of meta-analyses of 34 trials including 1314 participants demonstrated that PPIs were more effective than H_2-blockers and prokinetics in relieving heartburn both in patients with GERD who were treated empirically (PPI vs H_2-blockers: seven trials, RR 0.66, 95% CI 0.60–0.73 and PPI vs prokinetics: two trials, RR 0.53, 95% CI 0.32–0.87) and in patients with endoscopy-negative reflux disease (ENRD) (PPI vs H_2-blockers: three trials, RR 0.78, 95% CI 0.62–0.97 and PPI vs prokinetics: one trial RR 0.72, 95% CI 0.56–0.92) (**Figure 93-3**). Moreover, a meta-analysis of 134 trials involving 35,978 patients with esophagitis demonstrated a statistically significant benefit of taking standard dose PPI therapy (five trials, RR 0.22; 95% CI 0.15–0.31) and H_2-blockers (10 trials, RR 0.74, 95% CI 0.66–0.84) but not prokinetics (three trials, RR 0.71, 95% CI 0.46–1.10) compared to placebo in healing of esophagitis. In addition, 26 trials evaluating 4032 participants reported that there was statistically significant benefit of taking PPI therapy compared to H_2-blockers or H_2-blockers plus prokinetics in healing of esophagitis (RR 0.51, 95% CI 0.44–0.59). Thus, while PPI therapy resulted the most effective therapy for heartburn relief and healing of esophagitis, and H_2-blockers therapy was also superior to placebo, there is reportedly no evidence of the superiority of prokinetics over placebo (**Figure 93-4**).

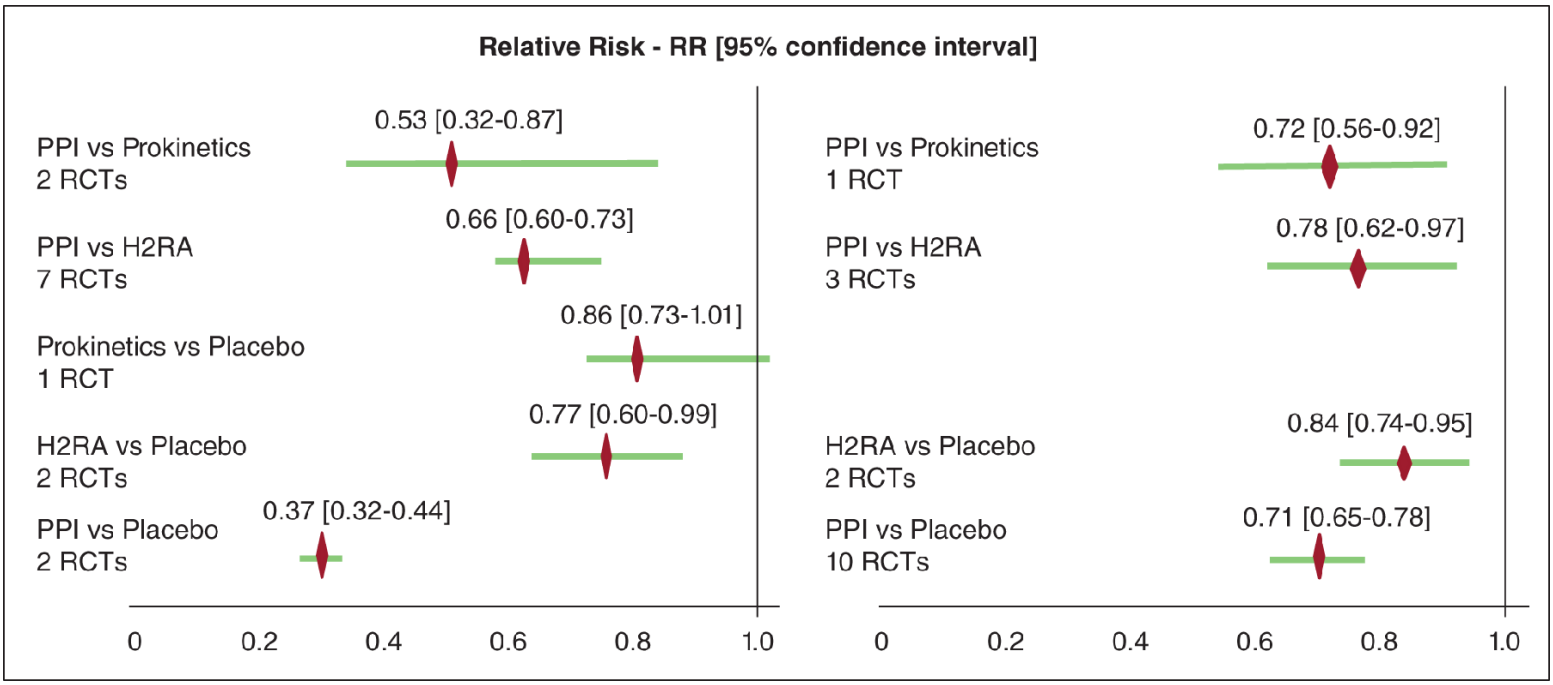


FIGURE 93-3. Efficacy of short-term use of proton pump inhibitors (PPI), H_2-receptor antagonists (H2RA), and prokinetics in adults with GERD treated empirically and in those with endoscopy-negative reflux disease (ENRD). (Adapted from Sigterman KE, van Pinxteren B, Bonis PA, et al. Short-term treatment with proton pump inhibitors, H_2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. *Cochrane Database Syst Rev*. 2013:31;5:CD002095.)

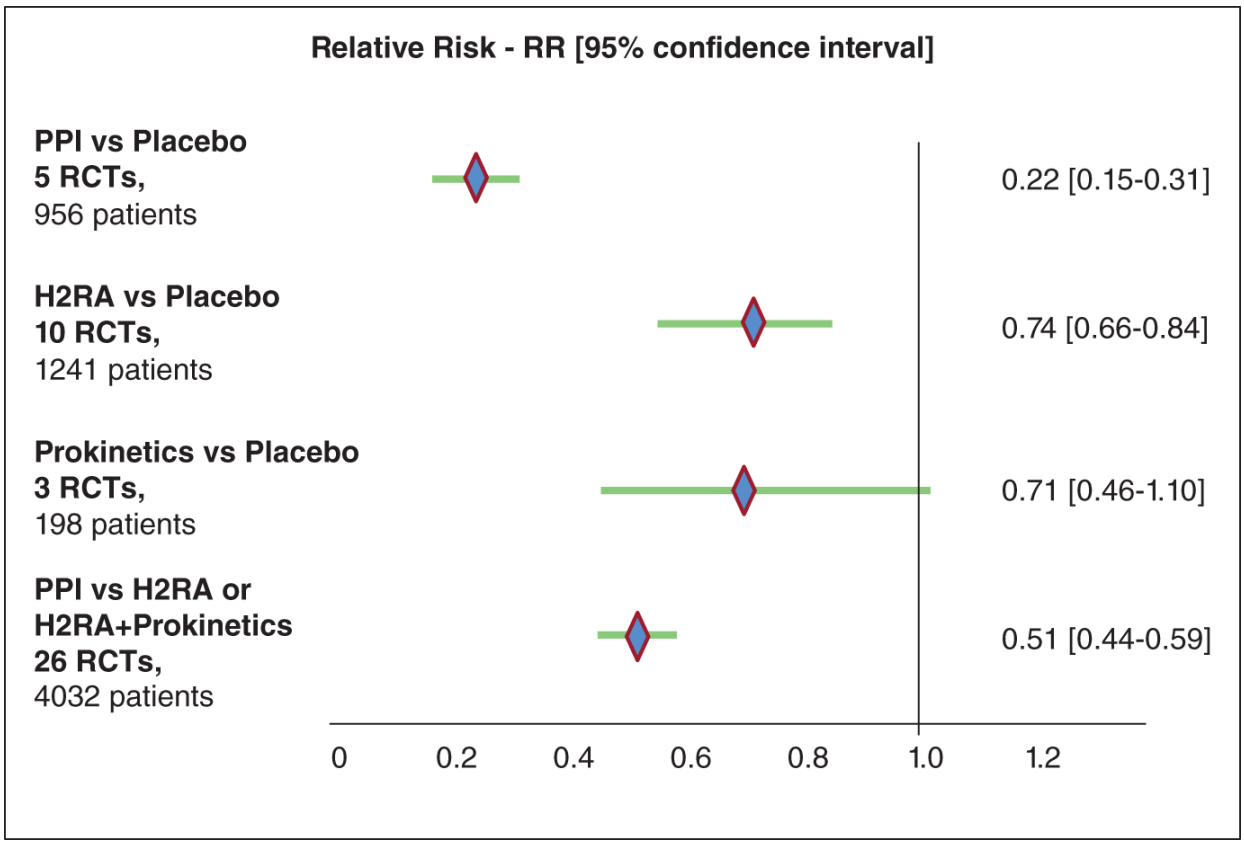


FIGURE 93-4. Effectiveness of proton pump inhibitors (PPIs), H_2-receptor antagonists (H2RAs), prokinetic therapy, sucralfate, and placebo in healing esophagitis. (Adapted from Khan M, Santana J, Donnellan C, et al. Medical treatments in the short term management of reflux oesophagitis. Update in *Cochrane Database Syst Rev*. 2011;(2):CD003244.)

Currently, five PPIs are available: omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. Some age-associated differences in pharmacokinetics and pharmacodynamics of the PPIs have been reported. However, it is

unknown if these differences are associated with different clinical effects, particularly in older patients. Indeed, a series of meta-analyses evaluating acute therapy of esophagitis reported that the PPIs were superior to ranitidine and placebo in healing erosive esophagitis, without significant differences in efficacy between omeprazole 20 mg daily and lansoprazole 30 mg daily or pantoprazole 40 mg daily or rabeprazole 20 mg daily. A systematic review of randomized controlled trials, however, comparing standard dose PPIs reported a lower 8-week healing rate of esophagitis with omeprazole 20 mg or lansoprazole 30 mg daily, but not with pantoprazole 40 mg daily, compared to esomeprazole 40 mg daily (**Table 93-5**). The recent finding that omeprazole has considerable potential for drug interactions, since it has higher affinity for the cytochrome CYP2C19 than other PPIs, may explain these differences in efficacy, especially in older patients who are treated with concomitant therapies.

TABLE 93-5 ■ RANDOMIZED CONTROLLED TRIALS COMPARING STANDARD DOSE PPIS IN THE HEALING OF ESOPHAGITIS AT 8 WEEKS

	TOTAL NUMBER OF PATIENTS	ESOPHAGITIS HEALED	%	P
Lansoprazole	3262	2698	82.7	0.0001
Esomeprazole	3264	2807	85.9	
Omeprazole	2431	1998	82.2	0.0001
Esomeprazole	2446	2167	88.6	
Pantoprazole	1709	1507	88.2	*Not significant*
Esomeprazole	1688	1523	90.2	

Data from Edwards SJ, Lind T, Lundell L. Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis—a comparison of esomeprazole with other PPIs. Aliment Pharmacol Ther. 2006;24:743–750.

Long-Term Maintenance Therapy GERD is a chronic disease with a 70% to 90% annual relapse rate after the interruption of an effective antisecretory regimen. Risk factors for relapse of the disease are shown in **Table 93-6**. Maintenance therapy with antisecretory drugs is a significant protective factor in reducing the occurrence of relapse of GERD in older patients. Several studies have shown higher efficacy of PPIs over H_2-blockers and prokinetics in maintaining a healed esophagitis. There are two main approaches to drug therapy for GERD: step-up and step-down. In the step-up approach, therapy is initiated with weak inhibition of gastric acid (eg, an H_2-blocker or half dosage of a PPI), and progresses to a higher degree of acid inhibition (standard and then escalating doses of PPI), until adequate symptom control is obtained. The step-down approach involves starting with the most effective regimen (full dosage of a PPI) and switching to lower doses of PPI for maintenance therapy once symptoms are under control. This latter approach is perhaps more rational, based on evidence showing superior efficacy of PPIs over H_2-blockers across all grades of severity of GERD. Withdrawal of maintenance therapy with PPI after 6 months significantly reduces the percentage of remission of esophagitis at 1 year from 95% to 33% in patients older than 65 years (**Figure 93-5**). Presently, no comparative studies have been carried out to evaluate which strategy (step-down vs step-up) is more cost-effective in older subjects.

TABLE 93-6 ■ RISK FACTORS FOR RELAPSE OF ESOPHAGITIS

RISK FACTORS

Patient's characteristics
Old age
High body mass index (BMI)
Clinical features
Long history of reflux symptoms
Latency prolonged between appearance of symptoms and therapy
Persistence of symptoms after the healing of esophagitis
Endoscopic characteristics
Severity of the esophagitis at baseline
Presence of a large hiatus hernia
Pathophysiology features
Reduced pressure of the lower esophageal sphincter (manometry)
Modified curve at the 24-h pH-metry

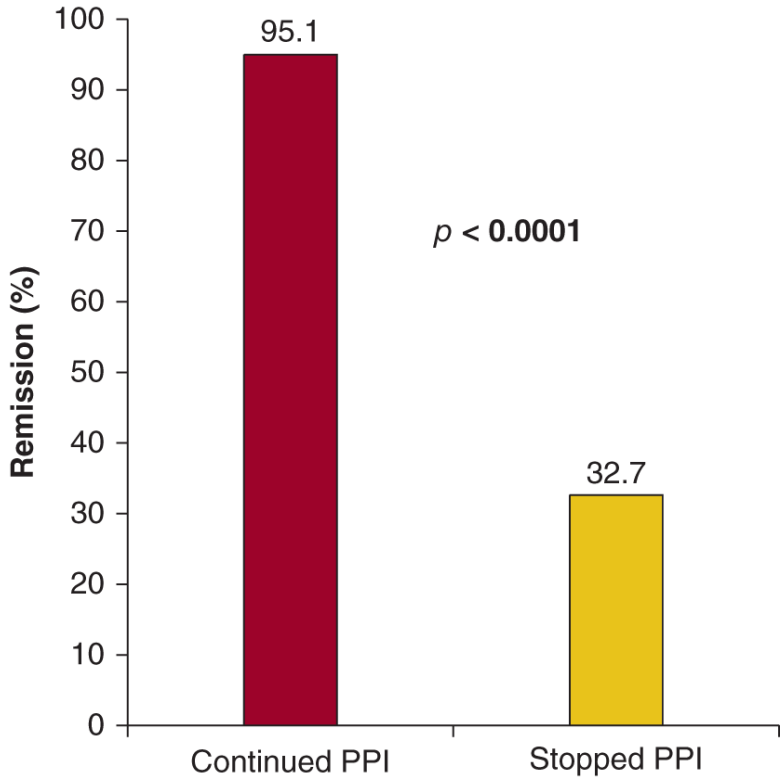


FIGURE 93-5. Remission at 12 months in older patients with esophagitis who continued versus stopped PPI maintenance treatment after 6 months. (Data from Pilotto A, Leandro G, Franceschi M, et al. Short- and long-term therapy for reflux oesophagitis in the older: a multi-centre, placebo-controlled study with pantoprazole. *Aliment Pharmacol Ther*. 2003;17:1399–1406.)

Safety of Long-Term Antisecretory Treatment

PPIs represent a very effective class of drugs widely prescribed in all age populations, including older subjects, and often for prolonged periods of time. Thus, safety evaluation of long-term treatment with PPIs is emerging as a major topic in clinical practice.

PPIs and esophageal and gastric histologic changes There is presently no evidence supporting the hypothesis that long-term PPI therapy may increase the risk of neoplastic degeneration in patients with Barrett esophagus. Conversely, based on meta-analysis of observational studies, the long-term use of PPIs was associated with a decreased risk of esophageal adenocarcinoma and/or high-grade dysplasia in patients with Barrett esophagus.

Similarly, there is no evidence that the long-term use of PPIs may cause or accelerate the progression of corpus

gastric atrophy or intestinal metaplasia. A study explored the long-term safety of omeprazole for up to 11 years in patients (including some older adults) with refractory reflux esophagitis. Annual incidence of gastric corpus mucosal atrophy was 4.7% in *H pylori*–positive individuals and 0.7% in *H pylori*–negative patients. Moreover, mucosal atrophy was mainly observed in older patients who had moderate or severe gastritis at entry into the study. Corpus intestinal metaplasia was rare and no dysplasia or neoplasms were observed.

A positive association between fundic gland polyps (FGPs) and acid suppression was first observed in 1992 and a study reported a 7.3% incidence of FGPs after a mean PPI treatment duration of 32.5 months, while polyp regression was noted following discontinuation of acid suppression therapy.

PPIs and hypergastrinemia The physiological role of gastrin is to stimulate gastric enterochromaffin-like (ECL) cells to secrete histamine, which in turn stimulates the secretion of hydrochloric acid from gastric parietal cells. Since PPIs inhibit the final step of gastric acid secretion by irreversible binding to the parietal cell H^+K^+ATPase (the proton pump), a secondary hypergastrinemia may occur in subjects long-term treated with PPIs. Indeed, a significant increase in the average serum gastrin level as well as a diffuse (simple) or linear/micronodular (focal) ECL-cell hyperplasia has been observed in patients who made continuous use of PPIs. The clinical relevance, however, of these findings is currently uncertain.

PPIs and iron and vitamin B_{12} deficiencies While gastric acid suppression may decrease iron absorption, it remains uncertain whether iron-deficiency anemia may result from chronic PPI therapy.

Recent studies suggest an association between long-term use of gastric acid suppressant drugs, particularly PPIs, and the development of vitamin B_{12} deficiency, especially in older subjects. A significant increase in vitamin B_{12}–deficiency anemia in long-term antisecretory drug users, however, has not been clearly established. With the current available information, it is appropriate to evaluate vitamin B_{12} status in long-term users of PPIs, especially in older subjects who may have poor nutrition (and therefore low vitamin B_{12} intake) and/or in patients requiring life-long PPI treatments, such as those with Zollinger-Ellison syndrome or other gastric acid hypersecretory states.

PPIs and magnesium Long-term PPI use can be associated with a subclinical magnesium deficiency status, as has been observed in hospitalized adult patients. Thus, the FDA has suggested monitoring serum magnesium levels in patients on PPI therapy. The mechanism and frequency of PPI-induced hypomagnesaemia are unclear.

PPIs, bone metabolism, osteoporosis, and risk of fractures Antisecretory drugs may interfere with calcium absorption through induction of hypochlorhydria; PPIs, moreover, may reduce bone resorption through inhibition of the osteoclastic vacuolar proton pump. Indeed, a long-term PPI therapy has been associated with an increased risk of hip, wrist, or spine fractures. The risk of fracture is higher in patients who receive multiple daily doses of PPIs and therapy is prolonged for a period of at least 1 year or longer. Additional risk factors for osteoporosis, such as old age and female gender, may also contribute to increase the risk of fractures in long-term acid suppression drug users.

PPIs and enteric infections Inhibition of acid secretion may induce an increase of the bacterial flora at the gastrointestinal level with potential to increase the incidence of systemic infections particularly in immune depressed older subjects. Indeed, the use of antisecretory drugs has been associated with an increased risk of infections of the lower gastrointestinal tract, mainly because of *Salmonella* spp. and *C difficile*. In a large population-based study, subjects treated with acid-lowering drugs had a threefold higher risk of developing bacterial diarrhea than those taking hypotensive or antiasthmatic medications. In older patients this susceptibility is increased even more so, particularly for *Salmonella* and *Campylobacter* infections. Some data suggest that a widespread use of PPIs, especially in the hospital setting, may contribute to the current in-hospital epidemic of *C difficile* infections. Indeed, a recent epidemiological study reported that 64% (88 out of 138) of all older hospitalized patients who developed this infection were on PPIs.

PPIs and community-acquired pneumonia A series of observational studies have suggested that the use of PPIs could increase the risk of hospitalization for community-acquired pneumonia (CAP), particularly in older subjects. The potential presence of confounding factors, however, seems to limit the conclusions of these studies. Indeed, recent meta-analyses have demonstrated that PPI and H_2-blockers long-term use is not associated with an increased risk of hospitalization for CAP. While the pathophysiological mechanisms which contribute to an increased risk of CAP in patients using PPIs are not well established, a significant increase in *Streptococcus pneumoniae* infection was reported in a recent study. Overall data suggest that concerns regarding this possible association should not influence prescribing of gastric acid-suppressing medications.

PPIs and functional decline and mortality Recently, chronic use of PPIs has been associated with a significant higher risk of functional decline in frail older subjects. Moreover, a study reported that in older patients discharged from acute care hospitals, the use of high-dose PPIs was associated with increased 1-year mortality. Although further studies are needed, these data suggest caution when continuing PPIs following an episode of hospitalization in older adults.

Bioavailability and metabolism of other agents Several studies have addressed the important clinical issue of a possible interaction between PPIs and other drugs, when they are given to patients treated with multiple medications. Since PPIs are mainly metabolized by the cytochrome P450 (CYP), particularly the subfamily CYP2C19, clinically relevant drug interactions may occur in case of concomitant administration of CYP-2C19-metabolized drugs.

Recently, it was shown that omeprazole competitively interferes with conversion of clopidogrel to its active metabolite through the CYP2C19 pathway. Despite the significance of this interference remains controversial, switching to another PPI that may not significantly use this pathway, such as pantoprazole, lansoprazole or rabeprazole, or to a H_2-blockers, may be warranted.

Special Issues: Overutilization of Acid Inhibitors

Acid inhibitors are among the most commonly used pharmaceuticals, that is, 14.9 million patients received 157 million prescriptions for PPIs in the United States in 2012. A recent study on 946 patients showed that 35% were prescribed PPI therapy for a documented upper GI disorder, 10% for empirical symptomatic treatment, and 18% for gastroprotection of NSAIDs or antiplatelet drugs, while up to 36% of subjects had no documented appropriate indication for PPI therapy. Other studies have reported that PPIs are frequently prescribed during hospitalization, especially in older adults, and that as many as 50% of such a prescriptions may be continued after discharge without clear indications. All these data suggest that older patients on long-term PPI therapy should be periodically evaluated for the indications for continued therapy.

The Role of Surgery

The role of surgery in the treatment of GERD is controversial. Laparoscopic fundoplication has greatly reduced the morbidity and mortality of antireflux surgery, this is also true for older adults. Thus, the indications for surgery are evolving. At present, evidence suggests that surgery may be indicated in older patients who (1) are medical treatment failures; (2) have severe complications, that is, strictures not treatable by endoscopy; (3) have severe dysphagia, aspiration, or atypical symptoms associated with a large hiatal hernia; and/or (4) have preneoplastic lesions, that is, Barrett esophagus with high-grade dysplasia. Randomized clinical studies are needed to compare the outcome of antireflux surgery with that of medical therapy in older adults. Furthermore, surgery for GERD should be centralized to units specialized in these techniques to reduce surgical complications and improve successful clinical outcomes.

PEPTIC ULCER DISEASE

Definition

Peptic ulcer is a break of the mucosa lining the stomach or the duodenum. According to their anatomical location, peptic ulcers are divided into *gastric ulcers*, that is, peptic ulcers of the gastric fundus, body, or antrum; *prepyloric and pyloric ulcers*, that is, located within 3 cm from the pyloric ring and in the pyloric ring, respectively; and *duodenal ulcers*, that is, located into the bulb or in the second portion of the duodenum (**Figure 93-6**).

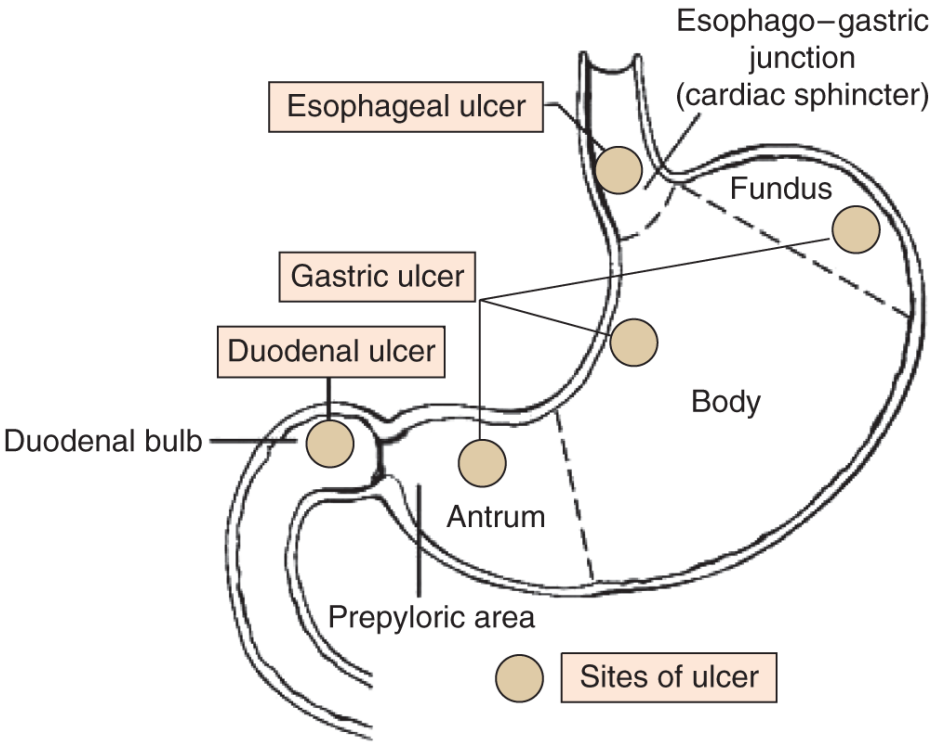


FIGURE 93-6. Anatomical location of peptic ulcers.

Epidemiology

The prevalence of peptic ulcer disease worldwide ranges from 0.1% to 4.7%, with an annual incidence ranging from 0.19% to 0.3%. The worldwide peptic ulcer prevalence differs, with duodenal ulcers dominating in Western populations and gastric ulcers being more frequent in Asia. Recent epidemiological studies indicate that the prevalence and incidence of the peptic ulcer show a constant decline in the general population, but the incidence of peptic ulcer and its complications increases with advancing age (**Figure 93-7**). Indeed, the rates of hospitalization for complicated peptic ulcer (**Figure 93-8**) and mortality rates for upper GI complications (**Figure 93-9**) remain very high in older patients.

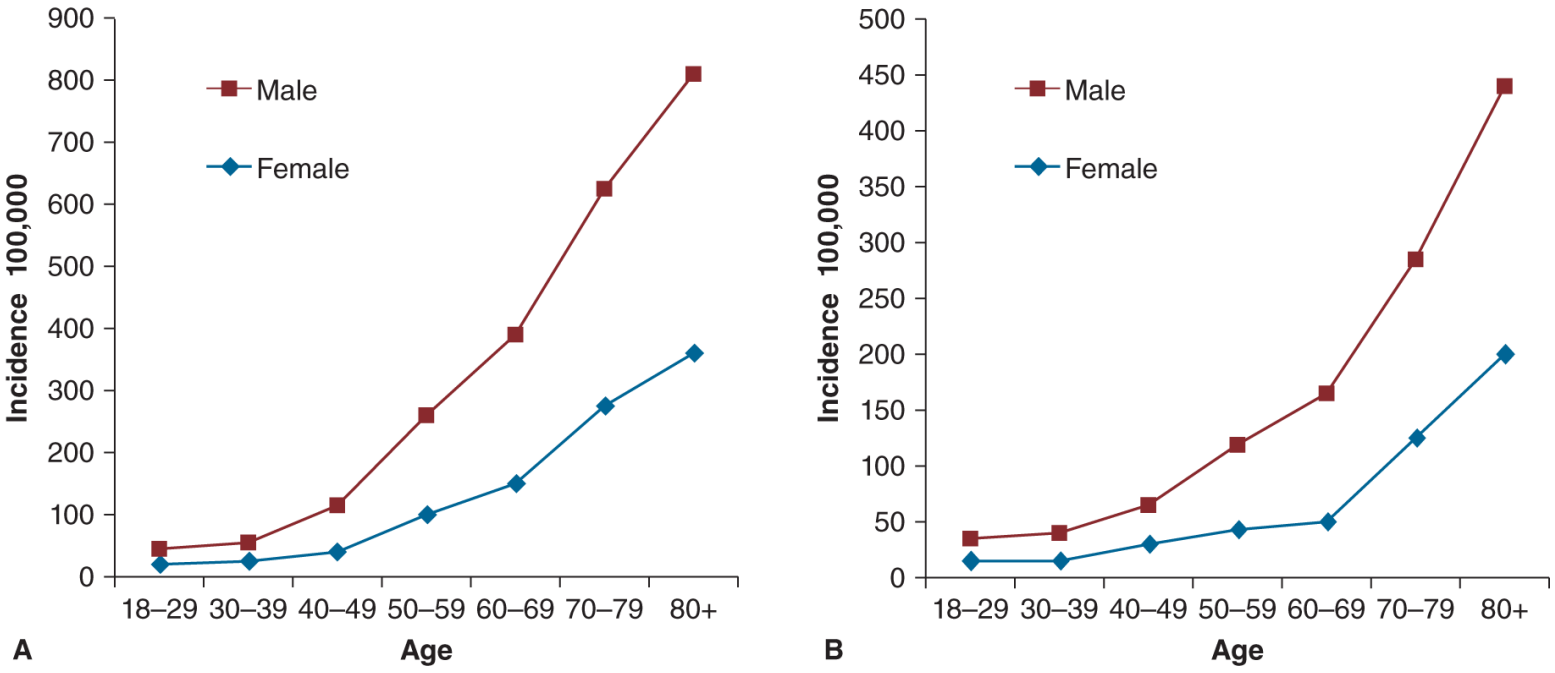


FIGURE 93-7. Age- and gender-specific annual incidence of peptic ulcer disease (**A**) and severe complications (**B**) (per 100,000) during

2000 to 2008 in Finland. (Adapted from Malmi H, Kautiainen H, Virta LJ, et al. Incidence and complications of peptic ulcer disease requiring hospitalisation have markedly decreased in Finland. *Aliment Pharmacol Ther*. 2014;39:496–506.)

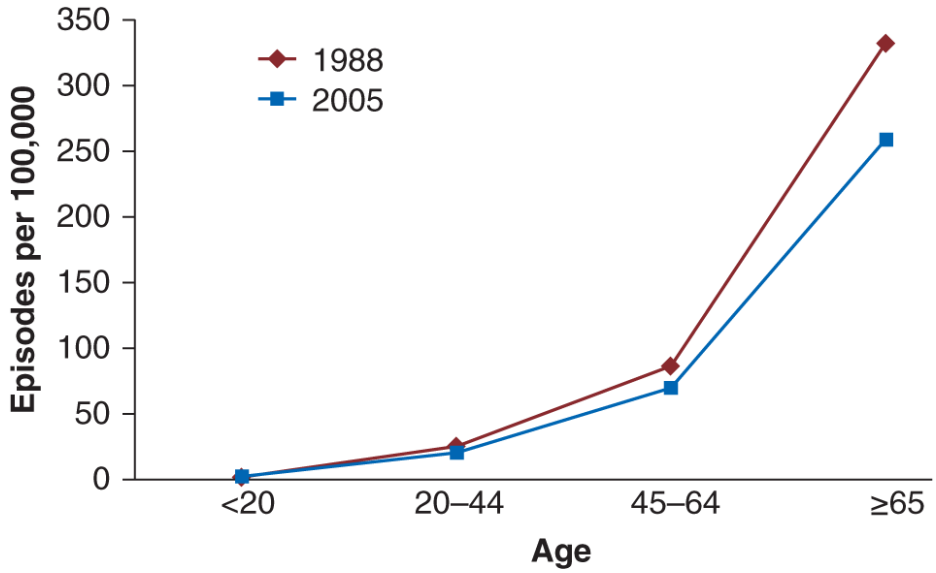


FIGURE 93-8. Trends in hospitalizations for peptic ulcer disease in United States according to age. (Adapted from Feinstein LB, Holman RC, Yorita Christensen KL, et al. Trends in hospitalizations for peptic ulcer disease, United States, 1998–2005. *Emerg Infect Dis*. 2010;16:1410–1418.)

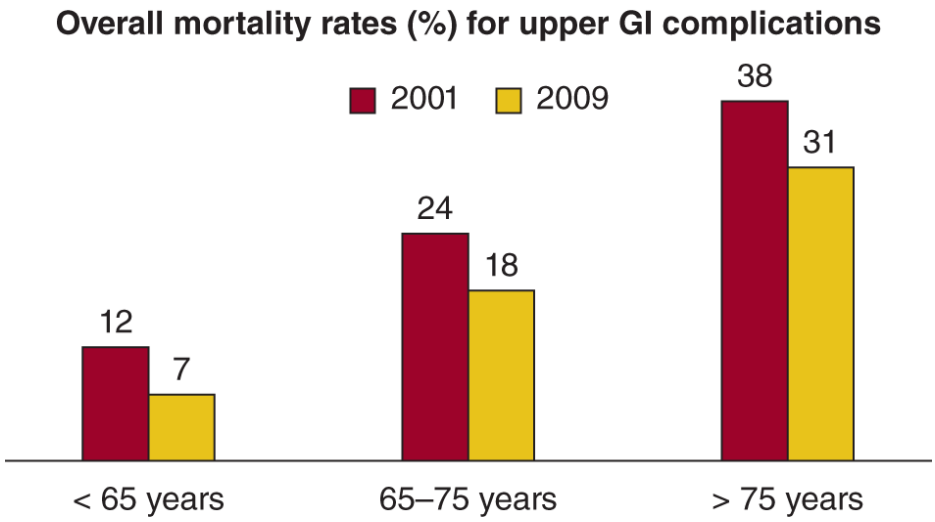


FIGURE 93-9. Mortality rates (%) for upper GI complications in the different age groups in United States in 2001 and 2009. (Adapted from Laine L, Yang H, Chang SC, et al. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol*. 2012;107:1190–1195.)

Pathophysiology and Classification

Two main factors that might explain the observed increase in peptic ulcer in older patients are the high prevalence of *H pylori* infection and the frequent use of mucosa-damaging drugs, that is, NSAIDs and/or aspirin. Nevertheless, in older subjects, around 20% of all peptic ulcers are not associated with either of these risk factors (**Figure 93-10**). Pathophysiology of the "idiopathic" non-NSAID, non-*H pylori* peptic ulcers is still uncertain; a critical disequilibrium between protective and erosive factors in the gastric or duodenal mucosa, however, seems to be involved. Several studies demonstrated that advancing age is associated with a reduction of the gastric mucosal barrier, that is, the capacity to resist external damage owing to secretion of gastric mucus, bicarbonate secretion, mucosal prostaglandins, gastric mucosal proliferation and/or mucosal blood flow. Moreover, in older patients with peptic ulcer, normal or high levels of gastric acid and pepsin secretions have been observed. Previous studies reported that advancing age was

independently related to chronic atrophic gastritis and a functional status of hypo/achlorhydria. More recent data suggested that atrophic changes of the gastric mucosa are associated with *H pylori* infection rather than with aging. Emotional stress, smoking tobacco, and/or alcohol use are potential risk factors that may contribute to the development of peptic ulcer in predisposed subjects.

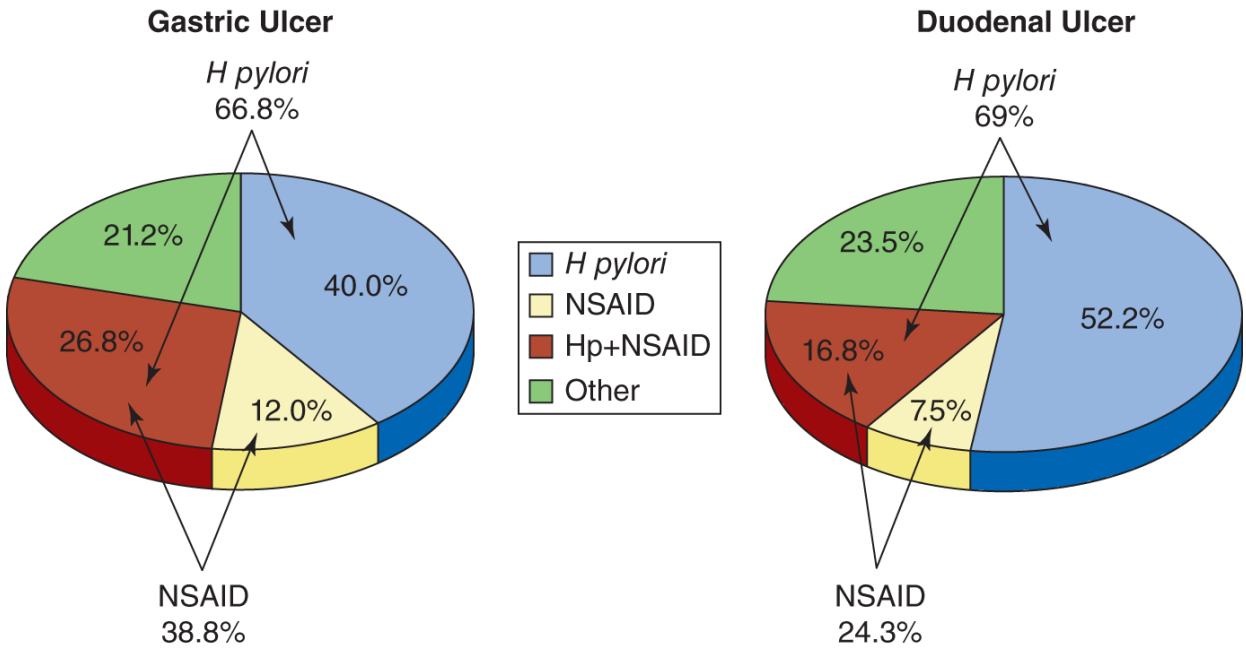


FIGURE 93-10. Prevalence of gastric and duodenal ulcer in older patients divided according to the presence of *H pylori* infection and/or NSAID use. (Adapted from Pilotto A, Franceschi M, Maggi S, Addante F, Sancarlo D. Optimal management of peptic ulcer disease in the older. *Drugs Aging*. 2010;27:545–558.)

H pylori–Associated Peptic Ulcer

Approximately, 70% of older peptic ulcer patients are *H pylori* positive (see **Figure 93-10**). Controlled studies, performed on older patients, reported that the treatment of *H pylori* infection healed ulcers in more than 95% of patients and improved symptoms in more than 85% of patients. Moreover, long-term studies performed in older patients with peptic ulcer demonstrated that the eradication of *H pylori* infection significantly improved clinical outcome, reducing ulcer recurrences and symptoms. Significant reduction of ulcer relapses after *H pylori* eradication is the main factor that demonstrated the pathogenic role of *H pylori* in peptic ulcer disease. Indeed, health programs leading to widespread eradication of *H pylori* infection in symptomatic patients have significantly reduced the prevalence of peptic ulcer, particularly of duodenal ulcer, both in Europe and in the Far East. Unfortunately, the percentage of older patients with peptic ulcer who are treated for their *H pylori* infection is still quite low. A study performed in the United States reported that of patients older than 65 years who were hospitalized for ulcer disease, only 40% to 56% were tested for *H pylori* infection; among the subjects who resulted *H pylori* positive, only 50% to 73% were treated with specific antibiotic-based anti-*H pylori* therapy.

NSAID/Aspirin-Associated Peptic Ulcer

In older patients, approximately 25% of duodenal ulcers and 40% of gastric ulcers are associated with the use of NSAIDs and/or aspirin (see **Figure 93-10**). The risk of NSAID-related peptic ulcers and their severe complications tends to increase linearly with age and becomes particularly high in the presence of disability, comorbidity, and polypharmacy. A case-control study performed in more than 3000 older patients who underwent an endoscopy documented that subjects undergoing treatment with NSAIDs and/or aspirin had a higher prevalence of gastric and duodenal ulcers compared to nonuser control subjects. Moreover, the risk of peptic ulcer is significantly higher in acute than chronic users of NSAIDs or aspirin (**Figure 93-11**). The injurious gastroduodenal effects of NSAIDs and aspirin are mainly caused by the inhibition of COX-1 and its role in mucosal defense mechanisms and also through the inhibition of thromboxane A2, which reduces platelet functions, resulting in a higher risk of bleeding. However, a direct effect on gastroduodenal mucosal surface cannot be excluded especially by those NSAIDs that have a high

acid/base pK ratio.

	NSAID Acute Users		NSAID Chronic Users	
	OR	95% CI	OR	95% CI
Gastric ulcer	4.47	3.19–6.26	2.80	1.97–3.99
Duodenal ulcer	2.39	1.73–3.31	1.68	1.22–2.33

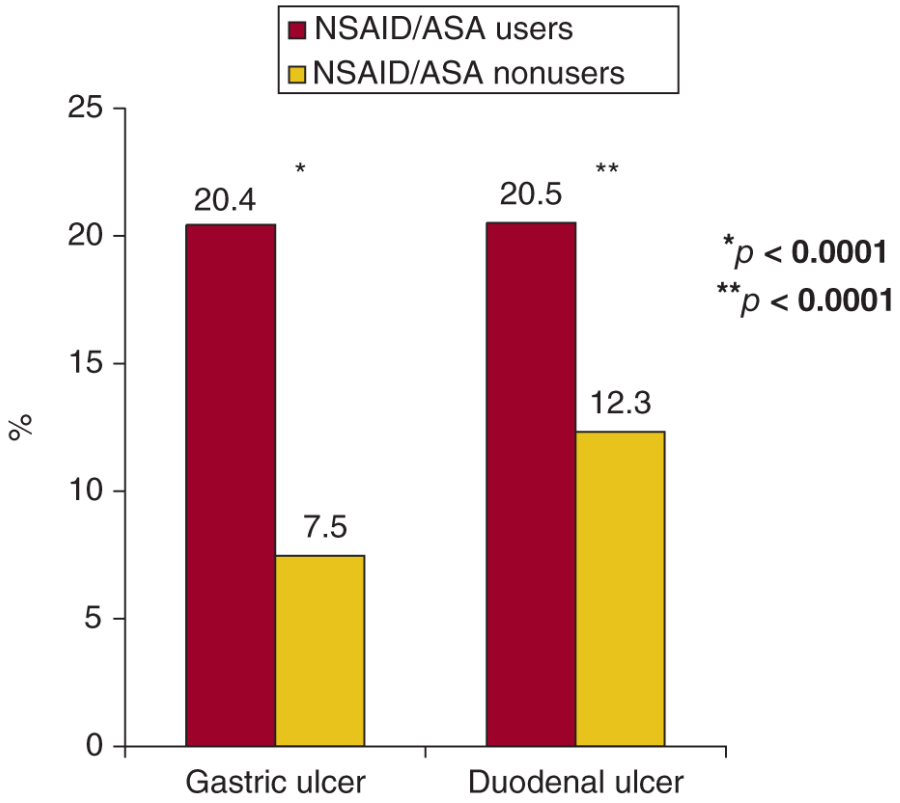


FIGURE 93-11. Prevalence of gastric ulcer and duodenal ulcer in NSAID users and NSAID nonusers. ASA, aspirin. (Data from Pilotto A, Franceschi M, Leandro G, et al. Proton-pump inhibitors reduce the risk of uncomplicated peptic ulcer in older either acute or chronic users of aspirin/non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther*. 2004;20:1091–1097.)

Different NSAIDs are associated with distinct GI adverse events, nevertheless none of them shows an absolutely safe profile. Drug-related pharmacodynamic and pharmacokinetic properties may explain the individual variability observed in terms of adverse effects on the upper GI tract. Recently, a genetic predisposition due to polymorphism of cytochrome P4502C9 that reduces the metabolism of some NSAIDs with a prolonged duration of drug levels, enhancing the risk of GI mucosal damage, has been reported as a significant factor influencing the ulcerogenic effect of the different NSAIDs.

Presentation

In older adults, peptic ulcer is often difficult to diagnose. Indeed, symptoms of peptic ulcer may be atypical in old age. The patient's concomitant diseases and treatments may cause symptoms that mask those of the ulcer. A study reported that in patients older than 60 years, only one-third suffered from typical epigastric pain, and two-thirds experienced vague abdominal pain as a main symptom. Moreover, the intensity of pain may be less severe in older subjects and therefore may not receive the full attention of the physician or may not be taken seriously by the patient him/herself. Frequently, symptomatology includes nausea, vomiting, weight loss, and/or anorexia as the first, or even the only, symptom of peptic ulcer in older adults. Unfortunately, it is not rare that the first symptom might be a severe complication, especially bleeding or stenosis. In a study carried out in patients aged 80 years or more, the most

common symptom was epigastric pain in both gastric and duodenal ulcers, while anemia and vomiting were most common among the patients suffering from duodenal ulcers. Because of the insidious clinical presentation of the disease in older patients, the consequences of peptic ulcer disease are more serious than those in younger subjects.

Evaluation

Since the clinical presentation of peptic ulcer may be insidious in older adults, a careful evaluation of both specific upper GI symptoms as well as a range of nonspecific symptoms, including anorexia, weight loss, anemia, vomiting, and dysphagia, may be useful in reducing incorrect and under-recognized diagnoses in older people with upper GI diseases. Recently, the Upper Gastrointestinal Symptom Questionnaire for the Elderly (UGISQUE) was developed and validated in two independent cohorts of older patients. Interestingly, this questionnaire had significantly higher diagnostic accuracy than individual clusters of symptoms for predicting the presence of esophagitis, peptic ulcer or any pathological condition diagnosed by endoscopy. Upper GI endoscopy is always indicated for older subjects with new abdominal symptoms because of the high prevalence of serious gastric diseases in this age group.

Upper GI endoscopy is safe and well tolerated in older adults. By direct visual identification, the location and size of an ulcer can be described. Peptic ulcer is a round to oval mucosal defect, from 5 mm to even 4 cm in diameter, with a smooth base and perpendicular borders. A series of biopsies for excluding malignancy is mandatory both in the center and on the borders of the gastric ulcer, even if they are not elevated or irregular as in ulcerative forms of advanced gastric cancer. Gastric *biopsies* allow for identifying the presence and the severity of chronic gastritis and/or the presence of *H pylori* infection. Endoscopic healing is the gold standard for evaluating ulcer healing in clinical trials. The surrounding mucosa may present radial folds, as a consequence of the parietal scarring. *Barium radiography* of the stomach and duodenum is indicated as part of the evaluation of the patient with suspected motility disorders, peptic strictures, or fistulas in which gastrografin may be used as an alternative to barium in contrast studies. Radiography is contraindicated in the presence of bleeding, severe vomiting with a high risk of pulmonary aspiration, or in cases of suspected gastric or duodenal perforation. If a peptic ulcer perforates, air will leak from the inside of the gastrointestinal tract to the peritoneal cavity. This leads to “free gas” within the peritoneal cavity that may be observed underneath the diaphragm on an erect or supine lateral *abdominal x-ray*.

Testing for *H pylori* Infection

H pylori infection may be easily diagnosed by means of either histology evaluation, rapid urease test, or culture performed on gastric biopsies taken during endoscopy.

However, the biopsy site needs to be selected with care, since *H pylori* may only be found in the fundus or body and not in the antral mucosa of older patients who are taking antisecretory drugs. Moreover, the presence of chronic atrophic gastritis as a result of a past colonization of *H pylori* may be associated with a lower prevalence of the bacterium in the gastric biopsy specimens in the older than in adult or young patients. For the same reasons, the rapid urease test performed on gastric biopsies has lower sensitivity in subjects 60 years and older compared with younger patients. The presence and severity of histologically proven gastritis can be investigated through the histological evaluation of morphological parameters of the gastric mucosa. The Operative Link on Gastritis Assessment (OLGA) group has developed a new system for reporting gastritis histologically. The description of the elementary lesions represents the core element in the histology report. The system places the histologic phenotype of gastritis on a scale of progressively increasing risk of gastric cancer, based on a semiquantitative score of some of the elementary lesions, such as (1) lymphoid-monocytic inflammation; (2) polymorphs (i.e., activity); (3) atrophy (distinguished as metaplastic and nonmetaplastic); and (4) *H pylori* status (positive vs negative). These findings suggest that in older adults (1) it is advisable to perform gastric biopsies from both the antrum and the body of the stomach; and (2) a second test for *H pylori* should be performed in this age group if a urease-based or histologic test is negative.

Post-Treatment *H pylori* Evaluation

Successful eradication should always be confirmed by a noninvasive or an invasive test if endoscopy is clinically indicated. Older patients with a diagnosis of peptic ulcer (especially gastric ulcer), gastric mucosa-associated lymphoid tissue, lymphoma, or severe gastritis should be evaluated by endoscopy and gastric mucosal histology after completion of anti-*H pylori* therapy. Most experts agree that this evaluation must be carried out at least 1 month after completion of therapy in order to minimize false-negative results. Older patients with mild or moderate forms of chronic gastritis may be evaluated after therapy by a noninvasive test. The ^{13}C-urea breath test demonstrated significantly higher

sensitivity, specificity, and diagnostic accuracy than serology (IgG anti-*H pylori* antibodies) in older subjects. An *H pylori*–stool antigen (HpSA) test for the detection of *H pylori* has been suggested as a valuable option with a high-potential role in the diagnosis after eradication therapy. The HpSA test is an easy and quick procedure that does not require expensive equipment. In hospitalized frail older patients, the HpSA was significantly less accurate than the ^{13}C-urea breath test, while antibiotic therapy and corpus atrophy decreased the positivity rate. Another study of geriatric subjects reported that HpSA test had a post-treatment diagnostic accuracy comparable to the ^{13}C-urea breath test (91% vs 92%) without influence by cognitive status, disability, concomitant diseases, and cotreatments.

Other Noninvasive Tests

Serum pepsinogen I and II levels (sPGI, sPGII) are known to increase in the presence of *H pylori*-related nonatrophic gastritis. sPGII levels are higher in subjects with both gastric and duodenal ulcer, and levels correlate with the severity of inflammation. A study in older people reported that sPGII levels decreased significantly after a successful *H pylori* cure. Moreover, sPGI or the ratio of sPGI/sPGII measurements may be useful to identify atrophic gastritis of the gastric corpus. Assays for gastrin (particularly gastrin-17) could be an indicator of the morphological status of the antral mucosa.

Management of Peptic Ulcer Disease

Eradication of *H pylori* infection There is currently a worldwide consensus that the first-line therapy for eradication of *H pylori* infection should be triple therapy with a PPI twice daily combined with clarithromycin 500 mg twice daily and amoxicillin 1 g twice daily or a nitroimidazole 500 mg twice daily for a minimum of 7 days. The cumulative results of clinical trials evaluating anti-*H pylori* therapies in older subjects confirmed that PPI-based triple therapies for 1 week were highly effective and well tolerated. Adverse event rates of less than 13% were reported, with less than 6% of patients discontinuing therapy owing to these effects (**Table 93-7**). In older patients, a reduction of the dosage of the PPI from a twice to once daily standard dose did not influence cure rates of the PPI-triple therapies. Since aging may modify the pharmacokinetic distribution of clarithromycin, independent of renal function, clinical trials evaluated the efficacy of PPI-based triple therapies including clarithromycin at a low dose of 250 mg twice daily in combination with a PPI and amoxicillin (at the standard dosage of 1 g twice daily) or metronidazole (at the dosage of 400 mg or 500 mg twice daily) in older patients. Results demonstrated no significant differences in cure rates and tolerability between clarithromycin 250 mg versus 500 mg twice daily. All these findings suggest that in older patients, 1-week PPI-based triple therapies should include low doses of both PPIs and clarithromycin, in combination with standard doses of either amoxicillin or a nitroimidazole, to obtain excellent cure rates and tolerability. Increasing the duration of treatment from 7 days to 14 days is associated with higher eradication rates. At present, however, no studies have evaluated the clinical usefulness of these 2-week triple therapy regimens specifically in older patients. Recent studies designed to assess the eradication rate of a 10-day sequential regimen of 5 day of PPI plus amoxicillin followed by five additional days with PPI plus clarithromycin and tinidazole have reported significantly higher eradication rates in comparison with standard triple therapy in both geriatric and adult patients.

TABLE 93-7 CUMULATIVE RESULTS OF CLINICAL TRIALS EVALUATING 1-WEEK PPI-BASED TRIPLE THERAPIES, SEQUENTIAL AND QUADRUPLE THERAPIES AGAINST *HELICOBACTER PYLORI* INFECTION IN OLDER PATIENTS

		ERADICATION			
	PATIENTS (N)	ITT (%)	PP (%)	DROP OUTS (%)	SIDE EFFECTS (%)
Triple Therapy					
PPI + C + M or T	296	88.2	90.9	3.0	3.4
PPI + A[a] + C	253	84.2	89.1	5.5	7.1
PPI + A[a] + M	154	79.8	83.7	4.5	7.1
PPI + A[a] + C	90	80.0	82.8	3.3	11.5
Sequential Therapy					
PPI + A, PPI C + T[b]	89	94.4	96.6	2.2	10.3

Quadruple Therapy					
PPI + TE + M + BS	95	91.0	95.0	4.2	28.4

ITT, intent-to-treat analysis; PP, per-protocol analysis; PPI, proton pump inhibitors, that is, omeprazole 20 mg daily or twice daily, lansoprazole 30 mg twice daily, pantoprazole 40 mg daily, or esomeprazole 20 mg daily or twice daily; R, rabeprazole 20 mg twice daily; A, amoxicillin; BS, bismuth subcitrate 240 mg twice daily for 10 days; C, clarithromycin 250 mg twice daily; M, metronidazole 250 mg four times a day or 500 mg twice daily; T, tinidazole 500 mg twice daily; TE, tetracycline 500 mg

[a] 1 g twice daily or 500 mg three times a day.

[b] For 5 days followed by 5 additional days.

Data from Pilotto A, Franceschi M. Helicobacter pylori infection in older people. World J Gastroenterol. 2014;20(21):6364–6373.

Low compliance and antibiotic resistance are the two major reasons for treatment failure. Primary resistance to amoxicillin remains uncommon, but the frequency of clarithromycin resistance is now around 10% in most European countries and the United States. Metronidazole resistance ranges between 20% and 30% and is more frequent among women and in developing countries. Consensus exists in using clarithromycin and metronidazole for *H pylori* eradication therapies when prevalences of antibiotic resistance is lower than 15% and 40%, respectively. A multicenter study from northeastern Italy, carried out in subjects 25 to 90 years old, documented that primary resistance to metronidazole was 15% and to clarithromycin 1.8%, without significant differences in patients of different ages. Because failure of therapy is often associated with secondary antibiotic resistance, retreatment should ideally be guided by data on susceptibility. Since, such information is often unavailable, the choice of a second-line treatment depends on which treatment was used initially. Thus, if a clarithromycin-based regimen was used first, PPI–amoxicillin or tetracycline and metronidazole regimens should be recommended if bismuth is not available. Quadruple therapies, in which a PPI or an H_2-blocker is added to a bismuth-based triple regimen with high-dose metronidazole, have been also proposed as second-line therapy. Another retreatment approach without susceptibility testing is to prescribe a second course of PPI-based triple therapy, avoiding antimicrobial agents against which prior therapy may have induced resistance. Unfortunately, no data in older patients are available on possible alternative rescue therapies including rifabutin or the new fluoroquinolones as well as probiotic agents as part of an eradication regimen. After two treatment failures with different antibiotics, however, the updated Maastricht Consensus Report recommends that culture and antimicrobial sensitivity testing should be performed. Indeed, eradication of *H pylori* infection is more difficult when a first treatment attempt has failed and the optimal strategy for retreatment has not yet been established in older patients.

Treatment of NSAID-related peptic ulcer NSAID- or aspirin-associated peptic ulcers usually heal after 4 to 8 weeks of treatment with a PPI. Healing rates are higher if NSAID or aspirin treatments are stopped. Presently, no consensus exists on the clinical usefulness of a maintenance therapy with antisecretory drugs in patients who stopped NSAID or aspirin treatment after healing an NSAID-related peptic ulcer.

The following strategies have been suggested to prevent NSAID- or aspirin-related gastroduodenal peptic ulcer in older adults (**Table 93-8**).

TABLE 93-8 ■ STRATEGIES FOR THE PREVENTION OF NSAID OR ASPIRIN-RELATED GASTRODUODENAL PEPTIC ULCER IN OLDER PATIENTS

STRATEGIES
1. Identify the high-risk patient • History of upper GI symptoms • History of peptic ulcer and bleeding • Old age • Disability • Comorbidity • Comedications (oral steroids, antiplatelet drugs, warfarin)
2. Reduce dosage and use less damaging NSAIDs
3. Use of coxibs
4. Cotreatment with gastroprotective drugs
5. Eradication of *H pylori* infection
6. Educational programs

Prevention

Identifying high-risk patients Current strategies to reduce ulcer relapse and/or complications are considered cost-effective in high-risk patients. Great importance is placed, therefore, on defining those patients who are at high risk for peptic ulcer when they are treated with NSAIDs or aspirin. A history of upper GI symptoms, peptic ulcer, and/or bleeding; old age; the presence of disability or comorbidity; and concomitant medications, particularly oral steroids, antiplatelet drugs, and warfarin increase the risk of NSAID-related peptic ulcer and/or its complications. Thus, a comprehensive geriatric assessment may be useful in the evaluation of the multidimensional risk of older patients.

Reduce dosage and use of less GI-toxic NSAIDs The risk of peptic ulcer and its complications appears to be directly related to the dose of the given NSAID or coxib. Lower risk of upper GI damage has been reported with NSAIDs with a short plasma half-life versus those with a prolonged plasma half-time. Independent of this, however, slow- release formulations present an augmented risk of ulcer complications.

Cotreatment with gastroprotective drugs Several meta-analyses of controlled trials on gastroprotective drug treatments reported that misoprostol and PPIs are more effective than H_2-blockers in preventing both gastric and duodenal severe damage. However, misoprostol administered at effective doses of 200 μg four times daily induced significantly higher adverse effects, particularly diarrhea, than PPIs and placebo. PPIs were very effective in preventing gastroduodenal injuries in both acute and chronic older users of NSAIDs (**Figure 93-12**). Similarly, significant efficacy of PPIs for the prevention of peptic ulcer and its complications has been reported in older patients treated with low-dose aspirin as antiplatelet therapy, independent of the presence of *H pylori* infection.

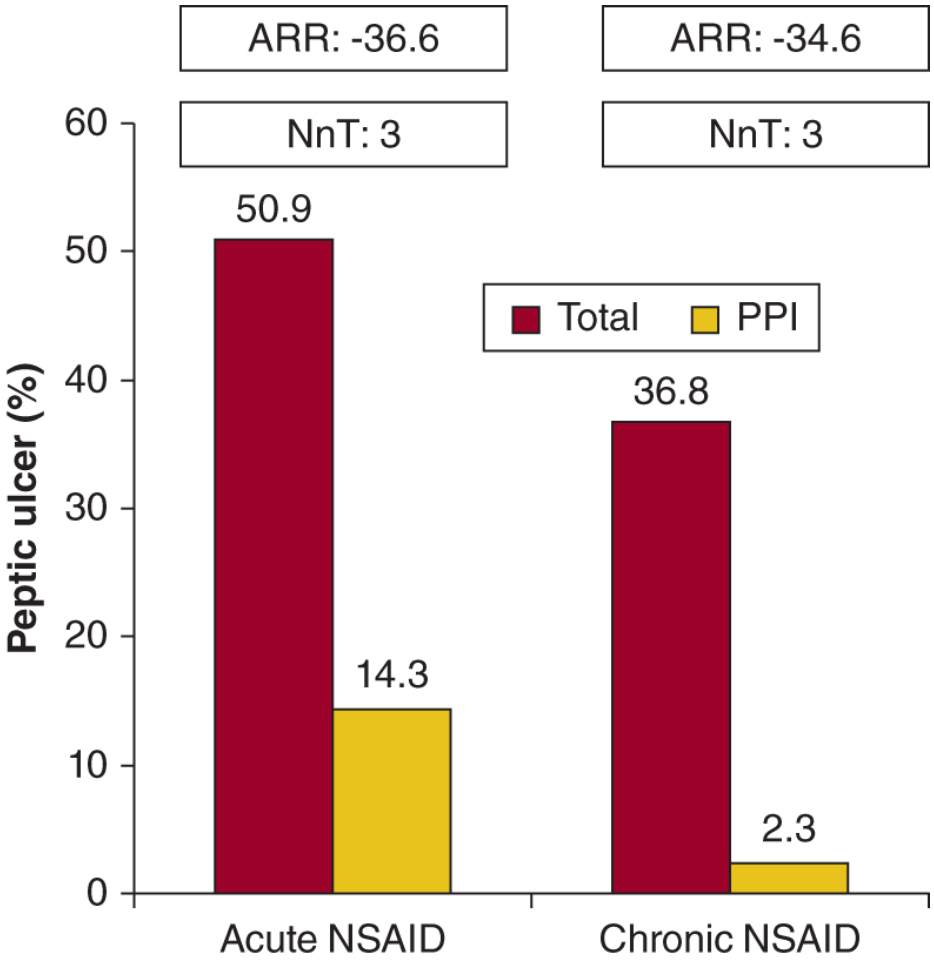


FIGURE 93-12. Absolute risk reduction (ARR) of peptic ulcer and the number needed to treat (NnT) in older acute and chronic users of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or aspirin concomitantly treated with proton pump inhibitors (PPIs). (Data from Pilotto A, Franceschi M, Leandro G, et al. Proton-pump inhibitors reduce the risk of uncomplicated peptic ulcer in older either acute or chronic users of aspirin/non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther*. 2004;20:1091–1097.)

Eradication of *H pylori* infection NSAID use and *H pylori* infection are independent risk factors for peptic ulcer and gastroduodenal bleeding in older subjects.

In *H pylori*–positive patients who are starting long-term treatment with NSAIDs, the cure of *H pylori* infection significantly reduces the 6-month risk of peptic ulcer. In older high-risk patients, however, the use of PPIs concomitantly with the NSAID reduces the occurrence of both acute and chronic NSAID-related gastroduodenal damage more effectively than the eradication of *H pylori* infection. Moreover, after the eradication of *H pylori*, maintenance treatment with a PPI is more effective than placebo in the prevention of ulcer bleeding in older patients. All these findings suggest that *H pylori* eradication may be a useful strategy to prevent NSAID-related peptic ulcer. Consequently, *H pylori* infection should be tested for and treated in older people in whom prolonged NSAID use is anticipated. Recent data, however, suggest that *H pylori* eradication alone is not sufficient for the prevention of severe gastroduodenal damage in older *H pylori*–positive NSAID and aspirin users.

Educational Programs

A crucial strategy in the prevention of NSAID-related adverse events is the discontinuation of NSAID therapy. Indeed, a study from Canada reported an estimated 37% of unnecessary NSAID prescriptions in older patients with osteoarthritis. Similarly, a study from the United States reported that almost 50% of NSAID prescriptions in older patients were inappropriate. Active interventions to improve appropriateness of drug prescription, particularly in older adults, demonstrated a reduction in NSAID prescriptions. A significant reduction in NSAID use was observed by a nurse-delivered advice intervention on NSAID use involving patients in general practice. A significant reduction in rehospitalization rates for peptic ulcer as well as mortality rates within 1 year was observed in older subjects who participated in a quality improvement project in the United States that involved counseling of patients and their caregivers about NSAID toxicity.

Non-NSAID, non–*H pylori* ulcers Antisecretory therapy remains the cornerstone of treatment to promote ulcer healing. Standard doses of PPIs should be prescribed for at least for 4 weeks in patients with duodenal ulcers and for 8 weeks in patients with gastric ulcers. Generally, patients respond well to these therapies, and no established evidence supports the need for a longer duration or higher dose of antisecretory therapy in uncomplicated idiopathic ulcer. Older nonresponders should be investigated for any possible underlying pathophysiology, including compliance, acid hypersecretory state, or use of damaging drugs.

UPPER GASTROINTESTINAL BLEEDING

Definition

Upper gastrointestinal bleeding (UGIB) is defined as bleeding derived from a source proximal to the ligament of Treitz, and can be categorized as variceal or nonvariceal hemorrhage. Gastrointestinal bleeding can be classified as acute (presenting with hematemesis, melena and/or hematochezia) or chronic, suspected because of the detection of occult gastrointestinal blood loss or anemia.

Epidemiology

Data from the United States demonstrated a decrease in both the incidence and mortality rates due to UGIB from 2001 to 2009 across all age groups. However, UGIB remains a significant cause of hospital admission and mortality in older subjects. It has been reported that the rates of admission for acute UGIB increase 30-fold between the third and ninth decades of age; 70% of acute UGIB episodes occur in patients older than 60 years. Moreover, a study performed in older residents in the United States has confirmed that the risk of hospitalization for UGIB was significantly associated with age above 80 years, limited instrumental activities of daily living (IADL), multiple comorbidities, and polypharmacy.

The mortality of patients who present with variceal hemorrhage has historically exceeded 30%, but has decreased over time, possibly as a result of advances in medical and endoscopic therapy; however, these data come from cohorts of patients with a mean age well below 65 years, and data about older patients with variceal bleeding are lacking.

Pathophysiology

UGIB can be caused by peptic ulcers, gastric erosions, esophageal varices, and other causes such as gastric cancer

(Table 93-9).

TABLE 93-9 CAUSES OF UPPER GASTROINTESTINAL BLEEDING ACCORDING TO RECENT EPIDEMIOLOGIC STUDIES

ENDOSCOPIC DIAGNOSIS	%
Peptic ulcer	31–67
Erosive gastritis	7–31
Variceal bleeding	4–20
Oesophagitis	3–12
Mallory-Weiss	4–8
Neoplasm	2–8
Other	2–8
None	3–19

Data from Holster IL, Kuipers EJ. Management of acute nonvariceal upper gastrointestinal bleeding: current policies and future perspectives. World J Gastroenterol. 2012;18:1202–1207.

Peptic ulcer disease Peptic ulcer is the most frequent cause of major, life-threatening acute nonvariceal gastrointestinal bleeding. Significant hemorrhage results from erosion of an underlying artery, and the magnitude of bleeding is related to the size of the arterial defect and the diameter of the artery. Consequently, bleeding may be particularly severe from large posterior duodenal ulcers which erode the gastroduodenal artery as well as from lesser curve gastric ulcers involving branches of the left gastric artery.

The high incidence of acute UGIB in older people has been attributed to many factors, including an increase in the use of NSAIDs as well as a high prevalence of upper GI disorders including GERD and peptic ulcer disease. Moreover, advanced age has been consistently identified as a risk factor for mortality among patients presenting with UGIB, presumably because of the high prevalence of comorbid illnesses—including pulmonary and cardiovascular disease—in older adults as compared with younger patients.

Esophageal varices and portal hypertensive gastropathy Esophageal and gastric varices are caused by increased venous collateral flow from the portal circulation through the gastric coronary veins, usually because of portal hypertension. Variceal hemorrhage can occur when the hepatic venous pressure gradient exceeds 12 mm Hg. Features predictive of variceal hemorrhage include large variceal size and the presence of red “wale” marks on varices. The vessels may leak blood or even rupture, causing life-threatening bleeding.

Portal hypertensive gastropathy results from venous congestion of the gastric mucosa; in most patients, this is caused by portal hypertension from cirrhosis.

Other causes

Esophagitis and Erosive Gastritis Esophagitis and erosive gastritis describe superficial mucosal injuries in the esophagus and stomach, respectively. These lesions are most commonly caused by hypersecretion of gastric acid and/or erosive medications, such as NSAIDs and alendronate (see above).

Mallory-Weiss Tears Mallory-Weiss tears occur at the esophagogastric junction and are due to prolonged retching. Alcohol abuse is the usual cause, but other causes including vomiting (eg, chemotherapy, digoxin toxicity, renal failure, advanced malignancy) may be responsible for the UGIB episodes from Mallory-Weiss tears. Bleeding usually stops spontaneously and active endoscopic or surgical intervention is seldom required.

Gastric Antral Vascular Ectasia Gastric antral vascular ectasia (also known as “watermelon stomach”) is an uncommon vascular anomaly characterized by linear, readily bleeding red streaks radiating from the pylorus into the gastric antrum. The prevalence of gastric antral vascular ectasia does not increase with age per se, but the condition can be associated with certain medical comorbidities, including end-stage renal disease and cirrhosis.

Dieulafoy Lesion Dieulafoy lesion is an unusual cause of acute bleeding in which a superficial submucosal artery is eroded. The diagnosis can be made only when endoscopy is undertaken during active bleeding. Arterial disruption is probably caused by a small ulcer, but no mucosal lesion can be identified after bleeding has ceased. The most common site of Dieulafoy lesion is the gastric fundus; it may also develop in the duodenum or other parts of the stomach.

Presentation

Hematemesis, bloody gastric aspirate, or melena usually indicates bleeding from the upper GI tract. The absence of blood in gastric aspirate, however, does not rule out a significant bleeding from the UGI tract.

Older people with UGIB may have specific aspects of clinical presentation that need a comprehensive clinical approach. Indeed, an UGIB may initially present with symptoms such as syncope, or postural hypotension, neurological symptoms, that is, transient ischemic attach and/or stroke, and cardiovascular symptoms, including ischemic heart disease, or light-headedness, or even a delirium episode or behavioral disorders due to the UGIB-related acute anemia. These general symptoms are more frequent in frail, comorbid and multitreated older subjects.

Evaluation

The initial evaluation of the older patient presenting with features of acute UGIB includes a complete medical history, physical examination, and laboratory assessment with the goal of assessing the severity of the bleeding. Medical history should include details of prior UGIB episodes, previous abdominal surgery and current medication use, particularly aspirin and NSAIDs. UGIB in cirrhotic patients has a nonvariceal origin in over 50% of cases. The physical examination should begin with an assessment of hemodynamics, including postural changes. Physical findings of chronic liver disease are suggestive of underlying portal hypertension. Laboratory evaluation should include serum electrolyte and coagulation parameter measurements, liver biochemical tests, and a complete blood count.

Upper GI endoscopy has three main purposes: (1) to provide an accurate diagnosis, (2) to give prognostic information, and (3) to carry out endoscopic therapy. Early endoscopic examination allows precise identification of the site and nature of the bleeding, and provides valuable prognostic information. Stigmata of recent hemorrhage should be recorded, as they predict risk of further bleeding and guide management decisions. Endoscopic therapy for peptic ulcer hemorrhage seems to be well tolerated in older adults.

In any case, endoscopy should not be carried out until the patient is adequately resuscitated. Endoscopy performed within 24 to 48 hours from the bleeding episode reveals an actual or potential site of bleeding in the majority of patients; 15% to 30% of all lesions are actively bleeding at the time of endoscopy.

Routine second-look endoscopy, in which repeated endoscopy is performed 24 hours after initial endoscopic hemostatic therapy, is not recommended. A second-look endoscopy however should be performed in patients with clinical evidence of recurrent bleeding.

Management

General management Hemodynamic status should be assessed immediately upon presentation and resuscitative measures begun as needed. Blood transfusions should be always carried out with hemoglobin levels less than or equal to 8 g/dL. In older patients with higher hemoglobin levels blood transfusions should be performed when clinical evidence of intravascular volume depletion or severe comorbidities, such as coronary artery disease, pulmonary diseases, and renal insufficiency, are present. Risk assessment should be performed to stratify patients into higher and lower risk categories and may assist in initial decisions such as timing of endoscopy, time of discharge, and level of care.

Peptic ulcer bleeding The best management of acute bleeding ulcer includes a combination treatment with endoscopy (eg, bipolar electrocoagulation, heater probe, clips and/or injection of sclerosant or vasoactive drugs) and intravenous PPI with a bolus followed by continuous infusion. These treatments reduce the rates of rebleeding and surgical interventions, but short- and long-term mortality rates are not reduced (**Table 93-10**).

TABLE 93-10 PPI THERAPY AND OUTCOME OF ENDOSCOPIC HEMOSTASIS IN BLEEDING PEPTIC ULCER

	REBLEEDING	SURGERY	MORTALITY
EndoTx + PPI vs PPI alone	0.2 (0.09–0.4)	0.17 (0.06–0.4)	NS
EndoTx + PPI vs EndoTx alone	0.5 (0.37–0.7)	NS	NS
EndoTx + PPI bolus vs infusion	NS	NS	NS
PPI after EndoTx vs EndoTx alone	0.52 (0.4–0.7)	0.53 (0.35–0.8)	NS

Oral PPI	0.32 (0.2–0.5)	0.38 (0.2–0.6)	NS
Intravenous PPI	0.57 (0.4–0.7)	0.67 (0.5–0.9)	NS

EndoTx, endoscopic treatment; NS, not significant.

Data from Andriulli A, Annese V, Caruso N, et al. Proton-pump inhibitors and outcome of endoscopic hemostasis in bleeding peptic ulcers: a series of meta-analyses. Am J Gastroenterol. 2005;100:207–219 and Leontiadis GI, Sharma VK, Howden CW. Systematic review and meta-analysis of proton pump inhibitor therapy in peptic ulcer bleeding. BMJ. 2005;330:568–570.

Preendoscopic PPI, that is, 80 mg omeprazole or pantoprazole bolus followed by 8 mg/h infusion, seems to decrease the need for endoscopic therapy but does not improve the final clinical outcome. Patients with flat spots or clean-based ulcers do not require endoscopic therapy or intensive PPI therapy.

After successful endoscopic hemostasis, intravenous PPI therapy with omeprazole/pantoprazole 80 mg bolus followed by 8 mg/h continuous infusion for 72 hours should be administered to patients who have an ulcer with active bleeding, a nonbleeding visible vessel, or an adherent clot. Patients with ulcers that have flat pigmented spots or clean bases can receive standard PPI therapy (eg, oral PPI once daily).

Recurrent bleeding after endoscopic therapy is treated with a second endoscopic treatment; if bleeding persists or recurs, treatment with surgery or interventional radiology is undertaken.

Variceal bleeding Endoscopic variceal band ligation has supplanted injection sclerotherapy under endoscopy, due to a significant lower rate of complications. The use of nonselective β-blockers seems to be effective for both primary and secondary prophylaxis of variceal hemorrhage; however, older patients should be monitored closely for adverse effects, which include orthostasis, fatigue, and affective disturbance.

Patients with portal hypertensive gastropathy (PHG) can present with or without endoscopically apparent gastroesophageal varices. If UGIB occurs in a patient with PHG, it is more commonly chronic and occult than overt and hemodynamically significant. Reduction of portal venous pressure with a nonselective β-blocker might be beneficial for patients with PHG and GI bleeding; however, the data to support this indication are limited, especially in older subjects.

Prevention

Long-term prevention of recurrent bleeding peptic ulcers Prevention of recurrent bleeding is based on the etiology of the bleeding ulcer. Patients with *H pylori-as* sociated, NSAID-associated, or idiopathic bleeding ulcers should receive therapy as outlined in the previous section. In patients who must resume NSAIDs, a COX-2 selective NSAID at the lowest effective dose plus daily PPI is recommended.

In patients with low-dose ASA-associated bleeding ulcers, the need for aspirin should be assessed. If given for secondary prevention (ie, established cardiovascular disease), aspirin should be resumed as soon as possible after bleeding ceases in most patients: ideally within 1 to 3 days and certainly within 7 days. Long-term daily PPI therapy should also be provided. If given for primary prevention (ie, no established cardiovascular disease), antiplatelet therapy likely should not be resumed in most patients.

Long-term prevention of recurrent bleeding variceal Although β-blockers have an established role as primary prophylaxis following variceal hemorrhage (ie, reducing the risk of variceal bleeding in patients who have never bled), their use as secondary prophylaxis (preventing variceal rebleeding) is not established, and endoscopic variceal ablation by a program of repeated variceal banding is the treatment of choice.

Special issues: prognostic evaluation of the older patient with UGIB Early stratification of patients into groups with different risk of rebleeding and mortality may be useful to support clinicians in the management of UGIB and in the choice of the most appropriate treatment, that is, medical, endoscopic, or surgical interventions. Indeed, prognostic scores have been developed that include endoscopy-based analysis of bleeding lesions, preendoscopic clinical scores, and combined clinical and endoscopic evaluation.

It is increasingly evident, however, that the prognosis of older patients with UGIB is strongly affected by a multiplicity of factors, that is, functional, cognitive, nutrition, multimorbidity, and polypharmacy, which are not directly related to the UGIB itself, suggesting that prognostic model for these patients should be multidimensional in nature (**Table 93-11**).

TABLE 93-11 CLINICAL PROGNOSTIC SCORES IN ACUTE UPPER GASTROINTESTINAL BLEEDING

	GLASGOW BLATCHFORD SCORING SYSTEM	ROCKALL SCORING SYSTEM	MULTIDIMENSIONAL PROGNOSTIC INDEX (MPI)
Variable	1. Blood urea nitrogen 2. Hemoglobin 3. SBP 4. Pulse (HR/bpm) 5. Presence of melena 6. Syncope 7. Hepatic disease 8. Cardiac failure	1. Age 2. Presence of shock 3. Comorbidity (CHF, IHD, major morbidity, renal failure, liver failure, metastatic cancer) 4. Endoscopic diagnosis nonmalignant, non-Mallory-Weiss diagnosis, upper GI tract malignancy 5. Evidence of bleeding adherent clot, active bleeding	1. ADL 2. IADL 3. SPMSQ 4. CIRS 5. MNA 6. ESS 7. Number of drugs 8. Cohabitation status
Items	8	5	8 domains
Score ranges	0–23	0–11	0–1
Score risk	Low risk (0) High risk (> 0)	Low risk (0–2) Intermediate risk (3–7) High risk (8–11)	Low risk: MPI-1 value < 0.33 Moderate risk: MPI-2 value 0.34–0.66 Severe risk: MPI-3 value ≥ 0.67
Type	Preendoscopic clinical score	Clinical and endoscopic score	Multidimensional, comprehensive, geriatric assessment-based
Evaluation	Management and timing of endoscopy of upper GI bleeding	Risk of rebleeding and mortality	Risk of mortality Risk of hospitalization Length of in-hospital stay

ADL, activities of daily living; CHF, congestive heart failure; CIRS, cumulative illness rating scale; ESS, Exton-Smith scale; GI, gastrointestinal; HR, heart rate; IADL, Instrumental-ADL; IHD, ischemic heart disease; MNA, mini nutritional assessment; SBP, systolic blood pressure; SPMSQ, short portable mental status questionnaire.

The Forrest classification Forrest classification is an endoscopy-based tool useful to stratify patients with UGIB into high- and low-risk categories for mortality and rebleeding and it has been used to evaluate the endoscopic intervention modalities.

The Glasgow-Blatchford score The Glasgow-Blatchford score (GBS) is a screening tool to assess the likelihood that a patient with UGIB will need blood transfusion or endoscopic intervention. It is calculated combining information on blood urea nitrogen, hemoglobin, systolic blood pressure, heart rate, presentation with melena and/or syncope, evidence of hepatic disease and/or heart failure. A score of 0 identifies low-risk patients who might be suitable for outpatient management; conversely a patient with a GBS greater than 0 is considered at high risk, and should receive clinical evaluation and surveillance.

The Rockall score The Rockall score (RS) is a prognostic tool based on age of patient, clinical parameters (heart rate and systolic blood pressure), the presence of comorbid diseases (heart, renal and/or liver failure, and ischemic heart disease), and endoscopic variables, that is, the endoscopic diagnosis and stigmata of recent hemorrhage. Based on the RS, patients are categorized into three groups: low risk (scores 0–2), intermediate risk (scores 3–7), and high risk (scores 8–11) group. Patients with clinical RS (before endoscopy) greater than 0 and patients with complete RS (after endoscopy) greater than 2 are considered to be at high risk for developing recurrent bleeding and death.

The Multidimensional Prognostic Index The Multidimensional Prognostic Index (MPI) is a prognostic tool based on a standard comprehensive geriatric assessment (CGA) that predicts short- and long-term mortality in older subjects. The MPI includes the evaluation of eight domains, that is, basal activities of daily living (ADL) and instrumental activities of daily living (IADL), cognitive impairment, nutritional status, the risk of developing pressure sores, comorbidity, the number of drugs taken by the patient, and cohabitation status. The MPI values range from 0 (low risk)

to 1 (severe risk of mortality). Also, the MPI can be expressed as three grades of risk: MPI-1 indicates low risk (MPI value ≤ 0.33), MPI-2 indicates moderate risk (MPI value between 0.34 and 0.66), and MPI-3 indicates severe risk of mortality (MPI value > 0.66). Moreover, patients with higher MPI grades have higher risk of in-hospital stay and instituzionalization after hospital discharge.

NEOPLASM OF THE ESOPHAGUS

Esophageal Cancer

Squamous cell carcinoma and adenocarcinoma are the most common histological types of esophagus neoplasm. The incidence increases progressively after 45 to 50 years of age; the average age is about 66 years. Although the incidence of squamous cell carcinoma has remained relatively static during the last decades, the incidence of esophageal adenocarcinoma has increased dramatically.

Epidemiology and Pathophysiology

Squamous cell carcinoma Esophageal squamous cell cancer accounts for 5% to 7% of all gastrointestinal malignancies. The annual incidence in the United States is 3 to 4 cases per 100,000 persons. The incidence increases with age, being most common in men in their sixth and seventh decades of life. Risk factors (**Table 93-12**) for squamous cell cancer include alcohol and tobacco use, caustic esophageal injury, chronic strictures, achalasia, squamous carcinoma of the nasopharynx, partial gastrectomy, and human papilloma virus. The incidence and mortality rates are much higher in older black men when compared to other group populations. Symptoms of esophageal cancer generally develop only when the tumor has grown to the extent that it has narrowed the lumen of the esophagus substantially, has invaded local structures, or has metastasized. Dysphagia is the most common symptom; other manifestations include coughing and/or choking (because of invasion of the tumor into of the tracheobronchial tree), hoarseness (because of invasion of a recurrent laryngeal nerve), or hematemesis (because of tumor invasion of aorta or the presence of an aortoesophageal fistula). Ulcerated tumors can cause odynophagia. Since anorexia and weight loss usually precede the onset of dysphagia, the physical examination of these patients at the time of the diagnosis often reveals malnutrition and dehydration. Metastatic disease may be responsible for bone pain.

TABLE 93-12 COMMON RISK FACTORS FOR ESOPHAGEAL CANCERS

SQUAMOUS CELL CARCINOMA	ADENOCARCINOMA
60–70 y of age	50–60 y of age
Achalasia	Barrett esophagus
Alcohol abuse	Gastroesophageal reflux disease
Black populations	Caucasian populations
Male sex	Male sex
High-starch diet without fruits and vegetables	
Lye ingestion	
Plummer-Vinson syndrome	
Previous head and neck squamous cell carcinoma	
Radiation therapy	
Smoking	

Adenocarcinoma Adenocarcinoma of the esophagus has been increasing in frequency at an alarming rate over the past few decades, now accounting for more than 50% of the newly diagnosed esophageal cancers. The annual incidence of adenocarcinoma of the esophagus and gastric cardias is 5.1 cases per 100,000 persons. Unlike squamous cell carcinoma, adenocarcinoma typically affects older white males. Barrett esophagus secondary to long-standing reflux disease is the single most important risk factor for adenocarcinoma (see **Table 93-12**). Patients with Barrett esophagus are 30 to 125 times more likely to have adenocarcinoma of the esophagus than the general population. The

estimated incidence of adenocarcinoma in patients with Barrett esophagus is 0.2% to 2.1% per year.

Independent risk factors are male sex, advanced age more than 75 years, and grade of dysplasia.

Presentation

The clinical presentation is similar to that of squamous cell carcinoma, but malnutrition, fistulas, and recurrent laryngeal nerve involvement are less common, and extension into the stomach, diaphragm, and the liver is more frequent. More than 80% of the tumors are in the distal esophagus. The diagnostic evaluation, treatment modalities, and prognosis are similar to those for squamous cell carcinoma. However, with increased use of endoscopic surveillance, adenocarcinoma can be diagnosed at an earlier stage than squamous cell carcinoma.

Evaluation

Endoscopy with biopsies and cytology is the best way to establish the diagnosis. The mid-esophagus and/or the distal esophagus are the most common sites affected. The majority of symptomatic lesions are ulcerated in the center with heaped up margins and encroachment on the lumen. However, early lesions may be subtle and almost normal in appearance. In vivo staining with Lugol iodine or toluidine blue may be helpful for discovering the abnormal mucosa. *Barium esophagogram* may show tumors, but has low sensitivity in the detection of early tumors. Usually *computed tomography* (CT) of the chest and abdomen is recommended to assess the extent of disease within the chest and to look for metastases. However, the sensitivity and specificity of CT for determining the depth of esophageal tumor penetration (the T status) and the presence of regional lymph node metastases (the N status) are poor. *Endoscopic ultrasonography* (EUS) is superior to CT in this regard, accurately predicting the T and N status in 70% to 80% of patients.

Management

Cancer of the esophagus usually is disseminated at the time of diagnosis, and because there is no treatment that reliably eradicates metastatic disease, cure is not possible in most cases. Initial treatment usually involves a choice between surgery, radiation therapy, chemotherapy, and some combination of these three modalities. Squamous cell cancer and adenocarcinoma are treated similarly, with similarly poor survival rates. Overall cure rates for cancer of the esophagus remain below 10%. Treatment and survival, therefore, depends on the stage of the disease. Older patients, especially white men, should be screened for Barrett esophagus, and if identified, patients should be placed in endoscopic *surveillance programs* and on aggressive antireflux therapy with PPIs. However, PPIs as well as antireflux surgery have not shown to consistently cause regression of the Barrett epithelium or prevention of esophageal cancer. Surveillance involves obtaining four-quadrant biopsies at 2-cm intervals in the Barrett segment using a jumbo biopsy forceps as well as biopsies of any other mucosal abnormalities such as nodules or ulcers. If the biopsies are negative for dysplasia, endoscopy should be repeated within 1 year, followed by endoscopy every 2 to 3 years. If low-grade or indefinite dysplasia is identified, the surveillance interval is shortened to every 6 months for 1 year, followed by annual surveillance. If high-grade dysplasia is found, endoscopy is repeated at 1 month. If high-grade dysplasia is confirmed by two independent pathologists, options include esophagectomy or continued surveillance every 3 months. Ablative endoscopic therapies such as photodynamic therapy, laser, argon plasma coagulation, and multipolar electrocoagulation appear to be very promising especially in patients who are poor surgical candidates (**Table 93-13**).

TABLE 93-13 ENDOSCOPIC SURVEILLANCE OF BARRETT ESOPHAGUS

DYSPLASIA	ENDOSCOPY
Absent	Every 3 y after at least two endoscopies with biopsy within 1 year negative for dysplasia
Low grade[a]	At 6–12 mo, every year (in absence of progression)
High grade[a]	Histologic confirmation Focal: every 3 mo to rule out esophageal adenocarcinoma Focal multiple: esophageal resection or endoscopic ablation.

[a] Expert pathologist confirmation.

Modified from Wang KK, Sampliner RE; Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines 2008 for the diagnosis, surveillance and therapy of Barrett's esophagus. Am J Gastroenterol. 2008;103:788–797.

Early cancers, that is, those limited to the mucosa and the submucosa, can be cured by esophagectomy, but cure is not always possible because of presentation of cancers at a late stage. In patients with *superficial cancers* limited to the mucosa who are poor candidates for surgery, options include endoscopic mucosal resection or ablation with electrocautery, argon plasma coagulation, laser or photo-dynamic therapy. In locally *advanced cancer*, a multimodality approach involving surgery, radiation, and chemotherapy provides the best chance for survival. Squamous cell cancer, unlike adenocarcinoma, is radiosensitive. Majority of patients have some response to radiation therapy, but the response is brief, averaging approximately 3 months. The most widely used combination for chemotherapy, cisplatin and 5-fluorouracil, has shown a response in 20% to 40% of cases, but has no impact on survival.

The SEER registry (surveillance, epidemiology, and end results) recently published data on the outcome of about 28,000 esophagectomies in patients aged more than 65 years, reporting that the operative mortality increases with age; in particular mortality increases by 8.8% in the group 65 to 69 years to 13.4% in the group 70 to 79 years up to 19.9% in patients aged more than 80 years versus young adults. Although cardiovascular and pulmonary complications are more likely to occur in older than younger adult patients during and after surgical intervention, recent data suggest that patients aged more than 70 years receiving neoadjuvant therapies for cancer of the esophagus or esophagogastric junction do not have a significantly increased prevalence of mortality and major postoperative complications compared to younger patients. Thus, advanced age alone should no longer be considered a contraindication to preoperative chemoradiation therapy preceding esophageal resection in selected patients.

In this context, the need for multidimensional geriatric assessment is increasingly clear and currently recommended by many cancer associations.

Palliative Therapy

In patients with metastatic disease, treatment is mainly palliative. Palliative measures for dysphagia include esophageal dilation, stent placement, or endoscopic tumor ablation. The 5-year survival rates for TNM stage I, II, III, and IV cancers are 60%, 31%, 20%, and 4.1%, respectively.

Benign Tumors

Benign tumors are a rare entity representing less than 1% of all the esophageal neoplasms. Leiomyoma is the most common benign esophageal tumor. Esophageal leiomyomas may produce dysphagia and retrosternal chest pain, but in most cases are asymptomatic. If leiomyomas are symptomatic, surgical enucleation is indicated. Others benign tumors are squamous cell papillomas, fibrovascular polyps, and granular cell tumors.

GASTRIC CANCER

Epidemiology

Gastric cancer is an important disease in older patients with an estimated 21,700 new diagnoses in the United States in 2001. On a global scale, gastric cancer remains the world's second most common malignancy after lung cancer. The incidence of gastric cancer shows marked worldwide variation; while in industrialized countries, the incidence of gastric cancer is decreasing, in less developed countries gastric cancer is extremely common and often affects younger people. While distal gastric adenocarcinoma is more common in Afro-Asian populations, carcinoma of the cardia and fundus are more common in Caucasians, and their incidence is rising at an alarming rate. Adenocarcinoma makes up 90% of malignant gastric tumors with lymphoma accounting for a further 5%. The Lauren classification is traditionally used to divide adenocarcinoma into (1) an intestinal form, where the malignant cells form a glandular like structure; and (2) a diffuse form, where the cells infiltrate through the wall of the stomach with relatively little disturbance of the mucosa itself, making endoscopic diagnosis more difficult. Despite significant advances in the understanding of its etiology and pathogenesis, the mortality rate remains high and no more than 10% of patients will be alive 5 years from diagnosis. The risk of gastric cancer is strongly related to age. The median age of patients presenting with this cancer is around 72 years, and from the early 1990s, one-quarter of newly diagnosed gastric cancer patients are older than 80 years.

Pathophysiology

Pernicious anemia with its hallmark of atrophic gastritis has long been known to confer an increased risk of gastric

cancer. Similarly, it is well established that benign ulcer surgery, such as partial gastrectomy, is associated with gastric cancer with a lead in time of 15 to 30 years. Following gastric surgery, inflammation of the gastric remnant is common and usually associated with the reflux of bile. Although the histological appearances are different, both pernicious anemia and the surgical stomach share a common pathophysiological abnormality—hypochlorhydria. Gastric cancer and gastric MALT lymphoma (lymphoma of the mucosa-associated lymphoid tissue) have been associated with *H pylori* infection, and the bacterium has been categorized as a group I carcinogen by the International Agency for Research on Cancer (IARC). *H pylori* infection induces, in genetically predisposed hosts, a cascade of events that could ultimately lead to gastric neoplasia. Several studies reported that the increased proliferation induced by inflammation creates a genetically unstable gastric mucosa, which is further compromised by the presence of genotoxic substances generated by inflammatory and bacterial products. The key pathophysiological events include the onset of gastric atrophy and hypochlorhydria. Hypochlorhydria itself contributes to bacterial overgrowth, which further exacerbates the inflammation and leads to generation of carcinogenic nitrogenous products. Diets that are high in salt content and lacking in fresh fruits and vegetables are likely to contribute to the malignant transformation (**Table 93-14**). The role of time, that is, a long-lasting infection with *H pylori*, is probably important in the development of all these mechanisms. Indeed, chronic atrophic gastritis and *H pylori* infection are commonly found in the same older subject. Most of the studies suggested that atrophic changes of the gastric mucosa are associated with *H pylori* infection rather than with aging itself. A prospective study was carried out in a group of older men with *H pylori* infection and atrophic corpus gastritis. During a 7.5-year period prior to eradication therapy, no significant changes were observed in the mean atrophy and intestinal metaplasia scores. However, after *H pylori* eradication, a significant improvement occurred in the mean histological score of inflammation, atrophy, and intestinal metaplasia. These findings suggest that advanced atrophic gastritis may improve after *H pylori* eradication also in older subjects.

TABLE 93-14 RISK FACTORS FOR STOMACH CANCER

RISK FACTORS
Male sex
Old age
H pylori infection
Foods that contain nitrites and nitrates
Tobacco use
Previous gastric surgery
Adenomatous polyps larger than 1 cm in diameter
Familial adenomatous polyposis (mutations in the *BRCA1* and *BRCA2* genes)
Hereditary diffuse gastric cancer
Atrophic gastritis
Type A blood group
Environmental cold dust, asbestos, and nickel exposure
Obesity

Presentation

A symptomatic presentation is very often indicative of advanced stage illness. In Western countries, the most common presenting symptoms are weight loss followed by abdominal pain, nausea and vomiting, anorexia, and dysphagia. Most of these symptoms are nonspecific and are very common in older patients for other reasons. In some studies, 40% of patients had symptoms for less than 3 months, but 60% were symptomatic for 3 months or longer and up to 20% for over 1 year. The late presentation of the disease probably explains why its prognosis remains so severe with only 10% of patients alive at 5 years. The clinical manifestations also depend critically on the anatomical location of the tumor. Large tumors in the fundus and body may simply manifest with occult blood loss. In contrast, tumors of the antrum will delay gastric emptying and lead to early satiety, anorexia, and eventually the features of gastric outlet obstruction. Tumors of the proximal stomach may involve the distal esophagus and present with dysphagia.

Evaluation

The diagnosis of gastric cancer is easy in advanced cases, but may require a high index of suspicion: a careful history and examination are essential. Physical examination is frequently unrewarding even in advanced gastric cancer. A hypochromic, microcytic anemia is a common finding and the fecal occult blood test may be positive, although this does not localize the source of blood loss and as such it is not a helpful diagnostic tool in old age. *Upper GI endoscopy* has been shown to be more accurate than *barium radiology* in the diagnosis of gastric cancer. Endoscopy allows a close inspection of the mucosa, which is generally the only circumstance under which early gastric carcinoma is found. *Histologic examination* of multiple biopsies is essential for diagnosis. As mentioned previously, gastric atrophy and intestinal metaplasia are common findings in older patients. The presence of dysplasia, however, should always be regarded as significant because it may indicate a high risk of malignant transformation, or it may reflect the presence of adjacent malignancy. Currently the diagnostic usefulness of the barium meal is limited in defining the extent of a tumor or in identifying eventual gastroenteric fistulas. *Ultrasonography* of the abdomen is useful for assessing the spread of gastric carcinoma. It may detect evidence of lymphadenopathy but can be particularly valuable in detecting metastases within the liver. A number of studies suggest that *endoscopic ultrasound* has an accuracy of 90% in defining the depth of invasion within the stomach itself. It is also sensitive to wall thickening and will pick up diffuse carcinomas, and it may allow for the identification of regional lymph nodes.

Management of Gastric Cancer

Age itself is not a contraindication to aggressive treatment including curative surgery. Nevertheless, the operative risk must be well defined by a comprehensive geriatric assessment.

Nonpharmacological: surgery and endoscopic procedures Surgical resection remains the only proven method of providing long-term survival in patients with gastric cancer, but it is effective only if a complete macro- and microscopic clearance of the tumor is possible (R_0 resection). In patients with very early tumors, alternatives to resection have been proposed including laser ablation, photodynamic therapy, and endoscopic mucosal resection. Clearly, such treatments avoid both the immediate and long-term morbidity associated with surgery, but can only be recommended for tumors limited to the gastric mucosa in which the incidence of lymphatic spread is minimal. In patients with mucosal disease, a policy of regular endoscopic surveillance combined with ablation of the surrounding mucosa is mandatory. As tumor invades into the submucosa, the incidence of lymphatic spread increases, and mucosal ablative techniques are unlikely to achieve clearance of the disease. If there is evidence of submucosal invasion, a formal resection is performed. Lesions that are ulcerated pose particular problems with infiltration and may also be difficult for the pathologist to interpret. Furthermore, some reports have indicated that such lesions may metastasize early to regional lymph nodes, and accordingly endoscopic mucosal resection is not recommended for these tumors.

Drugs: chemotherapy The low survival associated with gastric cancer has prompted investigation into postoperative (adjuvant) chemotherapy, and preoperative treatment (neoadjuvant). In patients with gastric cancer, there is no evidence that either adjuvant or neoadjuvant chemotherapy is of value in patients in whom a complete surgical resection is possible. Older patients are more likely to have cardiac and renal impairments and therefore less likely to tolerate chemotherapy well and have a greater risk of side effects.

A comprehensive geriatric assessment that exactly defines the multidimensional impairments of older patients is crucial in evaluating the role of adjuvant chemotherapy. This treatment must offer significant survival benefits weighed against the toxic effects and eventual hospitalizations and complications, particularly in very old subjects.

Palliative Therapy

The majority of older patients present with late gastric cancer at an advanced stage. Most will not be amenable to curative surgical resection, and the issue of palliation is therefore very important. Distal tumors involving the antrum frequently progress to *obstruction*. In some patients, this will be owing to physical stenosis of the pylorus, while in others gradual infiltration of the antrum leads to loss of functionality and a failure in gastric emptying. Medical treatment of outlet obstruction with prokinetics is usually unhelpful. The symptoms are usually unpleasant with vomiting, regurgitation and reflux, and rapid nutritional failure. Because of this, palliative surgical therapy is often justified and options include antrectomy or, more commonly, the formation of a gastroenterostomy to relieve obstruction. Alternative approaches may include laser to more localized lesions. If the distal esophagus is involved, patients with large tumors may also develop dysphagia. This complication is usually managed with stenting or

sometimes laser therapy. Large tumors frequently bleed and result in *chronic blood loss*. This may on occasion warrant consideration of surgery, although the difficulties of performing this on frail older patients should not be underestimated. Another alternative is to try to shrink the tumor using a neodymium YAG laser, but results of this technique for treating chronic blood loss are conflicting. Most patients with advanced gastric cancer develop *nutritional problems*, and weight loss is almost invariable. Extensive infiltration alters the compliance of the stomach and frequently leads to sensations of early satiety and loss of appetite. In addition, advanced gastric cancer frequently leads to profound metabolic effects such as cachexia and loss of muscle bulk. Some patients may benefit from radiotherapy, but adenocarcinoma is frequently not radiosensitive. The role of hospice and organized palliative care and pain teams is extremely important in improving the comfort of patients.

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Chapter 94

Common Large Intestinal Disorders

David A. Greenwald

Learning Objectives

- Identify various common disorders of the large intestine that affect older adult individuals.
- Understand the key differences in diagnosis and treatment for a variety of disorders of the large intestine between patients who are younger and those who are older.
- Determine the most suitable evaluation and management plans for disorders of the large intestine that are frequently encountered in clinical practice.
- Define optimal treatment for older adult patients with common disorders of the large intestine.

Key Clinical Points

1. **Endoscopic and radiologic testing for common disorders of the large intestine is safe; advanced age is not a contraindication to gastrointestinal endoscopic procedures, and indeed, such diagnostic testing is relatively high yield.**
2. **Symptoms ascribed to disorders of the large intestine may be manifestations of different diseases in older adults as compared to the young, and the high prevalence of comorbid illness and polypharmacy makes accurate diagnosis and effective treatment more challenging in older adults.**
3. **Disorders of the large intestine in older adults are a heterogeneous group of conditions, and include diverticular disease with its many manifestations, infectious and inflammatory colitides, bleeding, and ischemic disease. They are a major cause of morbidity and mortality in this age group. Appropriate and rapid diagnostic testing as well as personalized therapy is paramount to improve outcomes.**

In older adults, gastrointestinal (GI) disorders, especially those of the large intestine, account for a significant proportion of physician visits, inpatient hospitalizations, and health care expenditure in the United States. Not only are large intestinal disorders common, but in older adults their presentations, complications, and treatment may be different than in the young. This chapter focuses on diagnosis and treatment of a variety of diseases of the large intestine, including diverticular disease, *Clostridium difficile*–associated diarrhea, microscopic colitis, inflammatory bowel disease, colonic ischemia, colonic obstruction, and lower GI bleeding.

Diagnosis of GI disorders in an older adult patient poses several challenges to the physician in addition to those present for all patients. First, comorbid illnesses are frequent and often numerous, and some such as dementia and depression, may impair adequate communication between patient and caregiver. Second, medications and their side effects may cloud the clinical picture; polypharmacy is common in older adults. Lastly, symptoms attributable to the large intestine may be manifestations of different diseases in older adults than they would be in the young. The astute physician must take these factors into consideration when treating all patients.

DIAGNOSTIC TESTING

Symptoms of digestive diseases may be misinterpreted or atypical in the aged. For example, constipation may be a symptom of irritable bowel syndrome in a young patient, whereas it might herald an obstructing lesion in an older patient. Rectal bleeding in a young person is most commonly from hemorrhoids or inflammatory bowel disease. In older adults, diverticulosis, ischemic colitis or colon cancer more commonly cause rectal bleeding. A complete and thorough history is imperative in all patients, especially older adults. Subtle clues to the diagnosis are sometimes dismissed as physiologic aspects of aging. Physical examination and some laboratory tests including tests of liver function are unaffected by aging, and any abnormality should be evaluated for the presence of a disease state and not dismissed as an age-related change (**Table 94-1**).

TABLE 94-1 INFLUENCE OF AGE ON LIKELY DIAGNOSIS OF LOWER GASTROINTESTINAL SYMPTOMS

SYMPTOM	YOUNG PATIENT	OLDER PATIENT
Rectal bleeding	Hemorrhoids Inflammatory bowel disease Colonic polyp	Diverticulosis Vascular ectasia Colon cancer
Constipation	Irritable bowel syndrome	Obstructing lesion
Anal stricture	Inflammatory bowel disease	Neoplasm Radiation-induced injury

Endoscopic Procedures

Colonoscopy Colonoscopy in older adults is safe and well tolerated. Several studies of indications and outcomes of patients older than 80 years having elective and emergency endoscopic procedures found those tests to be safe; advanced age is not a contraindication to endoscopy. Moreover, the yield for diagnostic testing with colonoscopy in older adults is relatively high.

Adequate bowel preparation is critical to a successful colonoscopic examination. Bowel cleansing in older adults should be performed with care. Preparation with standard doses of polyethylene glycol–based lavage solutions (PEG-ELS) in older adults is well tolerated and produces satisfactory bowel cleansing in more than 95% of all cases. Split dose regimens, where a part of the preparation is given 6 to 8 hours before the procedure, is recommended for optimal bowel cleansing. Sodium phosphate osmotic laxative preparations should not be used in older adults, as they cause significant fluid shifts and may cause electrolyte abnormalities or phosphate nephropathy and renal failure in this subset of patients.

Most colonoscopies are performed under moderate sedation. Sedation for colonoscopy usually includes a combination of a benzodiazepine (midazolam or diazepam) and a narcotic (meperidine or fentanyl), or may include a short-acting anesthetic agent such as propofol. Older adults may be more sensitive to these agents used for sedation in GI endoscopy; small incremental doses should be given and the patient monitored closely for signs of cardiopulmonary compromise. Nevertheless, age alone is not a major determinant of morbidity; rapid or excessive dosing contributes more to complications from sedation than does age itself.

Endoscopic ultrasound Endoscopic ultrasound (EUS) can be used to diagnose and manage disease of the anorectum. EUS utilizes high frequency ultrasound waves emitted from a probe attached to an endoscope to delineate the layers of the rectal wall, the internal and external anal sphincters, and the pelvic floor muscles. EUS may be helpful in evaluating these structures in patients with fecal incontinence. EUS also is frequently used to stage rectal malignancy, providing information about the depth of tumor invasion and the status of regional lymph nodes. Direct tissue sampling is available through fine needle aspiration and biopsy at the time of the EUS.

Capsule endoscopy Wireless capsule endoscopy is an increasingly important test in the evaluation of obscure GI bleeding, which is not uncommon in older adults. The capsule transmits images of the small bowel to a hard drive that the patient wears, and following the completion of the study the images are downloaded to a computer for review. Common findings in older adults being evaluated for obscure bleeding or iron deficiency anemia include angioectasias and ulcers.

Radiology

Contrast studies Contrast studies of the large intestine involve coating the colonic mucosa with a contrast medium, usually barium sulfate, following thorough colonic preparation. Barium enemas may be performed by either the single- or double-contrast method; in the latter, air is insufflated as well as barium. The single-contrast technique often is used to diagnose colonic strictures, fistula, obstruction, or diverticulitis. Double-contrast barium enema more commonly is used to detect polyps or mucosal abnormalities.

There exists some controversy concerning whether double-contrast barium enema is effective as a screening tool for colon cancer. Many experts consider colonoscopy to be the gold standard screening test. Colonoscopy is safe in older adults and is widely available. However, contrast studies may be reasonable as a first-line test when colonic strictures are suspected or the presence of likely or known obstruction might make colonoscopy unsafe.

CT colonography CT colonography (virtual colonoscopy) is a radiographic technique that combines helical CT and graphics software to create a three-dimensional view of the colonic lumen. This technology was developed to detect colonic polyps. In clinical trials of CT colonography, detection rates for polyps greater than 5 mm are similar to those for optical colonoscopy. Debate remains about the significance of finding polyps of different sizes; comparisons of CT colonography with optical colonoscopy rest on what the investigators deem to be a "significant" polyp, with much disagreement about the significance of polyps less than 5 mm. Nonetheless, CT colonography may play an increasingly important role in colon cancer screening in the coming years.

There are several limitations of CT colonography. First, the procedure requires formal bowel preparation, similar to that required for optical colonoscopy. Moreover, polyps and other abnormalities found at CT colonography, detected in 10% to 30% of all examinations, require conventional colonoscopy for removal. Lastly, in addition to colonic lesions, incidental extracolonic findings on CT colonography such as gall bladder, liver, and renal/adrenal abnormalities may require evaluation and possibly further invasive testing.

DIVERTICULAR DISEASE

Colonic diverticula are herniations of colonic mucosa through the smooth muscle layers of the colon. Strictly speaking, because colonic diverticula do not involve the muscle layer but rather are herniations of the mucosa and submucosa, they are actually pseudodiverticula. Diverticulosis has been increasingly recognized in Western society and is thought to be a disorder of older individuals. Diverticula are present in approximately one-third of persons by age 50 and in approximately two-thirds by age 80. In Western society, the predominance of diverticula occurs on the left side of the colon, specifically the sigmoid colon, although diverticula can occur anywhere in the colon.

Pathophysiology

There are three factors implicated in the pathogenesis of colonic diverticulosis. First, altered colonic motility results in increased luminal pressure along segments of the colon, and the resulting high-pressure areas cause out-pouchings at areas of weakness. Second, low intake of dietary fiber predisposes to diverticular disease, because low stool weights and slower stool transit times allow for relative increases in colonic intraluminal pressure. Third, with age the structural integrity of the colonic muscular wall decreases, and diverticula are more likely to form as a result.

Asymptomatic Diverticulosis

Diverticulosis is usually an incidental finding in patients undergoing radiographic studies or colonoscopy for other reasons. There is no clear indication for therapy or follow-up in such patients. Large cohort studies suggest that complications of diverticular disease may be prevented by intake of a high-fiber diet. Although prospective, randomized studies are lacking, a diet high in fiber and low in fat appears to be reasonable, and one that likely provides other health benefits as well as potentially decreasing the risk of complications from diverticulosis.

Painful Diverticular Disease

Some patients with diverticulosis have left lower quadrant pain, and when examined, do not have evidence of inflammation. These patients may have painful diverticular disease. Pain often is described as crampy, located in the left lower abdomen, and may be associated with diarrhea or constipation as well as tenderness over the affected area. The pain is often exacerbated by eating and diminished by defecation or the passage of flatus. The symptoms of painful diverticular disease often overlap with those of irritable bowel syndrome, and therefore painful diverticular

disease is considered part of the spectrum of functional bowel disorders. It is important to consider other causes of left lower quadrant pain such as diverticulitis, colonic obstruction, and incarcerated hernias in such patients.

Diverticulitis

Diverticulitis, defined as having diverticulosis in association with inflammation, infection, or both, is probably the most common clinical manifestation of diverticular disease. Diverticulitis develops in approximately 10% to 25% of individuals with diverticulosis who are followed for 10 years or more; however, less than 20% of these patients require hospitalization.

The process by which a diverticulum becomes inflamed has been compared to appendicitis, in which the diverticulum becomes obstructed by stool in its neck. The resulting obstruction eventually leads to micro- or macroperforation of the diverticulum. Fever, leukocytosis, and rebound tenderness often ensue. In an older adult patient, absence of these findings unfortunately does not exclude diverticulitis, and an aggressive evaluation is indicated if this diagnosis is suspected.

An abdominal and pelvic CT scan often confirms the diagnosis when the clinical suspicion is for diverticulitis, and the radiographic findings may or may not include evidence of a pericolic abscess. Colonoscopy or barium enema should be delayed until inflammation has improved because of an increased risk of colonic perforation with these studies. Patients with severe pain, nausea, and vomiting often require hospitalization and benefit from intravenous antibiotics. Most patients with diverticulitis will improve within 48 to 72 hours, and then a 5- to 7-day course of oral antibiotics with gradual introduction of oral intake is adequate therapy. Selected patients with relatively mild symptoms and who are able to tolerate oral intake may be managed with close outpatient monitoring including oral antibiotics and bowel rest. Given the high incidence of complicated disease, there should be a low threshold for hospitalization in older adult patients with diverticulitis.

Patients with complicated disease, including those with abscesses, may need drainage by surgery or interventional radiology. Surgery is recommended for patients with diverticulitis who fail to respond to medical therapy within 72 hours, those with multiple episodes, and those with one attack complicated by abscess, obstruction, or when the inflammatory process involves the bladder. The operation can usually be done in one stage with a primary bowel anastomosis. Sometimes, however, a two-stage procedure with a temporary colostomy may be necessary.

Diverticular Hemorrhage

Three to five percent of patients with diverticulosis have hemorrhage from a diverticulum. Diverticular hemorrhage is the most common identifiable cause of significant lower GI bleeding, accounting for 30% to 40% of cases with confirmed sources.

Bleeding associated with diverticula is typically brisk and painless. While the majority of diverticula are located in the left colon, bleeding from diverticular disease usually arises from the right colon. Bleeding is said to arise from arterial rupture of the vasa recta as it courses over the dome of a diverticulum. Bleeding ceases spontaneously in 70% to 80% of patients, and rebleeding rates range from 22% to 38%. Rebleeding is more likely when the initial bleed is severe.

The initial step in the management of patients with hemodynamically significant bleeding from diverticulosis is stabilization with intravenous fluid and blood products as necessary. Stable patients with suspected diverticular hemorrhage may undergo colonoscopy following rapid colonic purge. Colonoscopy in this setting allows for the ability to identify a diverticular source, to exclude alternative diagnoses, and to provide therapy of actively bleeding lesions.

In patients with recurrent bleeding, nuclear tagged red blood cell scans (scintigraphy) or CT angiography may localize the bleeding site. Indeed, a positive bleeding scan often leads to angiography, which may allow for nonsurgical management of diverticular hemorrhage. Patients who require more than three units of packed red cell transfusions over 24 hours, have bleeding refractory to treatment, or are hemodynamically unstable may require surgical management. Preoperative nuclear red blood cell scans or angiography often help localize the diseased segment and allow for limited bowel resections. Blind total colectomy is rarely indicated.

CLOSTRIDIUM DIFFICILE COLITIS

Clostridium difficile, an anaerobic gram-positive, spore-forming toxigenic bacillus was first isolated in 1935. It was not until 1978 when the association between the toxin elaborated by this bacterium and antibiotic-associated

pseudomembranous colitis was made. The organism is now recognized as the single most important cause of nosocomial infectious diarrhea in the United States.

Pathogenesis

The pathogenesis of *C difficile* colitis involves several steps. Patients must first be exposed to an agent that disrupts colonic flora, typically antibiotics. While the most common antibiotics associated with *C difficile* colitis are ampicillin, amoxicillin, cephalosporins, and clindamycin, virtually all antibiotics (including those used to treat *C difficile* colitis) have been implicated in causing disease (**Table 94-2**).

TABLE 94-2 ANTIBIOTICS ASSOCIATED WITH *CLOSTRIDIUM DIFFICILE* COLITIS

COMMON	LESS COMMON
Ampicillin and amoxicillin	Chloramphenicol
Cephalosporins	Macrolides
Clindamycin	Sulfonamides
Fluoroquinolones	Tetracyclines
	Trimethoprim

Exposure to antibiotics leads to altered colonic microflora, which in turn changes the protective barrier typically present in the colon against *C difficile*. Colonization of the organism in the colon is then possible. *C difficile* infection may result in an asymptomatic carrier state, or patients may develop diarrhea and colitis. Patients with intact immune systems and an ability to mount an early antibody response to *C difficile* toxin usually become asymptomatic carriers of the organism. On the other hand, patients lacking sufficient ability to mount an adequate immune response develop diarrhea and colitis.

Risk factors for the development of *C difficile* colitis are outlined in **Table 94-3**.

TABLE 94-3 RISK FACTORS FOR *CLOSTRIDIUM DIFFICILE* INFECTION

Antimicrobial therapy
Older age
Use of nasogastric tube
Gastrointestinal procedures
Acid antisecretory medications
Intensive care unit stay
Length of hospitalization

Clinical Manifestations

Clinical manifestations of *C difficile* infection range from asymptomatic carriage to mild to moderate diarrhea to life-threatening pseudomembranous colitis (**Figure 94-1**). Asymptomatic carriage of *C difficile* is common in hospitalized patients, and in fact, studies have shown that 10% to 16% of hospitalized patients receiving antibiotics are carriers of *C difficile*. Asymptomatic carriers should not be treated. In patients who develop diarrhea with *C difficile*, symptoms often develop soon after colonization. Fever, abdominal pain, and leukocytosis accompany the watery, nonbloody diarrhea. Mucus or occult blood may be present, but hematochezia should prompt an evaluation for other disease states. Patients with more severe disease may develop colonic ileus or toxic dilation without diarrhea. Abdominal radiographs will often reveal the colonic dilation.

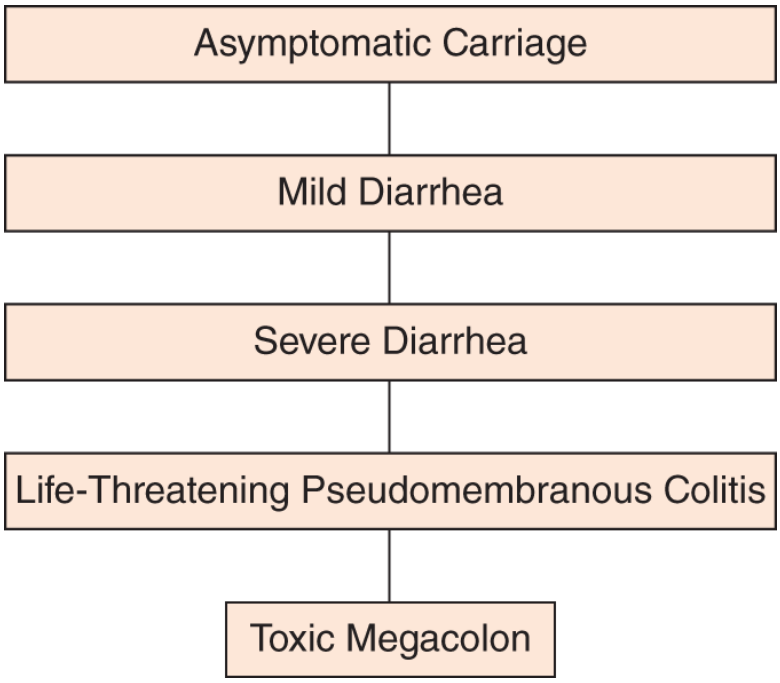


FIGURE 94-1. Clinical manifestations of *Clostridium difficile* infection.

Diagnostic Tests

There are several tests for diagnosing *C difficile* colitis. The most widely used is an enzyme linked immunoassay. This assay detects either one of the two *C difficile* toxins. While the main advantages are speed, cost, ease of testing, and high specificity, this immunoassay has relatively low sensitivity. Other diagnostic tests including *C difficile* culture, tissue culture cytotoxic assay, and PCR for detection of toxin genes are less commonly used because of their high cost, need for specialized laboratory techniques, and length of time to make the diagnosis.

Colonoscopy, or more often flexible sigmoidoscopy, may be helpful in making the diagnosis of *C difficile* colitis but is usually not necessary. Endoscopy is most useful when the diagnosis is in doubt or when disease severity demands rapid diagnosis. The finding of colonic pseudomembranes in a patient with antibiotic-associated diarrhea is almost pathognomonic for *C difficile* colitis (**Figure 94-2**).

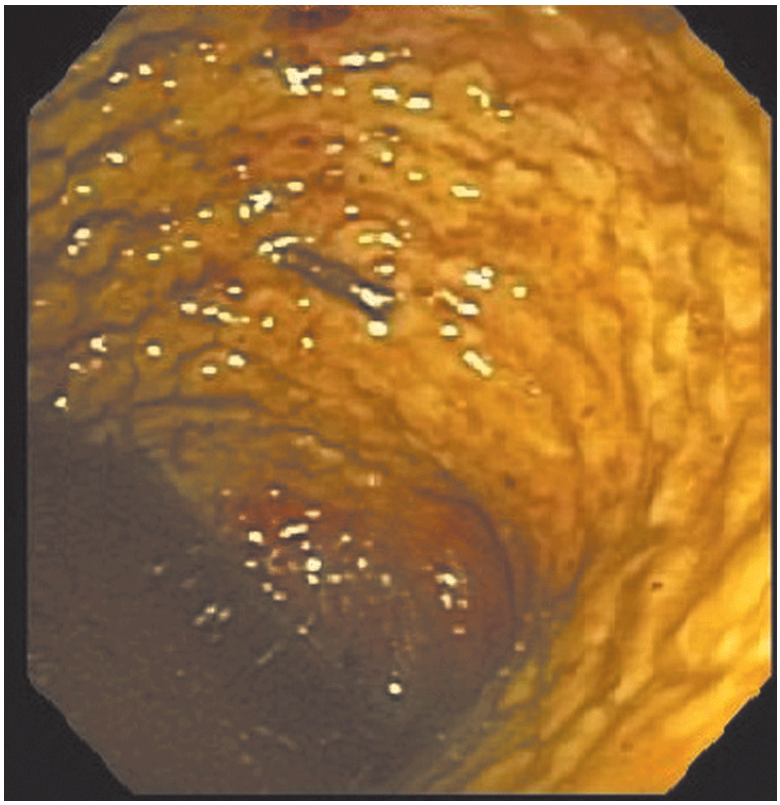


FIGURE 94-2. Pseudomembranes.

Treatment

Therapy for *C difficile* colitis begins with withdrawal of the precipitating antibiotics if possible. Metronidazole and vancomycin are both effective in the treatment of *C difficile*-associated disease. (Note that the only FDA-approved drugs for treating *C difficile* colitis in the United States are vancomycin and fidaxomicin.) Metronidazole is far less expensive, and the use of vancomycin carries with it a concern for the induction of vancomycin-resistant enterococci; therefore, the usual initial therapy in mild-moderate disease is with a 10- to 14-day course of oral metronidazole. This is effective in treating the majority of patients. In patients who are too ill or cannot take oral medication, IV metronidazole can be substituted. Patients who do not respond to metronidazole can be switched to oral vancomycin. Because intravenous vancomycin does not penetrate the colonic lumen, this formulation is not effective in treating *C difficile* colitis. Probiotic agents such as *Lactobacillus* GG and *Saccharomyces boulardii* have been used to reconstitute the colonic microflora, and are occasionally added to metronidazole or vancomycin to treat *C difficile* colitis, but their effectiveness has not been demonstrated in well-designed trials. Fidaxomicin is an oral-only FDA approved treatment of primary *C difficile* colitis and has equivalent initial efficacy with a lower relapse rate versus vancomycin (it has not been compared to metronidazole). The lower relapse rate was also seen in a subanalysis of older adults, but most clinicians do not use it as first-line therapy since it is much more expensive than either metronidazole or vancomycin.

Unfortunately, recurrent *C difficile* infection is a common problem and particularly prevalent in older adults. Symptomatic recurrence may result from relapse of the same strain (usually within 28 days) or reinfection with a different strain of *C difficile*. Resistance to metronidazole or vancomycin is seldom if ever an important factor in recurrence. Therefore, patients with recurrent *C difficile* colitis generally are given another trial with the antibiotic used to treat the initial infection. In some patients, a prolonged taper of vancomycin may be needed to prevent further recurrence (**Table 94-4A**). Fecal microbiota transplantation (FMT) has been shown to be highly effective in the treatment of recurrent *C difficile* infection, and is also very effective therapy for selected patients with severe or fulminant disease (**Table 94-4B**).

TABLE 94-4A VANCOMYCIN TAPER FOR SECOND RELAPSE OF *CLOSTRIDIUM DIFFICILE* COLITIS

Vancomycin 125 mg po QID for 7 d
Vancomycin 125 mg po BID for 7 d

Vancomycin 125 mg po QD for 7 d
Vancomycin 125 mg po QOD for 7 d
Vancomycin 125 mg po Q 3 d for 7 d

TABLE 94-4B INDICATIONS FOR FECAL MICROBIOTA TRANSPLANTATION FOR RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION

- ≥ 3 episodes of mild-to-moderate *Clostridium difficile* (CDI) and failure to respond to a 6- to 8-wk taper of vancomycin ± alternative antibiotic
- ≥ 2 episodes of CDI resulting in hospitalization and associated with significant morbidity
- Moderate CDI with no response to standard therapy for at least 1 wk
- Possibly severe (even fulminant) CDI with no response to standard therapy for 48 h

MICROSCOPIC COLITIS

The term *microscopic colitis* refers to two distinct but similar clinical entities, lymphocytic and collagenous colitis. Combined, they are characterized by chronic watery diarrhea and feature histologic evidence of chronic mucosal inflammation in the absence of endoscopic or radiological abnormalities of the large intestine. They differ principally by the presence or absence of a thickened collagenous band, which when present in collagenous colitis is located in the colonic subepithelium.

Both lymphocytic and collagenous colitis occur most commonly in people in their sixth to eighth decade. There is a strong female predominance. Most patients present with chronic watery stools for months to years. The pattern of symptoms in patients with microscopic colitis fluctuates and consists of exacerbations and remissions over years. Crampy abdominal pain is common, and symptoms often improve with fasting. Physical examination in patients with microscopic colitis is usually unremarkable, and occult blood in the stool is uncommon. Colonoscopic examinations are usually normal. It is important to exclude infectious causes of diarrhea by testing the stool for ova and parasites, bacterial pathogens, and *C difficile* toxin prior to making the diagnosis of microscopic colitis. The diagnosis relies on histopathologic evaluation of biopsied material from the diseased colon.

Pathology

Microscopic colitis is characterized by increased mononuclear cells in the lamina propria and between crypt epithelial cells, while collagenous colitis features a thickened subepithelial collagen layer. Contrasted to the normal colon where the collagen layer typically is 4 to 5 μm thick, in collagenous colitis the collagen layer is greater than 10 micrometers thick and averages 20 to 60 μm. The thickened layer is predominantly made up of type VI collagen, and it is this thickened collagen band that distinguishes collagenous colitis from lymphocytic colitis. Although inflammatory changes may be found diffusely throughout the colon in microscopic colitis, multiple biopsies of the left colon proximal to the rectosigmoid usually are sufficient to make the diagnosis.

Treatment

There have been few controlled trials regarding treatment for microscopic colitis, and therapy is largely empiric. Most reports suggest that no single agent works. The pattern of the diarrhea in microscopic colitis often is relapsing; patients sometimes find relief with one agent, but unfortunately symptom improvement may not be permanent. Almost one-third of patients respond to antidiarrheal agents like loperamide as well as stool bulking agents like psyllium or methylcellulose; however, these agents do not improve the subepithelial inflammation or reduce the thickness of the collagen band.

Other treatment trials in microscopic colitis have examined the effect of aminosalicylates, corticosteroids, and bile acid absorbing resins. Alone or in combination, these agents reduce subepithelial inflammation and collagen thickness. Budesonide, an orally administered, topically active synthetic corticosteroid with significant first-pass metabolism, is often effective in the treatment of microscopic colitis. Budesonide is an attractive agent here because of its limited systemic side effects and improvement of symptoms with once-daily dosing, but unfortunately relapse after stopping the medication is common. In severe refractory patients, diverting ileostomy or proctocolectomy is a treatment of last

resort.

INFLAMMATORY BOWEL DISEASE

Crohn disease and ulcerative colitis comprise the vast majority of inflammatory bowel disease (IBD) (**Table 94-5**). They are characterized by a tendency for immune activation and inflammation within the GI tract. IBD commonly has its onset in the young adult population, but is found with increasing frequency in older adults as well.

TABLE 94-5 DIFFERENTIATING CROHN DISEASE AND ULCERATIVE COLITIS

	CROHN DISEASE	ULCERATIVE COLITIS
Distribution	Throughout the GI tract, with skipped segments	Continuous disease from the rectum involving only the colon
Rectum	Relatively spared	Typically involved
Mucosal lesions	Aphthous ulcers, cobblestoning	Micro ulcers, linear ulcers
Rectal bleeding	Uncommon	Common
Depth of inflammation	Transmural	Mucosal
Fistulas	Present	Not present

The age of diagnosis may range from early childhood through the entire lifespan. Epidemiological studies suggest there is a bimodal distribution of the age of onset, with the peak incidence of IBD occurring in the second and third decades, and a second smaller peak in older adults between the ages of 60 and 70 years. “Late-onset” IBD accounts for approximately 12% cases of ulcerative colitis and 16% cases of Crohn disease. However, in older adults, presenting symptoms of IBD often are presumed to be attributable to another cause, and initially the correct diagnosis is sometimes overlooked. On the other hand, many experts believe that much of what was previously considered to be IBD in older adults is actually attributable to other causes, and in particular, to ischemic colitis.

Crohn Disease

Crohn disease is a chronic inflammatory process of unknown etiology, which most often affects the distal ileum, but can affect any segment of the GI tract including the colon. It is characterized by transmural inflammation of the bowel wall, the presence of apthae and ulcers, and the interspersing of segments of involved bowel with uninvolved bowel, that is, skip lesions. Fissures, fistulas, and strictures are common in Crohn disease. According to most published series, Crohn disease of the colon, also known as Crohn colitis, is more common in older adults than in the young.

Symptoms and Signs

The presentation of Crohn disease may be subtle and varies considerably. The clinical picture of Crohn disease in older adults as compared to the young has its roots in the propensity for Crohn disease in older adults to involve the colon. Consequently, intestinal obstruction, perforation, and fistula—features often associated with small bowel disease are less common. The majority of older adult patients with Crohn disease manifest their disease with abdominal pain, weight loss, fever, and diarrhea. The diarrhea, typically watery in Crohn disease of the small bowel can be bloody when the colon is involved.

Common laboratory abnormalities such as anemia, leukocytosis, thrombocytosis, hypoalbuminemia, and elevated erythrocyte sedimentation rate, as well as C-reactive protein levels vary with the severity of the illness. Interestingly, anemia in Crohn disease can be because of either iron deficiency from chronic GI blood loss or from vitamin B_{12} deficiency if the Crohn disease involves a large enough segment of the distal ileum, the site for vitamin B_{12} absorption in the small bowel.

Unfortunately, no single symptom, sign, or diagnostic test definitively establishes the diagnosis of Crohn disease, and prolonged delays in diagnosis probably occur more frequently in older adults. In the end, a constellation of suggestive symptoms and laboratory abnormalities should prompt further evaluation. Common intestinal infections should be excluded, and tests may include stool cultures, stool examination for ova and parasites, and assays for *C difficile* toxin.

Ultimately, the diagnosis of Crohn disease is confirmed by findings on barium studies, colonoscopy, and histopathology. Colonoscopy and barium studies can identify the characteristic linear ulcers, skip lesions, and mucosal edema in Crohn disease. Barium studies are superior for finding fistulas and defining the anatomic location of disease. CT and MR enterography may play an increasing role in the diagnosis of Crohn disease. Because of its ability to see the mucosa directly and sample it for histopathologic examination, colonoscopy complements radiologic studies in making the diagnosis of Crohn disease.

Computed tomography studies provide superior definition of the colon wall, can identify pyogenic complications like abscesses and perforations, and also can detect other intra-abdominal pathology that might mimic the presentation of Crohn disease, such as appendicitis or nephrolithiasis. On the other hand, CT does not demonstrate fine mucosal detail and often appears normal early in the course of disease.

Management

The principles of IBD management are the same regardless of the age of the patient. Nonetheless, there are several important considerations when treating older patients with IBD. The most commonly used medications in the treatment of Crohn disease include sulfasalazine, mesalamine (5-aminosalicylic acid), and corticosteroids; all of these are well tolerated in the older adult population. However, corticosteroid use confers a higher risk of complications in older adults, including accelerated bone loss and fractures, hypertension, and glucose intolerance (**Table 94-6**).

TABLE 94-6 DOSES AND ADVERSE REACTIONS WITH COMMONLY USED MEDICATIONS TO TREAT INFLAMMATORY BOWEL DISEASE

MEDICATION	DOSE	ADVERSE REACTIONS
Sulfasalazine	4–6 g/d	Nausea, folate deficiency, hemolytic anemia with glucose-6-phosphatase dehydrogenase deficiency
Mesalamine	Up to 4.8 g/d	Headaches
Prednisone	Up to 60 mg/d	Cushingoid appearance, glucose intolerance, osteoporosis, avascular necrosis, proximal myopathy, irritability, hypertension, cataract, glaucoma
6-Mercaptopurine, azathioprine	6-MP 1.5 mg/kg, AZA 3 mg/kg	Pancreatitis, pancytopenia, hepatitis
Metronidazole	Up to 1 g/d	Anorexia, nausea/vomiting, disulfiram-like effect, peripheral neuropathy
Ciprofloxacin	Up to 1 g/d	Nausea/vomiting, rash, hepatitis, spontaneous tendon rupture
Infliximab	5–10 mg/kg IV	Headache, nausea, vomiting, infections, induction and lupus-like syndrome, malignancy then maintenance

Immunomodulators like azathioprine, 6-mercaptopurine, and methotrexate are used effectively in the young to maintain remission of Crohn disease. These agents are usually well tolerated in older adults as well; however, some authorities argue against their use in older patients on the theoretical grounds that they may further impair the immune dysfunction associated with aging and result in increased risk of infection or possibly malignancy. Biologic agents, including the anti-TNF agents, infliximab and adalimumab, play an increasingly important role in the management of moderate to severe Crohn disease and may be used in older adults.

Finally, some antibiotics such as metronidazole and ciprofloxacin have been shown to be effective in inducing and maintaining remission, as well as healing perineal fistulas, in patients with Crohn disease. The long-term use of antibiotics typically is limited by the occurrence of significant side effects. Specifically, irreversible peripheral neuropathy can occur with the use of metronidazole, while antibiotic-associated diarrhea may be a complication of prolonged ciprofloxacin use.

Older adults with ileal or ileal–colonic Crohn disease occasionally require intestinal resection, but generally tolerate surgery well and appear to have low rates of postoperative recurrence. Proctocolectomy with ileostomy is a common surgical option for patients with extensive Crohn colitis. In older adult patients who are debilitated or malnourished, an initial subtotal colectomy with ileostomy is less debilitating and permits weight gain and improved physical well-being. If proctocolectomy is subsequently required, it can be done with a low complication rate, but may not be necessary at all if rectal disease is absent. A conventional ileostomy is generally favored in older patients

following colectomy, because anal sphincter sparing surgical procedures, such as an ileal pouch–anal anastomosis, often have poor functional results in older patients.

Ulcerative Colitis

Ulcerative colitis (UC) is a chronic inflammatory disorder of the GI tract of unknown etiology that affects the mucosa and submucosa of the large intestine in a continuous fashion. The inflammatory process invariably involves the rectum and extends proximally to variable distances, but does not involve the GI tract proximal to the colon. For many older patients, UC is a relatively mild illness, because colonic inflammation often is limited to the rectum or sigmoid colon. This distribution of disease is generally associated with less systemic manifestations, better response to medical therapy, and less need for surgery than more extensive UC.

Symptoms and Signs

The severity of UC may be subjectively classified as mild, moderate, or severe and is generally proportional to the extent of colonic inflammation. Symptoms in older adults are similar to those seen in young patients, and include bloody diarrhea, rectal pain, tenesmus, urgency, and abdominal pain. In comparison to Crohn disease, the diarrhea in UC almost always is bloody. Fecal urgency, a sensation of incomplete evacuation, and fecal incontinence also are common. Unfortunately, older patients appear to be more likely than younger patients to present with a severe initial attack, and that first severe manifestation is associated with a relatively high fatality rate.

Laboratory findings in UC are nonspecific and reflect the severity of the underlying disease. In patients with limited distal disease, laboratory abnormalities may be absent except perhaps for mild anemia. In patients with extensive disease, severe iron deficiency anemia, hypoalbuminemia, leukocytosis, and thrombocytosis are common.

Toxic megacolon is a feared complication of UC, and it occurs more frequently in older patients. One should be suspicious of toxic megacolon in a patient whose diarrhea improves but whose abdomen is distended and tympanic. Other markers of worsening systemic inflammation, such as fever and leukocytosis, will also be present. The diagnosis is usually made by abdominal radiography. Colonoscopy should not be attempted when there is a suspicion for toxic megacolon, as perforation may ensue.

Similar to the situation in Crohn disease, there is no single test that can definitively diagnose UC with acceptable sensitivity and specificity. In older adults, it is important to exclude other diseases that may mimic UC, like ischemic colitis, radiation proctocolitis, diverticulitis, malignancy, and infectious colitis.

Again, the constellation of characteristic signs and symptoms often prompts an endoscopic examination, which may show the classic findings of diffuse erythema, mucosal edema, granular mucosa, and ulcerations starting in the rectum without intervening areas of normal mucosa (**Figure 94-3**). In the proper clinical setting, flexible sigmoidoscopy with biopsy is usually sufficient to establish a diagnosis of UC. Complete colonoscopy with ileoscopy is necessary to determine the extent of disease and to exclude Crohn disease. However, complete colonoscopy is not recommended in patients with active UC for fear of perforation; the procedure can be safely performed once active disease has been controlled.



FIGURE 94-3. Ulcerative colitis as seen on colonoscopy.

Management

Most older adult patients with UC respond favorably to medical management. Once in remission, relapse occurs less frequently in older adults regardless of the severity of the initial attack. A range of agents is available for medical therapy of UC, and these may be administered orally, rectally, or parenterally depending on the site and severity of disease. Pharmacologic agents used to treat UC in older adults are similar to the ones used to treat Crohn disease and include sulfasalazine, mesalamine, corticosteroids, immunomodulators, and biologics.

The mainstays of treatment for UC are aminosalicylates, and they may be administered orally or rectally. Formulations designed either for enema or suppositories are reasonable choices when treating distal disease. Unfortunately, distal disease in older patients is more refractory to topical therapy than in the young, and so often older subjects with distal disease will require oral formulations of aminosalicylates to achieve and maintain remission.

In addition to aminosalicylates, corticosteroids are effective in achieving remission, but steroid use is associated with frequent side effects. Therefore, corticosteroids should only be used temporarily in UC as a means to induce remission. They should not be used for long term as they have not been shown to be effective at preventing relapses, and their side effect profile makes prolonged use unsatisfactory.

In patients who do not respond to aminosalicylates, immunomodulators such as azathioprine or 6-mercaptopurine can be introduced. These drugs are purine analogues, interfere with nucleic acid metabolism and cell growth, and exert their cytotoxic effects on lymphoid cells. Azathioprine and 6-mercaptopurine use is subject to a delayed response; patients may require up to 6 to 12 weeks to see an effect from these agents. Fortunately, they are effective at maintaining remission, once a response is achieved.

Surgery for UC is indicated in patients who fail medical therapy, have acute fulminant disease, are steroid dependent, or develop a dysplastic lesion or cancer. UC is cured following total proctocolectomy. In older adults, total proctocolectomy with ileostomy remains a popular choice, because restorative procedures like ileo–anal anastomosis are limited by functional morbidity. An alternative surgical procedure is a subtotal colectomy. In patients who have a subcolectomy, a rectal stump is left that provides the patient with an improved chance for fecal continence. Such patients, however, continue to have colonic mucosa, and thus have an ongoing increased risk for colon cancer to develop in the diseased segment and require periodic surveillance of the retained rectum.

Colon Cancer in IBD

The risk of colon cancer in patients with long-standing IBD is a significant complication of the disease. Colon cancer rates generally are higher in patients with UC than those with Crohn disease; it appears to be the degree and extent of ongoing inflammation in the colon that confers an increased risk of colon cancer. As such, patients with Crohn colitis are believed to have an equally high risk of developing colon cancer as their UC peers. In patients with long-standing UC, surveillance for colon cancer includes annual colonoscopy with random mucosal biopsies of the entire colon looking for evidence of early or advanced dysplasia. Areas that appear suspicious are also targeted. The risk of colon cancer increases substantially after 8 to 10 years of disease, and after many years approaches nine times the risk of the general population in patients of the same age group. During surveillance, patients found to have low- or high-grade dysplasia or carcinoma generally are offered proctocolectomy.

COLON ISCHEMIA

Colon ischemia (CI) is the most common intestinal vascular disorder in older adults. Until the 1950s, the only well-described form of CI was gangrene. During the 1950s, however, a variety of ischemic manifestations other than gangrene were noted after ligation of the inferior mesenteric artery during abdominal surgery. Careful review of these cases revealed a spectrum of diseases in addition to infarction that included healed ulcers, strictures, pseudotumors, and ischemic UC.

Pathophysiology

The colon receives its blood supply from branches of the superior mesenteric artery and inferior mesenteric artery. The colon is protected from ischemia by an abundant collateral circulation formed by the marginal arterial complex of Drummond, central anastomotic artery, and arc of Riolan. Occlusion of a major vessel results in opening of collateral pathways in response to arterial hypotension distal to the occlusion. Increased blood flow through collateral pathways maintains adequate perfusion for a variable but brief period of time. If blood flow is diminished for a prolonged period, vasoconstriction develops in the affected bed and may persist after the primary cause of the mesenteric ischemia is reversed.

In most cases, the cause of an episode of CI cannot be established with certainty, and no vascular occlusion can be identified. The causes of CI are vast and include thrombosis, embolus, shock, volvulus, hematologic disorders, infections, trauma, surgery, and medications (**Table 94-7**). The colon is particularly susceptible to ischemia, perhaps owing to its relatively low blood flow during periods of functional activity, and its sensitivity to autonomic stimulation. What triggers a specific episode of CI, however, usually is not known.

TABLE 94-7 CAUSES OF COLONIC ISCHEMIA

Inferior mesenteric artery thrombosis	Volvulus
Arterial embolus	Strangulated hernia
Cholesterol emboli	Vasculitis
Cardiac arrhythmia	Inherited and/or acquired hypercoagulable states
Shock	Medications

CI encompasses a spectrum of injury. The specific conditions resulting from ischemic injury to the colon are classified as reversible or irreversible, and then can be characterized further as reversible ischemic colonopathy, reversible or transient ischemic colitis, chronic ulcerative ischemic colitis, ischemic colonic stricture, colonic gangrene, and fulminant universal ischemic colitis.

Clinical Features

Despite a growing understanding of the pathophysiology of CI and its disparate clinical presentations, many cases of transient or reversible ischemia still are missed because diagnostic studies are not performed early enough in the course of disease. This is because patients may not seek medical advice for a disease that is self-limited, or the initial symptoms may be confused with other conditions such as IBD.

Approximately 90% of persons with CI are older than age 60 and have widespread evidence of atherosclerosis. Up to 10% of patients may have a potentially obstructing lesion of the colon, including carcinoma, benign stricture, and

diverticulitis. Patients with CI usually are not critically ill at the time of diagnosis, and their abdominal pain typically is mild. Mesenteric angiography plays little role in the diagnosis and management of this condition; since colonic blood flow usually has normalized by the time of presentation, the prognosis is excellent.

Typically, CI presents with the sudden onset of mild crampy left lower quadrant abdominal pain. The pain frequently is accompanied, or followed within 24 hours, by bloody diarrhea or bright red blood per rectum. In most cases, blood loss is minimal; hemodynamically significant bleeding should prompt consideration of other diagnoses, such as diverticular bleeding. Severe pain is unusual and may indicate irreversible transmural necrosis.

The differential diagnosis of CI includes infectious colitis, IBD, pseudomembranous colitis, diverticulitis, and colon carcinoma. In all patients suspected of having colonic ischemia, infection with organisms such as *Salmonella*, *Shigella*, *Campylobacter*, and *Escherichia coli* O157:H7 should be excluded. In fact, *E coli* O157:H7 infection induces a colitis that mimics or may even cause CI. Many commonly used medications are associated with CI, and include digitalis, nonsteroidal anti-inflammatory drugs, imipramine, danazol, and sumatriptan (**Table 94-8**).

TABLE 94-8 MEDICATIONS ASSOCIATED WITH COLON ISCHEMIA

Digitalis	Vasopressin
Gold	Pseudoephedrine
Sumatriptan	Cocaine
Methamphetamine	Nonsteroidal anti-inflammatory drugs
Imipramine	Saline laxatives
Estrogens	Psychotropic drugs

An older adult patient who presents with the sudden onset of abdominal pain and rectal bleeding or bloody diarrhea may benefit from a gentle barium enema or colonoscopy within 48 hours, once other more serious life-threatening diagnoses are excluded. Colonoscopy is preferable because it is more sensitive in demonstrating mucosal abnormalities and permits histopathologic evaluation of the colon mucosa. Conventional sigmoidoscopy is of value only if the segment of involved bowel is within reach of the sigmoidoscope; CI involves the sigmoid in 50% to 60% of patients and the rectum in less than 10% of cases. Findings vary greatly depending on the stage at which sigmoidoscopy or colonoscopy is performed. At the outset, purplish blebs representing mucosal and submucosal hemorrhage may be seen. As hemorrhage is absorbed, varying degrees of necrosis, inflammation, ulceration, and mucosal sloughing occur, resembling UC or Crohn disease.

Thumbprinting is the major radiologic finding in the acute presentation of CI. Thumbprints represent submucosal hemorrhage and edema. A barium enema repeated 1 week after an initial study should reflect evolution of the injury; either the areas of hemorrhage resorb and the study returns to normal or the thumbprints are replaced by a segmental pattern of colitis as the mucosa ulcerates.

Management

The treatment of CI is based on early diagnosis and continued monitoring, with special attention to the radiologic or colonoscopic appearance of the colon. This form of surveillance is essential in that it establishes the diagnosis and verifies its reversibility or shows progression to chronic ischemic colitis or stricture. Management includes stabilization of the patient, optimization of cardiac function, and bowel rest. Systemic antibiotics are administered routinely in most cases. Systemic glucocorticoids are of no proven value and increase the risk of perforation. If abdominal examination, fever, and leukocytosis suggest deterioration or if the patient experiences diarrhea or bleeding for more than 2 weeks, irreversible damage is likely, and surgical resection is usually indicated.

COLONIC OBSTRUCTION

Colonic obstruction results in dilation of the colon, abdominal distention and in some cases, colonic perforation. The majority of colonic obstructions are the result of mechanical obstruction from cancer, volvulus, stricture, impacted stool, surgical adhesion, or bowel intussusception. Patients with acute colonic obstruction can develop megacolon, the diagnosis of which is based on a cecal diameter of 12 cm or greater. Cecal distension is critical, because the cecum is the part of the colon that is most susceptible to ischemia and perforation. With obstruction, as fluid and gas accumulate

in the colon and intraluminal pressure increases, the radius of the colon increases. Wall tension is the greatest, and hence the risk for perforation most acute, at the area of greatest radius, which is generally in the cecum.

Acute Colonic Pseudo-Obstruction

Acute colonic pseudo-obstruction, also known as Ogilve syndrome, usually presents as intestinal ileus with massive bowel dilation postoperatively or in the setting of a severe intercurrent illness.

Pathophysiology

The colon is innervated extrinsically via the sympathetic and parasympathetic nervous systems and locally via the enteric neurons. The sympathetic nervous system, by inhibition of acetylcholine release, inhibits colonic motility. On the other hand, the parasympathetic nervous system, via acetylcholine release from the vagus and sacral nerves, stimulates colonic motility. An imbalance of these two systems favoring colonic inhibitory motor input results in colonic ileus and acute colonic pseudo-obstruction.

Clinical Features

Acute colonic pseudo-obstruction usually presents in patients with severe underlying illness like stroke, myocardial infarction, or sepsis, or after surgical procedures. It is most common after orthopedic procedures of the pelvis, hips or knees, abdominal surgery, or obstetric procedures.

The presentation of acute colonic pseudo-obstruction may be subtle and variable, although the most characteristic clinical feature is severe abdominal distention and failure to pass flatus or stool. Some patients report only mild distention and minimal pain. Indeed, a high level of suspicion is necessary to make the diagnosis, because patients often present after surgery with perioperative bowel cleansing and so early passage of stool is not expected.

The hallmark of the disease is colonic dilation on standard abdominal radiography. The entire colon can be affected, although in some cases just the right sided segments can be dilated. The presence of air in the rectum implies that there is no mechanical obstruction, and is therefore important to note before making a diagnosis of acute colonic pseudo-obstruction.

Management

Initial management of acute colonic pseudo-obstruction involves correcting reversible causes of colonic ileus such as electrolyte imbalances, hypoxemia, hypovolemia, and removal of medications that can exacerbate the problem. The vast majority of patients are successfully treated with these relatively simple measures. Bowel rest and intravenous hydration is imperative. Colonoscopic decompression, with or without placement of a decompression tube, is an option in patients with prolonged pseudo-obstruction. In fact, through the 1990s, the primary therapeutic approach for patients with acute colonic pseudo-obstruction who had not responded to conservative measures was endoscopic decompression of the colon.

Neostigmine, a cholinesterase inhibitor, given in doses of 1 to 2 mg IV or SC was confirmed to be effective in patients in a placebo-controlled study with acute colonic pseudo-obstruction. Relative contraindications to the use of neostigmine include a heart rate less than 50 beats per minute or systolic blood pressure less than 90 mm Hg; sick sinus syndrome or history of second- or third-degree arteriovenous block without a pacemaker; serum creatinine greater than 3 mg/dL; or active bronchospasm requiring medication (**Table 94-9**). Following neostigmine administration, patients should be monitored closely. A second administration of neostigmine can be attempted if there is partial or no response to the first trial.

TABLE 94-9 CONTRAINDICATIONS TO USE OF NEOSTIGMINE

ABSOLUTE	RELATIVE
Hypersensitivity to neostigmine	Recent myocardial infarction
Mechanical urinary or intestinal obstruction	Acidosis
	Asthma
	Bradycardia
	Peptic ulcer disease

In selected patients who fail conservative and medical management, colonoscopic decompression of the unprepped bowel can be attempted. However, care is required since during colonoscopy air is insufflated into an already dilated colon and the risk of colon perforation is increased. Surgical decompression, sometimes via placement of a cecostomy tube, remains another option for patients who do not respond to medical and endoscopic interventions.

The overall prognosis of patients with acute colonic pseudo-obstruction is poor, with an in-hospital mortality approaching 30%, attributable primarily to the severity of the underlying illness. The most significant complication of acute dilatation is colonic perforation, which occurred in 3% of cases in one retrospective series.

LOWER GASTROINTESTINAL BLEEDING

Lower GI bleeding is defined as that which arises distal to the ligament of Treitz. Lower GI bleeding occurs less frequently and is less severe than upper GI bleeding.

The incidence of lower GI bleeding increases significantly with age. The majority of lower GI bleeding in older adults is the result of diverticula, vascular ectasias, and CI (**Table 94-10**). This section will focus on the approach to the patient with lower GI bleeding and bleeding from vascular ectasias. Diverticular hemorrhage and CI were discussed previously.

TABLE 94-10 CAUSES OF LOWER GI HEMORRHAGE

Diverticulosis
Ischemic colitis
Vascular ectasia
Hemorrhoids
Neoplasm
Postpolypectomy
Inflammatory bowel disease
Infectious colitis
NSAID-induced colopathy
Radiation colopathy
Dieulafoy lesion
Colonic ulcerations
Meckel diverticulum
Rectal varices
Aortoenteric fistula
Small bowel sources

Acute lower GI bleeding presents with bright red blood per rectum, hematochezia, or melena depending on the location of the bleeding. Bright red blood per rectum usually indicates a distal colonic source or rapidly bleeding upper source. Melena usually indicates a right-sided colonic lesion or a source in the upper GI tract.

The first goal in the management of a patient with lower GI bleeding is resuscitation and hemodynamic stabilization. This may include administration of crystalloid intravenous fluids and blood products. Initial testing usually includes complete blood count, blood chemistry, coagulation profile, and blood type and cross-match, and the results help guide further management. For example, a low mean corpuscular volume often is a sign of chronic blood loss; a BUN-to-creatinine ratio of greater than 20:1 usually indicates an upper GI source; an elevated INR requires consideration of reversal in the face of hemodynamically significant bleeding.

Approximately 12% of patients thought to have lower GI bleeding have an upper GI bleeding source. It is important to exclude upper GI bleeding in patients with presumed lower GI bleeding, and often this can be accomplished with passage of a nasogastric tube and analysis of the gastric aspirate. Bilious fluid without blood in the nasogastric tube aspirate usually confirms the suspicion of lower GI bleeding. If an upper GI source is still in question,

urgent upper endoscopy may be performed.

Although urgent upper endoscopy for the diagnosis and treatment of upper GI bleeding is predicated on sound data, urgent colonoscopy in lower GI bleeding has been practiced less consistently. Colonoscopy has the advantage of allowing for the diagnosis and immediate treatment of actively bleeding lesions. A number of reports have shown that "urgent colonoscopy" is safe and yields a specific diagnosis in a high proportion of older adults patients with lower GI bleeding. On the basis of a high diagnostic yield, low rate of complications, and theoretical therapeutic potential, urgent colonoscopy following a rapid colonic purge has been recommended as the diagnostic procedure of choice in most patients with hemodynamically significant lower GI bleeding.

Other diagnostic tests in patients with active lower GI bleeding include scintigraphy (nuclear tagged red blood cell scans), CT angiography and conventional angiography. Approximately 45% of patients with lower GI bleeding have positive red blood cell scintigraphy. Tagged red blood cell scans can detect bleeding at a rate greater than 0.1 mL/min and are useful to localize the site of bleeding, but unfortunately offer no option for therapy. If a patient has a positive bleeding scan or CT angiography, traditional angiography with selective embolization can be performed to attempt to stop the bleeding. In order to detect active bleeding, angiography requires a higher rate of bleeding than scintigraphy, 0.5 mL/min compared to 0.1 mL/min. Transcatheter embolization of a lower GI bleeding source is usually effective in 70% to 90% of patients. If bleeding cannot be stopped with angiography, surgery to remove the bleeding colonic segment may be necessary. If a specific bleeding site can be localized with the above studies, a limited surgical resection can be performed rather than a subtotal colectomy.

Vascular Ectasias

Vascular ectasias, which arise from an age-related degeneration of previously normal blood vessels, typically occur in the cecum and proximal ascending colon. Along with diverticular bleeding, they are responsible for the majority of significant lower GI bleeding episodes in older adults. Ectasias are found in up to 25% of persons older than 60 years who do not have symptoms; they typically are multiple and less than 5 mm in diameter. Vascular ectasias probably arise as a result of repeated episodes of incomplete, low-grade obstruction of submucosal veins caused by increased tension in the colonic wall. The ultimate result is tortuosity and dilation of the venules and the arteriolar–capillary unit that feeds it, resulting in a small arteriovenous communication (**Figure 94-4**).

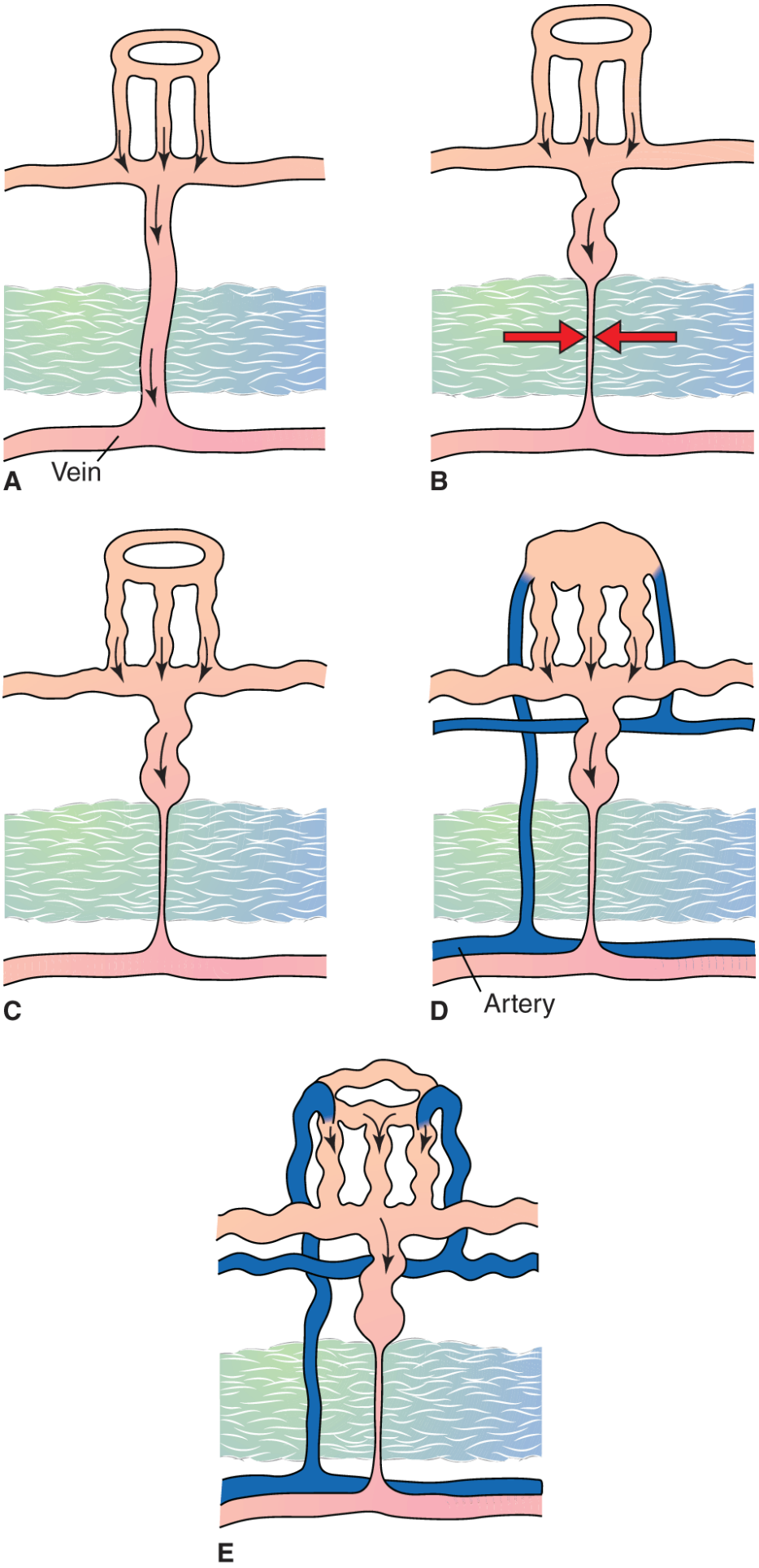

Vein
A
B
C
D
Artery
E

FIGURE 94-4. Proposed concept of the development of cecal vascular ectasias. **A.** Normal state of vein perforating muscular layers. **B.** With muscle contraction or increased intraluminal pressure, the vein is partially obstructed. **C.** After repeated episodes over many years, the submucosal vein becomes dilated and tortuous. **D.** Later, the veins and venules draining into the abnormal submucosal vein become similarly dilated and tortuous. **E.** Ultimately, the capillary ring becomes dilated, the precapillary sphincter becomes incompetent, and a small arteriovenous communication is present through the ectasia.

Lower GI bleeding caused by a vascular ectasia may be clinically indistinguishable from diverticular bleeding and is characterized by painless hematochezia. Bleeding from vascular ectasias may be hemodynamically significant, and a variety of treatment options exists including electrocoagulation, injection therapy, heater probe application, or argon plasma coagulation.

SUMMARY

Diseases of the large intestine that occur in older adults are a heterogeneous group of disorders, and are a major cause of morbidity and mortality in this population. The fundamental principle of thorough history and physical examination skills will aid the clinician at arriving at these diagnoses. With the aid of current therapeutic modalities, the pain and suffering associated with many of these diseases can be alleviated.

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Chapter 95

Constipation

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Learning Objectives

- Describe the definition and prevalence of constipation in the older adult.
- Understand the pathophysiology of constipation in the older adult.
- Identify diagnoses associated with and classification of constipation in the older adult.
- Summarize the assessment and management of constipation in the older adult.
- List the complications of constipation in the older adult.

Key Clinical Points

1. **Constipation is a common problem in older adults.**
2. **Constipation is an expensive condition, with high costs ranging from laxative expenditure to nursing time.**
3. **Health care providers should routinely inquire about constipation symptoms in older people, and be alert to the possible presence of constipation in individuals unable to communicate.**
4. **In many older people with constipation symptoms, lifestyle advice (diet, fluids, exercise, toileting habits) will preempt the need for laxative therapy.**
5. **In higher risk patients, a stepwise approach to prescribing laxatives, suppositories, or enemas should be used, with the goal of achieving comfortable and regular evacuation.**
6. **Rectal evacuation difficulties should be specifically addressed in order to identify conditions that may require additional interventions.**

INTRODUCTION

Constipation is a frequent health concern for older people in every health care setting. Primary care visits for constipation increase markedly in people older than 60 years, as does regular use of laxatives. Self-reported constipation in older people is associated with anxiety, depression, and poor health perception, while clinical constipation in vulnerable individuals may lead to complications such as fecal impaction, overflow incontinence, sigmoid volvulus, and urinary retention. Constipation is an expensive condition, with high costs ranging from laxative expenditure to nursing time. For instance, it is estimated that 80% of community nurses working with older people in the United Kingdom are managing constipation (particularly fecal impaction) as part of their case-load. An Australian study used in-depth, semistructured interviews to explore older individuals' experiences with constipation, and their findings largely summed up feelings and problems, no doubt, shared by many older people across the developed world:

- They feel "not right" in themselves when they are constipated.
- Physicians can have a dismissive attitude about constipation and do not consider the problem seriously.
- Patients are keen to find a solution, but feel useful and empathic advice and information are generally unavailable.

At the same time, patients have a strong imperative for self-management including use of over-the-counter laxatives.
- There are some barriers to lifestyle approaches, for example, expense of fruit and vegetables, fear of urinary incontinence with increased fluid intake, reluctance to walk out alone.
- One-quarter still need to do self-manual removal despite measures taken.

This chapter will describe the definition, epidemiology, risk factors, clinical presentation, assessment, and treatment of constipation in older adults. Data sources were searched of the English language literature (1966–2014), systematic review including the Cochrane database, reference lists from recent systematic reviews and book chapters, and expert committee reports, society guidelines, and expert opinion. Levels of evidence are as used by the US Preventive Services Task Force:

- Good evidence Level [1]: consistent results from well-designed, well-conducted studies
- Fair evidence Level [2]: results show benefit, but strength limited by number, quality, or consistency of studies
- Poor evidence Level [3]: insufficient because of limited number, power, or quality of studies

DEFINITIONS

Constipation is defined as a syndrome of difficulty moving bowels, characterized as difficulty or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation that may occur either in isolation or secondary to another underlying disorder. However, the definition of constipation can be broader and referred to as any condition which changes the bowel functions such as reduced stool frequency, straining to defecate, hard stool or inability to defecate. Patients and their physicians have vastly different perceptions on what constitutes constipation and a patient-centered approach generally takes patients at their word. Use of the Bristol Stool Scale also puts the patient and their practitioner on the same page (**Figure 95-1**). However, to study constipation in a more scientific manner, criteria have been developed.

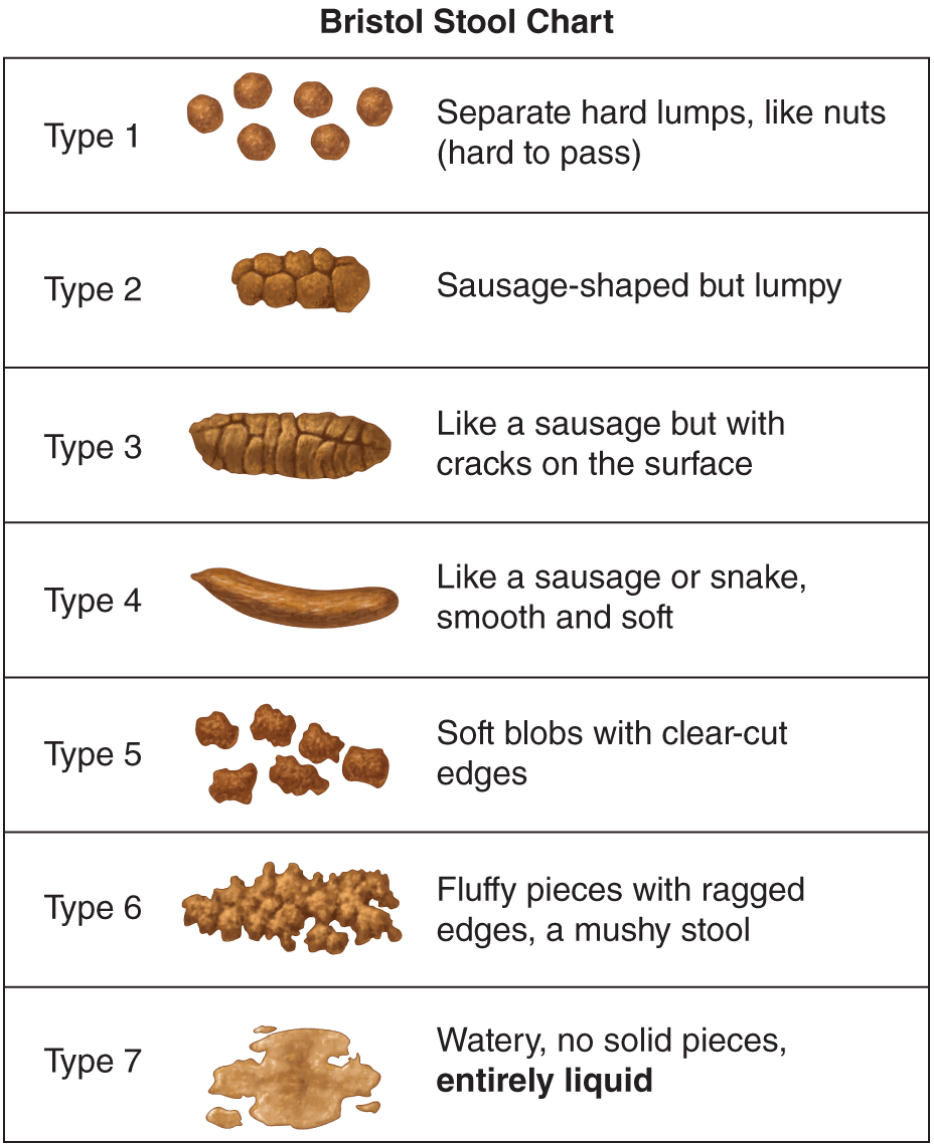


FIGURE 95-1. Bristol Stool Scale chart. (From Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32(9):920–924.)

The Rome III symptom criteria (**Table 95-1**) define functional constipation as symptoms for over 6 months and two or more of the following symptoms for more than one-fourth of the defecations during the past 3 months: straining; lumpy or hard stools; sense of incomplete evacuation; sensation of anorectal obstruction or blockade; manual maneuvers to facilitate defecations; less than three defecations per week; loose stools are not present and there are insufficient criteria for irritable bowel syndrome. The current Rome diagnostic criteria overlap with constipation predominant irritable bowel syndrome (IBS-C) and are difficult to separate them. Definitions of constipation in older people in medical and nursing literature have been inconsistent. Studies of older people have tended to define constipation subjectively by self-report, according to specific bowel-related symptoms, or by daily laxative usage. Thus, consider the same Rome criteria for defining constipation in the older population.

TABLE 95-1 ■ DEFINITIONS OF CONSTIPATION

C3. Functional Constipation

Diagnostic criteria*

1. Must include two or more of the following:
   a. Straining during at least 25% of defecations
   b. Lumpy or hard stools in at least 25% of defecations
   c. Sensation of incomplete evacuation for at least 25% of defecations
   d. Sensation of anorectal obstruction/blockage for at least 25% of defecations

e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

F3. Functional Defecation Disorders

Diagnostic criteria*

1. The patient must satisfy diagnostic criteria for functional constipation
2. During repeated attempts to defecate must have at least two of the following:
   a. Evidence of impaired evacuation, based on balloon expulsion test or imaging
   b. Inappropriate contraction of the pelvic floor muscles (i.e., anal sphincter or puborectalis) or less than 20% relaxation of basal resting sphincter pressure by manometry, imaging, or EMG
   c. Inadequate propulsive forces assessed by manometry or imaging

*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

PREVALENCE OF CONSTIPATION

Constipation prevalence is between 12% and 19% in North America and the prevalence increases with age. A systematic review reported that approximately 63 million people in North America meet the Rome II criteria for constipation with a disproportionate number being older than 65. **Table 95-2** provides practice guidance based on evidence from epidemiological studies (prevalence, symptomatology, and risk factors) of constipation in older people.

TABLE 95-2 PRACTICE GUIDANCE BASED ON EPIDEMIOLOGICAL EVIDENCE

Screening

Constipation symptoms should be routinely asked about in patients aged > 65 in view of the high prevalence of the condition in this population [2].

Men and women in their eighth decade and beyond should be regularly screened for constipation symptoms, as prevalence increases with advancing age [2].

Periodic objective assessment for constipation in older nursing home residents should be incorporated into routine nursing and medical care [2]. Patients unable to report symptoms owing to cognitive or communication difficulties should be especially targeted [3]. Such an assessment should occur at minimum every 3 mo (3 monthly incidence rate of new-onset constipation is 7% in nursing home residents), and optimally monthly [3].

Identifying Risk Factors

The identification of risk factors for constipation in older people is critical to effectively managing the condition [2].

Systematic identification of multiple risk factors in vulnerable older people with constipation should be incorporated into good practice guidelines in all health care settings [3].

Patients at increased risk of constipation from recognized comorbidities (eg, Parkinson disease, diabetes) should be regularly assessed for the condition [2].

Assessment

Identifying specific bowel symptoms in older individuals reporting constipation is important to guide appropriate management of this common complaint [2].

Reduced bowel movement frequency is not a sensitive clinical indicator for constipation in older people [2], though it is specific [3].

Difficulty with evacuation and rectal outlet delay are primary symptoms in older individuals [2].

An objective assessment should be undertaken in frail older people with constipation as these patients are at increased risk of developing complications [2].

Older patients being prescribed laxatives on a daily basis should be regularly reviewed for symptoms of constipation and the appropriateness of long-term laxative therapy [3].

Level [1] indicates good evidence, that is, consistent results from well-designed, well-conducted studies.
Level [2] indicates fair evidence, that is, results show benefit, but strength limited by number, quality, or consistency of studies.
Level [3] indicates poor evidence, that is, insufficient because of limited number, power, or quality of studies.

Self-Reported Constipation

One older community-based study of 3166 persons aged 65 years and older asked the question, “Do you have recurrent constipation?” and found a prevalence of 26% in women and 16% in men; in the plus 84 years age group, prevalence was 34% and 26%, respectively. Age was a strong independent risk factor for self-reported constipation. Other community studies support this relationship with age and show prevalence rates of up to 34% of women and 30% of men older than age 65 years. The preponderance of women over men reporting constipation tends to equalize after the age of 80 years.

Infrequent Bowel Movements

Two or fewer bowel movements per week are below normal range and tend to signify slow transit constipation. Weekly frequency of bowel movements does not, however, alter with age alone, in contrast to self-reporting of constipation. In community-based studies:

- Only 1% to 7% of both younger and older community-dwelling individuals report two or fewer bowel movements a week.
- This consistent bowel pattern across age groups persists even after statistical adjustment for the greater amount of laxatives used by older people.
- Among older people complaining of constipation, less than 10% report two or fewer weekly bowel movements, and more than 50% move their bowels daily.

Difficult Evacuation

Symptoms other than infrequent bowel movements drive self-reporting of constipation in older people. These symptoms are predominantly straining and passage of hard stools. Of older people reporting constipation in a US community study, 65% had persistent straining and 39% had passage of hard bowel movements. Difficult rectal evacuation is a primary cause of constipation in older people. Twenty-one percent of community-dwelling people aged 65 and older had rectal outlet delay (according to Rome II criteria), and many describe the need to self-evacuate. Among frailer individuals, difficult evacuation can lead to rectal impaction and fecal soiling.

Constipation in the Acute Care Setting

The number of hospitalizations due to constipation has dramatically increased in the last decade to 48,450 hospitalizations per year with a cost of approximated of $800 million per year. Older adults (65–84 years) accounted for the largest (42%) percentage of constipation discharges. The associated hospital cost per discharge associated with constipation was around $17,518 in 2010.

Constipation in the Long-Term Care Setting

Long-term care residents are at increased risk of developing complications of constipation (**Table 95-3**) that may precipitate acute hospital admissions. Physical frailty in older persons does increase the prevalence of infrequent bowel movements, with 17% of nursing home residents reporting two or fewer bowel movements a week. Among long-term care residents self-reporting constipation, 33% have two or fewer bowel movements a week. A Finnish study showed the prevalence of chronic constipation and/or rectal outlet delay to be 57% in women and 64% in men living in residential homes, and 79% and 81% respectively, in the nursing home setting. A UK study found that 64% of nursing home residents taking laxatives still reported straining on more than 1 in 4 occasions. This and the fact that 50% to 74% of long-term care residents use daily laxatives suggest that rectal evacuation difficulties are not being well managed in this population.

TABLE 95-3 COMPLICATIONS OF CONSTIPATION IN OLDER PEOPLE

Fecal incontinence [1]
Fecal impaction [1]
Stercoral perforation [3]

Urinary retention [2]
Sigmoid volvulus [2]
Acquired megacolon [2]
Rectal prolapse [3]
Diverticular disease [2]
Impaired quality of life [3]
Agitation in patients with dementia [3]

Level [1] indicates good evidence, that is, consistent results from well-designed, well-conducted studies.
Level [2] indicates fair evidence, that is, results show benefit, but strength limited by number, quality, or consistency of studies.
Level [3] indicates poor evidence, that is, insufficient because of limited number, power, or quality of studies.

PATHOPHYSIOLOGY

Physiologic studies suggest that changes in the lower bowel predisposing toward constipation in older people are not primarily age-related. This is compatible with the epidemiology showing that (1) bowel movement frequency does alter with aging, and (2) constipation symptoms are more prevalent in older people with comorbidities. Extrinsic causes such as reduced mobility, reduced fluid intake and dietary fiber, medical comorbidities and related medications all impact colonic motility and transit, and influence the pathophysiology of constipation.

Colonic Function

Colonic motility depends on the integrity of the central and autonomic nervous systems, gut wall innervation and receptors, circular smooth muscle, and gastrointestinal hormones. Propagating motor complexes in the colon are stimulated by increased intraluminal pressure generated by bulky fecal content. Studies of total gut transit time (passage of radiopaque isotope from mouth to anus, normally less than 72 hours), colonic motor activity, and postprandial gastrocolic reflex show no differences between healthy older and younger people. Older people with chronic constipation do, however, tend to have a prolonged total gut transit time, ranging from 4 to 9 days. Radiologic markers pass especially slowly through the left colon with striking delay in the rectosigmoid, suggesting that total transit time is prolonged due to a decline in propulsive activity in the colon; which may be secondary to a reduction in colonic enteric neurons producing nitric oxide and acetylcholine. The prolongation in transit time is even greater in institutionalized or bedridden patients with constipation, with total gut transit time ranging from 6 to more than 14 days. Slow transit results in a cycle of worsening colonic dysfunction by reducing water content of stool (normally 75%) and shrinking fecal bulk, which then diminishes the intraluminal pressures, and hence the generation of propagating motor complexes and propulsive activity.

Intrinsic Mechanisms for Colonic Dysfunction in Older People With Constipation

Certain intrinsic mechanisms for altered colonic function in older persons with constipation have been postulated from physiologic studies (see **Table 95-3**). The colonic epithelia decrease the secretion of water and electrolytes with aging due to a decrease of numbers of crypts and nongoblet epithelial cells. Overall collagen deposition in the left side of the colon increases with aging, and this could alter colonic compliance and motility. Direct electrophysiologic measurement of colonic motor activity in older subjects has shown that the sigmoid motor response to intraluminal bisacodyl (a direct stimulant of the myenteric plexus) is diminished in patients who are constipated, implying a deficit in intrinsic innervation. Myenteric plexus dysfunction may partially account for impaired gut motility in older persons with constipation. The total number of neurons in the myenteric plexus is decreased, and this neuronal loss bears no relation to the presence of pseudomelanosis coli cells, implying that use of anthraquinone laxatives is not the primary cause. Interestingly, these aging effects on the colon are not present in caloric restricted mice.

Another possible intrinsic factor is age-related deficit in the density of inhibitory nerves, or in the binding sites on smooth muscle for inhibitory gut neuropeptides. In vitro studies of colons across age groups showed an age-related reduction in the amplitude of inhibitory junction potentials, but no decrease in the levels of inhibitory gut neuropeptides. This age-related decline occurs earlier in women as compared with men. Such a decrease in inhibitory nerve input to the circular smooth muscle could result in segmental motor incoordination, which may lengthen transit

time and promote constipation in older persons with other predisposing risk factors. Individuals older than age 60 years have higher plasma concentrations of β-endorphin with increased binding to opiate receptors in the gut wall and myenteric plexus. Higher opiate binding has the effect of relaxing colonic tone, reducing motility, and inhibiting the gastrocolic reflex. Constipation is more prevalent in patients with nonulcer dyspepsia, the two clinical conditions being linked by gastrointestinal hypomotility.

Anorectal Function

In normal defecation, colonic activity propels stool into the rectal ampulla causing distension and intrinsically mediated relaxation of the smooth muscle of the internal anal sphincter (or anal canal). This is followed promptly by reflex contraction of the external anal sphincter and pelvic floor muscles, which are skeletal muscles innervated by the pudendal nerve. The brain registers a desire to defecate, the external sphincter is voluntarily relaxed, and the rectum is evacuated with assistance from abdominal wall muscle contraction.

Age-Related Changes in Anorectal Function

There is a tendency toward an age-related decline in internal sphincter tone, particularly in the eighth decade onward. Clinically, this predisposes older individuals to fecal incontinence, particularly with loose stools. There is a more definite age-related decline (greater in women than men) in external anal sphincter and pelvic muscle strength, which can contribute toward evacuation difficulties. Failure of the anorectal angle to open and excessive perineal descent in older women can lead to constipation. In simulated defecation studies, 37% of nonconstipated older subjects were unable to evacuate a small solid sphere. Consequent prolonged straining may compress the pudendal nerve, further exacerbating any preexisting weakness. There appears to be a reduction in rectal motility with normal aging, again in older old age. Rectal sensation does not alter with normal aging.

Anorectal Dysfunction in Older Persons

The most common form of anorectal dysfunction in older people is *rectal dysmotility*, characterized by reduced rectal motility, increased rectal compliance with a variable degree of rectal dilatation, and impaired rectal sensation such that the urge to pass stool is blunted (**Table 95-4**). Over time, an increasing degree of rectal distension is required to reflexly trigger the defecation mechanism. These patients have rectal retention of hard or soft stool on digital examination of which they may be unaware. The resulting rectal distension leads to relaxation of the internal sphincter and hence to fecal soiling. One study showed that rectal contractions could be elicited in only 14% of older people with a history of rectal impaction. One postulated cause for rectal dysmotility is diminished parasympathetic outflow as a result of impaired sacral cord function, for example, from ischemia or spinal stenosis. Rectal dysmotility can also develop through a persistent disregard or suppression of the urge to defecate as a result of dementia, depression, immobility, or painful anorectal conditions. Voluntary increase in intra-abdominal pressure during defecation could overcome rectal dysmotility to produce enough of an increase in rectal pressure for evacuation to occur, but older people often have weakened abdominal musculature, limiting their ability to compensate in this way.

TABLE 95-4 PATHOPHYSIOLOGIC MECHANISMS FOR CONSTIPATION IN OLDER PEOPLE

Chronic Constipation
Intrinsic myenteric plexus dysfunction
Increased collagen deposit in colon (age related)
Reduced inhibitory nerve input to circular muscle (age related)
Increased binding of plasma endorphins to gut receptors (age related)
Prolonged transit owing to extrinsic factors (immobility, diet, drugs, comorbidity)
Rectal Outlet Delay
Rectal dysmotility
Rectal dyschezia secondary to suppression or disregard of urge to pass stool
Sacral cord dysfunction
Pelvic floor descent
Pelvic floor dyssynergia (paradoxical contraction of pelvic floor muscles and external sphincter)

Irritable bowel disease
Weak abdominal musculature

Pelvic floor dyssynergia, though more common in younger women, can cause rectal outlet delay in older people (**Figure 95-2**). This is caused by paradoxical contraction or failure to relax the pelvic floor and external anal sphincter muscles during defecation, and manometric studies show paradoxical increases in anal canal pressure on straining. This abnormal expulsion pattern may be seen in individuals with severe and long-standing symptoms of rectal outlet delay, and in patients with Parkinson disease.

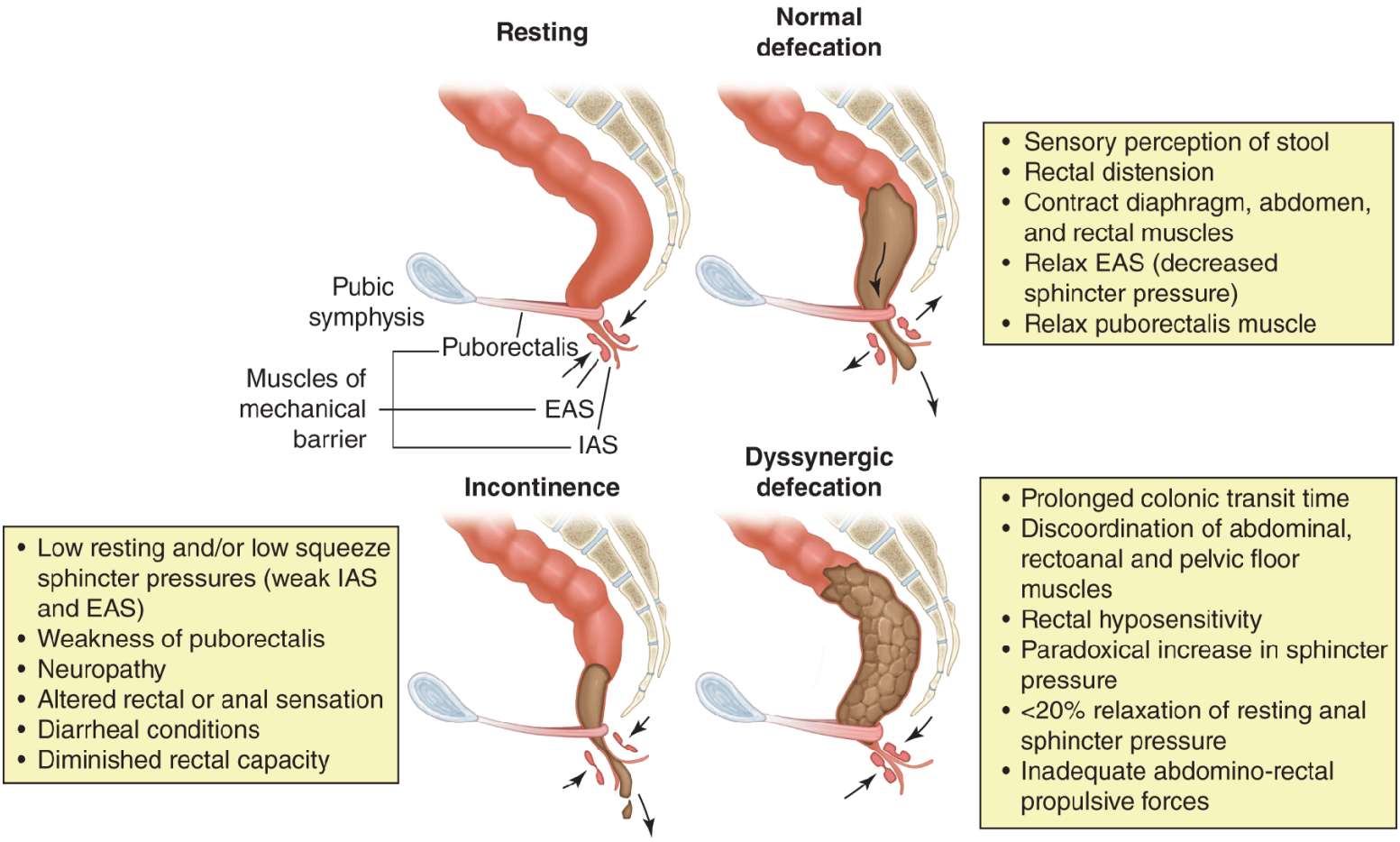


FIGURE 95-2. A series of schematic diagrams that reveal the normal anatomy and physiology of the pelvic floor in the sagittal plane at rest and during defecation, and the key pathophysiologic changes in subjects with fecal incontinence and dyssynergic defecation. EAS, external anal sphincter; IAS, internal anal sphincter. (Obtained from Rao SS. Advances in diagnostic assessment of fecal incontinence and dyssynergic defecation. *Clin Gastroenterol Hepatol.* 2010;8(11):910–919.e2.)

RISK FACTORS FOR CONSTIPATION IN OLDER PEOPLE

Both the epidemiology and pathophysiology of constipation in older people point to the enormous importance of identifying predisposing causes for the condition in each affected individual. One prospective study examined baseline characteristics predictive of new-onset constipation in older nursing home residents, using the US Minimum Data Set. Seven percent (n = 1291) developed constipation over a 3-month period. Independent predictors were white race, poor consumption of fluids, pneumonia, Parkinson disease, allergies, decreased bed mobility, arthritis, more than five medications, dementia, hypothyroidism, and hypertension. The authors postulated that allergies, arthritis, and hypertension were associated primarily because of the constipating effect of drugs used to treat these conditions. Other studies have shown that institutionalization itself is an independent risk factor for symptom-based constipation in older people. **Table 95-5** summarizes evidence-based risk factors of constipation in the older population.

TABLE 95-5 RISK FACTORS FOR CONSTIPATION IN OLDER PEOPLE

Medications
Polypharmacy (≥ 5 medications) [2]
Anticholinergic drugs (tricyclics, antipsychotics, antihistamines, antiemetics, drugs for detrusor hyperactivity) [1]
Opiates [2]
Iron supplements [3]
Calcium channel antagonists (nifedipine and verapamil) [2]
Calcium supplements [2]
Nonsteroidal anti-inflammatory drugs [2]
Impaired mobility [2]
Nursing home residency [2]
Neurological conditions
Dementia [2]
Parkinson disease [1]
Diabetes [1]
Autonomic neuropathy [2]
Stroke [3]
Spinal cord injury or disease [1]
Depression [3]
Dehydration [2]
Low dietary fiber [3]
Metabolic disturbances
Hypothyroidism
Hypercalcemia
Hypokalemia
Uremia
Patients receiving renal dialysis [3]
Mechanical obstruction (eg, tumor, rectocele)
Lack of privacy or comfort
Poor toilet access [3]

Level [1] indicates good evidence, that is, consistent results from well-designed, well-conducted studies.
Level [2] indicates fair evidence, that is, results show benefit, but strength limited by number, quality, or consistency of studies.
Level [3] indicates poor evidence, that is, insufficient because of limited number, power, or quality of studies.

Reduced Mobility

Impaired mobility is a common risk factor for constipation in older people. Greater physical activity (including regular walking) is associated with less self-reported and symptom-specific constipation in older people living both at home and in long-term care. Reduced mobility was found to be the strongest independent correlate of heavy laxative use among nursing home residents, following adjustment for age, comorbidity, and other relevant clinical factors. Gut transit time in older subjects was measured independently as 3 days in ambulant, and 3 weeks in bedridden patients, although comorbid factors were likely to be contributory. A study of healthy young male volunteers showed that after only 1 week of bed rest, both transit through the sigmoid colon and stool frequency were reduced. It is well documented that exercise increases colonic propulsive activity (“jogger’s diarrhea”), especially when measured postprandially. In a population survey of younger women (36–61 years), daily physical activity was associated with less constipation (defined as two or fewer bowel movements per week), and the association strengthened with

increased frequency of physical activity. This suggests that increasing physical activity in adulthood may reduce the likelihood of constipation problems in older age.

Drug Side Effects

Polypharmacy increases the risk of constipation in older patients, particularly in nursing homes where each individual takes an average of six prescribed medications per day. *Anticholinergic medications* reduce contractility of the smooth muscle of the gut via an antimuscarinic effect at acetylcholine receptor sites, and in some cases (eg, patients with schizophrenia taking neuroleptics), long-term use may result in chronic megacolon. In two cross-sectional studies of nursing home residents, anticholinergic antidepressants were independently associated with daily laxative use following adjustment for age, gender, function, and cognition. Anticholinergic neuroleptics and antihistamines were also independently associated in one of the studies; nonanticholinergic sedatives, however, were not found to be constipating. A study of 532 community-dwelling older US veterans found that among the 27% using anticholinergic drugs, the rate of constipation (42%) was significantly greater than those not using the drugs.

While older people are very susceptible to the constipating effects of *opiate analgesia*, a study of nursing home residents with persistent nonmalignant pain found that there was no increased rate of constipation in chronic opiate users over a 6-month period compared to those not taking opiates. They also observed a general improvement in functional status and social engagement. Constipation in chronic opiate users can be effectively managed (by laxative or suppository coprescription where needed)—an important finding as chronic pain is often undertreated in older people perhaps owing to fear of the adverse effects of analgesic drugs. Community-based studies of adults receiving opiates for chronic pain have shown equal constipation risk for all sustained-release oral preparations. Transdermal patches (eg, fentanyl), however, are associated with lower risk of constipation than oral preparations.

All types of *iron supplements* (sulphate, fumarate, and gluconate) cause constipation, the constipating factor being the amount of elemental iron absorbed. Slow-release preparations have a lesser impact on the large bowel, but this is because they tend to carry the iron past the first part of the duodenum into an area of the gut where elemental iron absorption is poorer. Administration of iron sulfate in doses greater than 325 mg/day does not substantially increase iron absorption in older persons and may significantly increase gastrointestinal side effects. Intravenous iron does not cause constipation and may be an alternative in patients with chronic anemia (eg, chronic kidney disease) who have symptomatic constipation on oral iron.

In a 5-year study of *calcium supplementation* in older women, the only side effect was constipation (treatment 13.4% vs placebo 9.1%). The study showed that calcium supplementation reduced bone loss and turnover and fracture rates in older women who took it, but long-term compliance was poor, and constipation may have contributed to this.

Calcium channel antagonists impair lower gut motility, particularly in the rectosigmoid, by inhibiting calcium uptake into smooth muscle cells and altering intraluminal electrolyte and water transportation. Severe constipation has been reported in older patients taking calcium channel antagonists, with nifedipine and verapamil being the most potent inhibitors of gut motility in this class of drugs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) increase the risk of constipation in older people, most likely through prostaglandin inhibition. In a large case-controlled primary care study, constipation and straining was a more common reason for stopping NSAIDs than dyspepsia. NSAIDs have also been implicated in causing stercoral perforation in patients with chronic constipation.

Aluminium antacids have been associated with constipation in older people living in both nursing homes and in the community.

Dietary Factors

Fiber Low consumption of wheat bran, fiber, vegetables, fruit, rice, and calories can all predispose toward constipation. A UK survey showed that consumption of fruit, vegetables, and bread decreases with advancing age. It has been suggested that the prevalence of constipation is rising because modern food processing produces refined food with low roughage. Community studies of older Europeans who eat a Mediterranean diet rich in fruit, vegetables, and olive oil show a low prevalence of constipation (4.4% in people aged > 50). Conversely, a German questionnaire survey of adults with and without constipation reported that chocolate, white bread, and bananas were the foodstuffs most strongly perceived to harden stools.

Calories Low-calorie intake in older people (adjusted for fiber intake) has been linked to constipation. One study looked at nutritional factors across all nursing homes in Finland and found that malnutrition and constipation were

associated. This may be a two-way association in that marked constipation or fecal impaction can cause anorexia, while low-calorie intake can promote constipation.

Enteral nutrition Constipation is a recognized problem in patients receiving enteral nutrition. A prospective survey from Spain of hospitalized patients (mean age 76) receiving nasogastric tube feeding identified constipation as a complication of treatment in 30%. Enteric feeding products containing fiber are available, though there are no data on whether constipation is any less of a problem with their use.

Fluid Intake

Amount Low-fluid intake in older adults has been related to symptomatic constipation in epidemiologic surveys and to slow colonic transit. In patients with Parkinson disease, low water intake is correlated with severity of constipation. Withholding fluids over a 1-week period in young male volunteers significantly reduced stool output. Older people are at greater risk of dehydration and resulting constipation because of

- Impaired thirst sensation
- Less effective hormonal responses to hypertonicity
- Limited access to drinks because of coexisting physical or cognitive impairments
- Voluntary fluid restriction in an attempt to control urinary incontinence

Alcohol and coffee A large Japanese survey of constipation symptoms found that alcohol consumption was a preventive factor in men. A population survey of middle-aged women in the United States showed that daily alcohol consumption (exceeding 12 g/day) and low-moderate caffeine intake were independently inversely related to infrequent bowel movements. Black coffee has been shown to increase colonic motility specifically in the rectosigmoid within 4 minutes of ingestion in young healthy volunteers (a reaction not observed with ingestion of hot water), implying that caffeine triggers the gastrocolic reflex.

Parkinson Disease

Patients with Parkinson disease suffer from three primary pathologies that lead to constipation:

- Primary degeneration of dopaminergic neurons in the myenteric plexus resulting in prolonged colorectal transit
- Pelvic dyssynergia causing rectal outlet delay and prolonged straining
- Small increases in intra-abdominal pressures on straining (compared with age-matched controls)

Constipation can become prominent early in the course of the disease, even 10 to 20 years prior to motor symptoms. In a 24-year longitudinal study in Honolulu, less than one bowel movement a day was associated with a threefold elevated risk of future Parkinson disease in men. A study of patients at a Parkinson disease clinic found that 59% were constipated according to the Rome criteria (vs 21% in age-matched control group without neurological disease), and 33% were very concerned by their bowel problem. Antiparkinsonian drugs can further exacerbate constipation. Pelvic dyssynergia affects 60% of people with Parkinson disease and may be hard to treat. Botulinum toxin injected into the puborectalis muscle has been used to improve rectal emptying in Parkinson disease patients with good effect, though repeat injections every 3 months are required to maintain clinical benefit.

Dementia

Dementia predisposes individuals to rectal dysmotility, partly through ignoring the urge to defecate. A study in which young men deliberately suppressed defecation resulted in prolonged transit through the rectosigmoid with a marked reduction in frequency of bowel movements. Epidemiological studies show a significant association between cognitive impairment and nurse-documented constipation in nursing home residents. Patients with non-Alzheimer dementias (Parkinson disease, Lewy body, vascular dementia) compared to those with Alzheimer dementia are more likely to suffer from autonomic symptoms, including constipation.

Mood-Related Disorders

Depression, psychological distress, and anxiety are all associated with increased self-reporting of constipation in older persons. In certain cases, the symptom of constipation is a somatic manifestation of psychiatric illness. A careful

assessment is required to differentiate subjective complaints from clinical constipation in depressed or anxious patients.

Stroke

Constipation affects 60% of those recovering from stroke while undergoing rehabilitation, and a high number of these have combined rectal outlet delay and slow transit constipation. For stroke survivors living in the community, problems relating to bowel evacuation are greatly worsened by difficulties accessing the toilet owing to functional impairment. Weakness of abdominal and pelvic muscles following stroke also contribute to problems with evacuation.

Spinal Cord Injury/Disease

Constipation affects the majority of people with spinal cord disease or injury. Age and duration of injury interact to promote complications of chronic constipation such as acquired megacolon, which affects more than half of patients with spinal cord injury. Lumbar stenosis in older people caused by degenerative joint disease may lead to cauda equina problems with severe rectal outlet delay. One study in younger people showed that an average of 27 of rectosigmoid emptying was achieved with each defecation in patients with cauda equina syndromes, versus 81% in healthy controls.

Diabetes

A Turkish study of outpatients with type 2 diabetes showed that 56% complained of constipation (vs 30% of controls). Neuropathy symptom scores correlated with laxative usage and straining. Diabetic patients with autonomic neuropathy are more likely to be constipated because of markedly slowed transit throughout the colon and impairment of the gastrocolic reflex. However, one-third of diabetic patients with constipation do not have neuropathic symptoms, so additional potentially reversible factors should be considered particularly in older people (eg, drugs, mobility, fluids). Indeed, a US community study found that constipation and/or laxative use was increased in type 1 versus type 2 diabetic men, but this difference was associated with use of calcium channel blockers rather than with neuropathy symptoms. Acute hyperglycemia inhibits the gastrocolic reflex and colonic peristalsis, so glycemic control is important. Colonic transit time in immobile older people with diabetes is extremely prolonged at 200 ± 144 hours. An Israeli study showed that this very long transit time in long-term care residents with diabetes can be significantly reduced by administering acarbose, an α-glucosidase inhibitor with a potential adverse effect of causing diarrhea. Overall, gut dysmotility can lead to bacterial overgrowth and the clinical problem of explosive diarrhea; treatment with erythromycin and long-term motility agents such as metoclopramide should be considered in these individuals.

Metabolic Disorders

Hypokalemia produces neuronal dysfunction that minimizes acetylcholine stimulation of gut smooth muscle and so prolongs transit through the gut. It should be excluded in cases of colonic pseudo-obstruction and sigmoid volvulus. *Hypercalcemia* causes conduction delay within the extrinsic and intrinsic innervation of the gut. Surgical treatment of hyperparathyroidism reverses the neuromuscular bowel dysfunction seen with this condition. Patients with *myxedema* have been observed to have edema of the gut wall with mucopolysaccharide deposition, although whether this contributes to the colonic hypomotility seen commonly in *clinical hypothyroidism* is uncertain. Patients on *long-term renal dialysis* have prolonged age-adjusted transit time, more so in hemo- than peritoneal dialysis. In a questionnaire study in Japan, 63% of hemodialysis patients complained of constipation. Important contributors to this problem were thought to be high (49%) use of resin to avoid hyperkalemia, suppression of the defecation urge while undergoing dialysis, and low-fiber intake. Resin administration also places older inpatients at risk of fecal impaction.

Colorectal Cancer

Colorectal cancer has been linked with both constipation and use of laxatives, although this risk association is likely to be confounded by the influence of underlying habits. One study, adjusted for age and potential confounders, found that having fewer than three reported bowel movements a week was associated with a greater than twofold risk of colon cancer, with the association being most strong in black women. As the prevalence of colorectal cancer increases with age, index of suspicion should be higher in older adults. Constipation alone, however, is not an indication for proceeding to colonoscopy (see below).

Rectocele

Posterior vaginal wall prolapse and rectocele are common in older multiparous women. These individuals have an increased risk of rectal outlet delay, particularly incomplete emptying and need for digital evacuation. This is presumably caused by mechanical obstruction, as this association is not seen in women with anterior pelvic prolapse.

COMPLICATIONS OF CONSTIPATION IN OLDER ADULTS

Fecal Incontinence

Constipation is a common, treatable, preventable, and often overlooked cause of fecal incontinence in older people (see **Table 95-4**). Few medical symptoms are as distressing and socially isolating for older people as fecal incontinence, a condition that places them at greater risk of morbidity, mortality, dependency, and nursing home placement. All too often, untreated overflow leads to hospitalization of vulnerable older patients. Many older individuals in the community with fecal incontinence will not volunteer the problem to their physician and, regrettably, physicians, and nurses do not routinely inquire about the symptom. This “hidden problem” therefore leads to social isolation and a downward spiral of psychological distress, dependency, and poor health. Even when older people are noted by health care professionals to have fecal incontinence, the condition is often poorly assessed and passively managed, especially in the long-term care setting where it is most prevalent.

Overflow (continuous fecal soiling and fecal impaction on rectal examination) was identified as the underlying problem in 52% of frail nursing home residents with long-standing fecal incontinence in one study. A therapeutic intervention consisting of enemas until no further response followed by lactulose achieved complete resolution of incontinence in 94% of those in whom full treatment compliance could be obtained. Notably, this study showed that only 4% of nursing home residents with long-standing fecal incontinence had been referred for further assessment, reflecting a tendency toward unnecessarily conservative nursing management (eg, use of pads and pants only). Another nursing home study found that daily lactulose and suppositories plus weekly enemas only effectively resolved overflow incontinence when complete rectal emptying was consistently achieved over a period of 2 months. An effective therapeutic program for overflow incontinence depends on the following:

- Regular toileting (ideally 2 hourly, which also promotes mobility)
- Monitoring of treatment effect by rectal examination and bowel chart
- Responsive stepwise drug and dosage changes
- Prolonged treatment (at least 2 weeks)
- Subsequent maintenance regimen to prevent recurrences

Fecal Impaction

Fecal impaction is an important cause of comorbidity in older patients, increasing the risk of hospitalization and of potentially fatal complications. A survey of patients admitted to acute geriatric units in the United Kingdom over 1 year reported that fecal impaction was a primary reason for hospitalization in 27%. In frail patients, fecal impaction may present as a nonspecific clinical deterioration; more specific symptoms are anorexia, vomiting, and abdominal pain. Findings on physical examination may include fever, delirium, abdominal distension, reduced bowel sounds, arrhythmias, and tachypnea secondary to splinting of the diaphragm. The mechanism for the fever and leukocytosis response is thought to be microscopic stercoral ulcerations of the colon. A plain abdominal radiograph will show colonic or rectal fecal retention associated with lower bowel dilatation. Presence of fluid levels in the large or small bowel suggests advanced obstruction; the closer the fecal impaction is to the ileocecal valve, the greater the number of fluid levels seen in the small bowel.

Urinary Retention/Lower Urinary Tract Symptoms

Rectosigmoid fecal loading may impinge on the bladder neck causing some degree of urinary retention. Two Finnish studies of older women and men showed an independent association between constipation and lower urinary tract symptoms (LUTS) in both genders. A case-control study in hospitalized women aged 65 and older found that after adjustment for relevant confounders, constipation was the primary predictor of urinary retention, increasing the risk of retention fourfold as measured be portable ultrasound postvoid residual (PVR) > 100 mL (other predictors were urinary tract infection and previous urinary retention). Urinary symptoms of difficult voiding were unreliable in

diagnosing retention in this study, suggesting that it is good practice to do screening PVRs in hospitalized older women with constipation, particularly in the context of coexisting urinary tract infection. A prospective cohort study examined the impact of treating chronic constipation on coexisting urinary symptoms in older people (mean age 72). After 4 months, there was a significant improvement in constipation, as well as urgency, frequency, and voiding difficulty), mean PVR (reduced from 85 to 30 mL), and fewer urinary tract infections. There are also case reports in frail older people of bilateral hydronephrosis associated with renal failure that resolved following fecal disimpaction.

Stercoral Perforation

Fecal impaction increases the risk of stercoral perforation of the wall of the colon (usually sigmoid) secondary to ischemic necrosis. Stercoral perforation can also occur in chronically constipated persons, where pressure from a hard fecaloma produces an ulcer with characteristically necrotic and inflammatory edges; these individuals tend to present with sudden onset of acute abdominal pain. Prompt surgical intervention and rigorous treatment of peritonitis are needed to prevent the high mortality rate associated with this condition. A case-control study found that the most prevalent risk factor for colon ischemia in 700 cases was the use of drugs that cause constipation (one in three cases compared to only one in nine controls).

Sigmoid Volvulus

Chronic constipation in frail older people is the leading cause of sigmoid volvulus in the developed world. Volvulus is

- The third commonest cause of large bowel obstruction in the United States
- More likely in constipated patients with Parkinson disease and neuropathic colon (eg, from spinal cord disease or long-term neuroleptic treatment)
- Associated with hypokalemia
- Treated initially by sigmoidoscopic deflation but with a high recurrence rate
- Managed surgically, usually by partial colectomy, when sigmoidoscopic deflation fails

Colonic Pseudo-Obstruction

Acute colonic pseudo-obstruction (Ogilvie syndrome) is most likely to occur in hospitalized frail older people with a history of chronic constipation who are acutely medically ill, or in postoperative phase. It presents with abdominal distension and colonic dilatation on x-ray, with a cecal diameter of 10 cm or more. Nothing by mouth, flatus tube, and correction of electrolyte imbalances (particularly potassium and magnesium) are initial treatments, progressing to neostigmine (if no cardiac contraindications), and then endoscopic decompression if dilatation persists. Administration of polyethylene glycol after initial resolution of colonic dilatation has been shown to reduce the likelihood of recurrence requiring escalation of therapy.

Rectal Prolapse

Prolonged straining at stool in constipated patients can result in rectal prolapse of varying degrees, and older people are more at risk from developing fecal soiling as a result. Surgery should be considered for full thickness prolapses, and laparoscopic versus transabdominal repair is now an effective treatment (including improving bowel-related symptoms) with a low recurrence rate.

Diverticular Disease

Left-sided diverticulosis coli affects 30% to 60% of people older than 60 in developed countries. Etiology has been attributed to high intraluminal pressures while straining at stool in people who have a low fiber diet. A case-control study of patients mean age 68 with acute uncomplicated diverticulitis showed 74% to have prolonged transit (longest in those with constipation symptoms), and 59% had small intestinal bacterial overgrowth. Newer approaches to preventing recurrence of symptomatic flare-ups of diverticular disease are use of mesalazine and *Lactobacillus casei*, separately or in combination.

Impact on Quality of Life

Quality of life and daily living are affected by functional bowel symptoms in older people, even following adjustment

for other chronic illnesses. Patients with constipation generally have an impaired quality of life compared with the general population, though few studies have looked at this specifically in older people. A Hong Kong study of community-living people aged 70 and older showed an independent association between constipation and low morale as measured by the Philadelphia Geriatric Morale Scale. A Canadian study of the general population found an association between constipation and a low SF-36 score, with the rate of physician visits for constipation being strongly predicted by the physical component of the SF-36. The Patient Assessment of Constipation Quality of Life questionnaire is a validated tool for assessing quality of life over time that has been used in older adults in long-term care; scores correlate with abdominal pain and constipation severity. Patients whose constipation is associated with abdominal pain or other irritable bowel symptoms score even lower on quality of life measures, plus have poor general health perception. Constipation in long-term care residents unable to communicate because of dementia has been linked to physically aggressive behavior. A US study of almost 9000 nursing home residents examined characteristics associated with the development of wandering behavior over a 1-year period and found that constipation increased the risk almost twofold. The authors postulated that residents with dementia may wander to alleviate constipation-related discomfort, and nursing home health professionals should be alert to this.

CLINICAL EVALUATION

General Assessment

A broad assessment should be undertaken in older patients with constipation, focusing on predisposing causes. In addition to bowel symptoms, the history should include over-the-counter medications, diet, and fluid intake. Physical examination should include cognition, mood, and function in addition to abdominal and rectal exams. Laboratory tests when indicated include complete blood count; plasma electrolytes; calcium; glucose; and liver and thyroid function tests. **Figure 95-3** illustrates a recommended approach to the patient with chronic constipation.

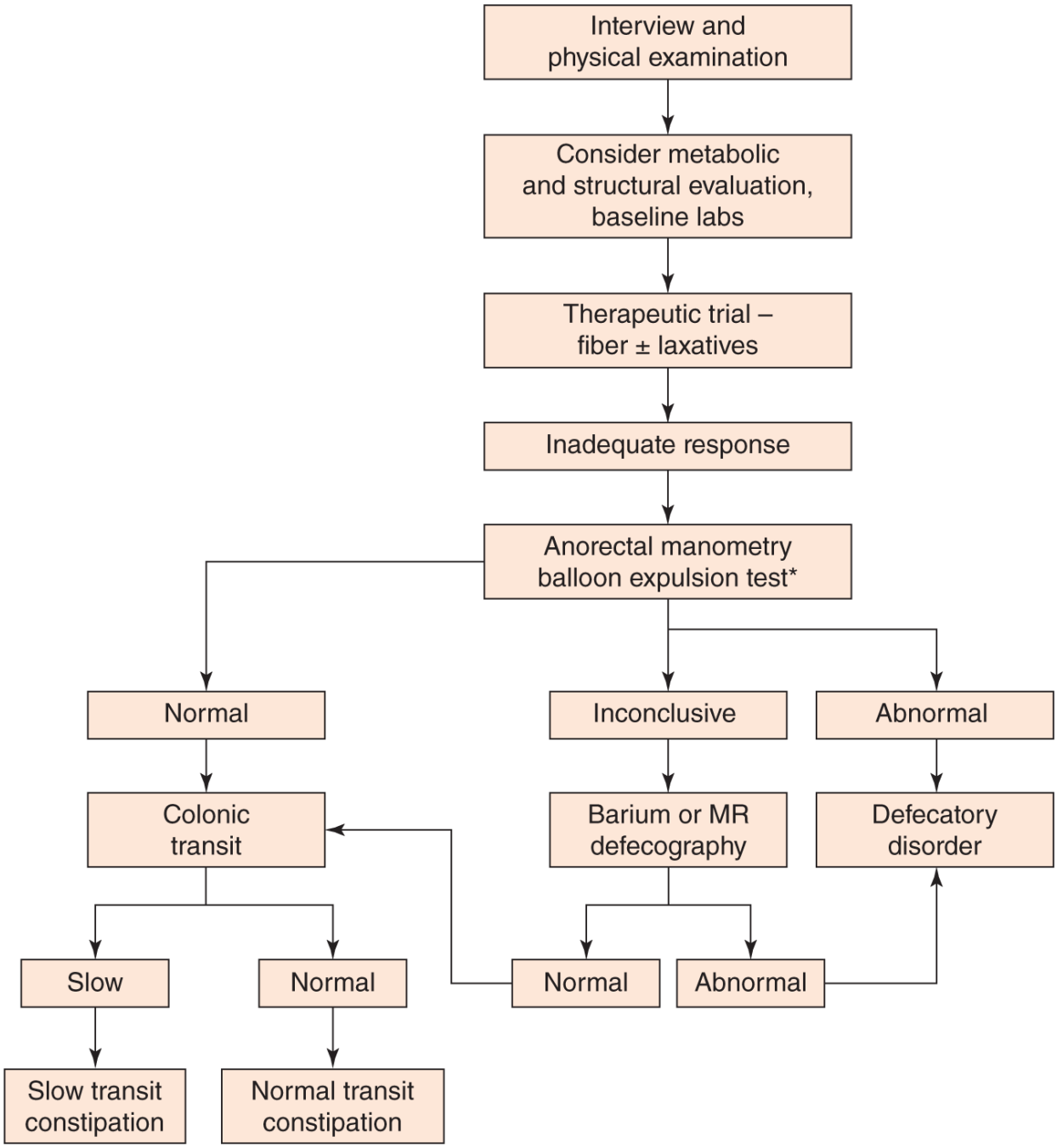


FIGURE 95-3. A practical approach to assessment of constipation in older people. (From Bharucha AE, Dorn SD, Lembo A, Pressman A. American Gastroenterological Association medical position statement on constipation. *Gastroenterology*. 2013;144:211–217; with permission.)

*Because anorectal manometry, rectal balloon expulsion test may not be available in all practice settings, it is acceptable in such circumstances, to proceed to assessing colonic transit with the understanding that delayed colonic transit does not exclude a defecatory disorder.

History

Table 95-6 lists the important aspects of the bowel history that should be elicited from an older person who complains of constipation. It is essential to identify rectal evacuation difficulties where present in order to manage the patient effectively. Although constipation may be underestimated in older patients with dementia and depression, studies have shown that adults complaining of constipation frequently underestimate the number of bowel movements. Thus it may be helpful to have them keep a stool chart for a week to document frequency and characteristics of their bowel movements and associated symptoms. A recent history of altered bowel habit should prompt an exploration of precipitants (eg, new medications, changes in diet), and where unexplained, an evaluation for colorectal cancer. Abdominal pain, rectal bleeding, and certainly any systemic features such as weight loss and anemia should prompt

further investigations for underlying neoplasm.

TABLE 95-6 DIAGNOSIS OF CONSTIPATION IN OLDER PEOPLE

Bowel History
Number of bowel movements per week
Stool consistency
Straining/symptoms of rectal outlet delay
Duration of constipation
Fecal incontinence/soiling
Irritable bowel syndrome symptoms (abdominal pain, bloating, passage of mucus)
Rectal pain or bleeding
Laxative use, prior and current
Psychological and quality of life impact of bowel problem
Urinary incontinence/lower urinary tract symptoms
General History
Mood/cognition
Symptoms of systemic illness (weight loss, anemia)
Relevant comorbidities (eg, diabetes, neurological disease)
Mobility
Diet
Medications
Toilet access (location of bathroom, manual dexterity, vision)
Specific Physical Examination
Digital rectal examination including external and internal sphincter tone
Perianal sensation/cutaneous anal reflex
Rectal prolapse/hemorrhoids
Pelvic floor descent/rectocele
Abdominal palpation, auscultation
Neurological, cognitive, and functional examination
Tests
Indications for plain abdominal radiograph
Empty rectum with clinical suspicion of constipation
Evaluation for fecal impaction
Persistent fecal incontinence despite clearing of any rectal impaction
Evaluation of abdominal distension, pain, or acute discomfort
Persisting complaints of constipation with increasing laxative usage
Indications for colonoscopy
Systemic illness (weight loss, anemia, etc)
Bleeding per rectum
Recent change in bowel habit without obvious risk factors
Indications for anorectal function tests
Severe or persistent symptoms of rectal outlet delay
Persistent fecal incontinence with clinical evidence of anal sphincter weakness

Perianal fecal soiling is a common and embarrassing symptom that patients are reluctant to volunteer. In one large

nursing home study, 38% of older individuals who complained of constipation reported fecal soiling of undergarments. Overflow fecal incontinence typically presents as frequent passive leakage of watery stool, sometimes confusing patients and caregivers into thinking they have “diarrhea” rather than constipation. Impaction must be ruled out in the presence of fecal soiling or incontinence. The other important diagnoses to consider in older people are loose stools caused by inappropriate laxative use, other drug side effects, or undiagnosed bowel disease.

Irritable bowel syndrome should be a diagnosis of exclusion in older people, and only made in those with a many year history of intermittent symptoms such as abdominal distension or pain relieved by defecation, passage of mucus, and feeling of incomplete emptying (Rome criteria). Rectal pain associated with defecation should alert the physician to rectal ischemia as well as to other more common anorectal conditions. Rectal bleeding should prompt further evaluation for an underlying tumor, unless examination clearly reveals bright red blood from anal fissure or hemorrhoids. Lower urinary tract symptoms may be exacerbated by constipation and should be documented.

A person’s attitude to their bowel problem (positive, acceptance, denial, distress, apathy) and the impact on their quality of life should be included when taking a history. Some health care providers share the generally held belief that constipation is an inevitable consequence of aging, and qualitative work has shown that patients can feel that their problem is not being taken seriously. A thorough clinical history and assessment is an important first step in developing a sound patient-physician partnership, which enhances successful outcomes in managing what is usually a chronic condition.

Digital Rectal Examination

Digital rectal examination is required in all patients who report constipation to reveal rectal impaction, rectal dilatation, hemorrhoids, anorectal disease, and perianal fecal soiling. Retained stool in rectal impaction does not have to be hard; loading with soft stool is commonly seen in older people taking laxatives who have problems with rectal outlet delay. Absence of stool on rectal examination does not exclude the diagnosis of constipation. A dilated rectum with diminished sensation and retained stool suggests rectal dysmotility. External sphincter tone is assessed by asking the patient to “squeeze and pull up” around the examining finger. Indicators of reduced internal anal tone are easy insertion of the finger into the anal canal and gaping of the anus on applying gentle traction to the anal margin. Anal sphincter weakness should prompt (1) careful prescribing to avoid causing fecal leakage though excessive laxative-induced softness of stool, and (2) instruction in anal sphincter strengthening exercises (**Table 95-7**).

TABLE 95-7 PATIENT EDUCATION

Toilet Habits and Positioning
Do not delay having a bowel movement when you feel the urge.
Put aside a particular time each day (we would advise after breakfast) when you can sit on the toilet without being in a hurry.
A relaxed attitude to bowel evacuation will especially help if you have problems with straining or a feeling of anal blockage.
If straining is a problem, it is helpful to have a footstool under your feet while sitting on the toilet as this increases the ability of your abdominal muscles to help evacuation of stool.
Abdominal Massage
Lie on the bed with pillows under your head and shoulders.
Your knees should be bent up with a pillow underneath them for support.
Cover your abdomen with a light sheet.
Massage your abdomen with firm but gentle circular movements starting at the right side and working across to the left side.
Continue the massage for approximately 10 min.
This massage should be a pleasant experience—if you feel any discomfort then stop.
Diet
To help prevent constipation you should eat more of the foods from list A and less of the foods from list B. Foods in list A tend to make the stool softer and easier to pass, because they are high in fiber. Foods in list B tend to make the stool harder, because they bind together the contents of the bowel.
List A: Fresh fruit, prunes and other dried fruit, whole meal bread, bran cereals and porridge, salad, cooked vegetables (with skin where possible), beans, lentils.
List B: Milk, hard cheese, yogurt, white bread or crackers, refined cereals, cakes, pancakes, noodles, white rice, chocolate, creamed

soups.

You should increase your fiber intake gradually because sudden change in fiber content may cause temporary bloating and irregularity. It is important to eat the foods that contain fiber all through the day and not just at one meal such as breakfast.

Increase the amount of fluid that you drink gradually up to 8 to 10 glasses a day. Try to drink more water, fruit juices, and fizzy drinks.

Sphincter Strengthening

Learning to do your exercises

Sit in a comfortable position with your knees slightly apart. Now imagine that you are trying to stop yourself passing wind from the bowel. To do this you must squeeze the muscle around the back passage. Try squeezing and lifting that muscle as tightly as you can. You should be able to feel the muscle move. Your buttocks, abdomen, and legs should not move at all. You should be aware of the skin around the back passage tightening and being pulled up and away from your chair. Really try to feel this. You are now exercising your anal sphincter muscles. (You do not need to hold your breath when you tighten the muscles!)

Practicing your exercises

Tighten and pull up the anal sphincter muscles as tightly as you can. Hold tightened for at least 5 s, then relax for at least 10 s.

Repeat this exercise at least 5 times. This will work on the strength of your muscles.

Next, pull the muscles to approximately half of their maximum squeeze. See how long you can hold this for. Then relax for at least 10 s.

Repeat at least 5 times. This will work on the endurance or staying power of your muscles.

Pull up the muscles as quickly and tightly as you can and then relax and then pull up again, and see how many times you can do this before you get tired. Try for at least 5 quick pull-ups. Try this quick pull-up exercise at least 10 times each day.

Do all these exercises as hard as you can and at least 5 times a day. As the muscles get stronger, you will find that you can do more pull-ups each time without the muscle getting tired.

It takes time for exercises to make muscle stronger. You may need to exercise regularly for several months before the muscles gain their full strength.

Instructions for Using Suppositories

These may be inserted into your rectum (back passage) by your nurse or caregiver or yourself if you are physically able to do it.

If necessary go to the toilet and empty your bowels if you can.

Wash your hands.

Remove any foil or wrapping from the suppository.

Either lie on your side with your lower leg straight and your upper leg bent toward your waist or squat.

Gently but firmly insert the suppository, narrow end first, into the rectum using a finger. Push far enough (approximately 1 in) so that it does not come out again.

You may find your body wanting to push out the suppository. Close your legs and keep still for a few minutes.

Try not to empty your bowels for at least 10 to 20 min.

Absent cutaneous-anal reflex (gentle scratching of the anal margin should normally induce a visible contraction of the external sphincter) and, in particular, perianal anesthesia point to significant sacral cord dysfunction with associated rectal dysmotility. Proctoscopy is a simple, quick, and useful test for diagnosing internal hemorrhoids and abnormalities of the rectal wall.

Pelvic Floor and Rectal Prolapse

Excessive perineal descent is observed by asking the patient to “bear down” while lying in the lateral position. Normal perineal descent is less than 4 cm (can be eye-balled by drawing an imaginary line between that ischial prominences). Rectal prolapse may also be observed in this manner, though lesser degrees of prolapse may only be identified by having the patient strain while sitting on a toilet or commode. An examination for posterior vaginal prolapse (bearing down in the gynecological position) is appropriate in all women with constipation, especially those reporting incomplete rectal emptying and the need to manually evacuate.

Plain Abdominal X-Ray

Clinical diagnosis can usually be made on the basis of a thorough history and examination. However, a plain

abdominal radiograph is useful in patients without rectal impaction in whom colonic loading is suspected because of a high-risk profile, constipation-related symptoms, or fecal incontinence. In those patients who continue to report troublesome constipation-related symptoms despite regular laxative use it can guide management by showing the following:

- No stool—patient may require education about what constitutes a normal bowel habit and no increase and possibly a reduction in laxative usage.
- Colonic fecal loading—patient requires education on lifestyle measures and a change in type or increased dose of laxative.
- Rectal loading with a clear colon—patient requires suppositories or enemas, and no increase and possibly a reduction in laxatives.

Rectal air with marked fecal loading in the descending colon may correlate with normal transit constipation or an evacuation disorder (**Figure 95-4A**). Marked fecal loading in the ascending and transverse colon correlates well with prolonged transit time, or slow transit constipation as does the presence of feces rather than air in the cecum (**Figure 95-4B**). Dilatation of the colon (> 6.5 cm maximum diameter) in the absence of acute obstruction points toward megacolon (**Figure 95-4C**). Rectal dilatation (> 4 cm) implies dysmotility and evacuation problems. Finally, in patients with abdominal distension and/or pain, an abdominal radiograph is necessary to rule out acute problems such as sigmoid volvulus and small bowel obstruction secondary to severe impaction.

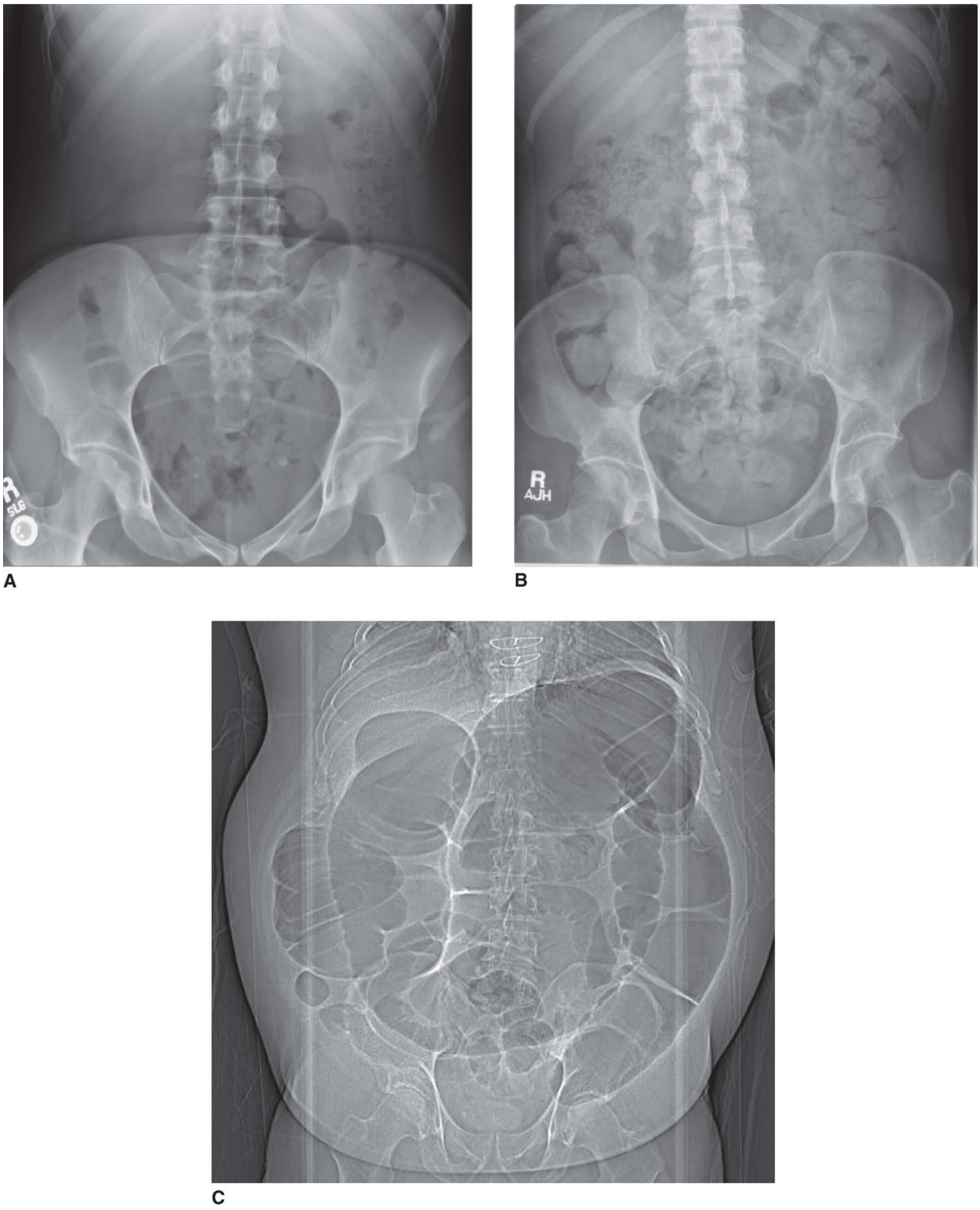


FIGURE 95-4. Plain radiographs of patients with constipation. **A.** Colonic or rectal fecal retention associated with air in rectum and cecum. **B.** Large amount of fecal material in the entire colon with no evidence of bowel obstruction or no free intraperitoneal air. **C.** Megacolon: Dilatation of the colon (> 6.5 cm maximum diameter) in the absence of acute obstruction.

Anorectal Function Tests

Anorectal function tests should be considered in assessment of constipation in older people (see **Figure 95-2**). Anorectal manometry and balloon expulsion should be considered as initial assessment in patients who have not responded to fiber. They may be indicated in patients with severe and persistent rectal outlet delay, in order to diagnose pelvic dyssynergia, which is more effectively treated by biofeedback than laxatives. Another indication is fecal incontinence of formed stool that persists despite clearing of fecal impaction. Balloon expulsion is a simple

procedure that evaluates the ability to defecate a water-filled balloon. During the balloon expulsion, the time required to expel the balloon should be recorded, with normal range between 1 and 5 minutes. Alternative, if spontaneous evacuation is not possible, the other outcome is to measure the additional weight added to assist in expelling the balloon. Anorectal tests (including endoanal ultrasound) can measure the integrity of the anal sphincters and thus guide management of incontinence toward conservative treatment (sphincter strengthening exercises and biofeedback therapy), or surgical intervention (sphincter reconstruction).

Defecography

There are several modalities to assess the defecatory movements and anatomy. Traditionally, barium and scintigraphy defecographies have been used, and more recently, magnetic resonance defecography was developed to identify anatomic abnormalities with higher resolution, visualization, and without radiation. Defecography should be use when the anorectal manometry and balloon expulsion are inconclusive or when there is a high suspicion for an anatomical disorder. The most relevant findings in defecography are inadequate or excessive perineal descent during defecation, excessive straining, internal intussusception, solitary rectal ulcers, rectoceles, and rectal prolapse. Unfortunately, these tests are not widely available.

Colonic Transit

Colonic transit is the rate at which fecal residue moves through the colon. There are several approved methods to measure colonic transit. The most common and inexpensive measurement is using radiopaque markers (sitzmarks), which consist of the Hinton technique. A capsule containing 24 radiopaque markers is swallowed and in 5 days, five or less markers should remain in the colon on an abdominal radiograph. Radionucleotide gamma scintigraphy and wireless pH-pressure capsule are other well-validated methods but less commonly used. The benefit of scintigraphy is that results could be obtained in 48 hours when compared to radiopaque markers. Colonic transit studies are useful to differentiate patients with slow-transit constipation versus normal transit constipation (**Figure 95-5**).

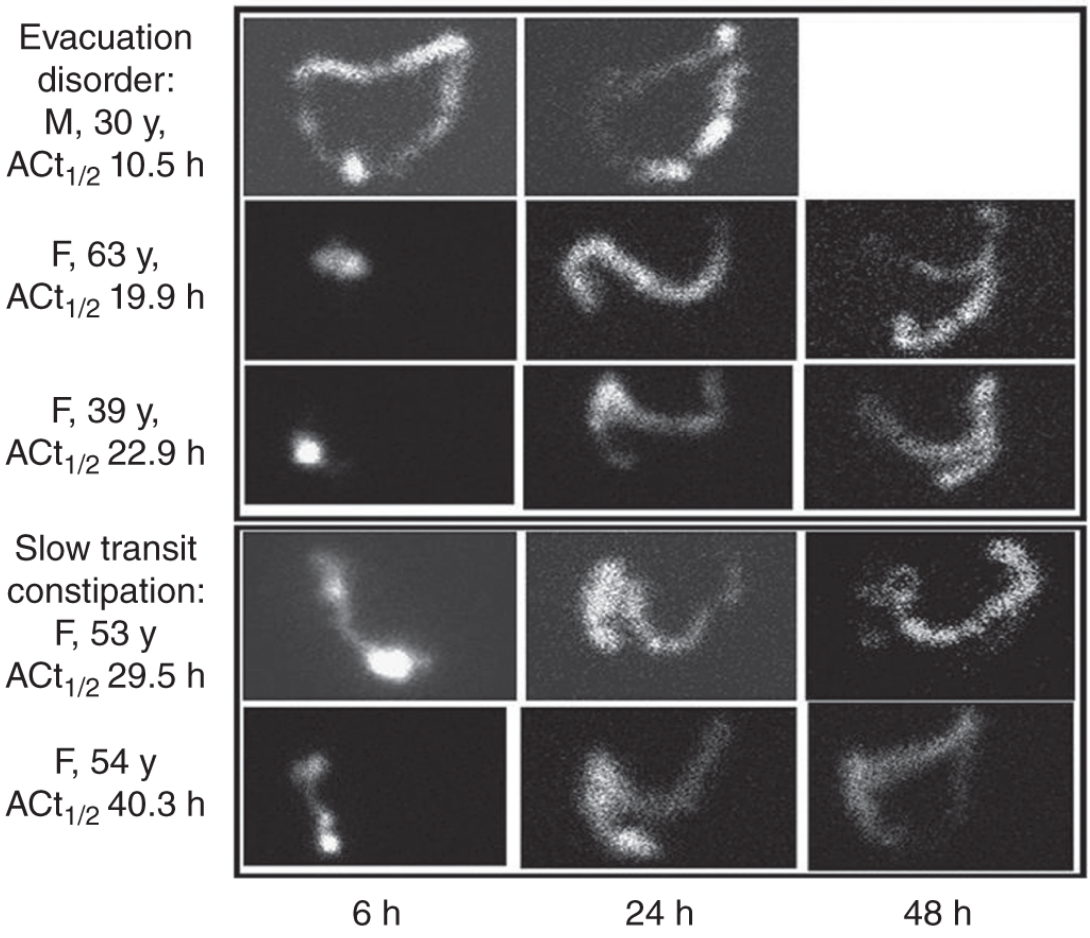


FIGURE 95-5. Examples of scintiscans at 6, 24, and 48 hours in patients with evacuation disorder and slow transit constipation; note the

delayed transit is also demonstrated at 48 hours in the patients with STC, and the retention of isotope in the left colon in patients with evacuation disorder. (Reproduced from Nullens S, Nelsen T, Camilleri M, et al. Regional colon transit in patients with dys-synergic defaecation or slow transit in patients with constipation. *Gut.* 2012;61(8):1132–1139.)

Colonoscopy

Chronic constipation alone is not an appropriate indication for colonoscopy; the range of neoplasia found is similar to that in asymptomatic patients undergoing primary colorectal cancer screening. Further investigation is warranted in the context of systemic illness or laboratory abnormalities. Barium enema has now largely been superseded by colonoscopy in older patients—colonoscopy causes significantly less discomfort than barium enema and is diagnostically more sensitive. A review of 400 colonoscopies in octogenarians and upward showed a good safety profile but low cancer detection rate for symptoms (eg, constipation, abdominal pain) other than bleeding (2% vs 12%). Inadequate colonoscopies are common in older people because of poor bowel preparation. Older age, constipation, reported laxative use, tricyclic antidepressants, stroke, and dementia have been associated with inadequate preparation and thus taking longer to instrument the cecum. Some recommendations include: Give regular laxatives and enemas or suppositories for at least 1 week before the procedure, with a longer run up period in patients known to have constipation, or with comorbidities such as diabetes; preempt unpleasant side effects ("Will the patient be able to reach the toilet in time to avoid fecal leakage?"); and use oral phosphosoda with caution as administration in older people increases serum phosphate, even in patients with normal creatinine clearance.

NONPHARMACOLOGIC MANAGEMENT

Nonpharmacologic treatments for constipation are underused as first-line management in constipation that is not acute or severe, and as adjunctive treatment even when laxatives are deemed necessary. Symptoms of difficult evacuation may be particularly amenable to nonpharmacologic management such as stool softening and bulking through increasing fiber and fluid intake, pelvic muscle strengthening exercises, and footstool elevation of the legs during evacuation (see below). A systematic review examining nonpharmacologic treatment of chronic constipation in older people found no studies evaluating the effect of exercise therapy and only a few nonrandomized trials examining fiber and fluid supplementation, and there has been little further research in this area since then. Available data, expert opinion, and practical recommendations are summarized below.

Education

Educating patients as to what constitutes normal bowel habit should be one of the first steps in managing self-reported constipation. Patients with no or mild symptoms of constipation should be encouraged to discontinue chronic laxative therapy. Patients who require laxative treatment for constipation should be told to aim for regular, comfortable evacuation rather than daily evacuation, which is often their preconceived norm. Educational interventions promoting lifestyle changes for patients with chronic constipation should focus on exercise and diet. In order to persuade older people with constipation to change their lifestyle, they need to be convinced that:

- Their current behaviors are "bad for their bowels."
- Bowel-related and general health improvements associated with recommended measures are worth the trouble and expense of changing.
- It is they who are responsible for what they eat and how much exercise they engage in.
- They have the skills and knowledge to modify their own lifestyle to improve their constipation, if they choose to do so.

It is important to provide people with clearly written educational materials. A randomized controlled trial in stroke survivors with constipation evaluated the impact of a one-off nurse-led assessment (with feedback to primary care physician) and educational session including provision of booklet. At 6 months, postintervention subjects reported improved bowel function in terms of number and normality of bowel movements; at 1 year, they were more likely to still be altering their diet and fluid intake to control their bowel problem. **Table 95-7** illustrates some of the patient-centered instructions from this study booklet, which are relevant to all older people with constipation.

Other trials have sought to influence fiber intake at a population level. Nutrition newsletters sent to older Americans in their homes significantly improved their dietary fiber intake. Another community intervention used

media and social marketing in educational targeting of small retirement communities under the theme “Bread: It’s a Great Way to Go,” and reported a result of a 49% decrease in laxative sales and 58% increase in sales of whole meal and whole grain bread.

Educating caregivers on maintaining fecal continence in patients with dementia (with focus on constipation and other contributing factors) is crucial, and the same applies for patients with chronic neurological diseases other than dementia such as Parkinson disease, stroke, and neuropathic bowel.

Diet

A meta-analysis of 20 nonrandomized studies in younger adults with constipation associated additional wheat bran with increased stool weight and decreased transit time. Evidence for the effectiveness of fiber in treatment of constipation in older people is more equivocal. In one community study, higher fiber intake was associated with lower laxative use among older women, but in another study, higher intake of bran was associated with no reduction in constipation symptoms and greater fecal loading in the colon on abdominal radiography. In older hospitalized patients, daily bran supplementation increased weekly bowel movement frequency and improved overall symptoms as compared with placebo. There have been several “before and after” studies in nursing home residents reporting that addition of dietary fiber (ranging from bran to processed pea hull) or fruit mixtures (apple puree to fruit porridge) to the daily diet improved bowel movement frequency and consistency, and reduced laxative intake and the need for nursing intervention. Bias cannot be excluded from these nursing home studies, including that of concomitant increased fluid intake contributing to these positive results. But despite these reservations, these observational studies emphasize the usefulness of increasing dietary fiber, fluid, and fruit in older people at high risk of constipation. Additional benefits should not be discounted; for instance, adding oat bran to the diet in one study reduced cholesterol levels more markedly in older versus younger women.

In practical terms, at least 12 to 20 g of fiber with additional fluids should be recommended. While coarse bran rather than more refined fiber is more effective in increasing stool fluid weight, it is far less palatable, and is more likely to cause initial symptoms of increased bloating, flatulence, and irregular bowel movements. Fiber should therefore be recommended to older individuals in the form of foods such as whole meal or whole grain bread, porridge, fresh fruit (preferably unpeeled), seeded berries, raw or cooked vegetables, beans, and lentils. A crossover trial in subjects aged 60 and older that entailed taking a daily kiwi fruit resulted in bulkier and softer stools and increased bowel movement frequency. Fiber supplementation should also be culturally appropriate. Chinese food is typically low in fiber, and dietary additives such as konjac glucomannan can serve as “natural laxatives.” Other examples of natural laxatives are aloe vera and rhubarb, both of which contain stimulant anthraquinone derivatives similar to *Senna*.

Fluids

An randomized controlled trial (RCT) in adults aged 18 to 50 with chronic constipation showed that the beneficial effect of increased dietary fiber was significantly enhanced by increasing fluid intake to 1.5 to 2 L daily. This level of fluid intake may, however, be challenging for many older people, especially those with symptoms of overactive bladder. Upping fluid intake by two 8-ounce beverages a day for 5 weeks in dependent nursing home residents significantly increased bowel movement frequency and reduced laxative use. This “hydration program” used a colorful beverage cart and four beverage choices to stimulate residents’ interest in drinking. Caffeine is known to increase both bowel and bladder smooth muscle activity, though its impact on constipation in older people is not documented. Subjects randomized to receive juice containing probiotics (*Lactobacillus rhamnosus* and *Propionibacterium freudenreichii*) for 4 weeks had a 24% increase in defecation frequency compared to those receiving unsupplemented juice.

Physical Activity

A RCT in middle-aged inactive patients with chronic constipation showed that regular physical activity (30-min brisk walk and 11-min home exercises a day) decreased colonic and rectosigmoid transit time and improved defecation. A review of physical activity interventions in older adults concluded that incorporating exercise naturally into a person’s day tends to provide the most effective means for increasing activity levels. Studies conducted in older nursing home patients showed the following outcome:

- Six months of moderate-intensity exercise training had no impact on constipation symptoms or habitual physical

activity (RCT).
- Six months of 2 hourly prompted toileting improved measures of daily physical activity and functional performance, but did not alter bowel movement frequency (RCT).
- Daily exercise in bed and the use of abdominal massage reduced laxative and enema use in chair-fast patients, although transit time was unaffected (non-RCT).

Existing evidence would tend to support exercise programs to influence constipation in nursing home residents within the context of also addressing other risk factors.

Abdominal Massage

Abdominal massage added to the standard bowel regimen in spinal cord patients has been shown to shorten colonic transit time and increase weekly bowel movement frequency. A vibrating device that applied kneading force to the abdomen once a day for 20 minutes was evaluated in older constipated nursing home residents, and after 12 weeks resulted in softening of stool, increased bowel movement frequency, and a 47% reduction in transit time. Case reports show that physiotherapists can incorporate daily 10-minute abdominal massage into home activity programs for community-dwelling people suffering from constipation with good effect.

Biofeedback: Pelvic Floor Rehabilitation and Sphincter-Strengthening Exercises

Biofeedback focuses on sensory and muscular retraining of the rectum and pelvic floor with the goals of improving to normalize the sensation, muscular relaxation or strengthening and improve the defecation dynamics (see **Figure 95-2**). Biofeedback is not well standardized and the best approach is unclear. A Cochrane review of 17 eligible studies with a total 931 participant showed that the heterogeneity of the different samples and large range of different outcome measures, meta-analysis was not possible. However, the larger studies are summarized here:

- Seventy percent (21/30) of biofeedback patients had improved constipation compared to 23% (7/30) of diazepam patients at 3-month follow-up (RR 3.00, 95% CI 1.51–5.98).
- In a 52-patient study, manometry biofeedback had 4.6 complete spontaneous bowel movements (CSBM) per week compared to 2.8 CSBM with sham biofeedback or standard therapy consisting of diet, exercise, and laxatives at 3 months (MD 1.80, 95% CI 1.25–2.35).
- EMG biofeedback reported at both 6 and 12 months, 80% (43/54) of biofeedback patients reported clinical improvement compared to 22% (12/55) of laxative-treated patients (RR 3.65, 95% CI 2.17–6.13).

The evidence recommended for these studies overall is low because the majority of trials are of poor methodological quality and subject to bias. Further well-designed randomized controlled trials with adequate sample sizes, validated outcome measures, and long-term follow-ups are required.

Where rectal outlet delay and/or persistent straining is associated with excessive pelvic floor descent, pelvic strengthening exercises should be employed. In women, it is helpful to do the teaching while undertaking a pelvic examination (with the examining hand resting on the posterior vaginal wall), so that positive verbal feedback can be given when the patient correctly contracts the pelvic floor. Pelvic floor retraining can help rectal outlet symptoms, but a greater degree of perineal descent is predictive of poorer treatment responses. Sphincter-strengthening exercises (see **Table 95-7**) should be taught to patients with fecal soiling and/or weak external sphincter.

Toileting Habits and Access

Small nonrandomized studies show that regular toileting habits (scheduled evacuation) restores comfortable evacuation in stroke survivors (with the assistance of digital stimulation) and in older postoperative inpatients. The preservation of the gastrocolic reflex with aging supports the rationale for postprandial toilet visits. Care should be given to treating hemorrhoids and any other anorectal condition in these patients. Expert opinion supports the use of footstools during evacuation in individuals with weakened abdominal and pelvic muscles to optimize the Valsalva maneuver.

Toilet access should be assessed and facilitated particularly in patients with mobility, visual, or dexterity impairments. Bathroom comfort and privacy must be considered, particularly for individuals in institutional settings. Reluctance to use the toilet in institutional settings has been linked to residents developing fecal impaction in case reports. **Table 95-8** summarizes basic but important recommendations relating to toileting and maintaining privacy and dignity.

TABLE 95-8 ■ TOILETS AND TOILETING—MAINTAINING PRIVACY AND DIGNITY

A multidisciplinary assessment should be made of older person's ability to access and use the toilet [3].
Commodes/sani-chairs/shower chairs: • Should be available to residents in institutional settings [3] • Should provide a safe seated position for prolonged use by older people with skin vulnerability and trunk support problems (eg, padded seat, footstool if feet are unsupported, back and arm support, grab rails, etc) [3]
Older people should be given the opportunity to use the toilet (either directly or by using a sani-chair or shower chair) rather than a bedside commode [3].
Bedpans should be avoided for defecation purposes.
Transportation to the toilet and use of the toilet or commode should be carried out with due regard to privacy and dignity.
A direct method of calling for assistance should be provided when an older person is left on the toilet/commode.
When using a commode: • Methods to reduce noise and odor should be offered • Methods to facilitate bottom wiping should be available • If in living area and cannot be emptied immediately, a chemical toilet should be offered instead [3]

Level [1] indicates good evidence, that is, consistent results from well-designed, well-conducted studies.
Level [2] indicates fair evidence, that is, results show benefit, but strength limited by number, quality, or consistency of studies.
Level [3] indicates poor evidence, that is, insufficient because of limited number, power, or quality of studies.
Data from Potter J, Norton C, Cottenden A, eds. Bowel Care in Older People. Royal College of Physicians of London, 2002.

PHARMACOLOGIC TREATMENT

Laxative and Enema Use and Abuse in Older People

A Food and Drug Administration (FDA) Advisory Panel has registered concern over the widespread overuse of over-the-counter (OTC) laxatives; laxatives are second only to analgesics as the most commonly used OTC medications by older people. OTC laxative use is common in the United States and Europe, and is encouraged by advertising and popular ignorance of adverse effects. Only 38% of OTC laxative users in Italy were guided in their choice of laxative by a physician; the remainder were influenced by pharmacists (21%), relatives or friends (16%), and advertisements (12%). Six percent of users reported adverse effects. One-fifth to one-third of regular laxative users do not consider themselves to be constipated, and many people take them through a misguided belief in the benefits of regular purgation. One study showed that 78% of older persons who used laxatives regularly had never gone for more than 3 days without a bowel movement. Habitual rather than surreptitious abuse is more likely in older individuals; repeated purging empties the colon of stool that would normally descend into and distend the rectal ampulla, thereby removing the urge to defecate, and prompting the patient to take further laxatives.

Although patients in hospitals and nursing homes are at higher risk for clinical constipation, this does not entirely justify the very high levels of cathartic prescribing in these settings. Seventy-six percent of hospitalized older adults are prescribed at least one type of laxative. A prospective study of 2355 nursing home residents in the Netherlands showed that over the course of 2 years, 47% were started on laxatives, with 79% of these continuing with the long-term treatment. Prescribing rates in US nursing homes are high at 54% to 74%, with almost half of these users being prescribed more than one agent. Most commonly prescribed agents are stool softeners (26%), magnesium salts (18%), and stimulants (16%). Two contributing factors may lead to over-prescribing of laxatives to older patients: lack of objective confirmation of the diagnosis by the prescribing physician or nurse; and prescribing patterns of laxatives that are clinically ineffective. In US nursing homes, docusate (a fecal softener with little or no laxative effect) is the predominantly prescribed agent.

Evidence-Based Summary of Laxative, Suppository, and Enema Treatment in Older Persons

Many reported trials of laxative and enema treatment in older people are low quality, limited by unclear definitions for constipation, inconsistent outcome measurement, and underreporting of potential confounding factors during the trial

period (eg, fiber intake). The absence of good level evidence may in part underlie the somewhat empirical way in which laxatives are prescribed to older people. The following conclusions are drawn from several meta-analytical reviews of efficacy of laxatives in treating chronic constipation in adults:

- Availability of published evidence is poor for many commonly used agents including *Senna*, magnesium hydroxide, bisacodyl, and stool softeners.
- In trials conducted in older people, significant improvements in bowel movement frequency were observed with a stimulant laxative (cascara) [3] and with lactulose [2], whole psyllium [2], and lactulose [2] were individually reported to improve stool consistency and related symptoms in placebo-controlled trials.
- Level [1] evidence supports the use of polyethylene glycol (PEG) in adults.
- Level [2] evidence supports the use of lactulose and psyllium in adults.
- None of the currently available trials include quality of life outcomes.
- In trials conducted in older adults (> 55 years), there is little evidence of differences in effectiveness between categories of laxatives.
- A stepped approach to laxative treatment in older people is justified, starting with cheaper laxatives before proceeding to more expensive alternatives.

Tables 95-9 and 95-10 summarizes the onset of action, mechanisms of action, potential side effects, and benefits of selected laxatives in current usage, and the following discussion describes efficacy and safety.

TABLE 95-9 MEDICATIONS USED IN OLDER PEOPLE WITH CONSTIPATION

TYPE	GENERIC NAME	TRADE NAME	DOSAGE	SIDE EFFECTS	TIME TO ONSET OF ACTION (*H*)	MECHANISM OF ACTION
Fiber	Bran	—	1 cup/d	Bloating, flatulence, iron and calcium malabsorption	—	Stool bulk increases, colonic transit time decreases, gastrointestinal motility increases
	Psyllium	Metamucil Konsyl	1 tsp up to 3 times daily	Bloating, flatulence	—	
	Methylcellulose	Citrucel	1 tsp up to 3 times daily	Less bloating	—	
	Calcium polycarbophil	FiberCon	2–4 tablets once daily	Bloating, flatulence	—	
Stool softener	Docusate sodium	Colace	100 mg twice daily		12–72	
Hyperosmolar agents	Sorbitol	—	15–30 mL once daily or twice daily	Sweet tasting, transient abdominal cramps, flatulence	24–48	Nonabsorbable disaccharides metabolized by colonic bacteria into acetic acid and other short-chain fatty acids
	Lactulose	Chronulac	15–30 mL once daily or twice daily	Same as sorbitol	24–48	
	PEG	Golytely Colyte Miralax	8–32 oz once daily	Incontinence due to potency	0.5–1	Osmotically increases intraluminal fluids
Stimulant	Glycerin		Suppository; up to once daily	Rectal irritation	0.25–1	Evacuation induced by local rectal stimulation
	Bisacodyl	Ducolax	10 mg suppositories or 5–10 mg by mouth up to 3 times/wk	Incontinence, hyperkalemia, abdominal cramps, rectal burning with daily use of suppository form	0.25–1	Bisacodyl and sodium picosulfate are prodrugs that are hydrolyzed by colonic bacteria (sodium picosulfate) or intestinal and colonic brush border enzymes (bisacodyl) to the active metabolite, bis-(p-hydroxyphenyl)-pyridyl-2-methane, which has antiabsorptive/secretory and prokinetic effects
	Picosulfate					Similar to bisacodyl
	Anthraquinones (senna, cascara)	Senokot Perdiem (plain) Peri-Colace	2 tablets once daily to 4 tablets twice daily 1–2 tsp once daily 1–2 tablets once daily	Degeneration of Meissner and Auerbach plexus (unproven), malabsorption, abdominal cramps, dehydration, melanosis coli	8–12 8–12 8–12	Electrolyte transport altered by increased intraluminal fluids; myenteric plexus stimulated; motility increases
Saline laxative	Magnesium	Milk of magnesia	15–30 mL once daily or twice daily	Magnesium toxicity, dehydration, abdominal cramps, incontinence	1–3	Fluid osmotically drawn into small bowel lumen; cholecystokinin stimulated; colon transit time decreases
		Haliey's M-O (with mineral oil)	15–30 mL once daily or twice daily		1–3	

Lubricant	Mineral oil	—	15–45 mL	Lipid pneumonia, malabsorption of fat-soluble vitamins, dehydration, incontinence	6–8	Stool lubricated
Enemas	Mineral oil retention enema	—	199–250 mL once daily per rectum	Incontinence, mechanical trauma	6–8	Stool softened and lubricated
	Tap water enema	—	500 mL per rectum	Mechanical trauma	5–15 min	Evacuation induced by distended colon; mechanical lavage
	Phosphate enema	Fleet	1 unit per rectum	Accumulated damage to rectal mucosa, hyperphosphatemia, mechanical trauma	5–15 min	
	Soapsuds enema	—	1500 mL per rectum	Accumulated damage to rectal mucosa, mechanical trauma	2–15 min	

Adapted from Locke GR, Pemberton JH, Phillips SF. AGA technical review of constipation. *Gastroenterology*. 2000;119(6):1766–1778.

TABLE 95-10 NEWER MEDICATIONS FOR TREATMENT OF CONSTIPATION

GENERIC NAME (TRADE NAME)	MECHANISM OF ACTION	METABOLISM, BIOAVAILABILTY	PHARMACODYNAMIC EFFECTS	CLINICAL TRAILS	COMMON SIDE EFFECTS	CARDIOVASCULAR SAFETY[a]
Secretagogues						
Lubioprostone (Amitiza)[b]	Stimulate instestinal chloride and fluid secretion by activating chloride channels	Intestinal degradation, minimal oral bioavailability	Accelerated small bowel and colonic transit in health	Phases 2 and 3 in CC, IBS-C	Diarrhea, nausea	No arrhythmic effects
Linaclotide (Linzess)[b]	Stimulate instestinal chloride and fluid secretion by activating CFTR	Intestinal degradation, minimal oral bioavailability	Dose-related acceleration of colonic transit in IBS-C	Phases 2 and 3 in CC, IBS-C	Diarrhea	No arrhythmic effects
Serotonin 5-HT_4 receptor agonists						
Prucalopride[C] (Resolor)	High selectivity and affinity for 5-HT_4 receptors; much weaker affinity for human D4 and s1 and mouse 5-HT_3 receptors	Limited hepatic, not CYP3A4	Accelerated colonic transit in health and CC	Phases 2 and 3 in CC	Diarrhea, headache	No arrhythmic activity in atrial cells; inhibits hERG at very high μmol/L concentration; no clinically relevant adverse cardia effects in large trials (>4000 subjects)

NOTE: Only agents that have been tested in phase 3 clinical trials are included.

CC. Chronic constipation.

[a]In addition to the listed effects, none of the agents shown in this table affect QTc in healthy subjects.

[b]Approved by the FDA

[c]Approved by the European Agency for Evaluation of Medical Products.

Stimulant Laxatives

Senna is a cheap and safe agent for use in older patients. A trial of cascara (a similar plant-derived stimulant laxative) in older hospitalized patients increased bowel movement frequency by an average of 2.6 bowel movements per week as compared to placebo. Administration of 20 mg of *Senna* daily for 6 months to patients older than 80 did not cause any significant losses of intestinal protein or electrolytes, and repeated studies in mice show no evidence of myenteric nerve damage resulting from its use. *Senna* generally induces evacuation 8 to 12 hours following administration, and should therefore be taken at bedtime. Some patients may require several weeks of daily use before achieving a regular bowel habit. Maintenance therapy with *Senna* is appropriate in patients with chronic constipation, and it can be used in higher doses for short-term treatment of fecal impaction. In patients with weak anal sphincters, *Senna* alone may be sufficient to treat constipation without causing or exacerbating fecal incontinence through excess stool softening.

Bisacodyl is a useful alternative stimulant laxative to *Senna*. Bisacodyl 10 mg daily improved stool frequency and consistency without side effects in a randomized, controlled trial among outpatients with a mean age of 62.

Phenolphthalein and *castor oil* should not be used in older people because of a high risk of side effects including malabsorption, dehydration, lipoid pneumonia, and, with heavy prolonged use, cathartic colon.

Bulk Laxatives

Bulk laxatives are generally underprescribed to older people, despite evidence that they increase bowel movement frequency (by a mean of 1.4 bowel movements per week as compared to placebo), and improve consistency and ease of evacuation. This may partly be because of intolerance in the form of bloating and unpredictable bowel habit in the first weeks of taking them, and also of caution on the part of prescribers because of the documented risk of impaction

with these agents in patients with poor fluid intake. Psyllium has been shown to increase stool frequency in people with Parkinson disease, but did not alter transit time. Bulking agents are generally useful in older individuals with mild to moderate constipation who are able to tolerate them and who drink sufficient fluids. They have the additional benefit of reducing abdominal pain in patients with irritable bowel syndrome, limiting flare-ups of diverticulitis, and facilitating painful defecation associated with hemorrhoids. Furthermore, psyllium significantly lowers serum cholesterol by binding bile acids in the intestine. Available preparations are natural nonwheat fibers such as psyllium and ispaghula husk, and synthetic compounds such as calcium polycarbophil and methylcellulose. The synthetic compounds tend to be cheaper and are available in more easily administrated tablet forms, as compared to reconstituted powder, which can be hard for older patients to swallow. The synthetic bulking agents and the natural fibers are equally effective in increasing stool frequency and volume. Bran in tablet form is considerably cheaper than bulk laxatives, but the former may cause even more bloating and unpredictability of bowel habit, and may also, unlike bulking agents, predispose to malabsorption of iron or calcium in older people.

Magnesium Salts

Magnesium salts are commonly prescribed to older hospitalized patients, and magnesium hydroxide is popular as an OTC laxative. There is only one published study evaluating magnesium hydroxide in older people—a small trial in nursing home residents, which suggested that this laxative was more effective than a bulking agent in increasing bowel movement frequency and softening stool. Magnesium salts may be favored by physician and patient alike because of their rapid action, but in general, a gradual catharsis is preferable to restore regular bowel habit in older persons. Their potent catharsis increases the risk of fluid and electrolyte losses, and of fecal incontinence in less-mobile people, or in those with weak sphincters. Furthermore, magnesium levels should be monitored in all older people who are using magnesium hydroxide on a regular basis, as hypermagnesemia can occur even with normal serum creatinine levels. Long-term use of magnesium hydroxide is contraindicated in chronic kidney disease. The more potent salt magnesium citrate carries an even greater risk of side effects, including promoting colonic pseudo-obstruction, and is therefore not recommended for use in the older population. Based on evidence and known side effects, there is no clear role for using magnesium salts in treatment of chronic constipation in older people.

Hyperosmolar Laxatives

Hyperosmolar laxatives are the most rigorously studied laxative group in the current literature. The following summarizes findings from nursing home studies:

- Lactulose (or the related agent lactitol) versus placebo shortened transit time, increased bowel movement frequency (by an average of 1.9 bowel movements per week), and improved stool consistency.
- In a comparison study with a bulking/stimulant combination agent, lactulose was a little less effective in influencing bowel pattern and consistency.
- Lactulose and sorbitol were equally effective in mostly eliminating the use of other laxatives and enemas in residents with dementia and chronic constipation, with sorbitol being considerably cheaper.

A well-designed trial in ambulatory older veterans with severe constipation also showed lactulose and sorbitol to be equally efficacious. Lactulose and sorbitol are effective agents in treating chronic constipation in older people in all health care settings, with sorbitol being the cheaper option.

PEG is a more potent hyperosmolar laxative than lactulose as demonstrated by its impact on transit time in normal subjects. In a randomized controlled trial in hospitalized patients (with a mean age of 55 years), PEG produced a greater increase in bowel movement frequency and a greater reduction in straining than lactulose, but at the expense of a higher mean number of liquid stools. A similar efficacy and side effect profile plus a reduction in laxative expenditures were shown with use in long-stay residents of a mental health institute. PEG treatment of fecal impaction (in combination with daily enemas) showed greater efficacy than lactulose, without the dehydration or hemodynamic side effects in older nursing home residents. Another trial in adults aged 17 to 88 with fecal loading on x-ray or rectal examination, and bowels not open for 3 to 5 days showed that 1 L (or 8 sachets) a day of PEG plus electrolytes for 3 days resolved impaction in 89% of patients, with few adverse effects. The current evidence base suggests that the role of PEG in older people is for acute disimpaction (ensuring that easy toilet access is guaranteed) and for regular use as a laxative only in high-risk people whose constipation has proved resistant to milder and cheaper alternatives.

Stool Softeners

Docusate sodium has been shown experimentally to have no effect on colonic motility, and little or no laxative action, even at doses of 300 mg/day. Current evidence suggests that docusate is not effective in the treatment of constipation or rectal outlet delay in older people. In a randomized controlled trial in adults with severe constipation docusate proved significantly inferior to psyllium for both softening stools and increasing bowel movement frequency. A systematic review of prospective controlled trials evaluating oral docusate in chronically ill people (though hampered by poor data) showed only a small trend toward increased stool frequency, and concluded that there was insufficient evidence to support its use in this population. Nevertheless, docusate is frequently recommended and used in older people as a laxative as well as fecal softener. This is of particular concern in the nursing home and hospital settings, where constipation may as a result be undertreated with an increased risk of fecal impaction. Furthermore, docusate (in combination with the stimulant danthron) increases the risk of fecal incontinence in nursing home residents.

Enemas

Enemas have a role in both acute disimpaction and in preventing recurrent impactions in susceptible patients. They induce evacuation as a response to colonic distension, as well as by plain lavage; the most common reason for a poor result from an enema is inadequate administration. In one study of nursing home residents with overflow incontinence associated with fecal impaction on rectal examination, daily phosphate enemas continued until no further results was effective in completely resolving incontinence in 94% of patients. Some patients with poor mobility or neurogenic bowel dysfunction may have recurrent stool impactions despite regular laxative and suppository use, and they will benefit from weekly enemas.

Regular use of phosphate enemas should be avoided in patients with renal impairment as dangerous hyperphosphatemia has been reported. Tap water enemas are the safest type for regular use, although they take more nursing administration time than phosphate enemas, and are not available in certain countries. Soapsuds enemas should never be administered to older patients. Arachis oil retention enemas are particularly useful in loosening colonic impactions. In patients who have a firm and large rectal impaction, manual evacuation should be performed before inserting enemas or suppositories, using local anesthetic gel if needed to reduce discomfort.

Suppositories

The predominance of rectal outlet delay (including manual evacuation) in older people, many of whom take regular laxatives, is likely to be linked to underuse of suppositories. Although research data are lacking, clinically suppositories are very useful in treatment of rectal outlet delay, or where symptoms of prolonged straining predominate. Regular suppository administration (usually three times a week, and ideally after breakfast) can effectively control symptoms in these patients. A study of nursing home patients with overflow incontinence found that a regimen of daily lactulose and suppositories plus weekly enemas was only effective in restoring continence when long-lasting and complete rectal emptying was achieved. Regular use of suppositories is indicated in older patients with impaired rectal motility and/or recurrent rectal impactions. With appropriate education, many older people can self-administer suppositories; they are easier to insert and more effective if used blunt end first, and people with impaired dexterity can be helped with suppository inserters designed for spinal cord injured patients. First-line suppository use is with glycerin, a hyperosmolar laxative used solely in suppository form. If ineffective, bisacodyl suppositories (in PEG base) should be used, although daily use can sometimes causes symptoms of rectal discomfort or burning. Bisacodyl suppositories have been shown to be effective in treating severe constipation in patients with spinal cord injuries. The onset of action of suppositories varies by individual from 5 to 45 minutes (most likely influenced by the state of the rectal innervation); thus patients should be advised to set a quiet time aside for effective evacuation.

Secretagogues

Lubiprostone is approved in the United States for the treatment of chronic constipation. It is classified as a prostone, a bicyclic fatty acid compound derived from a metabolite of prostaglandin E1, which acts locally in the small intestinal mucosa, inducing secretion of fluid and electrolytes through the activation of the type-2 chloride channels in the intestinal apical cell membrane. A secondary analysis of one trial showed that 24 µg twice daily lubiprostone significantly improved the number of spontaneous bowel movements, consistency and straining rate compared to placebo in a 4-week trial among 57 patients age 65 and older, and was well tolerated with less side effects than placebo. In another secondary analysis of 163 older adults, lubiprostone showed significant improvement in

constipation severity, abdominal bloating, and discomfort compared to placebo.

Linaclotide activates guanylate cyclase C on the intestinal mucosa, resulting in increased levels of intracellular and extracellular cyclic guanosine monophosphate, which results in increased luminal secretion of chloride and bicarbonate via the cystic fibrosis transmembrane conductance regulator. A meta-analysis of seven trials in patients with irritable bowel syndrome or chronic constipation showed that linaclotide increases the number complete spontaneous bowel movement per week and was associated with a 30% or more reduction from baseline in the weekly average of daily worst abdominal pain scores for 50% of the treatment weeks. Linaclotide also improved stool form and reduced abdominal pain, bloating, and overall symptom severity. Trials are lacking in the older population, and this drug, like lubiprostone, is expensive and not covered as a first-line agent by most insurance plans in the United States.

Enterokinetic Agents

Altered serotonin (5-HT) signaling may predispose to chronic constipation, and 5-HT4 agonists (e.g., prucalopride) have been shown to stimulate gastrointestinal motility and increase stool water content. The efficacy and safety of 5-HT4 agonists in treating chronic constipation were evaluated in a recent meta-analysis of 13 randomized controlled trials, where 5-HT4 agonists was superior for all outcomes: mean more than or equal to 3 spontaneous complete bowel movements (SCBM)/week (RR = 1.85; 95% CI 1.23–2.79); mean more than or equal to 1 SCBM over baseline (RR = 1.57; 95% CI 1.19–2.06). Two of these studies were done in older populations and prucalopride was superior to placebo. However, 5-HT4 agonists have a high risk of cardiac events and currently are not approved in the United States. If used in the geriatric population, careful use is recommended in patients with cardiac comorbidities.

TREATMENT GUIDANCE

Table 95-11 represents a combination of evidence-based and expert opinion in providing treatment guidance, and **Figure 95-6** provides an algorithmic approach. The recommendations can be summarized as follows:

- In ambulatory older patients with chronic constipation, a daily bulk laxative is appropriate for both rectal outlet delay and slow-transit constipation.
- If the bulking agent is not tolerated, or proves ineffective, then *Senna* may be substituted (1–3 tablets at night) with prn sorbitol (or lactulose) if needed to achieve patient-centered goals of comfortable regular evacuations.
- In less-mobile older people at higher risk of impaction, a combination of regular *Senna* and sorbitol (or lactulose) should be used with dosage titration.
- In patients with colonic impaction, oil retention enemas should be administered daily until there are no clinical or radiologic signs of obstruction, and then tap water enemas should be continued regularly until they produce no further result.
- Where the patient has easy access to a toilet, PEG 0.5 to 2 L daily should be given as long as is needed to clear the impaction, followed by a regular maintenance laxative regimen of *Senna* and sorbitol (or lactulose) to avoid recurrence of fecal impaction.
- In cases where toilet access is not easy (eg, at home with stairs), a more gradual clear-out using higher-dose *Senna* and sorbitol or lactulose is appropriate to limit problems with incontinence.
- For rectal outlet delay or a predominant complaint of straining, the first-line approach should be regular use of suppositories, and laxatives should only be given for coexisting symptoms of hard or infrequent bowel movements.

TABLE 95-11 PHARMACOLOGIC TREATMENT OF CONSTIPATION IN OLDER PEOPLE: A STEPWISE APPROACH

Chronic Constipation
In ambulant older people
Bulk laxative (psyllium) 1–3 times daily with fluids as required
If symptoms persist, add senna 1–3 tablets at bedtime
In individuals with questionable fluid intake or those intolerant of bulk laxatives, start with senna 1–2 tablets at bedtime
If symptoms persist, add sorbitol or lactulose 15 mL daily as needed, titrating the dose to achieve regular (≥ 3 times a week) and comfortable evacuation
In high-risk patients (bedridden individuals, patients with neurological disease, and patients with history of fecal impaction)

Senna 2–3 tablets at bedtime and sorbitol or lactulose 30 mL daily, titrating upward as needed
If symptoms persist, give PEG (half to two sachets daily)
Colonic Fecal Impaction
Clinical or radiological obstruction
Daily retention enemas (eg, arachis oil) until obstruction resolves, before starting oral laxatives
Colonic disimpaction
Daily enemas (preferably tap water) until no further washout result
PEG (0.5–2 L daily or 2–3 sachets of Movicol) with fluids
Ensure that patient has easy access to toilet to avoid fecal incontinence
When impaction resolves, give laxative regimen for chronic constipation in high-risk patients for long term to avoid recurrence
Rectal Outlet Delay
Rectal disimpaction
Manual disimpaction where necessary, followed by phosphate enema(s) for initial complete clearance of rectal impaction
Regular treatment
Glycerine suppositories at least once a week and as required to relieve symptoms
For persistent symptoms, use Bisacodyl suppositories instead of glycerine suppositories
In patients at high risk of rectal impaction (rectal dysmotility, neurological disease), give regular enemas (usually once weekly) and daily suppositories
If stool is hard or infrequent, add daily laxative as for chronic constipation

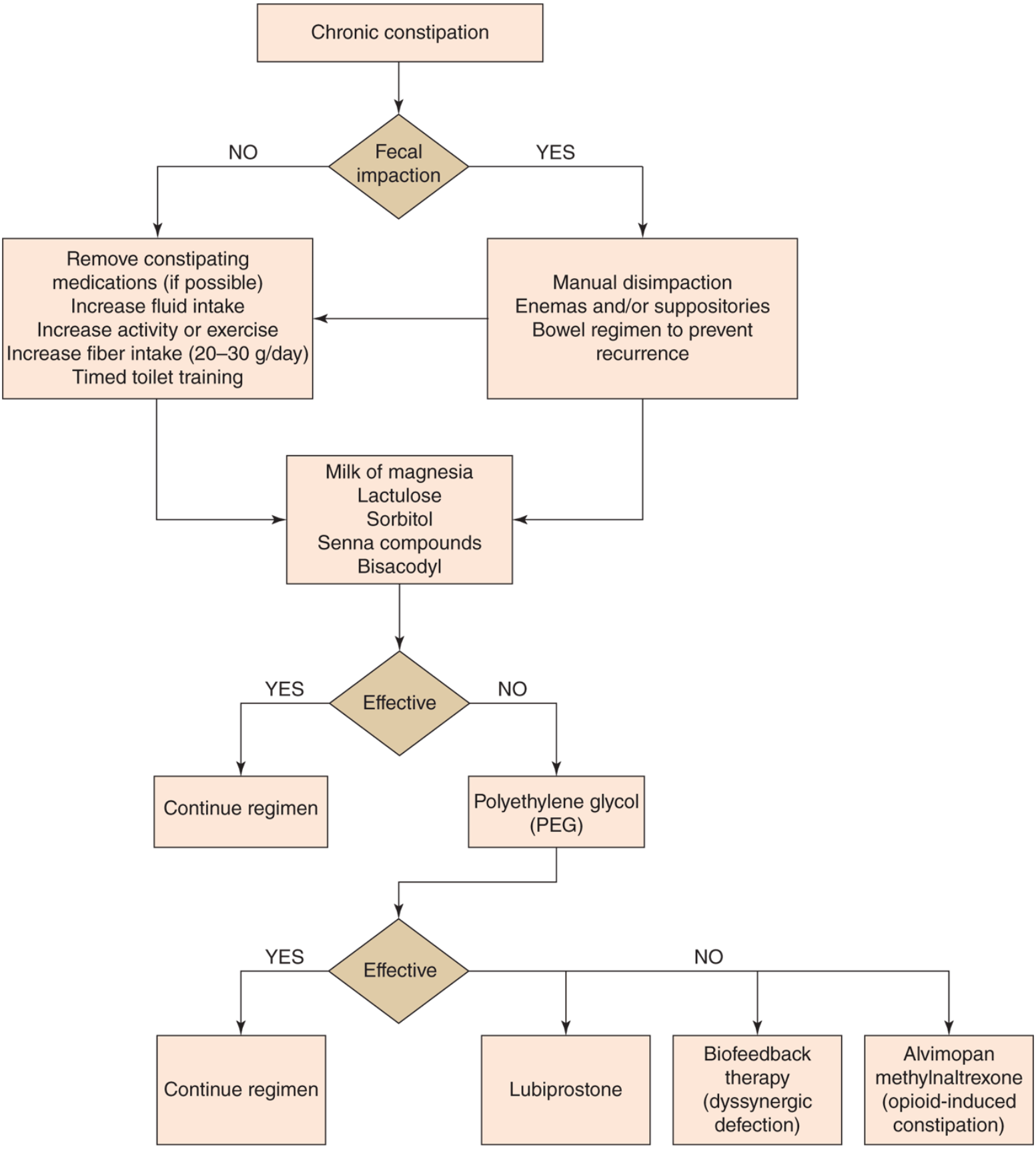


FIGURE 95-6. Treatment algorithm for the management of chronic constipation in older adults. (From Rao SS, Go JT. Update on the management of constipation in the elderly: new treatment options. *Clin Interv Aging*. 2010;5:163–171.)

CONCLUSION

A practical algorithmic approach to assessment and treatment of constipation in older people are illustrated in **Figures 95-3** and **95-6**. Health care providers should routinely inquire about constipation symptoms in older people and be alert to the presence of clinical constipation in individuals unable to communicate. In many older people with constipation symptoms, lifestyle advice (diet, fluids, exercise, toileting habits) will preempt the need for laxative therapy. In higher-risk patients, a stepwise approach to prescribing laxatives, suppositories, or enemas should be used, with the goal of achieving comfortable and regular evacuation. Rectal evacuation difficulties should be specifically addressed in order to identify conditions that may require additional interventions.

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Chapter 96

Oncology and Aging: General Principles

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Learning Objectives

- Identify factors inherent in the aging process that may promote neoplasia.
- Apply an understanding of lifespan and patient-centered choice to cancer screening recommendations.
- Integrate the concept of comprehensive geriatric assessment (CGA) and personal choice into cancer treatment decisions and individual management plans.
- Become aware of age-related factors that influence the risk of toxicity following radiation or chemotherapy.

Key Clinical Points

1. **Aging is associated with an increasing risk of developing cancer, with a number of mechanisms likely contributing including duration of exposure to carcinogens, susceptibility to DNA and other cellular damage with impaired repair mechanisms, a proneoplastic environment (eg, low-level inflammation), and impaired immune surveillance.**
2. **The 5-year survival rate for most cancers decreases with advanced age; many factors may contribute including altered tumor biology (ie, more aggressive tumor behavior), tolerance to therapy, and the presence of multiple comorbidities.**
3. **Age bias in diagnostic and treatment decisions for older patients with cancer exists and older patients are continually underrepresented in clinical trials.**
4. **Although performance status (eg, Eastern Cooperative Oncology Group [ECOG] performance score) is routinely applied to cancer patients, CGA that includes assessment tools to predict functional age of cancer patients based on physical function, comorbidities that may interfere with cancer therapy, nutritional status, polypharmacy, psychological and cognitive status, socioeconomic issues, and geriatric syndromes has been shown to add substantial prognostic information for older adults.**
5. **Patients and their caregivers should continually discuss goals of care throughout the course of their disease with the treating oncologist.**

INTRODUCTION

This chapter discusses many of the general relationships of oncology and aging. It focuses on the epidemiologic, basic etiologic, and biological relationships between the processes of aging and neoplasia, and, on the generalizable aspects of management of malignant disease in the older patient. This chapter discusses clinical management of individual

malignancies only as an example of general principles. The approach to specific malignancies is covered in subsequent chapters related to the appropriate organ system. It is now well recognized that cancer is a major problem for older individuals. It is the second leading cause of death after heart disease in the United States and age is the single most important risk factor for developing cancer. About 60% of all newly diagnosed malignant tumors and 70% of all cancer deaths occur in persons 65 years or older according to the National Cancer Institute (NCI). If one examines incidence and mortality data obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (**Figure 96-1**), one sees that the total cancer incidence rises progressively through the middle years and then falls off in the later years. However, the age-specific cancer incidence rises progressively throughout the age range. Thus, while the rate of increase diminishes somewhat in the oldest age groups, and the rate actually falls slightly in the very oldest (perhaps a survivor effect), the overall risk for developing cancer is certainly greatest in the later years. Because the number of people in this country older than age 65 is rising rapidly and the oldest of the old, that is, those older than age 85, are increasing at the greatest rate, geriatricians, generalists, and internists will be encountering increasing numbers of older individuals with cancer in their practices.

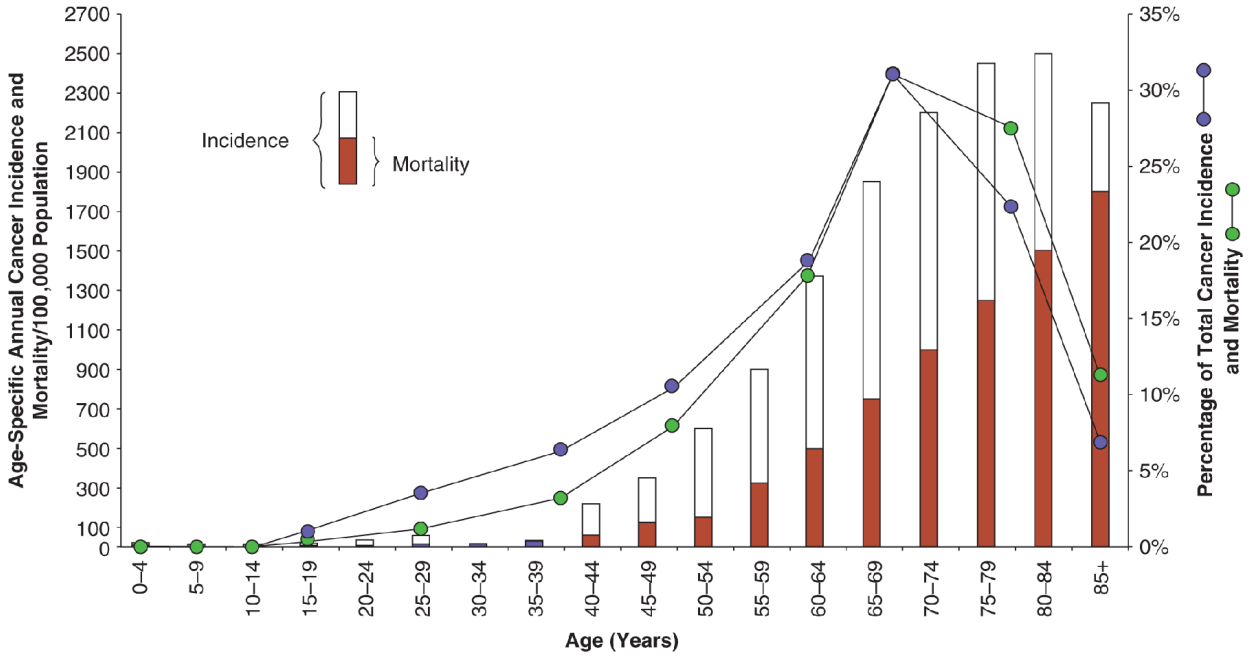


FIGURE 96-1. Comparison of the percentage of total cancer incidence and mortality by age with age-specific incidence and mortality. (Data from SEER Cancer Statistics Review: 1973–1994. Bethesda, MD: National Cancer Institute; 1997.)

The median age range for diagnosis for most major tumors, common to both men and women, is 68 to 74; the median age range at death is 70 to 79. The overall pattern for the incidence of age-specific cancer shows a rise with age, and, overall, 60% of cancers occur in people age 65 or older. This is not uniform for individual cancers and in some malignancies there is an apparent decrease in incidence in people older than age 80. This may be a result of a number of factors, including underreporting or natural selection, which would allow the less-cancer-prone population to survive. For most malignancies, the death rate is disproportionately higher for the older population. As **Figure 96-1** also demonstrates, the age-specific cancer mortality continues to rise as a function of age, as does incidence. In support of this observation is the report from the SEER Program that 5-year survivals for most types of cancer decrease with advancing age. Possible explanations include an altered natural history of some cancers, competing comorbid medical conditions, decreased physiologic reserve compromising the ability to tolerate therapy, physicians' reluctance to provide aggressive therapy, and barriers in the older person's access to care. Communication between health care providers and older patients may be hampered by deficits in hearing, vision, and cognition. The older cancer patient often has an older caregiver, and the diagnosis of cancer often affects the health-related quality of life of both individuals. Thus, not only does cancer occur at an increased rate in older individuals, but, it makes a significant impact on such people's lives, from the standpoint of both increasing morbidity and mortality. All of these challenges contribute to defining "geriatric oncology" as a true subspecialty and has led to the development of guidelines by the NCCN that addresses special considerations in older patients with cancer.

RELATIONSHIP BETWEEN AGING AND NEOPLASIA

The relationships between aging (senescence) and neoplastic transformation are complex, intertwined, and not fully understood. To explore the relationship, however, we must first briefly describe the current understanding of the multistep process of carcinogenesis. The first stage of cancer development is known as initiation. In this process, chemical or physical carcinogens, or certain viruses, cause a change in the cell that predisposes it to a subsequent malignant transformation. This change appears to be an irreversible lesion in the genomic deoxyribonucleic acid (DNA) of a stem cell; the lesion may remain stable for a long period. It is not clear whether such an initiated cell can be recognized clinically, but certain disorders such as myelodysplasia or carcinoma in situ, may be a manifestation of this phenomenon.

The next stage of carcinogenesis is called promotion and involves a proliferative phase. Promoters are agents that can induce mitogenesis, or cell division, in an initiated cell. This phenomenon includes the activation of a number of growth factors and transcription factors, which promote cell proliferation, and which may arise through the events related to changes in oncogenes or tumor-suppressor genes noted later. Whereas it appears that a single initiating event is sufficient to begin the process, promotion appears to be most successful when it is repetitive. This may occur shortly after initiation or after a delay and appears to be dose dependent as well as reversible. For this reason, researchers believe that cessation of cigarette smoking (containing both initiators and promoters) reduces the cancer incidence of former smokers when compared with those who continue to smoke.

The final stage of cancer development in this model is progression. This is actually multiphasic itself and involves the transformation of a cell from a premalignant to a malignant state, the potential clonal evolution of a subset of such cells, and the potential development of metastasis. The latter two phenomena are quite important and have led to the concept of tumor cell heterogeneity. Although we believe that tumors arise from a single “clone of cells,” tumor cells are genetically more unstable than normal cells, yielding progeny with variable proliferative and metastatic potential. Thus, not all cells within a given tumor are the same. Clinically, this may explain such diversity as variable chemosensitivity of tumor cells, the selection of resistant cells, the differential behavior of different metastatic lesions compared with the original tumor and with other metastatic lesions, and the sometimes unpredictable behavior of a particular cancer. Other factors relating to the tumor’s impact on host tissue may also play an important role at this stage. These include the ability to disrupt stromal elements such as the basement membrane and the ability to promote angiogenesis, which supports further tumor growth.

It is clear that alterations in growth regulatory gene function play a critical role in the development of neoplasia. There are two major classes of such genes—oncogenes and tumor-suppressor genes. Oncogenes, or cancer genes, were initially described as viral genes capable of transforming normal cells to malignant ones. Of the various genes, about 100 to 200 have been shown to be targets for oncogenic disruption of their DNA structure. Oncogene activation can result in one of two pathways: first the decision of a cell to divide or undergo senescence and apoptosis (programmed cell death) is altered such that the balance is shifted away from cell death and toward cell survival and proliferation. Secondly, the oncogene mutations might affect DNA repair, thus predisposing cells to additional DNA damage and activation of additional oncogenes. Oncogenes can be either dominant or recessive. Dominant oncogenes are those for which a functional alteration in one allele contributes to the malignant phenotype despite the persistence of the normal contralateral allele. Recessive oncogenes are called tumor-suppressor genes which normally limit cell growth, enhance apoptosis, and control differentiation and require both alleles to be disrupted to contribute to the cancer process.

A large number of oncogenes have been described. They appear to have the potential for growth-enhancing activity at a series of steps along the mitogenic pathway, including activating signal transduction at the cell surface, producing endogenous growth factors at the cytoplasmic level (eg, ras-like), and increasing the sensitivity of the cell to exogenous (or endogenous) growth factors at the nuclear level (eg, myc-like). Another oncogene, bcl-2, codes for an inner mitochondrial protein that blocks apoptosis, or programmed cell death. This mechanism may be of particular interest in the context of senescence, as it may operate by increasing cell longevity rather than proliferation. Increased cellular oncogenic expression has been noted in many tumors and can be mimicked experimentally by altering the DNA encoding for the oncogene, usually at or near the promoter. Thus, it is possible that the chromosomal damage noted in neoplasia during the initiation and promotion phases, if it occurred near the region of an oncogene, could result in transformation and clonal evolution of the cancer. The evolutions noted in Burkitt lymphoma and chronic granulocytic leukemia may be examples of this process. The expression of more than one oncogene is necessary to cause transformation.

A number of tumor-suppressor genes have been described, and mutations in such genes as *Rb* and *p53* have been

described in many human tumors. The normal function of such genes appears to prevent uncontrolled growth as a result of the action of various growth-promoting factors. It has even been suggested that senescence may act as a form of tumor suppression. In fact, the two tumor-suppressor genes just noted, *p53* and *Rb*, are essential for maintaining the senescent phenotype of cells in culture. Inactivation of either gene extends the replicative lifespan of such cells and mutations of *Rb* have been linked to both cancer incidence and longevity in mice. This phenomenon would appear to enhance the likelihood of acquiring further mutations, leading to the ultimate development of malignancy. Indeed deletions of *p53*, *Rb*, or both, are frequently found in common solid tumors, such as lung, breast, and colon. Although the inactivation of tumor-suppressor genes is important in the development of neoplasia, it is likely that alterations in both oncogenes and tumor-suppressor genes are necessary in many cases to achieve full malignant potential. It is also important to understand the theory of the "two-hit hypothesis." As described above, certain tumor-suppressor genes are responsible for suppressing the malignant phenotype. In normal individuals, both alleles of such genes would need to be eliminated by random or environmentally induced errors thus requiring "two-hits." In contrast, families with certain genetic mutations that make them susceptible to cancer, already have one abnormal allele of the tumor-suppressor gene. Thus, the "first-hit" preexists making them substantially more susceptible to carcinogenic action of the "second random hit."

There are several theories on how the aging process influences the process of neoplastic transformation to result in the markedly increased rates of cancer in older people. These include the following:

1. Longer duration of carcinogenic exposure: It is possible that aging simply allows the time necessary for the accumulation of cellular events to develop into a clinical neoplasm. There is evidence for age-related accumulation and expression of genetic damage. Somatic mutations are believed to occur at the rate of approximately 1 in 10 cell divisions, with approximately 10 cell divisions occurring in a lifetime of a human being. Certainly, the complex set of events required in the multistep process of carcinogenesis, for example, as described for colon cancer in humans, does occur over time. The passage of time alone, however, is not likely to explain the phenomenon, as the time for a mutated cell to become a malignant cell and then subsequently to become a detectable tumor has been estimated to be approximately 10% to 30% of the maximum lifespan for a given animal species, which may vary from just a few years to more than 100 years.
2. Altered susceptibility of aging cells to carcinogens: Data in this area are somewhat contradictory. In some cases, the incidence of skin tumors in mice produced with benzpyrene has been more related to dose than to age, whereas in other models, accelerated carcinogenesis as a function of age has been demonstrated, as, for example, when dimethylbenzanthracene (DMA) was applied to skin grafts of young and old mice. An age-related increase in the sensitivity of lymphocytes to cell-cycle arrest and chromosome damage after radiation has been demonstrated. It is also possible that there are alterations in carcinogen metabolism with age, but the findings from such studies have also been contradictory.
3. Decreased ability to repair DNA: It is possible that damage, once initiated, is more difficult to repair in older cells. A number of studies demonstrate decreased DNA repair as a function of age following damage by carcinogens as well as radiation. Such repair failures may also be reflected in increased karyotype abnormalities in aged normal cells as well as in older patients with neoplastic disease.
4. Oncogene activation or amplification or decrease in tumor-suppressor gene activity: These processes might be increased in the older host, resulting either in increased action or promotion or in differential clonal evolution. Although evidence is currently limited, there have been observations of increased amplification of proto-oncogenes and their products in aging fibroblasts in vitro as well as evidence for increased c-myc transcript levels in the livers of aging mice. Alternatively, such factors as genetic alterations or DNA damage could lead to inactivation of cancer-suppressor genes. Given that age-related mutations frequently appear to result in the loss of function, alterations in tumor-suppressor genes may prove to be an important mechanism.
5. Telomere shortening and genetic instability: The function of telomeres and the enzyme telomerase appears to be intimately involved in both the senescence and neoplasia processes. Telomeres, the terminal end of all chromosomes, shorten progressively as cells age. This functional decline begins at age 30 and continues at a loss of approximately 1% per year. This shortening appears to be causally related to controlled cell proliferation and limitation of population doubling. It is thought that each time a cell divided, an average person loses 30 to 200 base pairs from the end of that cell's telomeres. Because the major function of telomeres is to protect the stability of the more internal coding sequences, that is, allow cells to divide without losing genes; the loss of this function may lead to genetic instability, which may promote mutations in oncogenic or tumor-suppressor gene sequences.

Without telomeres, chromosome ends could fuse together and degrade the cells' genetic blueprint, making the cell malfunction, become cancerous, or even die. Telomere length is a predictor of mortality in people aged 60 or older. There are data to suggest that older people with shorter telomeres die more frequently and earlier than their peers with longer telomeres. The enzyme telomerase is responsible for adding back telomeric repeats to the ends of chromosomes, that is, regenerate the telomeres. This enzyme is generally not expressed in normal cells, but it is activated in malignant cells. It is thought that while telomerase can reverse replicative cell senescence, the indiscriminate expression of this enzyme might increase the likelihood of tumor formation. It is also possible that *p53* or *Rb* inactivation that occurs in senescent cells, or the inactivation of other tumor-suppressor genes, may allow the activation of the telomerase gene and promote cell immortalization and ultimately malignancy.

6. Microenvironment alterations: Older people have been shown to accumulate senescent cells as shown by β-galactosidase staining. They also have higher levels of interleukin 6 (IL-6), which has been labeled the "geriatric cytokine" and can contribute to frailty. A number of factors in the tumor microenvironment are critical for the development of the malignant phenotype, especially invasion and metastasis. Senescent cells can compromise tissue renewal capacity, and secrete multiple factors that alter tissue homeostasis. These factors include inflammatory cytokines like IL-1, and epithelial growth factors (eg, heregulin, and matrix metalloproteinases like MMP-3) and can disrupt the architecture and function of the surrounding tissue and stimulate or inhibit the proliferation of neighboring cells. More recently, there is accumulating evidence showing that senescent cells can have deleterious effects on the tissue microenvironment. The most significant of these effects is the acquisition of a "senescence-associated secretory phenotype" (SASP) that turns senescent fibroblasts into proinflammatory cells that have the ability to promote tumor progression. A variety of stresses can provoke cellular senescence and include telomere dysfunction resulting from repeated cell division (termed replicative senescence), mitochondrial deterioration, oxidative stress, severe or irreparable DNA damage and chromatin disruption (genotoxic stress), and the expression of certain oncogenes (oncogene-induced senescence). These stresses can be induced by external or internal chemical and physical insults encountered during the course of the lifespan, during therapeutic interventions (eg, radiation or chemotherapy), or as a consequence of endogenous processes such as oxidative respiration and mitogenic signals.
7. Decreased immune surveillance: A decrease in immune surveillance, or immunosenescence, could contribute to the increased incidence of malignancies. In animal models there is a considerable amount of evidence for a loss of tumor-specific immunity with progressive age. This includes the altered capacity of old mice to reject transplanted tumors, the close relationship between susceptibility to malignant melanomas and the rate of age-related T-cell–dependent immune function decline, and the ability by immunopharmacologic manipulation to increase age-depressed tumoricidal immune function and to decrease the incidence of spontaneous tumors. The evidence linking such data to age-associated immune deficiency and the rise of cancer incidence in humans, however, is mainly circumstantial and not likely to be fully explanatory, as the types of tumors seen in the most striking examples of immune deficiency are very different from those seen in the usual aging human.

Figure 96-2 summarizes in a schematic fashion the potential interaction of these many factors that may be of importance in the increase of cancer with age. It indicates the interface of time- and age-related events, such as free radical and other carcinogenic exposure, resulting in initiation, then cumulative promoting events, including mutations and other alterations in critical genes, which ultimately exceed a threshold of host resistance factors, which have been progressively reduced during the aging process.

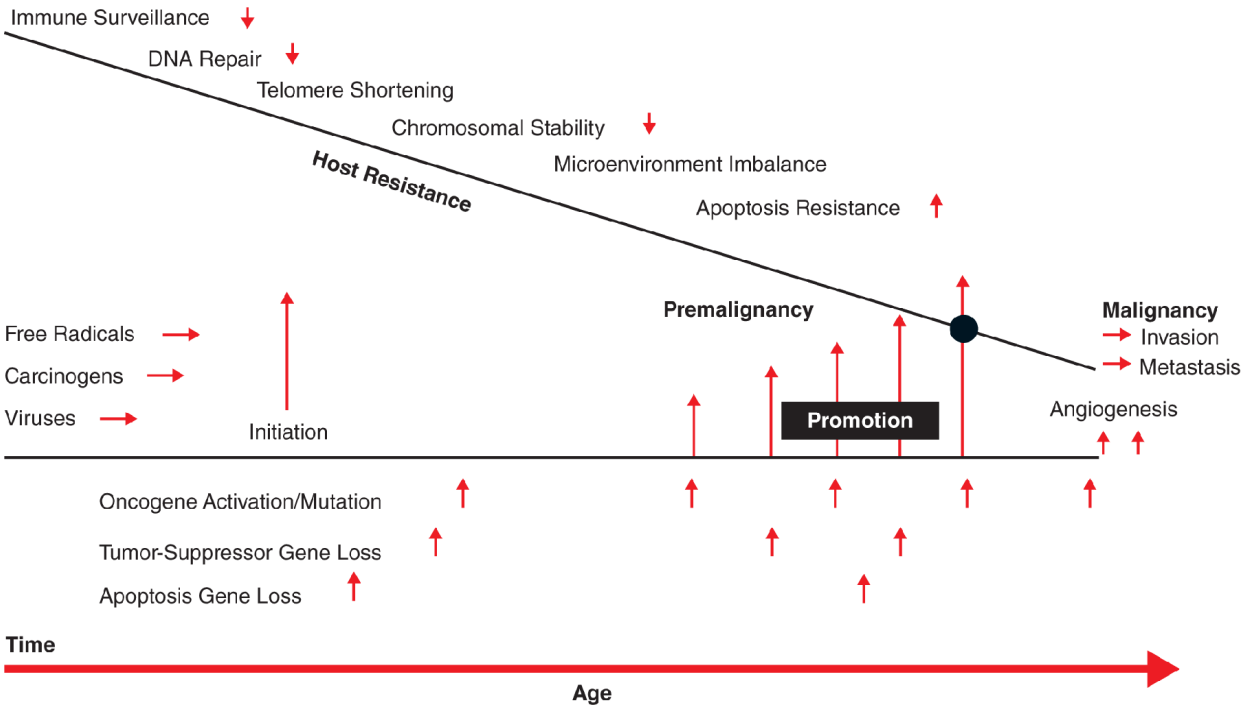


FIGURE 96-2. Age and cancer susceptibility. This figure presents a model incorporating the various factors that may play a role in the increased incidence of cancer with age.

Cellular senescence suppresses cancer by arresting cells at risk of malignant transformation. However, senescent cells also secrete molecules that can stimulate premalignant cells to proliferate and form tumors, suggesting that the senescence response is antagonistically pleiotropic. Thus a function important for the organism in early life (through the reproductive period) will be selected for, despite the fact that it may be quite injurious in later life. In this case, senescence could be viewed as the price we pay in later life for the rigorous attempt to control proliferation to avoid neoplasia early on. The progressive, and no doubt multifactorial, loss of the controls with aging ultimately results in an increase in neoplasia in advanced age despite the early control. From the standpoint of natural selection, both of these outcomes would be acceptable, as they tend to occur long after the reproductive lifespan. It is likely that through research at the basic level concerning the interactions of aging and neoplasia, we will learn a great deal about the fundamental basis of each. It is hoped that such information will enhance our ability to engage in prevention at the primary and secondary levels.

Current information suggests that a large proportion of cancers are potentially preventable. The most obviously available modalities in this regard are avoidance of known and suspected carcinogenic exposures such as tobacco smoke, occupational and environmental chemicals, excessive sunlight, and dietary factors such as excessive fat and smoked, salted, and pickled foods. Although older individuals have potentially acquired a lifetime exposure to such carcinogens, they should still accrue benefits from modifying these behaviors as well as from engaging in positive ones such as the suggested intake of fiber, vitamins, and fresh vegetables and regular exercise to prevent obesity a major risk factor for neoplasia.

CLINICAL PRESENTATIONS AND DISEASE BEHAVIOR

Screening in Asymptomatic Individuals

Older patients continue to be underscreened and thus underdiagnosed with cancer. It is well known that mammography and Papanicolaou (Pap) tests are underutilized in certain older racial and ethnic minority groups, and in those who have less than high school education or live below the poverty level. Only 17% of American Indian/Alaska Native women who are 60 years or older have ever had a mammogram, compared to 38% among all US women of that age. A number of organizations have made recommendations with respect to screening studies in older adults, and there is some variation among them. These recommendations are directed at mass screening of populations and it should be recognized that when applied to older persons, especially those older than age 75, such information is largely empirically derived. **Table 96-1** shows a synthesized recommendation by the authors of the current guidelines of the

American Cancer Society (ACS) relevant to the older adult, those of the US Preventive Services Task Force, and Medicare reimbursement. There is general agreement that routine cancer screening has little likelihood to result in a net benefit for individuals with limited life expectancy. The American Society of Clinical Oncology (ASCO), as part of their "Choosing Wisely Campaign," an initiative designed to highlight the misuse of medical tests, recently recommended avoiding prostate-specific antigen (PSA) screening in men who are expected to live fewer than 10 years. Similarly, the ACS and the American Urological Association (AUA) also recommend cessation of PSA screening in men with a life expectancy of fewer than 10 years. For colorectal cancer screening, the American College of Physicians recommends cessation of screening in individuals with less than 10-year life expectancy. Other guidelines in breast and cervical cancers have similarly used life expectancy and/or age (a crude surrogate for life expectancy) as a parameter for screening cessation. A recent large study evaluated data from the population-based National Health Interview Survey (NHIS) from 2000 through 2010 and included 27,404 participants ages 65 or older. Using a validated mortality index specific for NHIS, participants were grouped into those with low (< 25%), intermediate (25%–49%), high (50%–74%), and very high (≥ 75%) risks of 9-year mortality. The study demonstrated that in participants with very high mortality risk, 31% to 55% received recent cancer screening, with prostate cancer screening being most common (55%). For women who had a hysterectomy for benign reasons, 34%to 56% had a Papanicolaou test within the past 3 years. Screening was also common in individuals with less than 5-year life expectancy and the authors concluded that cancer screening in such patients not only has implications for utilization of health care resources in a setting unlikely to result in net benefit but may also cause net patient harm owing to subsequent diagnostic procedures and overtreatment.

TABLE 96-1 USPSTF GUIDELINES FOR SCREENING BY CANCER TYPE

TYPE OF CANCER	RECOMMENDATIONS
Colorectal	• Screen for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults beginning at age 50 and continuing until age 75 (Grade A). • Recommend against routine screening for colorectal cancer in adults aged 76–85. There may be considerations that support colorectal cancer screening in an individual patient (Grade C). • Recommend against screening for colorectal cancer screening in adults over the age of 85 (Grade D). • Evidence is insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer (I).
Lung	• Recommend annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55–80 who have at least a 30 pack-year smoking history and currently smoke or have quit within the past 15 y. Screening should be discontinued once a person has not smoked for 15 y or develops a health problem that substantially limits life expectancy or willingness to have curative lung surgery (Grade B).
Prostate	• Recommend against prostate-specific antigen (PSA)-based screening for prostate cancer (Grade D).
Breast	• Recommend biennial screening mammography for women 50–74 y (Grade B). • Decision to start regular biennial screening mammography before the age of 50 should be an individual one and take patient context into account, including patient's values regarding specific benefits and harms (Grade C). • Current evidence is insufficient to assess the benefits and harms of screening mammography in women 75 y and older (I). • Recommend against teaching breast self-examination (BSE) (Grade D). • Current evidence is insufficient to assess the additional benefits and harms of clinical breast examination (CBE) beyond screening mammography in women 40 y or older (I). • Current evidence is insufficient to assess additional benefits and harms of either digital mammography or MRI instead of film mammography as screening modalities for breast cancer (I).
Cervical	• Recommend screening for cervical cancer in women aged 21–65 with cytology (Pap smear) every 3 y or, for women age 30–65 who want to lengthen the screening interval, screening with a combination of cytology and HPV testing every 5 y (Grade A). • Recommend against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 (Grade D). • Recommend against screening for cervical cancer in women under the age of 21(Grade D). • Recommend against screening for cervical cancer in women over the age of 65 who have had adequate prior screening and are not otherwise at high risk for cervical cancer (Grade D).

	• Recommend against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (CIN grade 2 or 3) or cervical cancer (Grade D).

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; USPSTF, United States Preventive Services Task Force.

Modified from Wingfield S, Heflin MT. Clin Geriatr Med. 2016;32(1):17–33.

Grade A: The USPSTF recommends the service. There is high certainty that the net benefit is substantial.

Grade B: The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

Grade C:The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.

Grade D: The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.

I: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

Breast cancer screening Age is the major risk factor for developing and dying from breast cancer. Breast cancer risk factors that reflect hormonal exposures in the distant past, such as age at first birth or age at menarche, are less predictive of late-life breast cancer than factors indicating recent hormonal exposures such as high bone mass or obesity. A recent study evaluated PubMed for English-language studies in peer-reviewed journals published from January 1, 1990, to February 1, 2014, to identify risk factors for late-life breast cancer in women aged 65 and older and to quantify the benefits and harms of screening mammography for women aged 75 and older. Randomized trials of the benefits of screening mammography have traditionally not included women older than 74 years and it is thus not known if screening mammography benefits older women. Observational studies favor extending screening mammography to older women who have a life expectancy of more than 10 years. Modeling studies estimate two fewer breast cancer deaths per 1000 women who in their 70s continue biennial screening for 10 years instead of stopping screening at age 69. Potential harms of continued screening over 10 years include false-positive mammograms in approximately 200/1000 women screened and overdiagnosis (ie, finding breast cancer that would not have clinically surfaced otherwise) in approximately 13/1000 women screened. The authors concluded that providing information about life expectancy along with potential benefits and harms of screening may help an older women's decision making about screening mammography.

Cervical cancer screening The current ACS guideline for detection of cervical cancer in asymptomatic women appears to be a consensus position that states that "all women who are, or who have been, sexually active, or have reached age 18 years, [should] have an annual Pap test and pelvic examination. After a women has three or more consecutive satisfactory normal annual examinations, the Pap test may be performed less frequently at the discretion of her physician." This recommendation has no specific upper-age limitation, and the discussion of these recommendations contains a reminder that "mature women—those over 65—also require testing." In addition, in March 2003, the Food and Drug Administration (FDA) approved the human papillomavirus (HPV) DNA test to be used simultaneously with the Pap test to screen for cervical cancer in women age 30 and older. If both the Pap and the HPV DNA test results are negative, a woman's doctor may advise her to wait for 3 years before being retested, according to guidelines from the American College of Obstetricians and Gynecologists (ACOG). But more frequent testing is recommended if other high-risk factors are present, such as a weakened immune system or a history of cervical cancer. If only one of the tests is negative, the doctor may advise the woman to return for retesting in 6 to 12 months. Since there is little consensus, and minimal evidence, regarding the age at which to stop cervical screening one study examined the association between screening at age 50 to 64 and cervical cancer at age 65 to 83. Women (n = 1341) diagnosed with cervical cancer at age 65 to 83 between April 2007 and March 2012 in England and Wales were compared to randomly selected age-matched controls (n = 2646). Notably, women with adequate negative screening at age 50 to 64 had one-sixth the risk of cervical cancer at age 65 to 83 compared with women who were not screened.

Colorectal cancer screening The lifetime risk of colorectal cancer is approximately 5% with the incidence of 40 to 50/100,000 persons in persons over 75 years, and 15 to 20/100,000 in persons 60 to 65 years. Another important factor and potential benefit of screening for colon cancer with colonoscopy is the increase incidence of right-sided colon neoplasias. In the United States and other countries, the incidence of right-sided advanced adenomas and cancers increases with age, increasing from 15% of lesions in patients at 50 years to over 35% in patients over age 75. Right-sided lesions present symptomatically at advanced stages so early detection is important. Cancer screening in older

adults (those greater than 75 years) has been controversial and is not specifically addressed by most guidelines. Like with other tumors, older patients have not been included in randomized trials of the efficacy of screening studies. Recommendations for screening guidelines have been made based on detection rates, but do not address the impact of comorbidities, functional status, and life expectancy issues that are more important considerations in the older population. The US Preventive Services Task Force (USPSTF) recommends that in patients over 75 years who have been previously screened on a regular basis, no further screening should be offered. In patients 75 to 85 years, who have not been screened previously, the decision regarding first time screening should be based on the patient's health status and competing risks. Finally, it recommended not screening patients over the age of 85.

Prostate cancer screening Prostate cancer is the most common nonskin cancer in US men and one in six men will receive a diagnosis in their lifetime. The serum PSA test was approved by the US FDA in 1986, and its use for prostate cancer screening increased substantially in the mid-1990s. However, PSA testing is not specific to prostate cancer and elevated levels are seen with benign prostatic hyperplasia and prostatitis. Potential harms from PSA screening include additional medical visits, adverse effects of prostate biopsies, anxiety, and overdiagnosis. Based on the findings of two large systematic reviews in 2002, the USPSTF found insufficient evidence to recommend for or against routine screening for prostate cancer. The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but found mixed and inconclusive evidence that screening and early detection improved health outcomes. ASCO, as part of their "Choosing Wisely Campaign," an initiative designed to highlight the misuse of medical tests, recently recommended avoiding PSA screening in men who are expected to live fewer than 10 years. Similarly, the ACS and the AUA also recommend cessation of PSA screening in men with a life expectancy of fewer than 10 years.

Lung cancer Lung cancer is the leading cause of cancer-related mortality in the United States, with 159,000 deaths estimated in 2014. Age older than 55 years and smoking are the strongest risk factors for lung cancer. In 2010, the investigators of the randomized National Lung Screening Trial (NLST) reported that annual screening with low-dose computed tomography (LDCT) reduced lung cancer mortality by 20% compared with screening with chest radiographs. Subsequently, several clinical practice guidelines recommended annual screening, and many insurers agreed to cover screening. Most recently, the USPSTF recommended annual screening for 55- to 80-year-old individuals who had smoked at least 30 pack-years. The NLST population was not representative of Medicare: 25% of the study population was 65 years or older; only 9% was older than 70 years which is the median age at diagnosis of lung cancer. Centers for Medicare & Medicaid Services (CMS) now covers lung cancer screening with LDCT once a year for eligible individuals.

Physicians and other health care professionals should ensure that the older individual is aware of the importance of screening, that the opportunity for such examinations is provided, and that fears and anxieties about these tests are allayed to as great an extent as possible. Screening education materials made user friendly for the older person have been developed and should be used.

Initial Presentation

As an extension of the screening concept, the goal for initial cancer detection is to make the diagnosis as early as possible, with the hope that treatment at the earliest stages of disease would yield the best survival rates. It is, therefore, of great importance that both patient and physician pay attention to symptoms that may herald the onset of the neoplastic process. Current evidence suggests that once having noticed a symptom that appears to be related to cancer, older individuals do not delay appreciably in seeking medical help. In one study from New Mexico of 800 patients over 65 years, only 29.4% of the subjects were asymptomatic when cancer was detected, and 48% presented within 2 months of symptom onset. However, 19.2% of the subjects delayed seeking care for at least 12 weeks and 7.4% delayed at least 1 year. In another study from Finland, women over 80 years had a longer interval between first symptom and first medical examination for the diagnosis of colorectal cancer when compared to their younger counterparts. Older women, who are at greater risk of developing breast cancer, are also more likely to delay their presentation. In one study of 69 women (> 65 years) factors associated with delayed presentation were having a no-lump symptom, reservations about seeing a general practitioner, and fear of the consequences of cancer. Physicians, however, may also be guilty of delaying further diagnostic pursuits in older patients. One interesting study demonstrated that with the uncertainty of how to diagnose and treat older women with breast cancer, physician specialty, (surgeons vs nonsurgeons) length of time in practice (≤ 15 years vs >15 years), and concern over malpractice do influence clinical decisions. Part of the problem may lie in a failure to recognize some of the new signs

and symptoms in patients with multiple disease processes. It is easy to attribute such symptoms as anorexia, weight loss, or decrease in performance status to social or psychological changes. The increasing prevalence of findings such as anemia in older patients may lower the index of suspicion for attributing the factor to a new specific neoplastic process. The remarkable age-related increase in cancer incidence described earlier in this chapter should be sufficient to promote the maintenance of vigilance in this regard, although it must be balanced by judgment concerning the risk-benefit ratio for diagnostic evaluations in individual patients depending on their other medical status. Thus, the initial discovery of a new symptom in a previously totally well, active 80-years-old may be pursued rather differently than a similar discovery in a severely demented, bedbound individual with severe congestive heart failure, diabetes, and pulmonary failure.

Biological Behavior of Tumors in the Older Host

The effect of the aging process on the clinical course of cancer, or to put it another way, whether cancer behaves differently in the older individual, is not clear-cut. Although the SEER data noted previously suggested that in many cancers the 5-year survival rate is lower for older people, it is possible that this is related more to comorbid disease and other factors rather than simply to aging per se. On the other hand, there is a widespread belief that cancers may behave more indolently in older patients. These are important issues because they may to a considerable degree, affect decisions regarding treatment. Both clinical and experimental evidence support both sides of this issue, and it is likely that there is a spectrum of responses dependent on initial tumor types as well as individual host status. One indicator of the phenomenon is the extent of disease at presentation. For most cancers examined, there has been no consistent difference in the stage of disease or presentation for different age groups. For those that have been determined, the directions are not always the same. For malignant melanoma, older patients have been consistently found to have more advanced-stage local disease with deeper penetrating lesions at presentation. For breast cancer, some studies show a greater proportion of older patients with distant metastatic spread at presentation, whereas for lung cancer the opposite has been found, and older patients have been noted to present with localized disease in a greater proportion of cases. Uterine and cervical cancers have in some cases been noted to be later in the course of disease at presentation in older individuals. Of course, even these differences might be related to such phenomena as delay in the patient's presenting for diagnosis (which does not appear to be the case), delay in pursuing the diagnosis, intensity of diagnostic endeavors, or a combination of these factors, or, on the other hand, a greater chance for a serendipitous finding because of more frequent visits to physicians.

Another biological factor that may influence neoplastic behavior in differently aged hosts is the histologic subtype of the tumor. Thus, while thyroid cancer overall appears to behave more aggressively in the older host, it is also true that a larger proportion of thyroid neoplasia in older patients is made up by anaplastic carcinoma, which at any age has more aggressive behavior. Similarly, for malignant melanoma, although there is an increased proportion of older people who have melanomas of poor prognostic histologic type and location at presentation, older individuals have a poorer prognosis for survival than do younger ones independent of this phenomenon even for localized disease. Such biological differences may be manifested in other ways, as in the case of breast cancer, in which older women have an increased frequency of estrogen receptor–positive breast cancer, probably related to hormonal influences of the postmenopausal state. An additional factor is the longer tumor doubling time seen in breast cancer cells from older women. Because estrogen receptor (ER) positivity and longer doubling times are associated with better prognosis, with more slow-growing tumors, and with longer disease-free survivals, these phenomena, rather than age per se, might provide the reason why this cancer appears to behave more indolently in an older individual. Despite this, overall cancer-related survival is lower in older women, emphasizing the complex interactions of tumor and host that must be considered.

Acute myelogenous leukemia (AML) has a much poorer prognosis in older patients and the biology underlying the poor prognosis and poor treatment outcome of AML in the older adult has been extensively studied. Among the findings to date are a high incidence of poor-prognosis karyotypes (5q-, 7q-), high frequency of preceding myelodysplastic syndromes, and an increased expression of proteins involved in intrinsic resistance to chemotherapeutic agents. A recent study demonstrated that, compared to younger patients, leukemic blasts from older patients with AML had a lower propensity to apoptosis following traditional remission-induction treatment with ara-C and daunorubicin. Gene-expression studies have demonstrated that older AML patients tend to have worse survival compared to their younger counterparts and this may in part be driven by an increase expression of ras, src, and tumor necrosis factor (TNF) pathways in the bone marrow of older patients.

Biological Markers of Frailty

Aging is associated with increased levels of circulating cytokines and proinflammatory markers. Age-related changes in the immune system, that is, immunosenescence, and increased secretion of cytokines by adipose tissue, can lead to a state of chronic inflammation or "inflammaging." High levels of IL-6, IL-1, TNF-α, and C-reactive protein in older adults are associated with increased risk of morbidity and mortality. In particular, cohort studies in older subjects have indicated that increased TNF-α and IL-6 levels are associated with frailty. These biomarkers of frailty have now been evaluated in older and nonolder cancer patients in several studies of many tumor types (eg, colon cancer, AML, multiple myeloma) and have all demonstrated increased levels of proinflammatory cytokines in these patients. These frailty cytokines have not only been thought to play a role in carcinogenesis (eg, AML and multiple myeloma) but in fact are also responsible for several cancer-related symptom complexes including cancer cachexia, fatigue, poor performance status, and cognitive issues.

Experimental data in animal models likewise show this spectrum in rate of tumor growth and progression as a function of age. In these studies, the ability to contain tumor growth depends on the particular host tumor system used, thus mimicking the clinical situation to some extent. A proposed explanation for the situation in which the older host more effectively controls the rate of tumor is a paradoxical effect of decreasing immune function with age, that is, decreased activity of those cells in the old host's immune system, which, under the stimulation of the neoplastic process, produce tumor-enhancing factors such as angiogenesis factor. When this occurs, tumor growth might be expected to be diminished. To what extent these various factors play a role in the biological behavior of neoplasia in the human aging host remains a fascinating puzzle to be unraveled.

MANAGEMENT

General Principles

This section examines the utility of the major modalities of cancer treatment in the older individual. The treating physician is often placed in the position of weighing benefits versus risks of diagnostic and therapeutic interventions and should take into account the various biological, psychological, and social factors involved in the patient's well-being. Of great importance in this regard is the patient's own assessment of the value of both quantity and quality of potential survival during and after the treatment for malignancy. In this process, there is a clear need to individualize such decisions, and a decision made for a well older patient may be appropriately different than that for a frail older patient. Currently, it would appear that age bias in diagnostic and treatment decisions for older patients with cancer does exist and older patients are continually underrepresented in clinical trials. Analysis of data on approximately 60,000 patients treated in phase II and III trials sponsored by the National Cancer Institute between 1997 and 2000 found that only 32% of the participants were aged 65 or older, despite the fact that this age group accounted for 61% patients with cancer. Several follow-up studies have also confirmed that older adults continue to be underrepresented in the registration trials of new cancer therapies. Thus, while differences in decisions may be entirely appropriate in certain situations, these must be based on specific individualized patient information and not on categorical decisions made purely on the basis of chronological age.

We proposed one framework in which the general aspects of such decision making can be considered for the individual patient. This is shown in **Figure 96-3** and is called the Comprehensive Geriatric Model. It graphically presents a number of the concepts critical to the care of the older adult, that is, that there is a decreased functional reserve and that, as an extension of Engel's Bio-Psycho-Social Model, all of these various aspects of the individual's background must be taken into account when making decisions about the new process, that is, the cancer. Each of these levels, for example, biological or psychological, can create interactions that influence both the cancer and the host, and, likewise, any intervention directed at the cancer may influence both the cancer and each of these levels of the host's function. Conversely, each of these levels of function, when compromised by the aging process or other comorbid diseases, may influence the ability to deliver these various interventions. Thus, in a sense, a conceptual checklist is presented in which a four-way interaction of various factors can be systematically considered when making decisions. Examples of ways in which physiologic changes occurring with age can impact on cancer treatment are shown in **Table 96-2**.

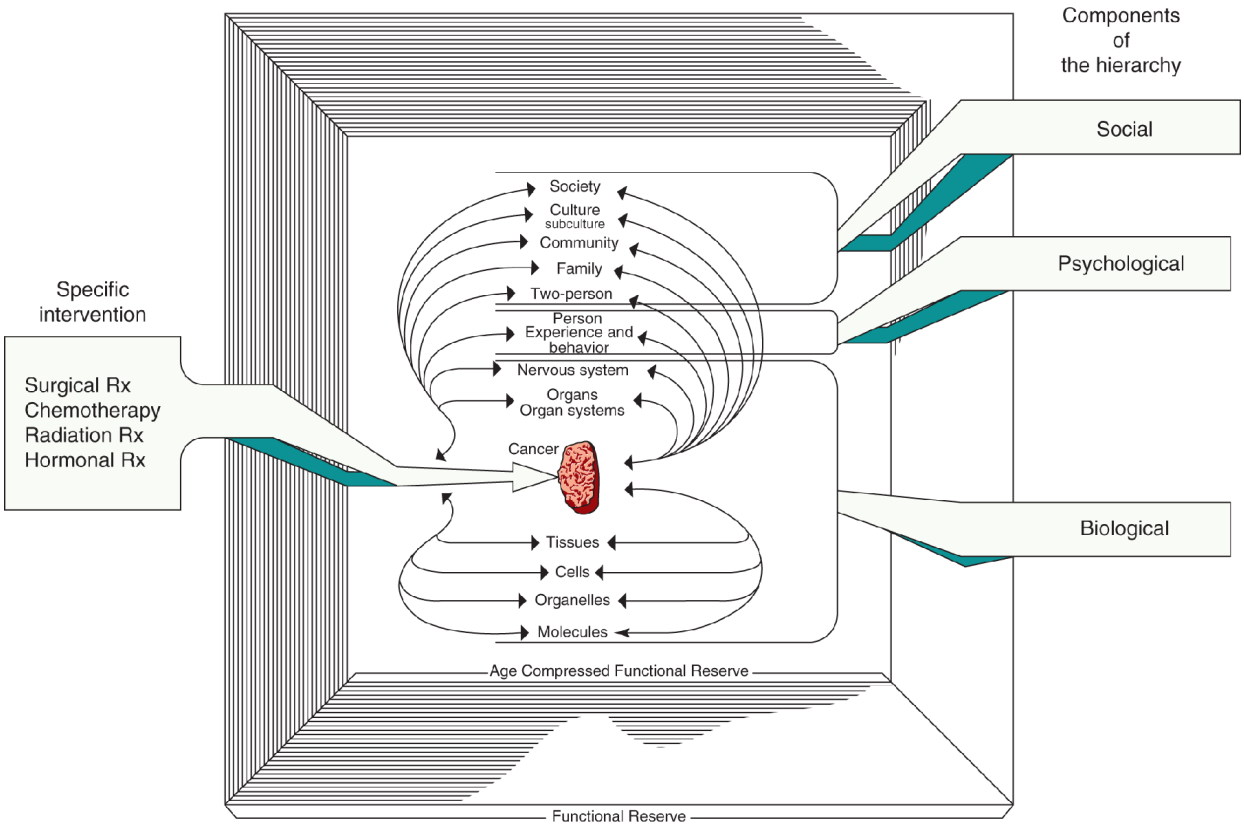


FIGURE 96-3. The Comprehensive Geriatric Model. (Reproduced with permission from Cohen HJ, DeMaria L. In Lazlo J, ed. *Physician's Guide to Cancer Care Complications*. New York, NY: Dekker;1986:240.)

Comprehensive Geriatric Assessment in Oncology

Aging is a heterogeneous process that is not captured by chronological age. Thus, a CGA (as described in detail in Chapter. 10) has been demonstrated to be very useful, since it is designed to capture the functional age of an older adult. This identifies those older adults who have a diminished life expectancy and/or are at risk for hospitalization and functional decline. Traditionally in oncology, performance status (PS) is used as an attempt to quantify cancer patients' general well-being and is also utilized to determine whether they can receive chemotherapy. The most commonly used measure, the Eastern Cooperative Oncology Group (ECOG) PS runs from 0 to 5, with 0 denoting perfect health and 5, death. However, in the geriatric oncology population, it has been demonstrated that ECOG PS alone is not sufficient, and CGA adds substantial information to the functional assessment of older cancer patients, including patients with a good ECOG PS. CGA includes assessment tools to predict the functional age of cancer patients based on functional status, comorbidities that may interfere with cancer therapy, nutritional status, polypharmacy, psychological and cognitive status, socioeconomic issues, and geriatric syndromes. There are a series of screening instruments that have been evaluated in older cancer patients as listed in **Table 96-3**. A complete assessment can be performed after screening and the one that is increasingly being used in North America in clinical trials performed by cooperative groups is described in **Table 96-4**. The measures included in this brief geriatric assessment were chosen for their reliability, validity, brevity, and prognostic ability to determine risk for morbidity or mortality in an older patient. The geriatric assessment tool primarily consisted of self-reported measures, which were completed by the patient. Three items were completed by the health care professional. The median time to complete the CGA tool was 22 minutes, and 87% of patients completed their portion without assistance.

TABLE 96–2 ■ AGING PHYSIOLOGY AND CANCER

AGING PHYSIOLOGY	CANCER RELEVANCE
Cardiopulmonary	
↓ Max CO, VO_2 max	Surgery
↓ Elasticity	C/P toxic drugs

Skin—↓ wound healing	Surgery
CNS—↓ brain weight, cerebral blood flow	Patient interactions CNS toxic drugs
Special senses—↓ taste, smell, salivary flow	Nutrition radiation therapy
Hematopoiesis—↓ response under stress	Chemotherapy and radiation therapy
Immune system—↓ response	Infection
Body composition—↓ lean, ↑ fat	Drug distribution
Liver—↓ mass and flow	Hepatic drug metabolism
Kidney—↓ GFR	Renal drug excretion

CNS, central nervous system; C/P, cardiopulmonary; GFR, glomerular filtration rate.

TABLE 96-3 ■ COMPARISONS OF VARIOUS SCREENING COMPREHENSIVE GERIATRIC ASSESSMENT (CGA) METHODOLOGIES

INSTRUMENT	METHOD	SCORING	INTERPRETATION	REMARKS
G8	Interview	Total score 17	Score 0–14 = presence of geriatric risk profile Score > 14 = absence of geriatric risk profile	Takes 2–3 min to complete screening
Groningen Frailty Indicator (GFI)	Conducting screening tests on patient	Total score 15	Score 0–3 = absence of geriatric risk profile Score 4–15 = presence of geriatric risk profile	Circle answers and use specific scoring rules set by the test
Vulnerable Elders Survey 13 (VES-13)	Self-report and interview	Total score 10	Score 0–2 = absence of vulnerability Score 3–10 = presence of vulnerability	Takes less than 5 min to complete
Senior Adult Oncology Program 2 (SAOP2)	Self-report and interview	N/A	If one item is positive: respective specialist consulted If several items impaired: geriatric referral for MDT	Clinic staff administers last page of interview
Abbreviated CGA (aCGA)	Interview 3 questions about ADLs 4 questions about IADLs 4 questions from the MMSE 4 questions from the GDS		GDS score ≥ 2: complete full 15-item GDS ADLs: any impairment: complete full ADLs IADLs: any impairment: complete full IADLs Cognitive screening score ≤ 6: complete full MMSE	

ADLs, activities of daily living; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; MDT, multidisciplinary team; MMSE, Mini Mental State Examination.

TABLE 96-4 ■ DOMAINS FOR CANCER-SPECIFIC COMPREHENSIVE GERIATRIC ASSESSMENT

DOMAIN WITH MEASURE	NO. OF ITEMS	DESCRIPTION
Functional status		

MOS physical health	10	Measures limitations in a wide range of physical functions (from bathing/dressing to vigorous activities such as running)
Instrumental activities of daily living (IADLs, subscale of the OARS)	7	Measures ability to complete activities required to maintain independence in the community (ie, meal preparation, shopping, making telephone calls, money management)
Karnofsky performance status (rated by the health care professional)	1	Global indicator of patient function determined by the health care professional on a scale of 0–100
No. of falls in last 6 mo	1	No. of times patient has fallen in last 6 mo
Timed Up and Go	1	Performance-based measure of functional status: amount of time it takes for seated patient to rise from a chair, walk 10 ft, walk back, and sit down
MOS social activities	4	Measures ability to participate in social activities and degree to which health status limits normal social activities
Comorbid medical conditions		
Physical health section (subscale of the OARS)	15	List of comorbid illnesses and the degree to which they impair daily activities; patient can add additional comorbid illnesses not listed; rating of eyesight and hearing
Psychological state		
Hospital Anxiety and Depression Scale	14	Measures of anxiety and depression
Social support		
MOS social support survey: emotional/information and tangible subscales	12	Perceived availability of social support
Nutritional status		
Body mass index	1	Weight/height
Percent unintentional weight loss in the past 6 mo	1	Unintentional weight loss in last 6 mo/baseline body weight × 100
Cognition		
Blessed Orientation-Memory-Concentration Test	6	Gross measure of cognitive function
Medications		
Comprehensive list of medications	1	List of medications including prescribed, herbal, and over-the-counter medications

CGA, comprehensive geriatric assessment; MOS, Medical Outcomes Study; OARS, Older American Resources and Services.
Note: Items completed by the health care professional include physician-rated Karnofsky performance status, Timed Up and Go, and Blessed Orientation-Memory-Concentration Test.

CGA has proved useful in studies in older cancer patients to predict for chemotherapy toxicity. In one study, by the Cancer and Aging Research Group (CARG), geriatric assessment variables along with sociodemographics, tumor/treatment variables, and laboratory test results were incorporated into a model that would predict for chemotherapy toxicity in older adults. Five hundred older cancer patients were followed through their chemotherapy course to capture grade 3 (severe), grade 4 (life-threatening or disabling), and grade 5 (death), toxicity. A scoring system in which the median risk score was 7 (range, 0–19) was utilized to risk-stratify patients (risk score: percent incidence of grade 3–5 toxicity). This identified older adults at low (0–5 points; 30%), intermediate (6–9 points; 52%), or high risk (10–19 points; 83%) of chemotherapy toxicity ($p < 0.001$). In another study of 518 older cancer patients, 24 parameters including geriatric assessment were incorporated to create the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score to predict grade 4 hematologic or grade 3/4 nonhematologic toxicity. Based on the

scores, risk categories were created and those patients with low-risk scores had only a 7% chance of hematologic and 33% chance of nonhematologic toxicity compared to high-risk patients, who had a 100% risk of hematologic and 93% risk of nonhematologic toxicity from chemotherapy. One limitation of these two studies was the small numbers of patients with hematologic malignancies (these patients tend to have lower bone marrow reserve, making them especially vulnerable to hematologic toxicities) and the inability to predict for grade 2 toxicities, which can also affect an older patient's QOL significantly.

CGA has also been used to aid the treating oncologist in the decision-making process. In the ELCAPA01 study 375 older cancer patients with cancer were assessed by geriatricians using the CGA to identify factors associated with changes in the cancer treatment: intensification, decrease, or delayed for more than 2 weeks. Multivariate assessment revealed that functional status assessed by the activities of daily living (ADLs) score, and the presence of malnutrition, were independently associated with changes in cancer treatment. CGA has also been utilized in the Preoperative Assessment of Cancer in the Elderly (PACE) trial to determine suitability of older patients for surgery. PACE incorporated a battery of validated instruments including the CGA, Brief Fatigue Inventory, ECOG PS, and American Society Anesthesiologists (ASA) grade in a large study of 460 older cancer patients prior to receiving elective surgery. Of these, 83% were observed to have at least one comorbidity, the most common being hypertension (53.5%). In a multivariate analysis, moderate-to-severe fatigue, a dependent instrumental activities of daily living (IADLs), and poor PS were identified as independent predictors of postoperative complications. Finally, one recent study has demonstrated that CGA predicts survival for older adults receiving induction chemotherapy for AML. In this study of 74 AML patients, median age 70, overall survival was significantly shorter in patients who screened positive for impairment in cognition and objectively measured physical function.

MAJOR THERAPEUTIC MODALITIES

Surgery

Surgery and other invasive procedures are frequently involved in initial diagnostic as well as in therapeutic approaches to the older patient with cancer. An increased number of comorbid medical conditions, decreased wound healing, and lack of physiologic reserve contribute to both prolonged hospital stay and rehabilitation following operative treatment. All phases of healing are compromised by the aging process. Both the inflammatory and proliferative responses are decreased, remodeling occurs to a lesser degree, and the collagen formed is qualitatively different from that in younger individuals. Normally, the repair process initiated by inflammation requires intact sensory nerves that stimulate increased blood flow and growth factor production. The loss of sensory neurons and the coexistence of other medical conditions, such as diabetes and vascular disease, contribute to delayed wound healing. Additionally, complications are more common when surgical intervention is performed on an emergency basis. Often, it is more appropriate to perform an operation as a preventive measure when dealing with older populations; for example, a hemicolectomy may be performed—even for patients with advanced colorectal cancer—to prevent the need for an emergency operation to treat bowel perforation or obstruction. The American Geriatrics Society Task Force and the American College of Surgeons provide general guidelines for older adults undergoing surgery and these may be applied to older cancer patients undergoing surgery.

Radiation Therapy

Radiation therapy (RT) can be used in the older cancer patient with both curative and palliative intent. RT is also used as an effective adjunct to surgery or chemotherapy or both. The International Society of Geriatric Oncology (SIOG) Task Force has put forth guidelines for best practices in radiation oncology in older cancer patients. Per these guidelines, patient selection should include comorbidity and geriatric evaluation. In older breast cancer patients shorter courses of hypofractionated whole breast RT are safe and effective. In patients with nonsmall-cell lung cancer (NSCLC) conformal radiotherapy and involved field techniques without elective nodal irradiation have improved outcomes without increasing toxicity. If comorbidities preclude surgery, stereotactic body radiotherapy (SBRT) is an option for early stage NSCLC and pancreatic cancer. In patients with lymphoma involved field radiotherapy (IFRT) may be based on pretreatment positron emission tomography (PET) data to reduce toxicity. In intermediate-risk prostate cancer patients 4 to 6 months of hormonal therapy combined with external-beam radiotherapy (EBRT) may be an option. Short-course EBRT is an alternative to combined modality therapy in older patients with rectal cancer without significant comorbidities. Endorectal RT may be an option for early disease. For primary brain tumors shorter

courses of postoperative RT following maximal debulking provides equivalent survival to longer schedules. Stereotactic RT provides an alternative to whole-brain RT in patients with limited brain metastases. Intensity-modulated radiotherapy provides an excellent technique to reduce dose to the carotids in head and neck cancer and improves locoregional control in esophageal cancer. It is crucial to monitor older patients receiving radiation since the effects of radiation on normal tissue may be enhanced by 10% to 15% in the older patient. Radiation to the oral pharynx and oral cavity can produce a loss of taste, dryness of mucous membranes, and involution of salivary glands, which when combined with a precarious nutritional intake in a frail and older individual might be lethal, or certainly contribute a considerable amount of morbidity, if not recognized. Moreover, if daily treatment is tolerated poorly owing to nausea or weakness, treatment may be compromised because of the decreased daily doses, the patient's unscheduled absences, or decrease in the total planned dose. Pulmonary complications like severe radiation pneumonitis has been noted in one study to occur more frequently in older lung cancer patients than in younger patients, regardless of radiation field size and concurrent therapies. Depression and cognitive decline are side effects of whole-brain RT.

Systemic Therapy: Chemotherapy, Hormonal Therapy, and Targeted Agents

A thorough discussion of the principles of pharmacology in older persons can be found in Chap. 24. Although still understudied, in recent years there have been more direct studies of the effect of age on the pharmacokinetics of orally or parenterally administered chemotherapeutic agents. The declining ability of senescent cells to repair DNA damage may prolong toxicity. Increased destruction of and lower numbers of rapidly renewing mucosal stem cells increase susceptibility to mucositis. Also, reduced hematopoietic stem cell reserve may slow recovery of cytopenias after chemotherapy in older persons. Age is definitely an independent risk factor for neutropenia in older patients with lymphomas and leukemias. There is lack of prospective data for older patients, particularly for those patients older than 80, for which data are almost entirely lacking. The SIOG Task Force has published guidelines for dose modification of chemotherapy in older patients with renal insufficiency and has reviewed the use of certain classes of drugs: alkylators, antimetabolites, anthracyclines, taxanes, camptothecins, and epipodophyllotoxins in older cancer patients. When oral agents are used, despite delayed gastric emptying, absorption is adequate but one must pay attention to concomitant medications like H_2 blockers, antacids, and proton pump inhibitors. Caution must be exercised when administering cytotoxic drugs like methotrexate, bleomycin, cisplatin, and ifosfamide. Both decreases in the number of nephrons and a decline in the glomerular filtration rate may contribute to excess toxicity. Also, there is a decrease in lean body mass in the older adult, thus, adjusting the dose based on a creatinine clearance and not merely the creatinine is very important. In addition, concomitant administration of drugs like nonsteroidal anti-inflammatory drugs may compromise renal function. Although the reasons are unclear, acute toxicities like nausea and vomiting occur less frequently in older patients, however the lack of functional reserve can lead to catastrophic outcomes quickly, that is, dehydration, renal insufficiency. Neurotoxicity secondary to taxanes, platinum agents, vincristine, high-dose cytarabine, and bortezomib, cardiotoxicity from doxorubicin, mucositis from 5-fluorouracil are all more common and severe in older patients. Comorbidity has a negative effect on survival in patients with cancer and one study found that hospitalization for chemotherapy-induced toxicity in older patients increased significantly with their comorbidity score. Patients with stage II, and III colon cancer treated with adjuvant therapy had a higher rate of cancer recurrence and mortality and grade 3 or 4 diarrhea if they also had concurrent diabetes. As described previously, CGA is helpful when incorporated with other parameters to predict for the risk of toxicity in older patients.

Older women are more likely to have ER-positive tumors and approximately 70% to 80% of all breast tumors in older patients express ER. Thus, tamoxifen, and aromatase inhibitors like anastrozole and letrozole have been used widely in the neoadjuvant, adjuvant, and metastatic setting. These drugs each have their own side effects. The well-known higher risk of thromboembolic events and cerebrovascular accidents reported with tamoxifen should be taken into account when proposing this treatment to a patient already suffering from severe peripheral venous insufficiency, hypertension, and/or atrial fibrillation. On the other hand, because of the increased risk of osteoporosis and bone fractures, aromatase inhibitors are probably not the optimal choice in a patient with previously reported osteoporosis and a very low risk of cancer relapse. Androgen-deprivation therapy with luteinizing hormone–releasing hormone (LHRH) agonists and antiandrogens is used in older men with prostate cancer. Side effects of impotence, breast tenderness, hot flashes, osteoporosis, and memory decline are common with these agents.

There has been an increased use of targeted therapeutic agents in the past decade and a recent, very elegant review highlights approved drugs in different therapeutic classes, including tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, drugs targeted to the human epidermal growth factor receptor 2, BRAF-mutation targeted drugs,

antiepidermal growth factor receptor inhibitors, checkpoint inhibitors, and antivascular endothelial growth factor therapy. While, there have not been older patient-specific trials of these therapies, the data have been extrapolated from larger trials in which older patients generally were a fraction of the participants. Many of these agents are orally administered, and older patients with comorbidities often are on many other medications, which may be metabolized by the cytochrome P450 liver enzymes. Thus, the treating oncologist should keep an eye out for significant drug interactions when these new agents are taken concomitantly with P450 inhibitors or inducers. One study has demonstrated that comorbidities and polypharmacy impacted cytogenetic response rates in older patients with chronic myeloid leukemia being treated with imatinib. In addition, while these drugs have a favorable safety profile compared to parenteral chemotherapy, there is still a higher risk of toxicity, leading to a higher rate of dose reduction and discontinuation when compared to younger patients.

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) is a widely utilized treatment modality for high-risk hematologic malignancies. Historically, the associated morbidity and mortality limited the use of allogeneic SCT to individuals age less than 50. However, autologous SCT for lymphoma and myeloma has been performed in patients 65 to 70 years. There are no guidelines for HSCT in older adults so, patient selection, choice of conditioning regimen, immunosuppression, stem cell source is arbitrary and may be based on cardiopulmonary and hepatorenal function. Risk-assessment tools such as CGA, and comorbidity measures have recently been applied to facilitate decisions regarding HSCT eligibility and tolerance. Reduced-intensity conditioning (RIC) for allogeneic HCT, has led to improved tolerance and decreased mortality and removed traditional age barriers. RIC regimens may vary in the degree of immunosuppression and myeloablation and transplant-related mortality is typically lower than myeloablative approaches. Another important issue is donor selection for older recipients. Older patients tend to have older human leukocyte antigen (HLA)-matched siblings, raising issues about the upper age or health limitations for donor collection since older donor age slightly diminishes hematopoietic stem cell yields. Numerous other geriatric domains such as nutrition, caregiver support, and cognitive assessment have not been evaluated in the setting of HSCT. For example, delirium occurs in up to 50% of allogeneic HSCT recipients and likely more often among older adults and needs further study.

Palliative and Supportive Care

Palliative care focuses on providing patients with relief from the symptoms caused by the tumor itself or treatment of the tumor with a goal to improve quality of life for both the patient and the family. Underlying problems requiring symptomatic relief need to be actively sought by the physician because older patients more frequently underreport their symptoms. Many of the specific aspects of supportive care are covered in other chapters and are only mentioned here to stress their importance for the management of the older cancer patient. These include the extreme importance of effective pain management (see Chapter 56); maintenance of appropriate nutritional support (see Chapter 35); the supportive role of nursing (see Chapter 26); the importance of patient, physician, and family discussions concerning decisions regarding terminal care and other issues (see Chapters 30, 55, 60, and 61); and the utility of hospice care (see Chapter 59).

Nausea and vomiting One complication frequently seen in treatment of the older patient with cancer is nausea and vomiting. These side effects can seriously compromise the ability to deliver effective chemotherapy, but also cause significant morbidity that is, dehydration and renal insufficiency. All older patients on chemotherapy should be well hydrated and environmental factors, such as food and other odors that may trigger vomiting should be avoided. If oral feeding is attempted patients should use dry bland foods that are generally well tolerated and avoid high-protein diets. Antiemetic drugs may be required for highly emetogenic chemotherapy, such as cisplatin. Corticosteroids are a useful adjunct to most antiemetic regimens that includes benzamides (eg, metoclopramide), butyrophenones (eg, haloperidol), and benzodiazepines (eg, lorazepam) and serotonin ($5HT_3$) antagonists such as ondansetron, palonosetron, and dolasetron. One recent study evaluated the comparative efficacy and tolerability of palonosetron and ondansetron/dolasetron in a retrospective post hoc analysis using pooled data from 171 older patients (age ≥ 65) with cancer enrolled in two randomized, double-blind, phase III clinical studies comparing single intravenous doses of these antiemetic agents given prior to receipt of moderately emetogenic chemotherapy. The authors concluded that palonosetron was more effective in controlling chemotherapy-induced nausea and vomiting in older cancer patients. One of the most common causes of nausea and vomiting in cancer patients is opioid-induced constipation.

Chemotherapeutic drugs like vincristine, vinblastine, thalidomide can also cause severe obstipation, in turn leading to nausea. Making sure patients are on a good bowel regimen with stool softeners and laxatives is very important.

Pain Cancer-related pain is experienced by 50% to 90% of patients with advanced disease and in about 60% to 70% patients who are receiving active treatment for their tumors. The Hospitalized Elderly Longitudinal Project (HELP) showed that one out of three patients in this study died in severe pain. Older patients are at risk for undertreatment of pain because of underestimation of their sensitivity to pain, the expectation that they tolerate pain well, and misconception about their ability to benefit from the use of opioids. In one study of 13,625 institutionalized patients over the age of 65 24%, 29%, and 38% of those aged greater than 85, 75 to 84, and 65 to 74, respectively reported daily pain. Age, gender, race, marital status, physical functioning, depression, and cognitive status were all independently associated with the presence of pain. Twenty-six percent of patients with daily pain received no analgesic treatment and those older than 85 years in daily pain were more likely not to receive any analgesia. There are several reasons for undertreatment of pain in the older cancer patient: older patients are less likely to complain about pain, pain is not assessed properly, clinicians fear that older patients will not tolerate opioids, many nursing homes are unwilling to dispense opioids and do not have adequate staff to monitor the frequent use of analgesics. The American Geriatrics Society has established guidelines for the management of chronic, persistent pain in older adults and this may be applied to the older cancer patient.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are very effective in managing bone pain but have side effects of kidney damage and gastritis. Opioids offer relief in almost 75% patients with cancer pain and it is now accepted that opioids should be used as first-line therapy for moderate-to-severe cancer pain. General principles for use of opioids in older adults include selecting the least invasive route, use long-acting or sustained-release preparations around the clock for continuous pain, prescribe one drug at a time and begin with low doses, increasing slowly, use drugs with a short duration of action, when changing opioids, decrease equianalgesic dose by 50% because of incomplete crossover, to be aware of additive effects, reassess, reexamine, and readjust therapy frequently until pain is relieved, anticipate, prevent, and vigorously treat side effects, for example, start prophylactic laxative in older adults to prevent constipation and continue the drug for adequate duration.

Adjuvant analgesics include tricyclic antidepressants (amitriptyline), anticonvulsants (gabapentin), N-methyl-D-aspartate (NMDA) receptor antagonists (dextromethorphan, ketamine), corticosteroids (prednisone, dexamethasone), topical agents (capsaicin, local anesthetics), and agents for bone pain (bisphosphonates, strontium-80). Comprehensive geriatric care involving other geriatric team members has shown a positive and sustained effect on pain management, pain in the frail older cancer patient. Finally, nonpharmacologic measures like massage therapy, foot reflexology, music therapy, and meditation have all been evaluated. One study indicated that an educational intervention (patients watched a 14-minute video that presented information on “Managing Cancer Pain” aimed at older patients with cancer) was effective in prevention and management of cancer pain in older adults.

Fatigue This is one of the most common symptoms and significantly affects a patient’s quality of life. In one systematic review, the prevalence of fatigue was 40% to 90% during treatment and 19% to 80% after completion of treatment. The etiology of fatigue is multifold ranging from immobility and deconditioning, to anemia, depression, pain, poor nutrition, drugs, and metabolic causes. Treatment of fatigue is to usually treat the underlying cause, for example, treat anemia with hematinics, iron, B_{12}, folate, transfusions. Exercise programs also play a very positive role in the treatment of cancer-related fatigue. Drugs like methylphenidate, corticosteroids and modafinil have also been used to treat cancer-related fatigue but all of these treatment modalities have yet to be studied exclusively in older cancer patients.

Cytopenias The ASCO 2006 guidelines recommend preventive use of white blood cell growth factors for patient’s whose risk of febrile neutropenia is 20% or higher and among other indications includes older patients with diffuse aggressive lymphomas treated with curative intent, and older patients with AML over 55 years during induction and consolidation chemotherapy. Different types of white cell growth factors have been studied in older patients and while these factors somewhat reduce the incidence of infections during aggressive chemotherapy, they have had little impact on treatment outcomes and on survival.

Anxiety and depression Recent studies indicate that the prevalence of depression in cancer patients is between 17% and 25%. Patients at greatest risk are women with severe illness, poor performance and functional status, and advanced cancer. Among cancer patients, there is a strong relationship between pain and depression. Before making the diagnosis in older adults, it may be prudent to rule out common causes of depression with the help of thyroid-stimulating hormone (TSH), B , calcium, and liver function tests. Selective serotonin reuptake inhibitors like citalopram,

fluoxetine, paroxetine, and sertraline are first-line choice of drugs in older patients, especially if patients have ischemic heart disease or conduction heart defects, prostatic hypertrophy, or uncontrolled glaucoma. Venlafaxine, mirtazapine, and bupropion are considered second-line drugs to use. Nortriptyline or desipramine is used as third-line drugs and for severe melancholic depression and they can be difficult to tolerate because of side effects or, in the case of monoamine oxidase inhibitors, because of dietary and medication restrictions.

Anorexia and cancer cachexia An older cancer patient's nutritional status can be compromised in direct response to tumor-induced alterations in metabolism and cachexia is characterized by advanced protein-calorie malnutrition involuntary weight loss, muscle wasting, and decreased quality of life. Tumor-induced weight loss occurs frequently in patients with solid tumors of the lung, pancreas, and upper gastrointestinal tract and less often in patients with breast cancer or lower gastrointestinal cancer. Anorexia and cachexia are common among dying patients. For family members, accepting their loved one not eating is often difficult because it means accepting that the patient is dying. Conditions that may cause poor intake and that can be easily treated—gastritis, constipation, oral candidiasis, pain, and nausea—should be treated. Several agents have been tried in clinical trials (not specifically in older patient) to stimulate the patient's appetite. These include oral corticosteroids, progestational agents like megestrol acetate, cannabinoids like dronabinol, antidepressants like mirtazapine, olanzapine, omega-3-fatty acids, etc. It is important to educate family members in advance that if a patient is close to death, neither food nor hydration is necessary to maintain the patient's comfort. Intravenous fluids, total parenteral nutrition (TPN), and tube feedings do not prolong the life of dying patients, and in fact may even increase discomfort and hasten death. Adverse effects of artificial nutrition in dying patients can include pulmonary congestion, pneumonia, edema, and pain associated with inflammation. Conversely, dehydration and ketosis due to caloric restriction correlate with analgesic effects and absence of discomfort. The only reported discomfort due to dehydration near death is xerostomia, which can be prevented and relieved with oral swabs or ice chips.

Older cancer survivor In 2012, there were 13.7 million cancer survivors and 59% were greater than or equal to 65 years. This success in the cure of cancer has come with a cost. Cancer and its therapies are associated with second malignancies and late effects that can affect any organ system. Given that older survivors are more likely to have multiple chronic health problems than younger survivors, it is imperative to understand the influence of cancer, its treatments, and associated late effects on the aging process. Surgery, radiation therapy, and hormone therapy can affect almost every system, but chemotherapy has the most pervasive effect. Compared with the young individual in whom such changes may produce a "premature aging syndrome," in the older adult these changes are superimposed on the usual age-related changes. The 2006 Institute of Medicine (IOM) report has highlighted the fact that cancer survivors are a high-risk, growing population of individuals that require specialized health care throughout their lifespan. It is important that all cancer survivors and their primary care providers be provided with a survivorship care plan, which represents a road map for posttreatment care created by their oncology treatment team. Geriatric Survivorship Care Plans that provide guidance on the management of these geriatric issues (eg, comorbidities, functional change, geriatric syndromes) and long-term side effects like neuropathy, cardiomyopathy, and osteoporosis may prove to be helpful. In addition, it is important to modify lifestyle behaviors and continue surveillance for secondary malignancies in this population.

Older caregiver Finally, the all-important area of psychological support for older patients with cancer and their caregivers must be considered. This begins with effective physician-patient communication and acknowledgment of the patient's views and values at every stage of the disease. An assessment of the patient's coping skills and strategies will be very helpful. The patient's spiritual state and use of religious coping strategies are also important to assess and support. It is ironic that despite the increase in physical frailty and other decrements in function with age, older cancer patients appear to cope better with the psychological stress of the illness than do younger patients. This may be a result of the development of effective coping strategies from dealing with many other stressors over the years.

CONCLUSION

Cancer is the leading cause of death in men and women aged 60 to 79. The biology of certain tumors is different in older patients and tend to run a more aggressive course compared to their younger counterparts. In addition, older patients have a lower physiologic reserve with decreased tolerance to intensive chemotherapy or other modalities of cancer treatment. Chronological age is not a reliable estimate of life expectancy, functional reserve, or risk of

treatment-related complications. CGA is increasingly being utilized in clinical trials of several tumor types and aids in decision making, and prediction of chemotherapy toxicity and should be incorporated in the care of older cancer patients. Therapy must include treatment of the tumor itself and aggressive and early symptom management with an aim to prevent complications. In one study of critically ill patients greater than 60 years of age, a majority of patients said they would not choose treatment if the outcome was survival but with severe functional or cognitive impairment. The patient and their caregivers should continue discussions with the treating oncologist with respect to goals of care throughout the course of their disease. Continued federal support funding research in this unique patient population is imperative and necessary so we can systematically and logically develop diagnostic and treatment plans that yield effective and gratifying results.

FURTHER READING

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Chapter 97

Breast Disease

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Learning Objectives

- Describe the key principles with regard to breast cancer in the older patient, including epidemiology, screening, risk factors, presentation, and initial evaluation of disease.
- Understand the basic local and systemic therapy approaches in the management of breast cancer in the older patient.
- Understand the basic approaches with regard to treatment of the older patient with metastatic breast cancer.
- Describe the usual surveillance recommended for patients with breast cancer.
- Understand potential prevention strategies.
- Become aware of special (understudied) populations with breast cancer, including men, racial/ethnic minorities, and those with advanced comorbidity.

Key Clinical Points

1. **Breast cancer in the older patient is common and will become more common as our population ages.**
2. **Although many older patients die from causes other than breast cancer, it remains a deadly disease for many, especially those with higher-risk cancers.**
3. **Older patients typically benefit from treatments (such as hormonal therapy and chemotherapy) as much as younger patients do, but may experience more toxicity with chemotherapy.**
4. **When discussing treatment, screening, and surveillance strategies with older patients, it is important to be mindful of each patient's competing medical issues, risk for cancer recurrence and cancer-related death, and functional status.**
5. **Older patients with breast cancer are often understudied. How to best optimize care with regard to treatment, comorbidity, functional status, and outcomes remains a priority for future research.**

DEFINITION

The breast, or mammary gland, is a fibrofatty organ that produces all the necessary nutrients for a newborn. In women of childbearing age, the breast responds to cyclic hormone production and contains an abundance of epithelial structures and stroma that enable the production of milk. In postmenopausal women, declining ovarian function in late menopause leads to regression of these structures. The postmenopausal breast contains a ductal system, but the lobules shrink and collapse, leaving an organ that is composed primarily of fat. While a breast lump in a premenopausal woman is likely to be a benign problem related to cyclic hormonal changes, in a postmenopausal woman, a breast mass is a major concern and is likely to be breast cancer.

EPIDEMIOLOGY

Cancer is the leading cause of death in women aged 55 to 74 and is second to heart disease in women aged 75 and older. The incidence of cancer increases dramatically with age. In particular, breast cancer—the most common cancer in American women—is a major health concern. According to 2014 American Cancer Society estimates, breast cancer is the most common cancer in women, accounting for 29% (232,670 new cases) of all newly diagnosed malignancies and the second leading cause of cancer-related death (40,000 deaths—15%). Moreover, current US incidence and mortality data suggest that 12% of all women (one in eight) will be diagnosed with breast cancer during their lifetime and that 3.5% will die from it.

Approximately half of the cases of breast cancer occur in women older than age 65. In addition, National Vital Statistics indicate that the incidence increases dramatically with age (**Figure 97-1**) from an invasive breast cancer rate of 15 per 1000 in women aged 40 to 50 to a rate of 43 per 1000 in women aged 70 to 80. Older age has also been associated with a lower breast cancer-specific survival rate (**Figure 97-2**).

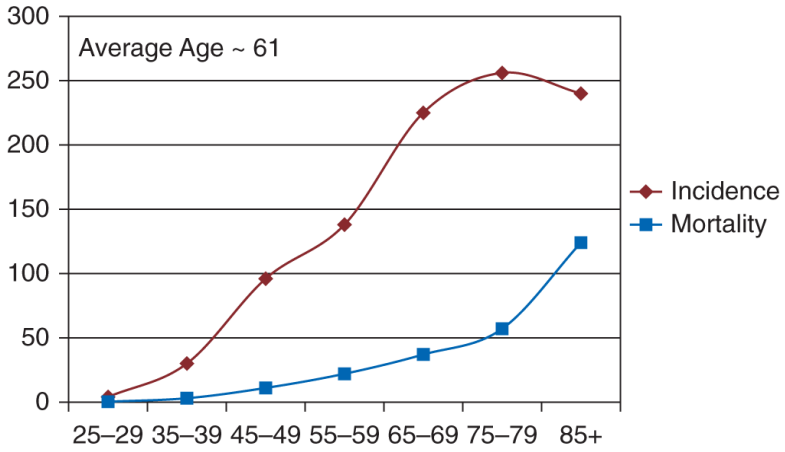


FIGURE 97-1. Breast cancer incidence and mortality rates by age. SEER data, 2007–2011. (From http://seer.cancer.gov/csr/1975_2011.)

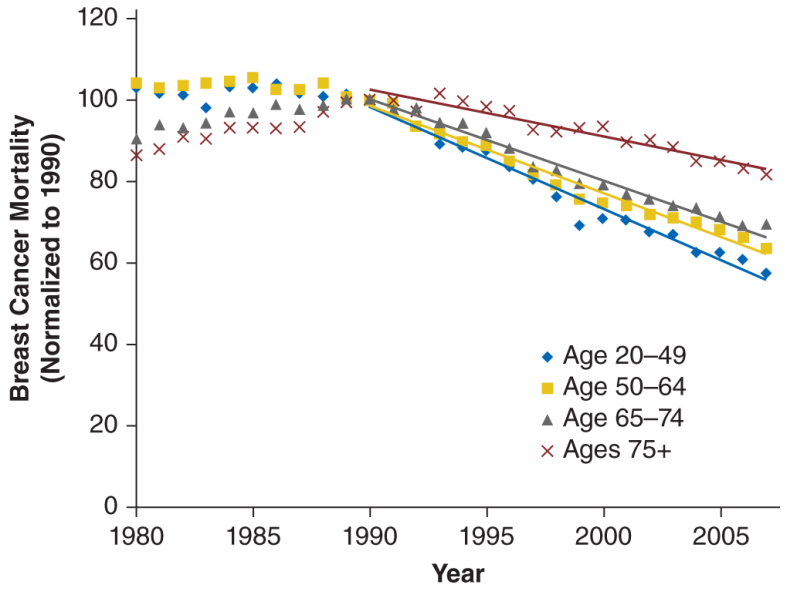


FIGURE 97-2. US breast cancer death rates by age and year (1980–2007 normalized to the group-specific death rate in 1990). (From Smith BD, Jiang J, McLaughlin SS, et al. Improvement in breast cancer outcomes over time: are older women missing out? *J Clin Oncol*. 2011;29:4647–4653. ©2011 by American Society of Clinical Oncology; printed with permission from the *Journal of Clinical Oncology*.)

Breast cancer is a major health concern in the United States and will become of greater importance since the size of the older population is growing dramatically. Although breast cancer is more common in older women, they are also less likely to be appropriately screened, more likely to present for care at a more advanced stage and to receive inferior surgical and postoperative management, and are less likely to be entered into clinical trials. This has resulted in older breast cancer patients sharing less in the dramatic decline in breast cancer mortality rates in the last two decades as compared with younger women.

PATHOPHYSIOLOGY

The specific cause of breast cancer is unknown. Many factors associated with increased risk have been identified. These include the following: increasing age, white race, family history of breast cancer (especially in a first-degree relative) or known genetic predisposition, early menarche, late age at birth of first child (older than 30 years), late menopause, dense breast tissue, history of benign breast disease (hyperplasia or atypical hyperplasia), heavy radiation exposure, obesity, postmenopausal estrogen replacement therapy, moderate-to-excessive alcohol use, and possibly cigarette smoking history. Most of these factors are associated with relative risks in the range of 1.4 to 2 times the risk in the general population. There is a breast cancer risk assessment tool, based on the Gail Model, which calculates the 5-year risk of breast cancer, using risk factors of age, age at first menses, age at first live birth, presence of first-degree relatives with breast cancer, number of past breast biopsies and whether or not atypical hyperplasia was found, and race/ethnicity. There is also geographic, economic, and racial variability in breast cancer incidence, with the highest incidence being found in affluent white populations. The reason for these differences is probably related to risk factor distribution, as well as genetic and environmental factors, but this is not fully understood.

A family history of breast cancer, implying a genetic defect, may be relevant in 5% to 20% of all cases of breast cancer. Genetic predisposition is particularly important in early-onset breast cancer (diagnosed before age 50), but is probably not a major factor in the geriatric population. *BRCA1* accounts for approximately 45% of familial breast cancers. Another gene, *BRCA2*, is responsible for approximately 35% of genetic abnormalities in high-risk families. Both *BRCA1* and *BRCA2* portend increased risks for breast cancer and ovarian cancer, ranging from 36% to 85% for breast cancer and 16% to 60% for ovarian cancer. Other, rarer mutations are also associated with breast cancer and have become better appreciated in recent years, including those present in the *ATM*, *TP53*, *PTEN*, *CHEK2*, and *PALB2* genes. In addition, there are many modifying factors, including genetic, hormonal, and environmental, that may determine whether a genetic mutation will lead to cancer.

Most breast cancers originate from ductal epithelium. Comparisons of older and younger patients with breast cancer reveal that infiltrating ductal carcinoma is the most common histologic type in both groups, accounting for 75% to 80% of cases, with lobular carcinoma accounting for approximately 5% to 10% and other subtypes accounting for the remaining cancers. Cancers in older patients are more likely to be well differentiated and moderately differentiated, be estrogen and progesterone receptor positive (60%–70% of patients), have lower rates of tumor proliferation (the number of cells synthesizing deoxyribonucleic acid [DNA]), and less frequently express the human epidermal growth factor receptor 2 (HER2) oncogene, when compared with cancers in younger patients. These data suggest that breast cancer in older patients is biologically less aggressive than it is in younger women. Mortality from breast cancer, however, is not lower in older women, leading us to explore issues associated with treatment choice and other patient- and tumor-related factors that might affect disease-specific survival.

PRESENTATION

Breast cancer usually presents either as a breast mass or a suspicious finding on a mammogram. The discovery of a breast mass in a postmenopausal woman requires prompt attention, as the majority of palpable masses in this age group are malignant and all breast masses require biopsy in this patient population. Mammography can help define the nature of a mass and detect other nonpalpable lesions if present and should be performed when a breast mass is found. A small percent of palpable breast cancers in older women may not show on mammogram (false negatives) but require biopsy. New mammographic findings also prompt evaluation.

Breast cancer screening in a postmenopausal woman includes mammography and a physical examination. After menopause, as estrogen levels diminish, breast glandular tissue and ductal tissue decrease and fat tissue increases. In addition, postmenopausal patients have fewer cysts and fibroadenomas. These age-related biological changes in breast tissue, especially the increased percentage of fat tissue, allow for improved contrast between small foci of malignancy and the surrounding breast tissue, resulting in fewer false-negative mammographic examinations. Several studies show that the routine use of screening mammography in women aged 50 through 70 improves survival by detecting breast carcinoma at an earlier stage and before metastatic dissemination and it is estimated that a 25% to 30% reduction in 5-year breast cancer mortality could be achieved in this age group if all women aged 50 to 70 were screened. Few clinical trials data are available to provide guidance for screening in women older than 70 years. Guidelines differ among experts; we suggest consideration of annual or biennial screening in older women with an estimated life

expectancy of at least 10 years. In addition, the pros and cons of screening including overdiagnosis should be carefully discussed. For women with life expectancies between 5 and 10 years, screening is not likely to be of value in improving breast cancer–related mortality and should be decided upon on an individualized basis. Medicare law currently provides for payment for screening mammography annually. Although the sensitivity and specificity of mammography is highest in older women, false-negative mammograms still occur. Physical examination by health professionals remains an essential and complementary adjunct to mammographic screening and is especially important in women who decline or are not likely to benefit by mammographic screening. **Table 97-1** presents our recommendations for the screening of older women.

TABLE 97-1 SCREENING GUIDELINES FOR BREAST CANCER IN WOMEN OLDER THAN 70 YEARS

	FREQUENCY	COMMENT
Breast self-examination	Monthly	Value uncertain, but many breast cancers are still detected by the patient
Physical examination	Yearly	By physician or other health professional; detects 15% of cancers *not* discovered on screening mammogram
Mammography	Every 1–2 y	Value in improving survival in women older than 75 y is unproven. We suggest screening in those with life expectancy of at least 10 y and discussion with patients about the pros and cons if life expectancy is 5–10 y

EVALUATION

Typically, a stepwise process of diagnosis and definitive surgery is followed, as depicted in **Figure 97-3**. This allows for pathologic confirmation of cancer and time to contemplate surgical treatment choice.

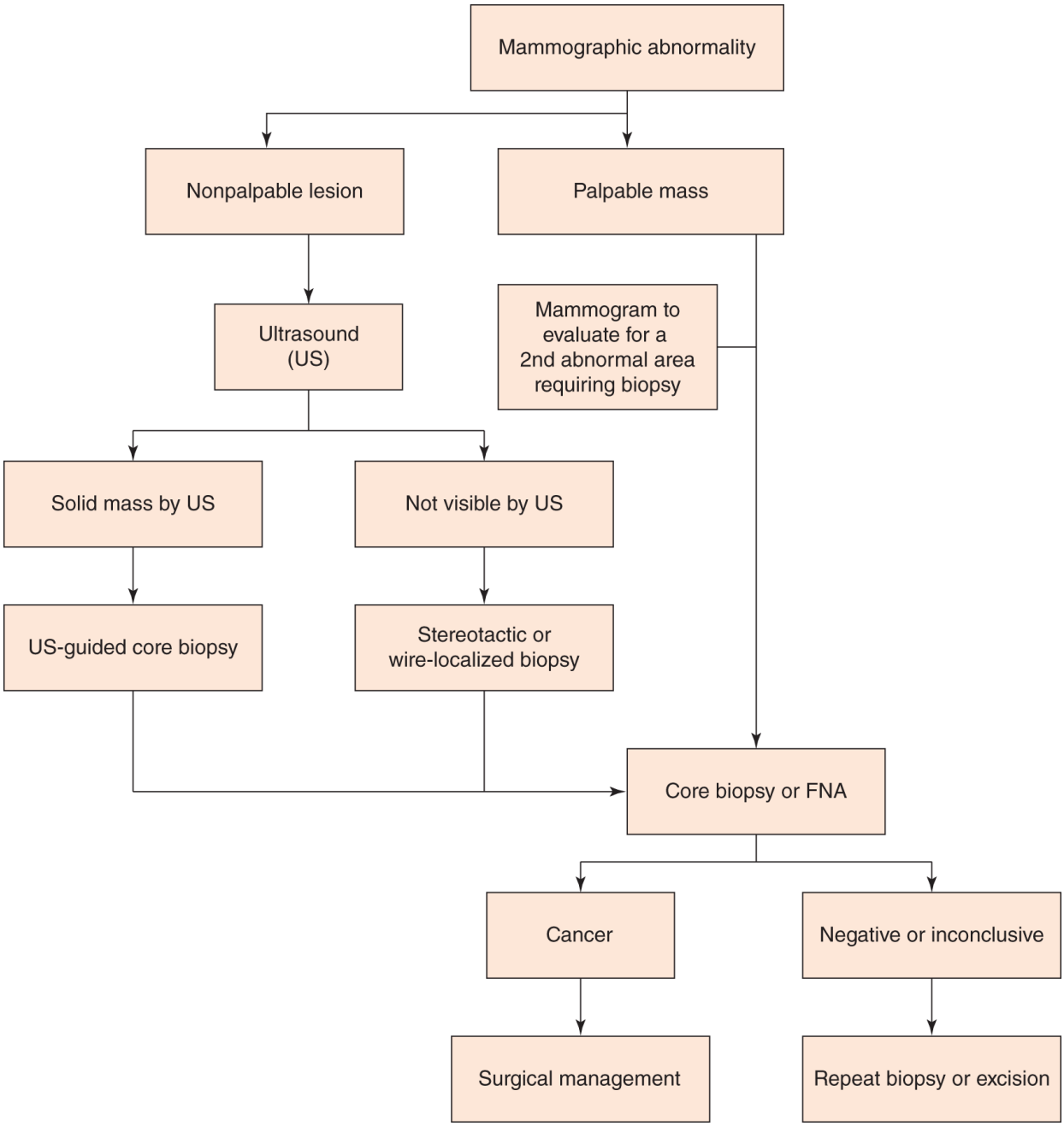


FIGURE 97-3. Stepwise evaluation of suspicious breast finding.

For palpable lesions, core needle biopsy is preferable to fine-needle aspiration biopsy, because core biopsy can distinguish invasive from in situ lesions in most patients and also allows better ascertainment of receptor status. Although concerns have been expressed that needle biopsy may be associated with tracking of malignant cells and a higher risk of local recurrence, such fears are unfounded. If the core biopsy or fine-needle aspiration is negative or inconclusive, unless the mass proves to be a cyst and resolves after aspiration, further biopsy, preferably excision, is necessary. For patients who have a mass that is characteristic of malignancy on physical examination or mammography, initial excision of the lesion or intraoperative biopsy to confirm invasive cancer and then lumpectomy or mastectomy, with or without sentinel lymph node biopsy or axillary dissection, may be preferable to a two-stage procedure involving a needle, core, or excisional biopsy.

For nonpalpable lesions that are found mammographically, ultrasound is recommended for further evaluation. If ultrasound finds a solid, suspicious lesion, ultrasound-guided biopsy can be done. If not visible by ultrasound, either stereotactic biopsy or needle-localized biopsy will be necessary. Stereotactic biopsy uses mammographic guidance to obtain a core biopsy specimen and is preferred because it allows pathologic diagnosis without anesthesia. The prone position required for the stereotactic procedure, however, may be difficult for some older patients. Needle-localized biopsy uses mammographic guidance to place a needle within the area of suspicion, after which the area is surgically

excised, a procedure that typically involves anesthesia. If atypical ductal hyperplasia is found on core biopsy, excisional biopsy is required, because a small proportion of suspicious lesions for which core biopsy finds only atypical hyperplasia will also contain in situ or invasive cancer when excised.

When biopsy is diagnostic of malignancy or definitive surgery is scheduled, preoperative evaluation typically includes a complete history and physical examination, a complete blood count and chemistry profile, and a chest x-ray. Magnetic resonance imaging (MRI) of the breasts may also be helpful in the management of older women in specific settings, but is not recommended for routine screening or diagnostic purposes. However, bilateral mammography should be performed on all patients during their diagnostic work-up to evaluate both the ipsilateral breast and the contralateral breast for other nonpalpable lesions.

MANAGEMENT

Staging

The American Joint Committee for Cancer (AJCC) guidelines set the standard for breast cancer staging. This system categorizes the extent of malignancy according to the size of the primary lesion (T), the extent of nodal involvement (N), and the occurrence of metastasis (M). **Table 97-2** presents the most recent AJCC breast cancer staging criteria (seventh edition). Tumor size (the largest diameter of the infiltrating component) and the extent of nodal involvement (the number positive) are determined from pathologic examination and are included in the pathology report and ascertainment of staging. Nodal assessment is done either by sentinel lymph node biopsy or by axillary dissection. Sentinel lymph node mapping and sampling is preferred as it allows identification and assessment of the one to four nodes most likely to contain cancer. If an axillary lymph node dissection is completed, a sample of at least six nodes (if possible) is ideal in order to reflect the prognosis accurately. Recent and ongoing large-scale clinical trials are underway to evaluate the optimal treatment of the axilla while minimizing toxicity and treatment-related complications such as lymphedema. Issues related to the management of the axilla are discussed in more detail below.

TABLE 97-2 AJCC STAGING CRITERIA FOR BREAST CANCER (7TH EDITION, 2010)[a]

SYMBOL TNM SYSTEM	MEANING
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Ductal carcinoma in situ, lobular carcinoma in situ, or Paget disease of the nipple with no tumor
T1	Tumor ≤ 2 cm in greatest dimension
	T1mi ≤ 1 mm in greatest dimension
	T1a ≤ 0.5 cm in greatest dimension
	T1b > 0.5 cm but not > 1 cm in greatest dimension
	T1c > 1 cm but not > 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size with direct extension to chest wall or skin (includes inflammatory carcinoma)
Pathologic regional lymph nodes (N)	
pNX	Regional lymph nodes cannot be assessed (eg, previously removed)
pN0	No regional lymph node metastasis; note: isolated tumor cells (ITCs) are defined as small clusters not > 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification. • pN0 (i –): No histologic nodal metastasis, and negative by immunohistochemistry (IHC) • pN0 (i +): No histologic nodal metastasis but positive by IHC, with no cluster greater than 0.2 mm in diameter

	• pN0 (mol –): No histologic nodal metastasis and negative molecular findings (by reverse transcriptase polymerase chain reaction, RT-PCR) • pN0 (mol +): No histologic nodal metastasis but positive molecular findings (by RT-PCR)
pN1	Metastasis in 1–3 ipsilateral axillary lymph node(s) and/or in internal mammary nodes with microscopic disease detected by SLND but not clinically apparent • pN1mi: Micrometastasis (> 0.2 mm, none greater than 2.0 mm) • pN1a: Metastasis in 1–3 axillary lymph nodes, at least one metastasis > 2.0 mm • pN1b: Metastasis to internal mammary lymph nodes with microscopic disease detected by SLND but not clinically apparent • pN1c: Metastasis in 1–3 ipsilateral axillary lymph node(s) and in internal mammary nodes with microscopic disease detected by SLND but not clinically apparent
pN2	Metastasis in 4–9 axillary lymph nodes or in clinically apparent internal mammary lymph nodes in the absence of axillary lymph nodes • pN2a: Metastasis in 4–9 axillary lymph nodes (at least one tumor deposit > 2 mm) • pN2b: Metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph nodes
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular (level III) lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph node(s) • pN3a: Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit > 2.0 mm), or metastasis to the infraclavicular lymph nodes • pN3b: Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary nodes; or in more than three axillary lymph nodes with microscopic metastasis in internal mammary lymph nodes detected by SLND but not clinically apparent • pN3c: Metastasis in ipsilateral supraclavicular lymph node(s)
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No evidence of distant metastasis
cM0 (I+)	No clinical or radiographic evidence of metastasis but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant metastasis as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm
Anatomic stage	
0	Tis N0 M0
1A	T1 N0 M0
1B	T0 N1mi M0
	T1 N1mi M0
IIA	T0 N1 M0
	T1 N1 M0
	T2 N0 M0
IIB	T2 N1 M0
	T3 N0 M0
IIIA	T0 N2 M0
	T1 N2 M0

	T2 N2 M0
	T3 N1 M0
	T3 N2 M0
IIIB	T4 N0 M0
	T4 N1 M0
	T4 N2 M0
IIIC	Any T N3 M0
IV	Any T, any N, M1

SLND, sentinel lymph node dissection.

[a] *Adapted from Edge SB, Byrd DR, Compton CC, et al, eds. The American Joint Committee on Staging (AJCC) Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010:347–376.*

Other key prognostic information from the pathology report includes the following: histologic type and tumor grade, assessment of vascular or lymphatic invasion and skin involvement, and percentages of ductal carcinoma in situ and invasive carcinoma in the primary lesion. Paraffin-embedded tumor is then analyzed for other prognostic markers. Immunohistochemical analysis of the invasive cancer cells is also done to determine estrogen receptor (ER), progesterone receptor (PR), and HER2 status. An intermediate result for HER2 by immunohistochemistry necessitates analysis by fluorescent in situ hybridization (FISH). Other markers, such as epidermal growth factor receptor and proliferative indices, are not of consistent benefit and are not recommended on a routine basis.

After definitive surgical management, asymptomatic patients with Stage 0 to II breast cancer, who have had an unremarkable preoperative evaluation, including history and physical examination, require no further staging procedures. Patients with Stage III breast cancer or those with signs or symptoms worrisome for metastatic disease should have imaging with computerized tomography of chest, abdomen, and pelvis and a radionuclide bone scan or a positron emission tomography–computed tomography (PET-CT) scan to rule out metastases. The use of tumor markers (such as the carcinoembryonic antigen [CEA] and mucin antigens CA27.29 and CA15.3) and circulating tumor cells is not recommended as part of the staging evaluation or in disease surveillance.

Carcinoma In Situ

The more widespread use of screening mammography has led to a major increase in the diagnosis of ductal carcinoma in situ (DCIS). Before the common use of screening mammograms, DCIS was uncommon, usually detected on physical examination, was large in size and the cure rate exceeded 95% with mastectomy. In a screened population, most DCIS lesions are nonpalpable and small and are suggested by microcalcifications found on screening mammography. Mastectomy cures almost all patients, but breast-conserving procedures followed by breast irradiation are as effective for patients with smaller lesions.

Axillary dissection or sentinel node biopsy finds metastases in less than 1% of patients and is generally not recommended. Excision alone, without local radiation therapy, may be appropriate for patients with lesions less than 2.5 cm with generous (> 1 cm) margins of normal tissue surrounding the in situ component. Most DCIS lesions are estrogen and progesterone receptor positive and clinical trials on tamoxifen have been shown to decrease the risk of recurrence and contralateral breast cancer in women with DCIS but without improvements in survival. For older women with DCIS the risks of tamoxifen are likely to exceed the benefits in many women and we recommend consideration of tamoxifen use on an individual basis.

Lobular carcinoma in situ (LCIS) is more common in premenopausal patients, lacks clinical and mammographic signs, is bilateral in 25% to 35% of cases, and is usually an incidental finding at breast biopsy. It is not a palpable lesion. Treatment options range from observation to bilateral mastectomy but observation is preferred. Of note, 20% to 40% of patients with LCIS subsequently develop infiltrating ductal cancer, with both the ipsilateral breast and the contralateral breast at similar risk. LCIS serves as a high-risk marker for subsequent invasive cancer, and treatment selection must rest on the desires of the patient. Most experts recommend close follow-up of these patients, without aggressive surgery. Tamoxifen dramatically decreases the risk of subsequent invasive breast cancer in patients with LCIS and should be considered on an individual basis.

Management of Early Localized Lesions (Stages I, II, and III)

Once a diagnosis of breast cancer is made, a woman is counseled about surgical choices, radiation therapy, and

systemic therapy. With regard to local therapy, breast-conserving procedures result in virtually identical relapse-free and overall survival compared with more extensive surgical treatment, including simple, modified-radical, and radical mastectomy. Reasonably healthy older women tolerate simple or modified mastectomies as well as younger women do, but should be offered the option of breast-conserving surgical procedures when clinically appropriate.

Management of the breast The breast-conserving approach to breast cancer management involves removing the tumor mass with a clear margin of surrounding normal breast tissue (lumpectomy, partial mastectomy, quadrantectomy, etc), assessing axillary lymph nodes when indicated, and for many, delivering local breast irradiation after surgery. Ipsilateral axillary node assessment is recommended by most medical, surgical, and radiation oncologists if it will provide important prognostic data that could change management. Breast-conserving procedures require close cooperation among the radiologist, surgeon, pathologist, and radiation oncologist in order to locate and remove the are a of concern, assure negative margins, and provide the best cosmetic result with the lowest risk of local recurrence. Breast irradiation after removal of tumor mass reduces the likelihood of recurrence in the affected breast from 30% to 40% to less than 10% and may improve survival in women with higher-risk breast cancers. Although radiation after breast conservation is standard therapy in younger women, older women with smaller, hormone receptor–positive breast cancers (≤ 2 cm in largest dimension) may be spared breast irradiation if they are willing to take adjuvant endocrine therapy. In such patients, survival is identical although there is a somewhat higher risk of breast recurrence over a 10-year period (about 10% without radiation and 2%–3% with radiation). Most breast relapses occur in or in close proximity to the previously resected lesion. Other techniques, such as brachytherapy (localized radiation therapy [RT]) may prove to be as effective as whole-breast RT and can be completed over a period of days to weeks. For healthy older patients at high risk for in-breast recurrence (tumors 2 cm or greater or positive lymph nodes) and reasonable life expectancy, breast radiation is recommended.

Contraindications to breast-conserving surgery include two or more gross tumors in separate quadrants of the breast, diffuse indeterminate or malignant-appearing microcalcifications, and a history of therapeutic irradiation of the breast region. Relative contraindications to breast-conserving surgery include the following: large tumor/breast size ratio (mass > 5 cm in size), which interferes with cosmesis; large breast size, which makes radiation delivery difficult and interferes with cosmesis; and a history of collagen vascular disease, which has been reported anecdotally to increase the likelihood of fibrosis associated with radiation. It is important, however, not to underestimate the value to a patient of preserving her own breast, with sensation intact, even if the cosmetic appearance is not perfect. It is now well established that preoperative (“neoadjuvant”) chemotherapy or endocrine therapy (for women with ER- or PR-positive breast cancer) can shrink large breast cancers, allowing breast conservation for many patients without sacrificing distant recurrence or survival outcomes.

Breast conservation may be more costly than mastectomy because of the time, inconvenience, and monetary expense of postoperative RT. Nevertheless, such treatment is preferred by many women, irrespective of age. The option for breast-conserving surgery also provides motivation for detecting early-stage lesions through screening. Patients who have had breast-conserving procedures also have higher self-appraisals of body image and sexuality than do women who have had more extensive surgical intervention.

Breast reconstruction For older women who have had a mastectomy, breast reconstruction represents another option for restoring body image. Many physicians, because of personal bias, are unlikely to discuss reconstruction with older patients. This procedure can be done safely in an older patient and should be discussed, with subsequent surgical consultation if desired.

Radiation after mastectomy The likelihood of local recurrence is directly proportional to both the size of the primary lesion and the number of involved axillary nodes. Postoperative adjuvant irradiation is generally recommended for patients with primary lesions greater than 5 cm or with four or more positive nodes. It is also considered reasonable for any woman with breast cancer that involves lymph nodes to receive postmastectomy “adjuvant” irradiation therapy to the chest wall and the contiguous regional lymph nodes (internal mammary, supraclavicular, and upper axilla), because it reduces the likelihood of local recurrence (recurrence in the mastectomy site or contiguous nodal areas) by 70% and improves overall breast cancer–specific survival rates by several percent. When necessary, delaying postoperative irradiation for 4 to 6 months to allow the completion of adjuvant chemotherapy is feasible and does not increase the risk of subsequent local recurrence.

Axillary assessment Tumor size and axillary nodal status are the most consistent predictors of the risk of recurrence and key in making decisions about the risk/benefit ratio of adjuvant systemic treatment. Node involvement is found in 5% to 37% of women with very small tumors (< 1 cm), and physical examination is only of modest benefit in

predicting nodal involvement, with false-negative and false-positive rates of 35% and 25%, respectively. Because arm problems, such as swelling (lymphedema), pain, numbness, weakness, and impaired shoulder mobility, may complicate axillary dissection, the argument has been made that its prognostic benefit is not worth the risk of side effects in women with primary tumors less than 1 cm in size. Sentinel lymph node mapping and sampling, with its lower risk of arm morbidity, is the procedure of choice, if axillary assessment is deemed necessary.

In older women, the role of assessing axillary nodes is quite controversial because of the risk of arm morbidity. If adjuvant chemotherapy is not a consideration because of physician or patient choice, the risk of axillary dissection is not worth its prognostic yield, regardless of the primary tumor size. It is generally acceptable to omit axillary assessment in older women with small (2 cm or less), clinically node-negative, ER-positive breast cancer, who will take adjuvant hormonal therapy for at least 5 years.

Lymphatic mapping with sentinel node biopsy is associated with minimal arm morbidity (< 5%) and is the standard method to assess axillary lymph nodes in women who have breast cancer and in whom there are no clinically evident ipsilateral axillary nodes. This procedure allows identification and sampling of the first nodes in the lymphatic basin to receive lymphatic flow which in about 95% of patients is the initial site of metastatic nodal involvement—irrespective of the location in the breast of the primary tumor. When one or two sentinel lymph node(s) are positive further axillary dissection can be omitted without any detrimental effects on local recurrence or survival. For patients with three or more sentinel nodes involved axillary dissection is indicated. Standard axillary dissection should be performed in any woman with breast cancer who has clinically palpable axillary lymph nodes.

Endocrine therapy as initial treatment For many older patients, especially those with advanced but localized lesions (T3 and T4) and those with significant comorbidity or frailty, initial treatment with hormonal therapy is appropriate in those with hormone receptor–positive tumors. Tumor shrinkage occurs in 40% to 70% of patients and control usually is maintained for 18 to 24 months. The majority of patients treated initially with hormonal therapy do not achieve complete tumor regression and will need surgery or other treatments to control the primary lesion if their life expectancy is longer than several years. Although surgery is more likely to be effective (and potentially curative) in patients with small lesions, several randomized trials comparing surgery with hormonal treatment for initial therapy suggest that long-term survival is not changed by using hormonal therapy as the initial treatment and reserving surgical management for patients with tumor progression. Radiation therapy also can be used as “salvage” treatment after hormonal therapy fails, but large tumor masses, especially those greater than 3 cm and those with extensive skin involvement, frequently respond only partially. For patients treated with hormonal therapy because comorbidity precludes surgical therapy, radiation therapy should be considered when tumor shrinkage is maximal to try to prolong the duration of local tumor control. In the authors’ opinion, older women with localized breast cancer amenable to surgery should be offered surgical treatment at diagnosis unless they are extremely frail or have dramatically reduced life expectancy.

Adjuvant Systemic Therapy

Adjuvant systemic therapy involves preoperative, perioperative, or postoperative administration of endocrine therapy and/or chemotherapy to patients with localized breast cancer for the purpose of reducing risk of and delaying relapse and improving survival. Such treatment is aimed at eradicating occult, clinically undetectable metastasis.

Figure 97-4 shows the cause of death for women with breast cancer by stage of disease and **Figure 97-5** shows the overall survival of older women by breast cancer stage. As demonstrated in these figures, women, and in particular older women, mostly die of non–breast cancer causes in the setting of early-stage disease. Adjuvant therapy is chosen on the basis of the risk:benefit ratio. The anticipated risk reduction for metastatic disease is weighed against the risk of toxicity from adjuvant therapy. Estimated improvements in relapse-free and overall survival for adjuvant systemic therapy are provided by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) (**Table 97-3**). This group provides collaborative meta-analyses of 194 randomized trials studying adjuvant chemotherapy and hormonal therapy every 5 years and was last updated in 2005, with the ability to show 15-year effects. These data clearly confirm the benefits of adjuvant endocrine therapy and chemotherapy in significantly reducing the risk of recurrence and death in women with early breast cancer, with the majority of the data applying to women younger than 70 years. **Table 97-4** summarizes the overview of results of adjuvant therapy for postmenopausal patients by age and depicts the benefits of adjuvant therapies by age group.

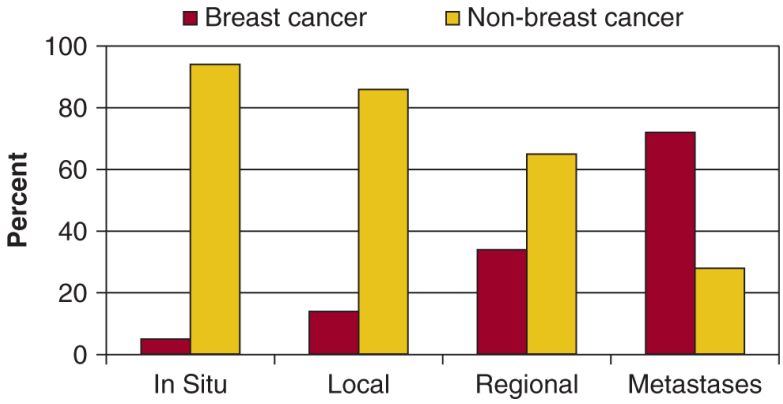


FIGURE 97-4. Cause of death after approximately 28-year follow-up for white women age greater than or equal to 70 with breast cancer. SEER data, *n* = 395,000; during 1973–2000. (Adapted from Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of death from breast cancer and other causes among female breast cancer patients. *J Natl Cancer Inst*. 2004;96(17):1311–1321; data used with permission from the Journal of the National Cancer Institute.)

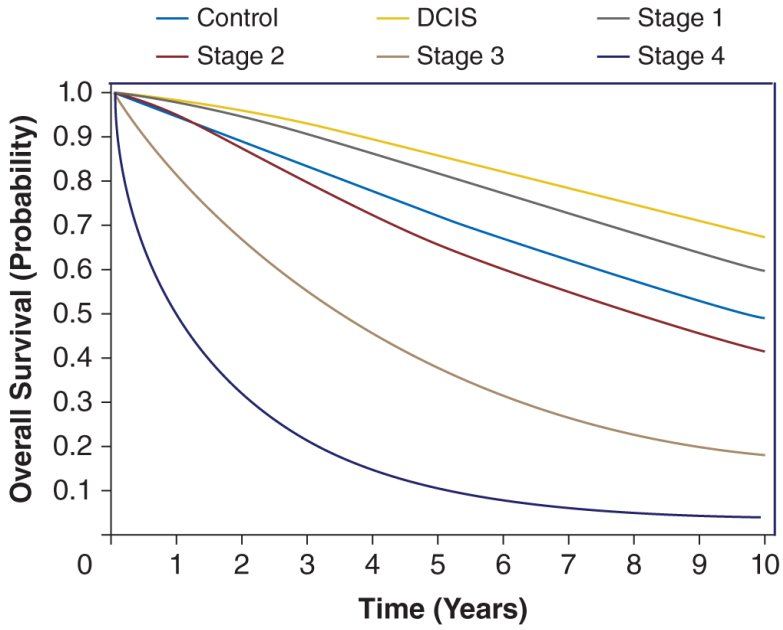


FIGURE 97-5. Overall survival of women age 67 and older by breast cancer stage and of their controls. (Schonberg MA, Marcantonio ER, Ngo L, Li D, Silliman RA, McCarthy EP. Causes of death and relative survival of older women after a breast cancer diagnosis. *J Clin Oncol*. 2011;29:1570–1577. ©2011 by American Society of Clinical Oncology; printed with permission from the *Journal of Clinical Oncology*.)

TABLE 97-3 RISK REDUCTION FOR ADJUVANT SYSTEMIC THERAPY IN WOMEN AGED 50–69

	ANNUAL EVENT RATIO[a] % (SE)	
	RECURRENCE	BREAST CANCER– SPECIFIC DEATH
Chemotherapy type (vs nil)		
CMF-based	0.81 (0.03)	0.90 (0.03)
Anthracycline-based	0.79 (0.04)	0.83 (0.05)
Other polychemotherapy	0.89 (0.06)	0.93 (0.07)
Presence or absence of tamoxifen		
Chemo + tam vs tam alone	0.84 (0.03)	0.90 (0.03)
Chemo then tam vs tam alone	0.77 (0.08)	0.80 (0.10)

Chemo alone vs nil	0.78 (0.04)	0.87 (0.04)
ER Status and Tam		
Polychemotherapy alone vs nil		
ER-poor	0.67 (0.07)	0.74 (0.08)
ER-positive	0.84 (0.07)	0.95 (0.08)
Unknown	0.81 (0.06)	0.88 (0.06)
Polychemotherapy + tamoxifen vs tamoxifen only		
ER-poor	0.75 (0.06)	0.86 (0.07)
ER-positive	0.85 (0.04)	0.89 (0.04)
Unknown	0.86 (0.07)	0.88 (0.08)
Nodal status		
Node-negative	0.77 (0.05)	0.77 (0.06)
Node-positive	0.83 (0.03)	0.90 (0.03)
Period of follow-up		
0–1 y	0.64 (0.03)	0.82 (0.06)
2–4 y	0.92 (0.04)	0.87 (0.04)
5–9 y	0.99 (0.05)	0.91 (0.05)
≥ 10 y	0.84 (0.10)	0.90 (0.08)

CMF, cyclophosphamide, methotrexate, and fluorouracil; ER, estrogen receptor; tam, tamoxifen.
[a]Annual event ratio for treatment versus control.
Adapted from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).

TABLE 97-4 ■ RISK REDUCTION IN RECURRENCE AND MORTALITY FOR ADJUVANT SYSTEMIC THERAPY BY AGE GROUP (YEARS)

	ANNUAL EVENT RATIO[a] % (SE)	
	RECURRENCE	BREAST CANCER–SPECIFIC DEATH
Single agent		
Age < 40	0.72 (0.15)	0.86 (0.16)
Age 40–49	0.82 (0.09)	0.91 (0.09)
Age 50–59	0.87 (0.08)	0.94 (0.08)
Age 60–69	0.94 (0.09)	1.06 (0.10)
Age ≥ 70	0.75 (0.20)	NS
Polychemotherapy		
Age < 40	0.60 (0.06)	0.71 (0.07)
Age 40–49	0.64 (0.04)	0.70 (0.05)
Age 50–59	0.77 (0.03)	0.85 (0.04)
Age 60–69	0.87 (0.03)	0.91 (0.04)
Age ≥ 70	0.88 (0.11)	0.87 (0.12)
Anthracycline-based regimen vs CMF		
Age < 50	0.90 (0.04)	0.90 (0.03)
Age 50–69	0.87 (0.05)	0.83 (0.05)
Age ≥ 70	NS	NS
Approximately 5 y of tamoxifen vs not in ER-positive (or unknown)		

Age < 40	0.56 (0.10)	0.61 (0.12)
Age 40–49	0.71 (0.07)	0.76 (0.09)
Age 50–59	0.66 (0.05)	0.76 (0.07)
Age 60–69	0.55 (0.05)	0.65 (0.06)
Age ≥ 70	0.49 (0.12)	0.63 (0.15)

CMF, cyclophosphamide, methotrexate, and fluorouracil; NS, not specified and not significant.

[a]Annual event ratio for treatment versus control.

Adapted from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-1717.

In postmenopausal women, the majority of trials using adjuvant endocrine therapy compared tamoxifen with either no treatment or with chemotherapy and tamoxifen. In women older than 70 years, there was a significant decrease in the annual recurrence rate (51%) and deaths (37%) among those treated with approximately 5 years of tamoxifen versus not. Patients with positive ER or PR derived greatest benefit from tamoxifen. In addition, tamoxifen significantly decreased the annual odds of developing contralateral breast cancer by approximately 40%. Several studies have confirmed that tamoxifen decreases cardiovascular morbidity, lowers cholesterol and low-density lipoprotein levels, and increases or preserves vertebral bone density in postmenopausal women, but there is a small increased risk of thrombotic events and of endometrial cancer. Based on this information, adjuvant hormonal therapy for 5 years is recommended for most women with estrogen and/or progesterone receptor node-negative and node-positive early breast cancer. More recent data suggest that extension of therapy to 10 years may be important for some women, although extension of therapy may not be appropriate for all patients, particularly those with significant comorbidity, lower risk tumors, or poor tolerance to endocrine therapy.

Newer data, included in a subsequent EBCTCG meta-analysis of adjuvant aromatase inhibitors versus tamoxifen in 2010, show that treatment with aromatase inhibitors (anastrozole, letrozole, and exemestane), agents that inhibit the enzyme involved in estrogen production, result in an approximate 3% lower recurrence rate and a possible, slight decrease in breast cancer mortality compared with tamoxifen, irrespective of postmenopausal age. However, additional follow-up is required to provide a clearer distinction in outcomes for women treated with endocrine therapies. Use of the aromatase inhibitors (AIs) is not associated with increased blood clot risk or endometrial cancer. However, side effects of AIs include menopausal symptoms, musculoskeletal aches and pains, and accelerated osteoporosis. In women who have osteopenia or osteoporosis, bone density is monitored carefully during treatment with AIs. In general, there are three options for use of AIs in the adjuvant setting: (1) 2 to 3 years of tamoxifen followed by 2 to 3 years of an AI to complete a 5-year course of adjuvant hormonal therapy, (2) 5 years of an AI, or (3) 5 years of tamoxifen followed by an AI for 2 to 5 years. The optimal duration of adjuvant hormonal therapy with AIs is still not defined and may be longer than 5 years for some patients. The forthcoming results from MA17R (NCT00754845), large randomized trial which assigned women to receive letrozole or placebo after completing 5 years of adjuvant letrozole therapy, will answer this question in the coming years. As of now, the only large-scale prospective trials for extension of therapy reported include those for women treated with tamoxifen monotherapy or those with sequential tamoxifen and aromatase inhibitor therapy.

The overview found a significant decrease in the annual odds of recurrence and death for both node-negative and node-positive tumors in women aged 50 to 70 who were treated with combination chemotherapy (polychemotherapy); unfortunately, not enough data were available to see a statistically significant benefit of chemotherapy in patients older than 70 years. In postmenopausal women in general, however, the combination of tamoxifen and chemotherapy was superior to tamoxifen alone in prolonging relapse-free and overall survival. Chemotherapy programs using anthracycline-containing combinations were superior to nonanthracycline regimens in improving both relapse-free and overall survival. Current controversies revolve around the optimal duration and intensity of adjuvant chemotherapy and the choice of adjuvant therapy based on the breast cancer cell type.

With regard to the optimal duration of adjuvant chemotherapy, short treatment courses of 3 to 6 months appear to be as effective as treatment of longer duration in multiple, prospective evaluations. With regard to the optimal dose intensity of adjuvant chemotherapy (the dose administered during a specific time period), more intense regimens are more effective, even in older patients. Adjuvant chemotherapy regimens that have shown a survival benefit for women aged 50 to 70 are also well tolerated in healthy women older than 70 years. More intense regimens, such as eight versus four cycles and delivered every 2 versus every 3 weeks, are more effective in women with high risk of recurrence. Current standard polychemotherapy regimens for HER2-negative tumors include the following:

doxorubicin (Adriamycin) and cyclophosphamide (AC); AC plus a taxane (paclitaxel and docetaxel) (AC-T); docetaxel and cyclophosphamide (TC); cyclophosphamide, methotrexate, and 5-fluorouracil (CMF); cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF); cyclophosphamide, epirubicin, and 5-fluorouracil (CEF); cyclophosphamide, epirubicin, and 5-fluorouracil followed by docetaxel (CEF-T); and docetaxel, doxorubicin, and 5-fluorouracil (TAC). Unlike tamoxifen, however, chemotherapy had little effect on the risk of developing contralateral breast cancer in the overview analysis.

With regard to tumor type, molecular strategies have defined three categories of breast cancer—hormone receptor positive, HER2 positive, and hormone receptor/HER2 negative (triple negative)—and ongoing research will continue to further classify these traditional, clinical subtypes and define sensitivity to adjuvant treatments. Benefit of adjuvant therapy for women who have hormone receptor–positive breast cancer is derived primarily from hormonal agents, and the additional benefit of chemotherapy is questionable in some cases. Techniques to define risk—based on the molecular profile of these tumors, especially those that are node negative—are increasingly used in practice to help decide which patients are at high enough risk to justify the addition of chemotherapy to hormonal adjuvant therapy.

The addition of trastuzumab (Herceptin), a humanized monoclonal antibody targeted against the *HER2* gene product, to adjuvant chemotherapy for HER2-positive tumors further decreases the risk of recurrence and death by approximately 40%, according to randomized trials with over 8 years of follow-up. Serial cardiac monitoring, with echocardiogram or multigated acquisition (MUGA) scan to evaluate cardiac ejection fraction, is recommended during treatment, as trastuzumab may cause reversible decline in cardiac function. Up to one-fifth of the women will not complete the entire year of therapy owing to asymptomatic decline in ejection fraction (15%), development of congestive heart failure or other cardiac event (5%). For patients with hormone receptor– and HER2-negative tumors, more intense chemotherapy regimens are generally utilized. In recent years, we have seen approvals for new, anti-HER2 agents such as pertuzumab (Perjeta) and ado-trastuzumab emtansine (T-DM1, Kadcyla) in the metastatic setting with pertuzumab also granted accelerated Food and Drug Administration (FDA) approval when administered along with taxane-based, preoperative chemotherapy and trastuzumab. Ongoing trials will further characterize the potential role of these novel agents in the neo/adjuvant setting.

As a result of the paucity of data, the role of adjuvant chemotherapy in the management of older patients remains unclear to most oncologists. More carefully designed trials of chemotherapy for older women are needed and should include drug combinations that provide dose intensity similar to that of other currently effective therapies. One such trial, comparing standard chemotherapy (AC or CMF by provider/patient choice) with an oral chemotherapeutic agent (capecitabine) (Cancer and Leukemia Group B trial 49907; www.calgb.org), showed a significant benefit for standard chemotherapy in improving both relapse-free and overall survival. Another upcoming trial will administer ado-trastuzumab emtansine to patients aged 65 and older with higher-risk, HER2-positive disease who are considered "unfit" for standard trastuzumab-based chemotherapy. This trial will carefully examine toxicity and outcomes for patients on study with the hypothesis that ado-trastuzumab emtansine will be more tolerable and equally efficacious as traditional trastuzumab chemotherapy–based adjuvant regimens. More prospective clinical trials are urgently needed which are either dedicated to older patients with breast cancer or which are largely inclusive of older patients.

With regard to follow-up after completion of active therapy for breast cancer, surveillance with routine blood work and body imaging is not recommended. **Table 97-5** presents updated guidelines developed by the American Society of Clinical Oncology. In addition to mammograms and follow-up visits with the oncologist, patients should be educated about the symptoms of breast cancer recurrence so that those symptoms are reported and evaluated promptly.

TABLE 97-5 FOLLOW-UP OF EARLY BREAST CANCER AFTER DIAGNOSIS AND INITIAL TREATMENT

	FREQUENCY OF EXAMINATION		
	1–3 Y	3–5 Y	5+ Y
History and physical examination	Every 3–6 mo	Every 6–12 mo	Yearly
Breast self-examination	Monthly	Monthly	Monthly
Mammogram[a]	Yearly	Yearly	Yearly
Gynecologic examination[b]	Yearly	Yearly	Yearly
Other[c]	PRN	PRN	PRN

[a]

Breast MRI is not currently recommended as part of routine screening unless jn the setting of a known genetic predisposition or other higher-risk condition.
[b]Yearly gynecologic examinations are recommended, particularly for those on tamoxifen who have an intact uterus.
[c]Tumor marker studies, complete blood count, automated chemistry studies, chest and skeletal x-rays, ultrasound, and radionuclide, computed tomographic, and positron emission tomographic scans are not recommended in asymptomatic patients. Appropriate studies should be obtained for patients with signs or symptoms of recurrence only.
Data from Recommended Breast Cancer Surveillance Guidelines. American Society of Clinical Oncology (www.asco.org).

Treatment of Metastatic Disease

Patients with metastatic breast cancer are currently incurable and have a median survival of approximately 2 to 7 years after the discovery of recurrence, depending on what series is considered. Nevertheless, patients may derive considerable palliative benefit from judiciously chosen therapy. Bone, soft tissue (skin and lymph nodes), pleural, and pulmonary metastases are the most common sites of breast cancer recurrence. Women with localized, symptomatic lesions in brain, skin, lymph nodes, and bone should also be considered for palliative radiation therapy, which relieves symptoms in the majority of patients.

Patients with disseminated metastases should be considered for palliative systemic treatment and consideration for clinical trial enrollment should occur at every line of therapy. **Table 97-6** describes endocrine and cytotoxic agents used in the treatment of breast cancer and their common and major side effects. Endocrine therapy usually is associated with minimal toxicity, while the toxicity associated with chemotherapy is frequently substantial and, in a small percent of patients, may be life threatening. Provided that metastases are not rapidly progressive or life threatening, all women with hormone receptor–positive, metastatic breast cancer should have an initial trial of endocrine therapy.

TABLE 97-6 ENDOCRINE AND CYTOTOXIC AGENTS USED IN THE TREATMENT OF BREAST CANCER

CLASS	COMMON AND MAJOR TOXICITIES
Endocrine Therapy	
Selective estrogen receptor modulators (SERMs)	
Tamoxifen	Hot flashes; vaginal effects; rare: thrombosis, endometrial hyperplasia/carcinoma
Toremifene	
Aromatase inhibitors	
Anastrozole	Hot flashes, arthralgias, bone mineral density loss
Letrozole	
Exemestane	
Pure antiestrogen	
Fulvestrant	Injection site pain, hot flashes, malaise, nausea
Progestin	
Megace	Weight gain, gastrointestinal side effects
Cytotoxic Agents	
Alkylating agents	
Cyclophosphamide	Myelosuppression (M), N + V, cystitis
Carboplatin or cisplatin	M, N + V (mild)
Antitumor antibiotics	
Doxorubicin, epirubicin, liposomal doxorubicin	M, N + V, mucositis (MS), alopecia, cardiomyopathy, vesication
Antimetabolites	
Methotrexate	M (uncommon), nephrotoxicity, MS
Fluorouracil	M (uncommon), N + V (uncommon), rash (rare)
Capecitabine	Diarrhea, “hand-foot” syndrome

Gemcitabine	M, N + V (mild)
Taxanes and antimicrotubule agents	
Paclitaxel	M, hypersensitivity reactions (HR), neuropathy, MS, arthralgia/myalgia, alopecia, MS (rare)
Docetaxel	M, HR (rare), neuropathy, fluid retention, rash, alopecia
Nanoparticle albumin-bound paclitaxel	M, neuropathy, arthralgia/myalgia, alopecia
Ixabepilone	M, neuropathy, arthralgia/myalgia, alopecia
Eribulin	M, fatigue, neuropathy
Vincas	
Vinorelbine	Peripheral neuropathy, alopecia, M (rare), vesication
Immunotherapy	
Trastuzumab	Cardiomyopathy, infusion reactions
Lapatinib	Diarrhea, rash, decrease in left ventricular function
Pertuzumab	Diarrhea, rash, decrease in left ventricular function
Ado-trastuzumab emtansine	Transaminitis, thrombocytopenia, fatigue

N + V, nausea and vomiting.

The choice of initial hormone agent for therapy of metastatic breast cancer may depend on what agent was used in the adjuvant setting and on the interval between initial diagnosis and recurrence. If relapse occurs soon after starting adjuvant hormonal therapy, it is reasonable to try one more, non–cross-resistant hormonal agent. If the tumor progresses soon after changing to the second hormonal agent, it is generally deemed hormone refractory and chemotherapy should be considered, along with available clinical trials. If relapse occurs 6 months or more after starting adjuvant hormonal therapy, another hormonal agent is generally tried. Historically, the most experience is with tamoxifen and response rates of approximately 30% are seen in unselected patients. As first-line treatment for metastatic disease, AIs (agents that block the synthesis of estrogens in postmenopausal women) are as effective as or more effective than tamoxifen. Responses to endocrine treatment generally last an average of 1 year, but in a small percentage of patients, response may last many years. Patients with hormone receptor–positive tumors, time intervals greater than 2 years from initial diagnosis to recurrence, soft tissue or bone metastases only, or a prior response to endocrine therapy are the most likely to respond and experience durable disease control. For patients who have responded to one agent or who have prolonged periods where the tumor does not grow (stable disease), other hormonal agents should be used in succession, until it is clear that the metastases are refractory to endocrine therapy. Patients who respond to one endocrine agent are likely to respond to another at the time of progression; the use of successive endocrine agents in patients with minimally symptomatic metastases is an excellent treatment strategy. In addition to tamoxifen, fulvestrant, and AIs, progestins and estrogens may also be effective; moreover, patients who have previously responded or had prolonged stable disease and then had tumor progression may respond to the same agent after being treated with other therapy. Data also support use of fulvestrant in the first-line setting, when appropriate.

Once breast cancer is deemed refractory to hormonal therapy or in the setting of triple negative disease, chemotherapy is usually the treatment of choice. There is some controversy regarding the benefits of single-agent versus combination chemotherapy for first-line treatment for metastatic breast cancer. Although response rates are often higher when multiagent chemotherapy is administered, overall survival for doublet versus single-agent treatment strategies is equivalent, and a sequential, single-agent chemotherapy approach allows for reduced toxicity, improved quality of life, and preservation of options for the next line. In addition, given the greater toxicity experienced by older patients compared with younger patients receiving chemotherapy, avoiding combination chemotherapy in this setting is optimal for the vast majority of patients—unless faced with extenuating circumstances (ie, visceral crisis).

Older patients with metastatic disease, whose general health is otherwise satisfactory, display response and toxicity profiles to chemotherapy similar to those of their younger counterparts. Most cytotoxic drugs are metabolized in the liver with only a select few dependent on renal excretion (methotrexate, carboplatin, and cisplatin); major liver dysfunction probably is required to alter drug metabolism significantly. Chemotherapy-related myelosuppression is more common in older patients as a result of diminished bone marrow reserve with aging; nausea and vomiting are seen less frequently than they are in younger patients. Of importance, psychosocial adjustments to chemotherapy

appear to be better for older than for younger patients. Complete and partial responses to most single chemotherapy agents range from 20% to 30%, while responses to combination chemotherapy average 50% to 70%. Responses generally last an average of 6 to 12 months; response rates to subsequent "salvage" regimens are generally low and last only several months.

In the treatment of metastatic, HER2-positive breast cancer, biologically engineered monoclonal antibodies with antitumor activity are the mainstay of treatment and are typically partnered with chemotherapy. For breast cancer, the following have been shown to be beneficial for use in combination with chemotherapy agents: trastuzumab (Herceptin, the humanized-monoclonal antibody that inhibits erbB-2 [Her2/neu]), lapatinib (Tykerb, an epidermal growth factor receptor [EGFR] and Her2/neu dual tyrosine kinase inhibitor), pertuzumab (Perjeta, an inhibitor of HER2 dimerization), and ado-trastuzumab emtansine (T-DM1, Kadcyla, a HER2 antibody-drug conjugate). All of these agents were approved for treatment of HER2-positive, metastatic breast cancer during 1998 to 2013. Trastuzumab is well tolerated and associated with tumor response rates of approximately 25% when used as a single agent. And, similar to other HER2-directed therapies, concomitant use of trastuzumab with chemotherapy often improves in response rates when compared to chemotherapy alone. Lapatinib is approved for use in combination with capecitabine for treatment of HER2-overexpressing advanced or metastatic breast cancer that has been previously treated with an anthracycline, a taxane, and trastuzumab. Pertuzumab is approved for use when combined with both taxane-based chemotherapy and trastuzumab in the first-line setting, and ado-trastuzumab emtansine is approved as monotherapy in patients who have received prior lines of therapy, including a taxane and trastuzumab.

PREVENTION

Except for draconian measures such as prophylactic mastectomy, which is not 100% effective, there is no known simple strategy to prevent breast cancer in older women. As the pathogenesis of breast cancer is likely to be related to interactions of estrogens, other hormones, and breast tissue, agents that lower breast tissue estrogen exposure, such as selective estrogen receptor modulators (SERMs) and aromatase inhibitors have been studied and found to be effective in breast cancer prevention. The SERMs, tamoxifen and raloxifene, and the aromatase inhibitor exemestane, decrease the incidence of hormone receptor–positive breast cancer by about half when used as preventive agents. Large trials that have included substantial numbers of older patients have confirmed these results but have not shown any survival advantage in spite of decreased breast cancer occurrences in the treated patients. In clinical practice, the benefits of SERM or exemestane treatment must be weighed against risk and can be estimated from a model developed from Gail and colleagues. At present, we believe that only a few older high-risk patients should be considered for preventive therapy and that these patients should have an estimated life expectancy of at least 10 years. Like younger patients, older patients should be encouraged to maintain an ideal body mass and engage in exercise. In addition, prophylactic, contralateral surgery as a method for prevention is not recommended in most patients unless in the setting of a genetic predisposition to cancer such as *BRCA1* or *BRCA2*. Prophylactic surgery has not been shown to improve long-term outcomes, including survival, in most patients.

Follow-Up for Women With Early Breast Cancer

There is good evidence that close follow-up after diagnosis or adjuvant therapy does not result in improved overall survival, but that detection of early skin or lymph node (soft tissue) recurrence may result in more effective palliation. Mammography is an exception, and in women with reasonable life expectancy, should be performed yearly or every other year to detect new primary lesions. Because a history of breast cancer is a risk factor for another breast cancer, follow-up visits do provide an opportunity for patients to express concerns and for physicians to give them reassurance. Extensive laboratory and radiologic procedures are now available for the detection of metastatic disease, but trials have indicated that a brief, focused history and a limited physical examination (skin, chest, breast, and abdominal examination) detect more than 75% of metastases. National guidelines suggest that optimal follow-up consists of periodic clinic visits and annual screening mammography in asymptomatic patients with a history of breast cancer. Available data do not support the use of routine laboratory work, imaging, or tumor markers for routine follow-up and should not be used in asymptomatic patients (see **Table 97-5**).

SPECIAL POPULATIONS AND ISSUES

Male Breast Cancer

Male breast cancer is uncommon and accounts for less than 1% of all breast cancer incidence. The natural history of male and female breast cancer is similar, but males usually present at a later stage, probably because of a delay in diagnosis. Almost all cases are sporadic, except for males with Klinefelter syndrome (sex chromosomes XXY)—in which the prevalence of breast cancer ranges from 3% to 6%—or men with the *BRCA2* gene, which is associated with a 5% to 10% risk of male breast cancer. A careful family history is mandatory in all males with breast cancer. Mastectomy with axillary dissection is the standard approach to treatment but breast-conserving surgery and irradiation is appropriate for males with small tumors. Histologically, most lesions are infiltrating ductal carcinomas, and the frequency of estrogen receptor–positive lesions is 70% to 80%. Because of the rarity of male breast cancer, there are few data on the role of adjuvant systemic therapy, and it is unlikely that large randomized trials will be undertaken. We suggest using the same guidelines for adjuvant therapy in men that are used in women with a similar stage and receptor status. Uncontrolled trials suggest that such treatment is similar in efficacy in men to that in women, although tamoxifen is the preferred adjuvant hormonal therapy in men.

Males with metastatic breast cancer are incurable but frequently respond to endocrine therapy, including tamoxifen and orchiectomy if they are hormone receptor positive. There is little experience with AIs in men with breast cancer. The results with systemic chemotherapy are similar to those in females.

Geriatric Assessment and Comorbidity

Robust, prospective data on the degree of toxicity suffered and benefit gained from standard treatments are lacking for older patients due to their persistent underrepresentation in clinical trials. Consequently, providers face significant challenges when trying to optimize treatment selection for older patients, with the expected therapy benefits and toxicities often extrapolated from observations in younger women despite differing life expectancy and frailty. Because of these issues, studies have increasingly focused on optimizing care for older patients with cancer, including the importance of functional status, toxicity prediction, and treatment selection.

In recent years, a greater emphasis has been put on functional age rather than chronological age given the vast heterogeneity of medical comorbidity and functional status for any given age. An abbreviated geriatric assessment has been developed by Dr. Arti Hurria and colleagues with this in mind and identifies older adults who have diminished life expectancy and/or are at risk for hospitalization and functional decline. The geriatric assessment includes multiple reliable measures which are primarily self-administered and require minimal resources and time by providers. Incorporation of this assessment in 500 patients starting chemotherapy for various cancers resulted in improved prediction of which patients experienced severe treatment-related toxicities and complemented clinical data. This assessment is feasible (as tested within Alliance studies) now being incorporated more widely across protocols in older patients with cancer and will likely become a part of routine clinical practice in the future as a tool to predict who may do poorly with treatment and to enhance treatment discussions. **Table 97-7** presents a list of key references for providers who care for older patients with cancer.

TABLE 97-7 KEY WEBSITES AND RESOURCES FOR HELP IN CARING FOR OLDER PATIENTS WITH CANCER

ORGANIZATIONS	DESCRIPTION	URL/LINK
American Society of Clinical Oncology (ASCO)	ASCO University modules explore treatment options for older patients with cancer. Also has Maintenance of Certification (MOC) Course on Geriatric Oncology.	http://university.asco.org/geriatric-oncology
International Society of Geriatric Oncology (SIOG)	Website has links to geriatric oncology guidelines and other educational materials.	http://www.siog.org/
Portal of Geriatrics Online Education (POGOe)	Comprehensive site with free access to expert-contributed geriatrics materials.	http://www.pogoe.org/about
Cancer and Aging Research Group (CARG)	A group of researchers with major interest in geriatric oncology research. Opportunities for mentoring. Also online chemotherapy toxicity calculator and geriatric assessment tools.	http://www.mycarg.org/
Lineberger Comprehensive Cancer	Free core lectures, resources, links in geriatrics.	http://unclineberger.org/geriatric

Center Geriatric Oncology		
ONLINE TOOLS AND CALCULATORS	**DESCRIPTION**	**URL/LINK**
Adjuvant! (adjvuvantonline.com)	Allows calculation of benefits of adjuvant therapy for patients with breast cancer. Can add estimates of comorbidity to calculations.	https://www.adjuvantonline.com/index.jsp
ePrognosis	A series of calculators based on systematic review of literature that allows for estimation of life expectancy in older adults (not specific to cancer).	http://eprognosis.ucsf.edu/default.php
Moffitt Cancer Center Senior Adult Oncology Program Tools	Online tools for estimating chemotherapy toxicity ("CRASH" score) and other geriatric calculators.	http://moffitt.org/cancer-types—treatment/cancers-we-treat/senior-adult-oncology-program-tools

Palliative Care, End-of-Life Care, and Hospice

For many patients and families with metastatic breast cancer, palliative care is synonymous with end-of-life care. This certainly is not the case and especially in the care of older patients with symptoms, early palliative care at the time of diagnosis of metastases can make the cancer journey much more endurable for both the patient and their family. Studies have shown that integrating palliative care with standard cancer treatment, including chemotherapy, can lead to significant improvements in quality of life and even survival. Although many oncologists are capable of managing the complex array of symptoms related to both metastatic breast cancer and its treatment, partnering with a trained team of palliative care experts results in better outcomes and relieves the oncologist from providing the extensive array of supportive services needed for their patients. We suggest that a palliative care consultation be considered for all older patients with metastatic breast cancer early in their course and preferably at the time of diagnosis.

Irrespective of their response to treatment of metastasis, the vast majority of older patients will succumb to their breast cancer. Those receiving palliative care can be easily transitioned to end-of-life care and hospice care. For those who have not had palliative care interventions, end-of-life care provided by palliative care experts and transition to hospice is recommended.

Disparities

Racial and age disparities in breast cancer care and outcomes have been well documented and have persisted over time, despite increasing awareness of this issue. Past examinations of receipt of care and outcomes for women have consistently demonstrated lower rates of treatment and worse outcomes for black and older patients compared to their white and younger counterparts. Furthermore, studies within cohorts of older patients also demonstrate racial disparities, including more delays to treatment, less standard therapy, shorter durations in therapy, and higher mortality rates for older black versus white women. Patients with less access to care, those who are underinsured, and those from lower socioeconomic groups also suffer from worse outcomes from breast cancer. Assurance that all patients receive guideline-concordant care is a national priority and rigorous interventions to better understand optimal ways of delivering care to all women are desperately needed. Patients felt to be at risk for problems with system navigation and social issues should be referred for patient navigation, social work, and resource assistance whenever possible.

CONCLUSION

Breast cancer is a major gerontologic problem. Both physician and patient education concerning screening, early diagnosis, and management of breast cancer in this age group are required. Available data indicate that optimal treatment of breast cancer in older women results in outcomes similar to those from treatment of younger women. Although significant comorbid illness is encountered more frequently in older patients and may complicate breast cancer treatment, most patients can be managed with judicious "state-of-the-art" therapy. Barriers to the treatment of breast cancer in older women are generic to the treatment of all illnesses in this age group and include access to care, transportation, adequate family and social support, physician bias, and treatment costs. Changes in health care policy, as well as focused research related to cancer in the geriatric population, will be needed to overcome these obstacles.

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Chapter 98

Prostate Cancer

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Learning Objectives

- List the risk factors for the development of prostate cancer.
- Understand the screening recommendations for prostate cancer in older men.
- Describe the treatment options for localized and advanced prostate cancer in older patients.

Key Clinical Points

1. **There is no Food and Drug Administration (FDA)-approved treatment shown to reduce the risk of developing prostate cancer.**
2. **Life expectancy and comorbidities should be considered before initiating prostate cancer screening.**
3. **Localized prostate cancer in an older patient can be effectively treated with a range of therapies including watchful waiting, active surveillance, surgery, and/or radiation.**

EPIDEMIOLOGY AND RISK FACTORS

Prostate cancer remains the most common noncutaneous malignancy diagnosed in American men and is the second leading cause of cancer-related deaths. Currently about 233,000 U.S. men per year are diagnosed with prostate cancer and about 29,000 U.S. men per year die of the disease.

The only undisputed risk factors for prostate cancer are older age, African-American race, and positive family history. Prostate cancer is generally a disease of older men; risk increases exponentially with age, with a median age at presentation of 66 years. More than half of prostate cancer diagnoses and 90% of prostate cancer deaths occur in men older than 65. The incidence rates of the disease among African-American men are higher than rates for men in *any* other racial or ethnic background. African-American men are more likely to be diagnosed with prostate cancer and to die from it than their Caucasian counterparts. The estimated lifetime risk of prostate cancer is 17.6% and 20.6%, respectively for Caucasians and African-Americans, while the estimated lifetime risk of death is 2.8% and 4.7%. Early-onset prostate cancer may be inherited in an autosomal dominant fashion, and it is estimated that approximately 10% of all prostate cancer cases are hereditary. A large twin study suggests that genetic factors may account for as much as 42% of prostate cancer risk, although the absence of clear, highly penetrant markers suggests that in the majority of men, prostate cancer risk involves a complex interaction of multiple genetic and environmental factors.

Additional factors such as diet, obesity, hormones, inflammation and sexually transmitted diseases, and occupational exposure have all been implicated in prostate carcinogenesis, but without consistent results. Dietary fat may be a risk factor for prostate cancer. Multiple epidemiologic, case-control, and cohort studies have suggested a moderate-to-strong increased risk of developing prostate cancer, particularly advanced disease, associated with total dietary fat, saturated fat, α-linolenic fatty acid, and cooked red meat. Two large prospective studies and a smaller case-control study suggest that fish intake may be protective, possibly owing to marine omega-3 fatty acids—known antagonists of arachidonic acid, which suppress the production of proinflammatory cytokines. Evidence for the association with dietary fat is further correlated with worldwide incidence patterns; prostate cancer is more common in

the United States and northern European countries and is relatively rare in Asia and Africa. When Asian men migrate to the West and change from a low-fat to a high-fat diet, their risk of prostate cancer increases. However, many of the men migrating from low-fat diet areas also consume green tea and soy products, which contain isoflavones and estrogen that may act as antioxidants and chemoprotectants against prostate-specific carcinogenesis. There appears to be an inverse relationship between soy intake and prostate cancer risk.

There is no consistent association between obesity and prostate cancer incidence. However, there are associations between obesity and aggressive prostate cancer, recurrence after primary therapy, and death from prostate cancer. Data from the Prostate Cancer Prevention Trial (PCPT) suggest that obesity increases the risk of higher-grade cancers, but decreases the risk of low-grade prostate cancer. While body mass index (BMI) greater than or equal to 30 was associated with an 18% decrease in low-grade cancers (Gleason grade < 7), there was a 29% increase in Gleason grade of 7 and above and a 78% increase in high-grade cancers (Gleason 8–10). These data suggest that obesity may differentially affect the development of aggressive and nonaggressive prostate cancer and may somehow play a role in the progression from latent to clinically significant prostate cancer. Although the specific role of obesity in prostate cancer risk is unclear, it may be linked to other risk factors such as dietary fat and meat intake, hormone metabolism, and insulin metabolism. The prevalence of obesity also correlates with prostate cancer risk across populations and may provide a link between the increased risk of prostate cancer with westernization.

A diet rich in fruits and vegetables is associated with reduced risk for several cancers, but their effect on prostate cancer risk is unclear. There is an inverse association with use of tomatoes and tomato products, presumably owing to the effects of lycopene, the most common carotenoid in the human body and one of the most potent carotenoid antioxidants. The Health Professionals Follow-Up Study (HPFS) found that frequent consumption of tomato products is associated with a decreased risk of prostate cancer, and in a meta-analysis of 21 case-control and cohort studies, a significant 10% to 20% risk reduction was associated with high versus low intake of tomatoes. The majority of these studies also show a stronger effect for cooked versus raw tomatoes.

Although it seems intuitive that testosterone levels may influence the incidence of prostate cancer, no evidence confirms this association. Dihydrotestosterone, the active hormone produced from the conversion of testosterone by the enzyme 5α-reductase, is associated in some studies with increased risk. A prospective, population-based study of 1156 men showed no correlation between 17 different hormones and prostate cancer development, with the possible exception of androstanediol glucuronide. Importantly, no dose-response relationships were seen, suggesting that serum hormone levels may not be useful even in risk stratification.

There is some evidence that chronic inflammation may increase prostate cancer risk. One meta-analysis of 11 studies on prostatitis and prostate cancer showed an overall relative risk of 1.6, while another meta-analysis of aspirin and cancer showed that regular aspirin use was associated with an approximately 15% decrease in prostate cancer risk. Population studies have suggested an increased risk of prostate cancer in patients with sexually transmitted diseases (STDs), including syphilis, recurrent gonorrhea, human papilloma virus (HPV), and HIV. A meta-analysis of 17 studies of prostate cancer and sexual patterns suggested that an increased number of sexual partners is associated with an increased prostate cancer risk, possibly through an increased exposure to STDs. There are currently no strong data to suggest a link between benign prostate hypertrophy (BPH) and prostate cancer risk.

PREVENTION

Chemoprevention is an area of ongoing research, and in many ways, prostate cancer is an ideal disease for this approach—relatively slow growing, centered in the older adult population, yet with devastating effects and difficult management after the onset of metastasis. To date, many promising agents have failed to show a protective benefit against developing prostate cancer.

5α-Reductase Inhibitors

Finasteride blocks the actions of 5α-reductase, the enzyme that converts testosterone to dihydrotestosterone. The PCPT enrolled 18,000 men between January 1994 and May 1997 to study the efficacy of finasteride for decreasing the prevalence of prostate cancer. The trial was based on two observations: androgens are required for prostate cancer development and men with congenital 5α-reductase deficiency develop neither BPH nor prostate cancer. This randomized, double-blind, placebo-controlled trial was closed early because of a perceived risk reduction with finasteride. After 7 years of treatment, prostate cancer was diagnosed in 18.4% of the men on finasteride and 24.4% of the men on placebo, a 6% absolute risk reduction and 24.8% relative risk reduction. The risk reduction associated with

finasteride was apparent across all risk groups defined by age, family history, race, and prostate-specific antigen (PSA). Finasteride use was also associated with increased sexual dysfunction, but decreased lower urinary tract symptoms. Results from the trial, however, were tempered by an apparent increase in high-risk cancers in the finasteride group; 6.4% of the cancers in the finasteride group were Gleason grade 8 to 10 versus 5.1% in the controls. This represented a significant 1.3% absolute increase in the risk of high-grade cancer associated with finasteride. High-grade prostate cancers are associated with a poorer prognosis after definitive therapy.

The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial further investigated the role of 5α-reductase in prostate cancer prevention. This randomized, double-blind, placebo-controlled trial enrolled 8200 patients in Europe and the United States. Men were randomized to dutasteride (Avodart), an inhibitor of both isoforms of 5α-reductase, versus placebo. Prostate biopsies were mandated at years 2 and 4 and as clinically indicated. After 4 years of treatment, men receiving dutasteride had a 5.1% absolute risk reduction in the number of prostate cancers diagnosed. However, similar to the PCPT, a statistically significant increase in Gleason 8 to 10 cancers was observed in years 3 to 4 of treatment with dutasteride. Both the PCPT and REDUCE trials led the FDA to issue a safety announcement that 5α–reductase inhibitors may increase the risk of more serious prostate cancers and so are not approved for chemoprevention.

Vitamin E and Selenium

Oxidative stress may play a role in the development of prostate cancer. Reactive oxygen species can damage deoxyribonucleic acid (DNA), lipids, and proteins. The association of prostate cancer and a high-fat diet may be secondary to the generation of increased fatty acids, which can cause lipid peroxidation.

Selenium is an essential trace nutrient with antioxidant properties. It enters the food chain via consumption of plants and plant-eating animals. α-Tocopherol is the most active and abundant source of vitamin E, and its antioxidant properties have been studied extensively in a variety of prostate cell lines and animal models. Selenium was initially investigated in the prevention of recurrent basal and squamous cell skin cancers, and although it did not affect the incidence of recurrent skin cancer, an unexpected finding was a decrease in the risk of prostate, colorectal, and lung cancer. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC) randomized 29,133 male smokers to either α-tocopherol (50 mg daily), β-carotene (20 mg daily), both, or placebo. Although the primary end point was lung cancer incidence and mortality, the trial demonstrated a significant 32% decrease in prostate cancer incidence and a 41% decrease in prostate cancer mortality in the groups taking α-tocopherol supplements. These trials generated interest in exploring the role of antioxidants in prostate cancer prevention.

Selenium and Vitamin E Cancer Prevention Trial (SELECT) was an National Cancer Institute (NCI)-sponsored, randomized, prospective, double-blind trial designed to determine whether selenium and vitamin E decrease the risk of prostate cancer in healthy men. Over 35,000 healthy men with a normal digital rectal examination (DRE) and a PSA less than or equal to 4 ng/mL were randomized to four study arms: vitamin E + placebo, selenium + placebo, vitamin E + selenium, and placebo + placebo. The primary end point of the trial was prostate cancer incidence. In 2008, the trial was stopped early when an interim analysis demonstrated no evidence of clinical benefit of either agent. In addition to the lack of benefit of either agent alone or combined, after a median overall follow-up of 5.46 years, there was a nonsignificant increased risk of prostate cancer in the vitamin E alone group. With additional follow-up in 2011, the number of prostate cancers in patients treated with vitamin E alone was significantly increased compared to the placebo arm (7.1% vs 6.08%).

Thus, although there was great excitement about antioxidant supplementation for prostate cancer prevention, particularly in older people, randomized prospective trials have shown no overall benefit.

PRESENTATION/SCREENING

Most men who present with prostate cancer are asymptomatic, particularly in the era of PSA testing, which detects many cancers long before they are clinically apparent. Patients rarely have urinary symptoms, as the majority of cancers arise in the posterior aspect of the prostate. Most men undergo evaluation after routine screening reveals either an elevated PSA or abnormal DRE. Since the advent of PSA testing and regular screening, in the United States the majority of patients have clinically localized, intermediate-risk prostate cancer at diagnosis. A minority of patients are diagnosed when they present with symptomatic metastatic disease, usually manifested as bony pain. For example in 1988, 14% of new prostate cancer patients presented with metastatic disease, but that number had fallen to 3.3% by 1998 and has remained stable since that time. Although screening has strongly influenced this downward stage

migration, there is still a debate as to whether it has significantly decreased prostate cancer–specific mortality.

Two large-scale, long-term, randomized clinical trials were designed to evaluate whether screening decreases mortality. The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) trial was based in the United States and randomized over 76,000 men (age 55–74) to either an annual screening arm or control group. Those patients randomized to get screened had an annual PSA value for 6 years as well as a DRE for 4 years. After 7 years, screening was associated with a 22% relative increase in prostate cancers diagnosed with no difference in prostate cancer–specific mortality after both 7 and 10 years. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial randomized over 180,000 men (age 50–74) to screening versus control. In contrast to the PLCO trial, PSA screening resulted in a significant 20% relative reduction in prostate cancer–specific mortality after 9 years of follow-up. At 10 and 11 years, the relative reduction in mortality was 38%. Potentially important differences between the trials were noted. First, the PLCO trial used a higher PSA value of 4 ng/mL compared to the 3 ng/mL in the ERSPC and may have missed several, clinically significant, cases of prostate cancer; second, the number of patients in the control group who received screening in the PLCO trial was estimated to be 40% to 52%. This contamination of the control arm may have reduced the statistical power of the study.

Based on these trials, the US Preventative Services Task Force (USPSTF) recommended against PSA screening, giving it a grade D recommendation. If a patient requests PSA testing, the task force recommends shared decision making between the patient and physician as well as an explicit understanding of the risks/benefits of screening. There are certain populations (ie, African Americans, patients with a strong family history) to which these recommendations do not apply. The National Comprehensive Cancer Network (NCCN) still recommends PSA screening in informed, healthy men. In men age 70 or greater, the NCCN acknowledges that PSA screening is unlikely to affect life expectancy, but a subset of patients will harbor high-risk disease and may benefit from therapy.

The risk of overdiagnosis may outweigh the benefits from treating a select few with aggressive disease. One study predicted a 27% relative decrease in the probability of lives saved if the stopping age for PSA screening was changed from 74 to 69. This was tempered with a 50% relative decrease in overdiagnosis. The NCCN proposes several strategies for screening older adults including the following: (1) Discontinue PSA screening at age 69. (2) Continue screening through age 74 with an increase in PSA threshold for biopsy. (3) Discontinue screening at age 70 if the PSA value is less than 3 ng/mL. In 2013, the American Urological Association (AUA) released a revised set of clinical guidelines for prostate cancer screening. The AUA made the following statements: (1) No screening is recommended for men less than age 40. (2) Routine screening for men ages 40 to 54 at average risk is not recommended. (3) Shared decision making and review of risks/benefits for men ages 55 to 69 are necessary prior to PSA screening. (4) If electing to undergo PSA screening, an interval of 2 or more years may be preferred over annual screening. (5) No screening is recommended in men over age 70 or with less than 10 to 15 years of life expectancy.

A summary of the various screening recommendations is provided in **Table 98-1**. These recommendations do not apply for men at higher risk for prostate cancer. In the absence of unified guidelines, a difficult task for primary care physicians is thus deciding which patients should undergo screening for prostate cancer. In the absence of definitive data, a reasonable approach to screening should involve an active discussion between the physician and patient, taking into consideration the patient's overall health and treatment preferences. Men with a life expectancy of less than 10 to 15 years (owing to age or comorbidities) should be informed that screening may not be beneficial. Younger men with a family history of prostate cancer and African-American men should be encouraged to undergo screening, as the disease prevalence is high in these groups. Any patient with symptoms that may be attributable to prostate cancer (bone pain, hypercalcemia, symptomatic pelvic lymphadenopathy) warrants a PSA evaluation as a part of his initial evaluation, since symptomatic patients can enjoy significant improvement with the institution of hormonal therapy. An ongoing challenge for the geriatrician is the need to remain current on the development of new treatments. In the future, as more targeted and less toxic therapies are identified, PSA screening may become a routine part of health maintenance for all men.

TABLE 98-1 SCREENING RECOMMENDATIONS IN OLDER ADULTS

ORGANIZATION	RECOMMENDATIONS
NCCN	Consider testing in men > 70 y with few or no comorbidities. Possible strategies to discontinue screening: 1. Stop screening at age 69. 2. Screen until 74 y, increase PSA threshold for biopsy between ages 70 and 74. 3. Stop screening at age 75 and PSA < 3 ng/mL.

USPSTF	Grade D recommendation for PSA screening. No evidence to support screening in men > 70 y.
AUA	Recommends against screening in men > 70 y with less than 10–15 y life expectancy.

AUA, American Urological Association; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; USPSTF, US Preventative Services Task Force.

EVALUATION

The appropriate screening examinations for prostate cancer include a serum PSA and DRE. PSA is a protein produced and secreted by both normal prostate and prostate cancer cells. It provides a sensitive but not highly specific screening test, as it is also elevated with BPH, inflammation, and infection of the prostate. The usual cutoff is 4 ng/mL, but 15% of men with normal PSA levels will have prostate cancer and 2% will have high-grade prostate cancer. PSA is, however, more sensitive than DRE, detecting more cancers at earlier-stage and smaller-sized cancers than rectal examination alone. PSA-doubling time is also a factor in prostate assessment, and any patient with a rapid PSA-doubling time should be sent for further evaluation, even if the absolute value of the PSA is below the normal cutoff level. DRE yield alone is low; estimates are that only 3% to 6% of examinations yield suspicious results. On the basis of an elevated PSA or an abnormal DRE, the patient should be referred for a transrectal ultrasound-guided prostate biopsy. In general, 6 to 12 cores are taken for evaluation; areas that are abnormal on DRE may receive more biopsy attempts.

If the biopsy is positive, a Gleason score is assigned. This score is one of the most important determinants of prognosis. The pathologist assigns a numerical value (on a scale of 1–5) to the most prevalent and the second most prevalent grades of cancer seen in the specimens. The score is then reported on a scale of 2 to 10, with 10 being the most aggressive cancer. Gleason scores should be reported separately, for example, 3 + 4 = 7, as the primary pathology has prognostic implications.

Risk stratification plays an important role in both the selection and timing of treatment and is an important part of the initial evaluation. After diagnosis, the natural course of prostate cancer can be estimated from tumor volume, aggressiveness, PSA level, and extent of disease. Tumor volume assessment includes local stage, the number of positive biopsy cores, and the extent of cancer in affected cores. Gleason score is currently the standard measurement of aggressiveness with Gleason 5 to 6 cancers considered low grade, Gleason 7 intermediate grade, and Gleason 8 to 10 high grade. Taking all of these prognostic factors into effect, newly diagnosed patients are classified as having low-, intermediate-, or high-risk disease. In addition to these broad risk groups, multiple nomograms are available to help clinicians estimate an individual patient's probability of localized disease, risk of progression without intervention, and risk of recurrence after definitive therapy. Several of these tools are available online, and they can sometimes be more helpful than the broad categories in assessing an individual's risk, as they allow integration of discordant factors (eg, high PSA with low Gleason score). PSA velocity prior to diagnosis may also provide valuable information in risk assessment; a PSA velocity greater than or equal to 2 ng/mL in the year prior to radical prostatectomy (RP) is predictive of greater risk of biochemical recurrence, cancer-specific mortality, and overall mortality.

Table 98-2 provides guidelines for preoperative staging. The staging evaluation for men with known prostate cancer or symptoms that could be attributable to metastatic prostate cancer includes serum chemistries, PSA, bone scan, and computed tomography (CT) scan of the abdomen and pelvis. These initial tests provide evaluation of the most likely sites of metastatic disease to avoid inappropriate surgical intervention or radiation therapy. The extent of evaluation for metastatic disease relates to the likelihood of finding disease. A prospective survey of 3690 men described the positive yield of bone scan and CT as fewer than 5% and 12%, respectively, for men with a PSA of 4 to 20 ng/mL. The yield decreased to 2% and 9% for those who also had a Gleason score of less than or equal to 6. Only the combination of a Gleason score of 8 to 10 and a PSA greater than 20, or a PSA greater than 50 alone, identified a group of men who had a greater than 10% yield on bone scan and a 20% yield on CT scan. To stage in an appropriate and cost-effective manner, patients with low PSAs and low-to-intermediate Gleason scores do not require evaluation. More risk factors increase the degree of preoperative evaluation. These studies also provide a baseline for follow-up. **Figure 98-1** illustrates a stepwise approach to evaluation, monitoring, and treatment.

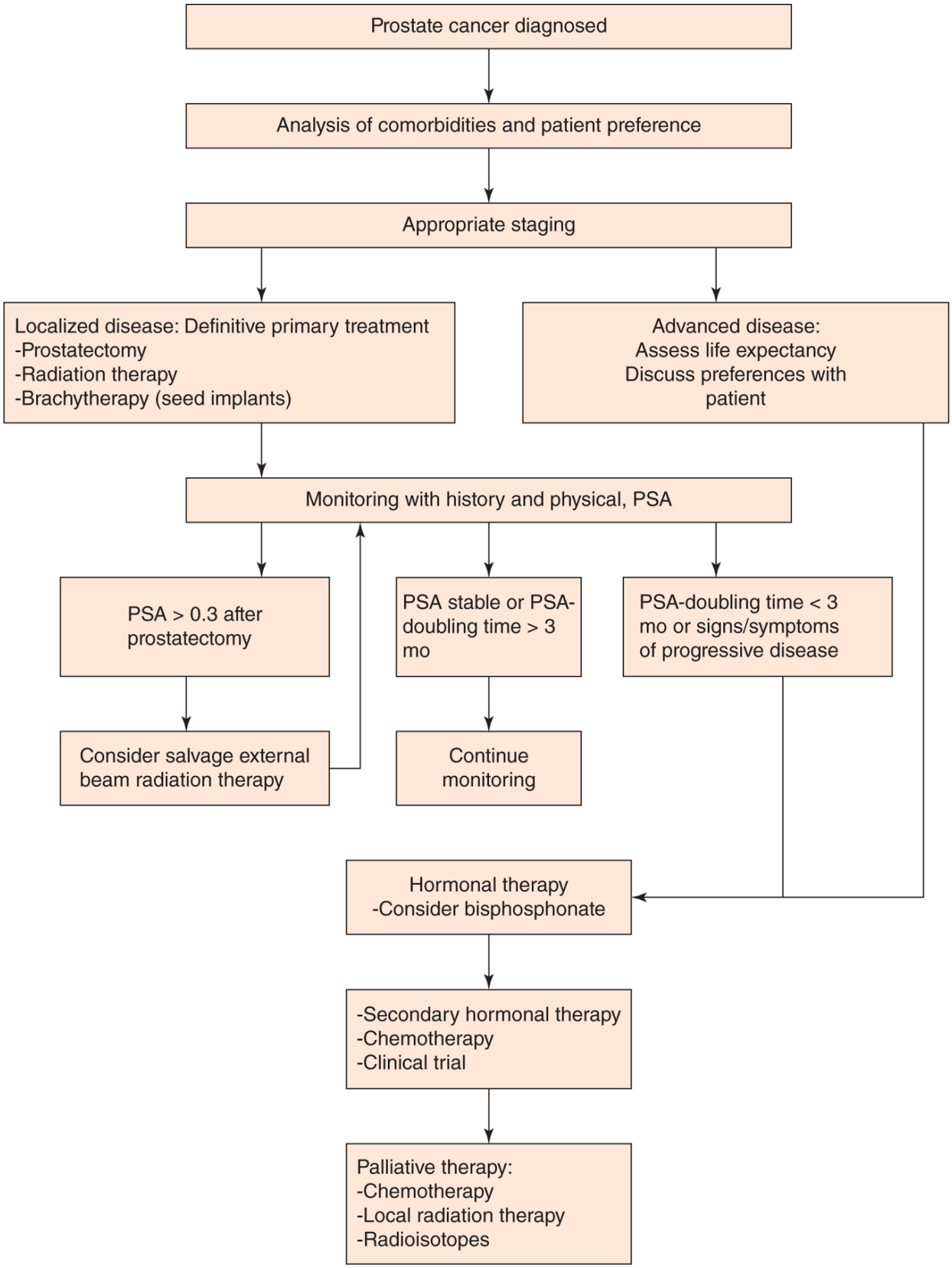


FIGURE 98-1. Prostate cancer evaluation and management flowchart. PSA, prostate-specific antigen.

TABLE 98-2 GUIDELINES FOR STAGING EVALUATION

PARAMETERS	RISK	METASTATIC EVALUATION	REFERENCES
PSA < 10, Gleason 2–6, clinical stage < T2b	Low	No screening	All 237 patients had negative bone scans and all 244 patients had

			negative CT scans in this category
PSA 10–20, Gleason 7, clinical stage T2b-T2c	Intermediate	Consider bone scan and perform CT scan of abdomen/pelvis	3 of 308 patients had a positive bone scan and 8 of 174 patients had a positive CT scan in this category
PSA > 20, Gleason 8–10, clinical stage ≥ T3a	High	Perform bone scan and CT scan of abdomen/pelvis	OR for positive CT scan 6.17 for Gleason 8–10 vs 2–6
Symptoms		Appropriate evaluation for symptoms noted	

CT, computed tomography; OR, odds ratio; PSA, prostate-specific antigen.

MANAGEMENT

After an initial diagnosis of prostate cancer, treatment decisions should take into consideration a number of factors including the individual patient's remaining life expectancy (which can be estimated using social security tables), comorbidities, baseline quality of life, treatment preferences, and disease characteristics/risk factors.

Observation

The concept of observation or watchful waiting involves deferring treatment until patients develop symptomatic disease. It was first proposed in the 1970s after the results of the Veterans Administration Cooperative Urological Research Group (VACURG) trial suggested that delaying therapy until the onset of symptoms did not increase prostate cancer–specific mortality in patients with locally advanced or metastatic disease. To evaluate watchful waiting in the modern era, from 1985 to 1993 the Medical Research Council Trial randomized 938 men with locally advanced or asymptomatic metastatic prostate cancer to either immediate or deferred treatment with hormonal therapy. In this study, 67% of patients died secondary to prostate cancer, a substantial increase from the findings of the VACURG trial. Overall survival was significantly longer in the patients treated immediately, with the most pronounced difference in men who initially had no evidence of metastatic disease. The rate of complications, such as bone pain, pathologic fractures, spinal cord compression, and ureteral obstruction was higher in the deferred group. Because PSA testing allows detection of cancers some 5 to 15 years earlier than DRE, men with T1c (PSA detected) tumors treated with watchful waiting may have better than 20-year disease-specific survival. Among a prospective cohort of 300 men (mean age 72) with localized disease, an equivalent 15-year overall survival was observed in those who deferred therapy versus those who received initial treatment. Watchful waiting, either at the time of initial diagnosis or at the time of progression, may be applicable in older men without metastatic disease. However, if the patient is not a candidate for treatment and has no symptoms attributable to the disease, both the patient and the physician should reflect on why screening was undertaken.

Active Surveillance

Active surveillance or expectant management differs from watchful waiting in the intensity of monitoring and the expectation of delayed but successful definitive, potentially curative therapy. This strategy is based on the observation that there is tremendous heterogeneity in the natural history of prostate cancer, and a significant number of men may be "overdiagnosed" in the sense that diagnosis and treatment may not improve either quality of life or survival. Active surveillance involves regular monitoring with PSA every 3 months, clinical examination with DRE every 6 months, and repeat biopsies as warranted by PSA and DRE (which can occur as frequently as once a year). An increase in PSA velocity (doubling time fewer than 3 years), primary Gleason pattern of 4 or 5 on repeat biopsy, or an increased number or extent of positive biopsy cores suggests progression of disease, and intervention with appropriately selected therapy should be initiated. Many experts feel that this is a reasonable approach for men with low-risk disease and may represent a practical compromise between radical treatment for all patients and watchful waiting with palliative treatment only (a strategy that undertreats aggressive disease). Although active surveillance may avoid overtreatment and allow patients to maintain their baseline quality of life, the strategy carries with it a risk of local or metastatic progression before active treatment is initiated. It is important, therefore, that patients are made aware that even the most careful monitoring may miss the window for administering curative therapy.

Local Therapy: Surgery, Radiation, or Brachytherapy

Surgery, radiation, or brachytherapy for early-stage disease is performed with curative intent.

Radical prostatectomy RP involves removal of the prostate and seminal vesicles, and is an appropriate therapy for any patient with disease confined to the prostate, a life expectancy more than 10 years, and no contraindications to surgery. Data have shown that outcomes are generally better with high-volume surgeons within high-volume medical centers. Laparoscopic and robotic prostatectomies have been refined and moved into mainstream care. Outcome data to date suggest that in the hands of an experienced surgeon, these approaches are comparable to open surgery and may involve less morbidity. Randomized clinical trials have shown no benefit for neoadjuvant hormonal therapy with RP. A randomized, prospective trial of 98 patients demonstrated that patients with positive lymph nodes at the time of surgery have decreased prostate cancer–specific mortality with a trend toward overall survival when immediate and continued androgen deprivation therapy is added to their initial treatment compared to no adjuvant therapy. Pathologic examination after surgery allows for verification of organ confinement and margin status as well as complete histologic examination. Almost 50% of patients with biopsy Gleason 6 disease are upgraded to Gleason 7 or higher once the entire gland is removed and evaluated.

External beam radiation therapy External beam radiation therapy (EBRT) in most centers is now delivered using advanced CT planning or intensity-modulated radiation therapy. These newer techniques, collectively known as "three-dimensional conformal therapy," have become standard of care. They allow for increased accuracy and thus the delivery of higher doses to the prostate while sparing normal tissues, ultimately decreasing both acute and delayed side effects. Often gold fiducial markers are implanted in the prostate prior to EBRT to provide landmarks for accurate daily dosing.

Radiation dosing is currently based on risk of recurrence. Patients with low-risk prostate cancer are generally treated with 70 to 75 Gy in 35 to 41 fractions. Higher doses of 75 to 80 Gy are recommended for patients with intermediate- and high-risk features. In addition, intermediate risk patients benefit from 4 to 6 months of neoadjuvant and adjuvant androgen deprivation therapy (ADT), while high-risk patients should receive neoadjuvant and adjuvant ADT for a total of 2 to 3 years. Because the prostate is not removed with EBRT, there is no pathologic confirmation of the extent of disease or adjustment of the biopsy Gleason score. Relative contraindications to EBRT include active collagen vascular disease, inflammatory bowel disease, and microvascular damage from hypertension or diabetes.

Brachytherapy Brachytherapy involves radioactive iodine (^{125}I) or palladium (^{103}Pd) implants, which are placed in the prostate under general anesthesia. They emit short-range radiation within the prostate, generally avoiding the bladder and rectum, and lose their radioactivity gradually. Prostate brachytherapy as monotherapy is indicated for patients with low-risk disease and small prostate volume (< 60 g). For intermediate-risk patients, brachytherapy is frequently combined with external beam radiation (40–50 Gy). High-risk patients are generally considered poor candidates for this treatment modality.

Although there are no good randomized data comparing local treatment modalities, a review of 2991 patients treated at the Cleveland Clinic and Memorial Sloan Kettering Cancer Center showed similar 5-year biochemical relapse-free survival rates for RP, EBRT, and brachytherapy, leading the authors to conclude that intrinsic tumor characteristics rather than treatment modality play the larger role in determining progression after definitive therapy. Given similar outcomes between EBRT and prostatectomy, logistics and potential side effects may play a significant role in treatment decisions. Some men may not be candidates for major pelvic surgery, and therefore prostatectomy may not be an option. Others may find the 8 to 9 weeks of daily radiation treatments unacceptable and opt for prostatectomy or brachytherapy, which is completed in a single surgical procedure. Incontinence is the primary side effect noted after prostatectomy, though reported rates vary significantly from surgeon to surgeon. EBRT causes short-term irritative bladder symptoms; long-term incontinence is rare. Bowel dysfunction is a potential short and/or delayed side effect of radiation therapy. Impotence occurs in as many as 50% of patients treated with any of the three local approaches, though it tends to occur later with EBRT than with prostatectomy. Primary care providers may want to refer patients to both urology and radiation oncology in order to fully educate patients about their choices.

Primary Androgen Deprivation

Patients with unfavorable prognostic factors, or those patients who are not interested in the risk:benefit ratio of local therapy, may choose primary hormonal therapy. Approximately 12.5% of the 3486 men in the Prostate Cancer Outcomes Study chose hormonal treatment as initial therapy, considered to be a surprisingly high number. Clearly,

there is no chance of cure with this modality, but for some patients the risk of relapse may be too high to pursue aggressive local therapy. There is also scant evidence about the outcomes associated with this approach.

Adjuvant Therapy

At this time, there is no standard adjuvant chemotherapy for patients at high-risk of recurrence, although there are several intergroup trials examining the role of adjuvant chemotherapy with both RP and EBRT. Adjuvant hormonal therapy, as noted earlier, is now standard of care with EBRT in patients with intermediate- and high-risk disease; after RP, it is recommended only for patients with node-positive disease.

POSTTREATMENT SURVEILLANCE

The scheduled follow-up after definitive local therapy depends on the risk of recurrence and the potential for curative salvage therapy. Patients at high risk of recurrence who would be good candidates for further intervention should have regular PSA testing (every 1–3 months) and DRE at least annually. Patients at low risk of recurrence or poor intervention candidates are more appropriately followed with evaluations every 4 to 6 months for the first 5 years and annually thereafter. Forty-five percent of patients who recur after prostatectomy do so within 2 years. Seventy-seven percent of recurrences occur within the first 5 years after prostatectomy and 96% within 9 years. Any patient with symptoms referable to local or systemic relapse (particularly new bone pain) should be evaluated with repeat serum and radiologic tests.

Biochemical Recurrence

Biochemical recurrence after RP is defined as a PSA level greater than 0.3 ng/mL and rising on two or more determinations. Recurrence after EBRT has been redefined by consensus as nadir PSA plus 2. The pattern of local recurrence is usually 1 to 3 years after primary therapy, with a slowly rising PSA or new finding on DRE; these patients should be followed closely and referred for local salvage therapy, if appropriate. The need for biopsy of radiologically proven disease in this setting is controversial. Patients who relapse quickly after local therapy (< 6 months) are more likely to have metastatic disease that was not discovered prior to definitive local therapy and are therefore unlikely to respond to local salvage therapy.

Patients with a rising PSA and no clinical, symptomatic, or radiographic evidence of disease present a therapeutic dilemma, as there is no clear consensus as to the timing of further therapy. Some men with biochemical recurrence will eventually die of prostate cancer, while others will have indolent disease and ultimately die of other causes. Prognosis is best estimated by considering initial stage, Gleason grade, and PSA in addition to the absolute value of the PSA at the time of recurrence and the PSA-doubling time. PSA-doubling time has been shown to be a useful parameter for monitoring patients and deciding when to initiate treatment after biochemical recurrence. One analysis of 587 men who had undergone an RP for clinically localized disease analyzed the significance of PSA-doubling time as a predictor of clinical progression after biochemical (PSA) failure. In a multivariate model, PSA-doubling time was a significant risk factor ($p < 0.001$) for both metastatic progression and local recurrence. The mean 5-year progression-free survival was 99% with a PSA-doubling time of more than 10 years, 95% with a PSA-doubling time of 1 to 9.9 years, 93% with a PSA-doubling time of 6 to 11 months, and 64% with a PSA-doubling time of fewer than 6 months. As expected, patients with a PSA-doubling time of fewer than 6 months were far more likely to have metastatic disease than local recurrence. PSA-doubling time of fewer than or equal to 3 months has been shown in multiple studies to predict cancer-specific mortality among patients with biochemical recurrence after either RP or EBRT.

Salvage Local Therapy

Patients whose PSA levels do not fall to an undetectable level after surgery should be evaluated for salvage therapy, including EBRT with or without ADT, or ADT alone. Approximately 20% to 25% of men with local recurrence postprostatectomy can be cured with early salvage EBRT. Several factors have been demonstrated to predict long-term response to salvage ERBT: Gleason score less than or equal to 7, positive surgical margins at RP, negative nodal or seminal vesicle involvement, and post-RP PSA kinetics consistent with local failure (> 3-year interval from RP to biochemical failure, PSA-doubling time > 10 to 12 months, and an absolute PSA at salvage of ≤ 1.0). Patients who recur immediately after definitive radiation therapy are candidates for ADT, observation, or, in selected cases, salvage prostatectomy.

ADVANCED DISEASE

A positive bone scan and pain in a weightbearing area correlating to the scan should prompt an x-ray to assess for impending pathologic fractures. Patients should be made nonweightbearing and immediately referred for both surgical and radiation consultation. The possibility of cord compression should be suspected in any man with a history of prostate cancer and new-onset back pain. Pain from spinal cord compression is often severe and generally predates neurologic symptoms. A negative neurologic examination should not delay a definitive radiologic study (preferably magnetic resonance imaging [MRI] or CT myelogram), and patients with suspected cord compression should be initiated and maintained on steroids until compression is ruled out.

Hormonal Therapy

First-line hormonal therapy Patients with advanced disease at presentation, or patients who relapse after definitive local therapy are initially treated with some form of ADT. The timing of hormonal therapy for a biochemical recurrence after definitive therapy is controversial. Early initiation of ADT in these patients reduced prostate cancer–specific mortality (17% relative risk) when compared to symptom-driven initiation. However, overall mortality was similar in both groups. Without clear guidelines, ADT is typically initiated based on PSA doubling time, Gleason score, and patient preferences. Hormonal therapy for patients with advanced disease is usually initiated at presentation.

The goal of ADT is to decrease the level of testosterone available to potentiate growth of the prostate cancer cells. A variety of treatments can achieve this goal; **Table 98-3** outlines the spectrum of drugs, which either alone or in combination are used as ADT. Currently, the majority of men on ADT are treated with luteinizing hormone–releasing hormone (LHRH) agonists or antagonists alone (monotherapy) or in combination with an antiandrogen (combined androgen blockade). Although some physicians routinely use combination therapy, others prefer LHRH monotherapy, and there are no clear data showing benefit of one strategy over the other. Patients with known metastatic disease, however, need to be on an antiandrogen for at least 30 days, starting 7 to 10 days prior to initiation of LHRH agonist therapy to avoid the initial testosterone flare associated with LHRH therapy.

TABLE 98-3 COMMONLY USED HORMONAL THERAPY OPTIONS

TREATMENT	MECHANISM	EXAMPLE	ADMINISTRATION
Orchiectomy	Removal of major source of testosterone		Surgical
LHRH agonist/antagonist	Stops the pulsatile secretion of LHRH from the pituitary and production of testosterone by the testes	Zoladex, Lupron, Trelstar	By depot injection, every 3–4 mo
First-generation antiandrogen	Androgen receptor antagonist	Casodex, Eulexin, Nilandron	Daily pill
CYP17 inhibitors	Inhibit synthesis of adrenal and testicular androgens	Abiraterone acetate	Daily pill
Second-generation antiandrogen	Androgen receptor antagonist	Enzalutamide	Daily pill

Orchiectomy (surgical castration) may be an underused and underappreciated form of hormonal treatment. Clearly, with advances in surgical techniques, the morbidity associated with the procedure is minimal and barring unforeseen complications, it is an outpatient procedure. Data from the Prostate Cancer Outcomes Study provided an update on quality-of-life issues for patients receiving hormonal therapy. Men who chose LHRH agonist therapy reported greater problems than orchiectomy patients did with their overall sexual functioning, despite both groups having similar levels of function prior to beginning treatment. LHRH patients were also less likely to perceive themselves as free of cancer, likely because of the need for ongoing injections.

The duration of response to first-line ADT is typically 18 to 24 months, although patients who initiate therapy for biochemical relapse alone may show PSA responses for much longer. The continuation of ADT in the setting of hormone refractory disease is a subject of some controversy. A retrospective analysis by the Southwest Oncology

Group (SWOG) showed no improvement in survival for patients remaining on LHRH therapy, while an Eastern Cooperative Oncology Group (ECOG) analysis showed a slight survival benefit. Given the potential for improved survival for patients remaining on testicular androgen suppression, many physicians continue to administer LHRH agonists for the duration of treatment with secondary hormonal therapies and chemotherapy.

Side effects from hormonal therapies include hot flashes, insomnia, decreased libido, erectile dysfunction, weight gain/fluid retention, diabetes, increased risk of cardiovascular events, and breast enlargement/nipple tenderness. Breast enlargement can be curtailed, although not reversed, by a few treatments of electron beam radiation directly to the breast stem cells underneath the areola. This low-risk treatment can provide significant physical and psychological benefit. Antiandrogen treatment can lead to hepatic dysfunction, requiring monitoring of liver function tests after the initial month of therapy, and every 3 months thereafter. Antiandrogens are also associated with gastrointestinal effects, including nausea, diarrhea, and constipation. Estrogens can predispose patients to thromboembolic complications, including deep vein thrombosis, pulmonary embolism, and myocardial infarction.

Patients with decreased testosterone caused by orchiectomy or ADT also have a significantly increased risk of bone loss. Most studies have demonstrated a 2% to 3% decrease per year in bone mineral density (BMD) of the hip and spine during initial testosterone suppressing therapy, and BMD continues to decline during long-term therapy. Fracture rates are also higher in patients on ADT. Three large, claims-based studies have shown that LHRH treatment is independently associated with fracture risk. Patients on testosterone suppressing therapy should, therefore, be encouraged to take daily calcium (500 mg) and vitamin D (400 IU) supplements to prevent bone loss. In addition, patients may benefit from BMD testing to evaluate overall bone health. Men with osteopenia or osteoporosis should be considered for treatment with oral bisphosphonates (see section on “Supportive Care”).

Intermittent androgen deprivation Intermittent androgen blockade has been advocated as a way to decrease side effects from ADT, and also to, potentially, increase the time to androgen independence. With this strategy, patients are cycled on and off hormonal therapy based on PSA response. Once patients achieve an undetectable PSA in response to ADT, they are taken off therapy and monitored; treatment is reinitiated based on absolute PSA value and/or PSA-doubling time. In 2012, a prospective trial randomized 1386 men with PSA relapse to continuous versus intermittent ADT. After an initial 8 month cycle of ADT, patients in the intermittent group restarted hormonal therapy once the PSA value was greater than 10 ng/mL or with evidence of disease progression. With respect to the primary outcome of overall survival, intermittent therapy was shown to be noninferior to continuous treatment. Additionally, quality-of-life indicators were better in the intermittent treatment group. The S9346 trial was similarly designed for patients with metastatic, hormone-sensitive prostate cancer randomized to intermittent versus continuous therapy. The results of the trial released in 2013 showed intermittent therapy to be not noninferior to continuous ADT, which remains the standard of care for such patients.

Second-line hormonal therapy Castration-resistant prostate cancer (CRPC) is defined as a rising PSA (or radiographic progression) with a castrate level of serum testosterone (< 50 ng/dL) and after withdrawal or addition of an antiandrogen. For instance, if the patient is receiving combined androgen blockade (ie, a gonadotropin-releasing hormone [GnRH] agonist and antiandrogen), the first treatment modality is antiandrogen withdrawal. The maximum duration of response is approximately 5 months. To date, there have been no identified predictors of androgen withdrawal response, although a longer duration of treatment with flutamide has been associated with response in two larger trials.

Since 2010, there have been five new antineoplastic agents that have shown a survival benefit in metastatic CRPC (mCRPC). In the majority of instances, a medical oncologist will manage the treatment regimens described below. However, recognizing the side effects of each treatment is paramount in the care provided by the geriatrician, which may require a dose adjustment or cessation of therapy. Abiraterone acetate and enzalutamide were recently approved for the treatment of mCRPC, both of which target androgen signaling. Abiraterone acetate is an irreversible inhibitor of the cytochrome P450 isoform-17 (CYP17), a key enzyme for androgen synthesis in the testes and adrenal glands. The precursor to abiraterone acetate, ketoconazole, can inhibit multiple P450 enzymes resulting in off target effects and toxicities. In combination with prednisone, abiraterone acetate increased overall survival in both the pre- and postchemotherapy setting in 2011 and 2013, respectively, leading to its FDA approval. Its ability to inhibit androgen synthesis can lead to mineralocorticoid excess, resulting in edema (31%), hypokalemia (17%), and hypertension (10%). Less common side effects are liver function test (LFT) elevations and cardiac abnormalities (tachycardia, atrial fibrillation). In addition to the survival benefit, abiraterone acetate delayed the use of opioids for pain and skeletal-related events. Enzalutamide is an androgen receptor antagonist, which prevents androgen from binding to the receptor and also inhibits nuclear translocation of the receptor. Similar to abiraterone acetate, enzalutamide increased overall

survival regardless of chemotherapy status. Common side effects include fatigue, headaches, and hot flashes. Seizures were observed in approximately 1% of patients and should be used with caution in patients with a known seizure disorder. Since enzalutamide is used without prednisone, the side effects of mineralocorticoid excess are not seen. The most effective sequence of abiraterone acetate and enzalutamide is not known and may be dictated by the side effect profile of each medication or physician preference.

Estrogens, such as diethylstilbestrol, have shown promise both singly and in combination, although estrogen therapy is associated with side effects such as edema and increased incidence of thromboembolic complications. Judicious use of prophylactic agents, such as warfarin or low-dose aspirin, has been included in these trials, but not prospectively. With the development of next-generation androgen signaling antagonists, use of estrogens has fallen out of favor.

The decision to pursue secondary hormonal manipulations will likely depend on several factors. Available data suggest that patients with a significant and prolonged response to initial hormonal therapy, or a significant antiandrogen withdrawal response, may be good candidates for a trial of secondary hormonal therapy. Poor performance status and the presence of other medical problems may render attempts at further hormonal manipulation an attractive option, as these patients are often intolerant of the side effects associated with chemotherapy. Patients with rapid PSA-doubling times are likely to have more aggressive disease and may receive more benefit from chemotherapy or a clinical trial with a novel agent.

Chemotherapy

The use of chemotherapy in mCRPC still has an important role to play in treatment after progressing through the multiple lines of hormonal therapy. Although mCRPC was once labeled “chemotherapy resistant,” a number of agents now show great promise in both palliative and response end points. Docetaxel is the first chemotherapeutic agent with demonstrated survival benefit in prostate cancer and has become standard of care for first-line therapy in castration resistant disease. In phase II and III clinical trials, docetaxel in combination with prednisone showed an increased median survival, PSA response, and quality of life compared with mitoxantrone. Mitoxantrone with prednisone has demonstrated palliative benefits in patients with bone metastases and is generally well tolerated; However, mitoxantrone has been supplanted by cabazitaxel as second-line chemotherapy. Cabazitaxel is a semisynthetic taxane with a similar mechanism to docetaxel. In a randomized, prospective phase III trial, cabazitaxel increased overall survival when compared to mitoxantrone in the post-docetaxel setting. Mitoxantrone is currently third-line chemotherapy and used less frequently due to side effects and lack of survival benefit.

SUPPORTIVE CARE

Bisphosphonates/RANKL Inhibitors

Bisphosphonates are synthetic analogues of inorganic pyrophosphates with high avidity for calcium and areas of bone mineralization. These compounds have been used for many years to treat disorders associated with bone resorption such as osteoporosis, Paget disease, and metastatic bone disease. Although various bisphosphonates have been tested in multiple clinical trials in the setting of advanced prostate cancer, only zoledronic acid—a potent, intravenous bisphosphonate—has a demonstrated effect on bone metastases in this population. In two placebo-controlled, randomized clinical trials, zoledronic acid decreased the incidence of skeletal events by 25% compared with placebo. Intravenous bisphosphonates are generally well tolerated, though patients should have regular creatinine assessment as renal toxicity is a known, but relatively uncommon, side effect. In addition, bisphosphonate use is associated with osteonecrosis of the jaw—a rare but potentially devastating complication, which appears to be most prevalent in patients who have received these drugs over a period of several years. It may be prudent, therefore, for patients to have a dental examination prior to initiating therapy, and clinicians should ask patients regularly about their dental health.

As both increasing age and androgen deprivation place men at higher risk of osteoporosis, bisphosphonates may also be useful in prevention of secondary fractures in this population. Even with intermittent androgen blockade, osteopenia of the lumbar spine was found in 46% and osteoporosis in 20% of patients, with similar values seen for the hip. A similar study found that 50% of men on androgen blockade for at least 12 months had asymptomatic vertebral fractures. A study of 47 men with hormone-sensitive prostate cancer compared BMD in men receiving the LHRH agonist leuprolide alone to BMD in men receiving the combination of pamidronate and leuprolide. Pamidronate showed significant protection of BMD in the lumbar spine, greater trochanter, and total hip. Although the study was

only of 48 weeks duration, it underscored the startling amount of bone loss in patients on LHRH monotherapy for this period: 3.3% in the lumbar spine, 2.1% in the trochanter, and 1.8% in the total hip. As bone is a ready target for prostate cancer metastases as well, bone protection should be paramount, especially in the early stages of the disease. Zoledronic acid is commonly used in the outpatient setting in patients with bony metastatic deposits. Denosumab is a monoclonal antibody directed against the RANK ligand to prevent pathologic fracture and osteopenia/osteoporosis. In a head-to-head comparison, denosumab was shown to be noninferior to zoledronic acid with respect to preventing skeletal related events in men with mCRPC. Although designed as a noninferiority trial, denosumab was found to be superior to zoledronic acid as first-line treatment. Additionally, denosumab can be administered as a subcutaneous injection and used safely in patients with renal insufficiency.

Pain Control

The majority of men with advanced prostate cancer have bone metastases, which are frequently very painful. Pain control is thus a critical issue in these patients and needs to be frequently monitored. Bone pain generally responds well to treatment with both nonsteroidal anti-inflammatory drugs and opioids, used alone or in combination. Although some older patients are very tolerant of narcotic analgesics, as a rule they should be started on low doses with careful dose titration and individualized treatment plans to achieve maximal analgesia and maintain quality of life. Constipation, the most common side effect of pain medications, should be aggressively addressed, but is generally well controlled with laxatives.

Palliative Radiation and Systemic Radioisotopes

Palliative radiation therapy can provide significant pain relief for symptomatic bony metastases and is also used to prevent impending pathologic fracture. Thus, patients with one or two areas of severe bone pain, which is either inadequately controlled with narcotics or which requires unacceptably high doses of narcotics, should be referred to radiation oncology for consultation. Most palliative radiation is given in one to 10 dose fractions, and 80% to 90% of prostate cancer patients who receive palliative radiation for bone metastases experience significant and durable pain relief. The onset of pain relief may be as soon as 48 hours after the initiation of therapy, although some patients will not experience maximal relief for up to 2 weeks after therapy is complete. Systemic radioisotopes can deliver high-dose radiation to bone lesions without significantly affecting normal bone and can provide palliative benefit to patients with widespread, painful bone metastases, which are refractory to palliative chemotherapy or narcotic analgesia. Strontium-89 and Samarium-153 are both β-emitters, which were FDA approved in the 1990s for palliation and pain relief. These agents have the potential to cause significant myelosuppression and thrombocytopenia. More recently, Radium-223, a calcium mimetic, was shown to increase overall survival as well as provide pain relief, making this an attractive treatment for castration-resistant, symptomatic, bony metastases. Radium-223 is an α-emitter, which can transmit higher energy over shorter distances compared to β-emitters, making this treatment more effective with less side effects.

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Chapter 99

Lung Cancer

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Learning Objectives

- Become familiar with the general principles of lung cancer evaluation and its inherent need for a multidisciplinary approach to management.
- Identify the broad treatment paradigms for different stages of lung cancer, including more recent developments in therapeutics, and their potential risks and complications.
- Discern geriatrics-oriented issues in the multidisciplinary care of older adults with lung cancer and apply geriatric assessment and palliative care principles to their care trajectory.

Key Clinical Points

1. **Lung cancer remains a cancer of older adults and confers substantial morbidity and mortality in an aging patient population.**
2. **Although advances have been made in molecular diagnostics and therapeutics for a select group of patients with advanced nonsmall-cell lung cancer (NSCLC), the risks of cytotoxic chemotherapy among other modalities have to be apprised on an individual basis.**
3. **Given the trade-offs of various lung cancer treatment options and poor prognosis in most patients with advanced disease, geriatricians play a key role in helping older adults with lung cancer and their caregivers define goals of care, optimize the management of geriatric syndromes and comorbid conditions, and better assess functional, cognitive, and psychosocial reserve to undergo treatment.**
4. **Early integration of palliative care improves mood and quality of life and may prolong survival in patients with advanced NSCLC and such interventions may be particularly relevant in older adults.**

EPIDEMIOLOGY AND RISK FACTORS

Lung cancer remains the second most common cancer diagnosis and the most common cause of cancer deaths among men and women in the United States. In 2014, it is estimated there will have been 224,210 new cases of lung cancer with 86,930 men and 72,330 women dying from their disease. The median age at lung cancer diagnosis is 70 and the American population greater than or equal to 65 years is predicted to increase to over 20% by the year 2030. This combination of a burgeoning geriatric oncology population and newly recommended annual low-dose computed tomography (CT) scan screening will likely increase the number of older patients needing evaluation and treatment for lung cancer. Despite advances in screening, diagnosis, and treatment, the majority (80%) of lung cancer is diagnosed with either spread to regional lymph nodes or distant sites (ie, stage III or IV). More patients die from lung cancer than from colon, breast, and prostate cancers combined.

The major modifiable risk factor for the development of lung cancer is tobacco use, accounting for approximately 80% of lung cancer cases. Smokers and nonsmokers are at risk for lung cancer; however, the risk is much higher (10-fold) among patients who have smoked cigarettes. The risk is directly proportional to the number of pack-years and tar

content. Patients exposed to passive tobacco smoke are also at risk, accounting for 25% of lung cancer cases. Men or women who smoke cigars and pipes are at an increased risk as well; however, their risk may be less than that of cigarette smokers. Smoking cessation even in long-time smokers decreases the risk of lung cancer development and is a major public health priority.

Lung cancer in never-smokers accounts for approximately 10% of patients with lung cancers in the United States, disproportionately affecting women. Never-smokers are more likely to have an activating mutation in the epidermal growth factor receptor (EGFR) and are therefore more likely to respond to oral anti-EGFR tyrosine kinase inhibitors. Possible pathogenic theories have included exposure to environmental or occupational etiologic factors such as asbestos or radon. Occupational and environmental exposures are important questions to ask patients particularly if they have worked in construction, naval shipyards, or live in areas with high air pollution, diesel exhaust, or smoke from cooking and heating. Prior radiation therapy to the chest for other malignancies also increases the risk of a second primary lung cancer, particularly among smokers.

SCREENING

Despite smoking cessation efforts and declining rates of heavy cigarette smoking, millions of Americans remain at increased risk for the development of lung cancer. To address this issue, the National Lung Screening Trial (NLST) was performed and reported a 20% relative reduction in lung cancer mortality using low-dose CT screening (LDCT) compared to chest radiography. Based on these results, in December 2013, the US Preventive Services Task Force (USPSTF) released its updated recommendations to perform annual screening for lung cancer with LDCT in adults aged 55 to 80 who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Ideally, most cancers would be diagnosed at an early stage; however, among older patients with increasing comorbidity, it is critical to understand the impact of undergoing screening as they may be more likely to die from other comorbid conditions and not from cancer. The impact of these screening guidelines remains to be determined with regard to the diagnosis and treatment of early-stage lung cancers. Centralized Medicare Services and the Veterans' Administration (VA) have recently approved health care coverage for this new screening recommendation. The issues of lead-time bias and additional morbidity and mortality are particularly relevant in the population of older adults in whom competing causes of death and multiple comorbidities are frequently encountered. In addition to the overdiagnosis of small tumors detected during screening, which could otherwise remain silent until the patient dies from other causes, screening for lung cancer with LDCT could potentially cause harm secondary to morbidity and mortality associated with biopsies and surgery, since lung tumors often appear as noncalcified nodules. In the NLST trial, only 25% of patient enrolled in the screening arms were of age 65 to 74 and less than 1% were greater than or equal to 75 years. Over 96% of the patients with a positive screen led to a false-positive result after further work-up. This has important implications for screening among the oldest old with comorbid conditions. Among older adults, there is a higher risk for false-positive LDCT screening findings. Earlier trials using chest radiography, cytologic examination of the sputum, or both, however, failed to decrease cancer-specific mortality; therefore, screening with LDCT is the new standard of care. The NLST created a biomarker repository with biological specimens that have the potential to further investigate candidate diagnostic biomarkers for early diagnosis in both retrospective and prospective screening trials. Several molecular biomarkers have been described using specimens along the airway, in exhaled breath, or blood, but none are currently validated for use in the clinical setting.

PATHOLOGY

In general, lung cancer is broadly characterized into NSCLC versus small-cell lung cancer (SCLC) (**Table 99-1**). Distinguishing between these two histopathology subtypes is critical as the subtype dictates treatment course. For example, SCLC is more responsive to chemotherapy and radiation, requires prophylactic cranial irradiation (PCI), and often has a more aggressive clinical course compared to NSCLC. NSCLC is the most common subtype accounting for up to 85% of diagnoses. Among NSCLC, adenocarcinoma accounts for the most common histologic type followed by squamous cell carcinoma. Less prevalent subtypes recognized by the World Health Organization (WHO) include large-cell carcinoma, adenosquamous carcinoma, sarcomatoid carcinoma, and carcinoid tumors. Bronchoalveolar carcinoma is currently classified under adenocarcinoma.

TABLE 99-1 OVERVIEW OF LUNG CANCER STAGING, EPIDEMIOLOGY, AND TREATMENT

STAGE	TNM STAGING	DEFINITION	% CASES AT DIAGNOSIS	% 5-YEAR SURVIVAL	MANAGEMENT STRATEGY
Nonsmall-Cell Lung Cancer					
I	T1a–T2a N0 M0	Localized	15%	54% (70%–80%)	Surgery +/– postoperative chemotherapy Stereotactic body radiation therapy (SBRT): nonsurgical candidate patients
II	T1a–T2a, N1 T2b, N0–1 T3, N0	Spread to regional lymph nodes	22%	40%–60%	Surgery + postoperative chemotherapy RT +/– chemotherapy
III	Any T, N2–N3 T3, N1–N2 All T4 disease	Spread to regional lymph nodes	22%	10%–25%	Most IIIA/all IIIB: concurrent or sequential chemoradiation Select IIIA: preoperative chemotherapy/radiation + surgery if potentially resectable
IV	Any T Any N M1a or M1b	Distant spread	57%	< 5%	Chemotherapy Targeted therapy (if applicable) Clinical trial
Small-Cell Lung Cancer					
Limited stage (stages I–IIIB)		Primary tumor and involved lymph nodes can be safely encompassed in a single radiation port	35%–40%	10%–15%	Concurrent chemoradiation (Occasionally detected after surgical resection for small lesion; then postoperative chemotherapy)
Extensive stage (stage IV)		Usually metastatic	60%–65%	≤ 2%	Chemotherapy

COMMON CHEMOTHERAPY REGIMENS AND TOXICITIES

STAGE	COMMON CHEMOTHERAPY REGIMENS	COMMON ADVERSE SIDE EFFECTS
Nonsmall-Cell Lung Cancer		
I/II	Carboplatin/paclitaxel	Carboplatin: fatigue, nausea, myelosuppression (particularly thrombocytopenia) Paclitaxel: alopecia, neuropathy, infusion reactions, myelosuppression, myalgias/arthralgias
	Cisplatin/etoposide	Cisplatin: fatigue, nausea (including delayed), ototoxicity, nephrotoxicity, less myelosuppression than with carboplatin Etoposide: fatigue, nausea, myelosuppression, alopecia
	Cisplatin/pemetrexed	Pemetrexed: fatigue, nausea, rash, myelosuppression (anemia most common)
	Cisplatin/vinorelbine	Vinorelbine: fatigue, nausea, myelosuppression constipation > diarrhea, neuropathy
III	Usually with radiation: cisplatin/etoposide Carboplatin/paclitaxel	(See above)

IV	Doublets: carboplatin/cisplatin *plus* Paclitaxel +/– bevacizumab Pemetrexed Nab-paclitaxel Gemcitabine Single agents: Erlotinib Crizotinib Docetaxel Pemetrexed Gemcitabine Vinorelbine	Bevacizumab: hypertension, proteinuria, bleeding/hemorrhage, thrombotic events, impaired wound healing Nab-paclitaxel: less neuropathy and infusion reactions than with paclitaxel Gemcitabine: fatigue, myelosuppression, nausea, drug fever, pneumonitis (rare) Erlotinib: acneiform rash, diarrhea; fatigue, nausea, pneumonitis (rare) Crizotinib: visual disturbances (day/night changes, peripheral vision changes, photopsias), edema, nausea, fatigue, LFT abnormalities, pneumonitis (rare) Docetaxel: fatigue, nausea, alopecia, myelosuppression (more so than with paclitaxel), edema, myalgias/arthralgias, ungual toxicity, neuropathy (less common)
Small-Cell Lung Cancer		
Limited stage (stages I–IIIB)	Cisplatin or carboplatin/etoposide *plus* radiation	See above for stage III NSCLC
Extensive stage (stage IVA/B)	Carboplatin or cisplatin/etoposide Carboplatin or cisplatin/irinotecan Topotecan Paclitaxel	Topotecan: fatigue, nausea, myelosuppression Irinotecan: fatigue, nausea, myelosuppression, diarrhea (early/late)

TNM, tumor, node, metastasis.

Changes in smoking and environmental factors have thought to contribute to a shift in histology from squamous cell carcinoma to adenocarcinoma, particularly in the United States. Squamous cell carcinoma classically is central in location, endobronchial in nature, sometimes with central cavitation, and commonly associated with lobar collapse, obstructive pneumonia, or hemoptysis, with relatively late development of distant metastases. Adenocarcinoma is classically a peripheral, solitary lung nodule, often associated with malignant pleural effusion and early development of metastases frequently involving the brain and bone. SCLC has the strongest association with smoking and commonly forms rapidly growing, central masses.

The pathologic classification of lung cancer is evolving due to new sampling and radiologic techniques, molecular biomarkers, and histologic/pathologic advances. In 2011, the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society International (IASLC/ATC/ERSI) developed a multidisciplinary international team to incorporate advances in the molecular and histologic lung cancer subtypes of resection specimens, small biopsies, and cytology into a new, separate classification schema from the WHO. Many of the IASLC/ATC/ERSI classification revisions will inform the expected new WHO pathologic classification guidelines in 2015, including the elimination of bronchoalveolar carcinoma and mixed subtype adenocarcinomas. Mutational analysis is now routinely done on adenocarcinomas as oral targeted therapies exist for EGFR mutations, anaplastic lymphoma kinase (ALK) rearrangements, and *ROS1* mutations, particularly prevalent in never-smokers.

CLINICAL PRESENTATION

The initial clinical presentation of lung cancer patients is changing. With new screening guidelines and regular use of chest CT scans for several medical indications, many new lung cancers are diagnosed during evaluation of incidental pulmonary nodules that require serial follow-up CT scans. Despite these practice changes, patients still present with

classic symptoms of cough, unintentional weight loss, and/or hemoptysis. Symptoms related to the primary tumor depend on the location of the tumor. Central tumors produce cough, dyspnea, hoarseness, stridor, hemoptysis, and postobstructive pneumonia. Superior sulcus tumors may produce shoulder pain, arm pain, brachial plexopathy, or Horner syndrome. Peripheral lesions may cause pleuritic chest pain due to pleural involvement. Symptoms related to mediastinal disease include hoarseness caused by the involvement of the left recurrent laryngeal nerve with left-sided tumors and obstruction of the superior vena cava with right-sided tumors or associated lymphadenopathy.

Because more than half of patients have metastases at presentation, initial symptoms related to a metastatic site are frequent, particularly in patients with adenocarcinoma or small-cell carcinoma. Often, the initial presentation is due to symptomatic brain metastases and associated vasogenic edema causing seizures, new headaches, or neurologic deficits. Subsequent metastases from lung cancer are common. Sites of spread include the brain, pleura, bone, liver, adrenal glands, and contralateral lung. Rarely, lung cancer is diagnosed due to a paraneoplastic syndrome such as hypertrophic pulmonary osteoarthropathy leading to hypercalcemia in squamous cell carcinoma. SCLCs are known to cause syndrome of inappropriate secretion of antidiuretic hormone, Cushing syndrome, and various neurologic syndromes such as Eaton-Lambert reverse myasthenia syndrome among others. More commonly in advanced disease, hypercoagulability results in venous thromboembolic disease either concomitantly at the time of diagnosis or during the disease trajectory.

Special Presentation Issues

Lung cancer is unique in that it can present in several ways including but not limited to superior sulcus (Pancoast) tumors, chest wall tumors, or solitary brain metastases. Superior sulcus tumors are carcinomas that develop in the apex of the lung with invasion into the thoracic inlet. The most common initial symptom is shoulder pain due to invasion of the brachial plexus. This invasion into the sympathetic chain and stellate ganglion is Horner syndrome in patients presenting with the classic triad of miosis, ptosis, and anhidrosis. Chest wall tumors are bulky primary lung tumors that directly invade the chest wall. Treatment options for both superior sulcus and chest wall tumors include combinations of surgery, radiation, and chemotherapy. A third unique presentation is superior vena cava (SVC) syndrome in which edema develops in the face and neck with dilated veins in the neck and torso due to compression of the SVC outlet. Small-cell carcinoma is a common histology encountered with this presentation. Urgent radiation therapy is often appropriate before histologic confirmation depending on the patient's clinical status. Lastly, patients who present with solitary brain metastases after curative treatment intent for early-stage NSCLC, are eligible for resection of the solitary metastases, achieving prolonged disease-free survival in the absence of other distant metastatic disease. Performance status (PS), extent of extracranial disease, and age are key prognostic factors in this scenario. Surgical resection followed by radiation typically in the form of whole-brain irradiation (WBI) has been the standard for surgical candidates; however, surgery followed by stereotactic radiosurgery (SRS) to the surgical bed is an emerging option that spares late cognitive side effects of whole-brain radiation therapy (WBRT). For unresectable tumors or nonoperable patients, SRS versus WBI are reasonable alternatives. Patients with multiple larger tumors are generally treated with WBI. Approximately one-half of patients treated with resection and postoperative radiation therapy will develop recurrence in the brain; some of these patients may still be suitable for additional radiation treatments.

EVALUATION

Diagnostic Approaches

Although patients may present with symptoms outlined above, it is becoming increasingly common for solitary pulmonary nodules (SPNs) being detected on chest x-ray and/or CT scans of the chest that are ordered for other indications. The pretest probability of SPNs being benign or malignant depends on several factors, including the size and appearance of the nodule, as well as patient risk factors including smoking exposure. Assessing for dynamic changes of an SPN over serial CT imaging may be recommended at first if there is a low or intermediate level of suspicion. If the clinical suspicion is high and CT imaging supports an early-stage process, patients may be eligible for video-assisted thoracoscopic surgery (VATS) via wedge resection or lobectomy that may be both diagnostic and therapeutic if lung cancer is confirmed. Otherwise percutaneous imaging-guided biopsies or transbronchial biopsies of SPN or thoracic lymph nodes via bronchoscopy and endobronchial ultrasound, respectively, may be indicated to obtain a tissue diagnosis. Certainly if more distant lesions are noted in the liver or elsewhere that may be more accessible to a percutaneous approach, this ought to be considered as well. Finally, in patients with a suspected malignant pleural

effusion, thoracentesis with cytologic evaluation may provide sufficient material to render a diagnosis.

Staging Work-Up

When there is strong clinical suspicion for lung cancer and definitely when a diagnosis of lung cancer is confirmed, CT staging imaging of the chest and upper abdomen (ie, liver and adrenal glands) is warranted. Current guidelines also warrant brain imaging even among patients with suspected early-stage disease, preferably with magnetic resonance imaging (MRI), and especially for those with confirmed SCLC. Integrated positron emission tomography (PET)/CT is mostly incorporated in the evaluation of patients with potentially resectable early-stage NSCLC (stages I–II) and some cases of stage IIIA, for which a noninvasive evaluation of the mediastinal lymph nodes (ie, N2 disease) can be important in surgical and nonsurgical treatment planning. Endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) are less invasive approaches to evaluating hilar and mediastinal lymphadenopathy on staging imaging to guide treatment planning and are becoming more readily adopted into pathologic staging approaches. However, patients may still need mediastinoscopy (ie, surgical staging) prior to surgery if there are concerns about accessibility or yield by EBUS/EUS, particularly in NSCLC arising from the left upper lobe.

If metastatic disease is identified on initial CT staging imaging, a PET/CT is unlikely to change management. Evaluation for brain metastases with MRI or contrast-infused CT is indicated for any SCLC diagnosis, and most experts advocate for its use in patients with stage III or IV NSCLC, or in any patient with suggestive signs or symptoms regardless of stage. Since SCLC is still conventionally staged into limited versus extensive stage (see "Small-Cell Lung Cancer" later), this distinction invariably can be made with staging imaging alone since the treatment of choice is nonsurgical with the rare exception of resection of early-stage–appearing SPN that turns out to be SCLC.

Molecular Markers

With earlier studies demonstrating driver mutations being more prevalent in adenocarcinomas of the lung in never- or light-smokers such as *EGFR* gene mutations (10%–15% of all cases) or *ALK* gene translocations (6%–8%), molecular testing on tumor specimens for these molecular markers has now been adopted as part of standard of care since each of these has targeted therapies available in the first line that lead to improved response rates and progression-free survival compared with standard chemotherapy (gefitinib, erlotinib, and afatinib for EGFR; crizotinib or ceritinib for ALK). Current guidelines recommend that these markers be tested in tumors from patients with stage IV adenocarcinoma, large-cell carcinoma, or those with mixed adenosquamous histology. However, given that the prevalence of these mutations in a specific center's patient population may be relatively low, the cost-effectiveness may also be variable and should be taken into account.

TREATMENT OF NONSMALL-CELL LUNG CANCER

Stage I

Despite advances in surgical, radiation, and chemotherapeutic techniques, overall survival even for early-stage lung cancer remains low. At diagnosis, only 15% of patients have localized disease which corresponds to a 50% to 75% 5-year overall survival. Depending on a patient's comorbidity burden and pulmonary function status, a curative treatment approach with either radiation or surgery is pursued for those with NSCLC (see **Table 99-1**). The treatment of SCLC will be discussed separately.

A NSCLC tumor that is less than or equal to 5 cm without mediastinal involvement is considered stage I and curative resection with a surgical approach is the standard treatment per current practice guidelines. The North American Lung Cancer Study Group 821 trial demonstrated the superiority of lobectomy over sublobar resection in terms of local control but not in overall survival. Comparative effectiveness research has found an improvement in both overall survival and local control for older patients treated with lobectomy versus sublobar resection.

The preferred definitive treatment for early-stage NSCLC is surgery; however, this is often not possible in older patients with coexisting medical comorbidities. Thoracic surgery is often not an option in patients with serious coexisting medical conditions such as severe chronic obstructive pulmonary disease, diabetes, or heart disease termed "medically inoperable." The use of stereotactic body radiotherapy (SBRT) is increasing in older patients with early-stage NSCLC who are considered medically inoperable or prefer to avoid definitive surgery. The Radiation Therapy Oncology Group (RTOG) 0236 trial demonstrated high rates of primary tumor and locoregional control with low rates

of clinically significant toxicity, and a 3-year overall survival approaching 56% in medically inoperable early-stage NSCLC patients treated with SBRT. Historically, 3-year survival rates for medically inoperable disease remain low at 20% to 35% with conventional radiation treatment or observation alone. Retrospective evaluation of older patients treated with SBRT both in the United States and Europe has also demonstrated excellent tumor control and limited toxicity. In response, the use of SBRT is increasing in older patients with early-stage lung cancer who are medically inoperable; however, outcomes data detailing both short- and long-term complications and associated costs with this newer treatment remain unknown. A recent retrospective comparative effectiveness study found no statistical difference in overall survival or local control in patients treated with SBRT versus lobectomy among Medicare recipients. There are no currently available randomized phase III data comparing SBRT to surgical resection.

Currently, the NCCN guidelines do not support the use of molecularly targeted therapies, adjuvant (ie, postoperative) radiation, or adjuvant chemotherapy in stage I disease outside of a clinical trial setting. Based on phase III clinical trial data and the LACE meta-analyses, the role for adjuvant chemotherapy in stage IA disease was detrimental to overall survival and inconclusive in stage IB disease due to a statistically insignificant improvement in survival. Therefore, most experts would recommend a risk/benefit discussion should be held for patients with resected NSCLC tumors greater than or equal to 4 cm.

Stage II

Stage II NSCLC is usually due to a larger primary tumor size (> 5 cm or local obstruction without nodal involvement) and/or ipsilateral hilar nodal involvement (ie, N1 disease). These patients are also treated by surgical resection (lobectomy or pneumonectomy) with curative intent. Patients with stage II NSCLC are at higher risk for recurrence than those with stage I, and even with adjuvant chemotherapy and/or radiotherapy where appropriate, 5-year overall survival rates remain only 40% to 60%. Postoperative (ie, adjuvant) chemotherapy utilizing cisplatin-based doublets has improved cancer-related and overall survival, but no single preferred regimen has been established. Preoperative (ie, neoadjuvant) chemotherapy may allow for more cycles of chemotherapy to be administered without interruption or delay due to toxicities but have not been shown to improve outcomes compared to postoperative administration. Routine incorporation of postoperative radiation after curative resection has been shown to be detrimental to overall survival. However, postoperative radiation therapy should be considered in patients with a positive surgical margin or those upstaged to IIIA disease due to mediastinal nodal (ie, N2) involvement as they may have improved survival with adjuvant radiation therapy following chemotherapy.

Although the standard treatment for stage II disease involves surgery followed by chemotherapy, the median age of patients enrolled in many of these seminal trials evaluating postoperative chemotherapy were 60 to 65 years, some of which had excluded patients age greater than or equal to 75. Furthermore, many of these trials incorporated cisplatin-based regimens, which may be more difficult for older adults to tolerate, particularly those with age- and/or comorbidity-related renal dysfunction. To date, large, prospective trials evaluating carboplatin-based regimens remain sparse. Regardless of chemotherapy regimen choice, there still remains a clinical benefit in select older adults with stage II disease and good performance status.

Moreover, nonsurgical approaches to older patients with stage II disease who have medically inoperable disease due to poor pulmonary reserve or unresectable disease pose a unique challenge for an otherwise “surgical disease.” Several approaches in these patients have been utilized: SBRT or hypofractionated RT alone, SBRT followed by “adjuvant” chemotherapy, or definitive concurrent chemoradiation. There are no prospective data to guide decision making for this patient subset and currently requires multidisciplinary input from medical and radiation oncology team members to individualize therapy based on patient- and cancer-related factors, intensity and toxicities of each approach, and patient preferences. Finally, older patients with stage II disease due to two small lesions in the same lobe of the lung (ie, cT3N0) remain an understudied subgroup and treatment approaches should likewise be individualized.

Stage III

Patients with stage III NSCLC remain a clinically heterogeneous patient population necessitating a multidisciplinary approach to navigate the multiple surgical, radiation, and chemotherapy treatments available. Patients with stage III NSCLC due to chest wall involvement with limited or no nodal involvement should generally be assessed for surgical resection because of associated improved local control. However, stage III is usually attributable to mediastinal nodal involvement and thus precludes upfront surgical resection. Therefore, accurate mediastinal staging is critically important in clinically appearing early-stage disease with the incorporation of PET/CT imaging for staging and pathologic confirmation by tissue either by EBUS-guided biopsy and/or surgically by mediastinoscopy when

appropriate. Preoperative chemotherapy or concurrent chemoradiation for potentially resectable disease has led to conflicting results in cancer-related survival. Those patients able to undergo lobectomy (as opposed to pneumonectomy) after preoperative chemoradiation can achieve a median overall survival rates of 2 to 3 years, depending on pathologic mediastinal nodal response, as opposed to 12 to 18 months typically reported with definitive chemoradiation alone.

For unresectable IIIA disease or stage IIIB disease (due to contralateral hilar or mediastinal nodal disease), more functionally fit patients are usually offered definitive concurrent chemoradiation therapy over sequential chemotherapy and radiation therapy, as the former approach has conferred improved cancer response rates as well as improved cancer-related and overall survival. However, concurrent chemoradiation significantly increases the risk of short-term radiation toxicities such as esophagitis as well as neutropenia that may be more difficult to tolerate in vulnerable older adults with stage III NSCLC. Although the absolute benefit of concurrent versus sequential therapy is relatively small in younger adults, it can still be seen in select older adults (ie, age $\geq$ 70) as evidenced in several subset analyses of phase III clinical trials. Consolidation chemotherapy after chemoradiation remains a controversial area but data are accumulating that older adults with stage III NSCLC may not benefit from this additional treatment. Because of the treatment intensity involved, among older patients, geriatric assessments may play an important clinical role in the selection of those patients who are most likely to benefit from more intensive combined modality treatment since no prospective data exist to guide decision making. Certainly optimization of comorbidities, functional status, cancer symptoms, social support, and geriatric syndromes would prove useful because of the increased morbidity of these therapeutic approaches employed in stage III NSCLC.

Stage IV

Over half of patients with NSCLC will have distant metastases at the time of diagnosis, for which platinum-based doublets have become the standard of care as first-line therapy in improving survival among fit older patients. Aging is associated with physiologic changes in body composition, drug metabolism and clearance, and functional status. Comorbidity, polypharmacy, nutrition, cognitive function, and psychosocial factors should ideally be taken into account when caring for older adults with metastatic lung cancer. Historically, we have known since 1999 after the phase III Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) that older patients have improved survival and quality of life with single-agent chemotherapy versus supportive care alone. This was followed by two more large phase III randomized trials showing that docetaxel was at least as good as vinorelbine, slightly favoring docetaxel with a relative improvement in median progression-free survival (5.5 vs 3.3 months). The Multicenter Italian Lung Cancer in the Elderly Study (MILES) trial demonstrated the combination of vinorelbine plus gemcitabine was no more effective than either agent alone.

More recently, older adult–specific phase II studies and the phase III CALGB 9730 showed improved response rate and failure-free survival with platinum-based doublet chemotherapy compared to singlet therapy within older and patients with borderline performance status (ie, PS = 2 on the ECOG scale). Quoix et al. reported in the IFCT-0501 phase III randomized trial, a 10-month overall survival versus a 6-month overall survival in older patients with stage IV NSCLC treated with doublet chemotherapy versus monotherapy, respectively. An increase in toxic effects was observed in those who received doublet chemotherapy. The study authors acknowledged that most of older adults included in this study as “fit.” Thus, the difficulty remains in how to correctly identify and select which older patients are most likely to benefit from more aggressive doublet versus singlet chemotherapy regimens. Few data exist regarding the outcome of chemotherapy in frail older patients with advanced NSCLC, particularly in those age greater than or equal to 80.

To date, only one trial (Elderly Selection on Geriatric Index Assessment [ESOGIA]) has incorporated a geriatric assessment into treatment decision making among older patients with stage IV NSCLC. This study showed that the geriatric assessment can help gauge older patients who were more likely to have toxicity when stratified to different treatment arms (doublet versus singlet versus best supportive care [BSC]). However, this geriatric assessment–based stratification did not lead to improved survival outcomes than those decisions made by “usual care” incorporating “conventional” factors such as age and performance status.

For older patients with adenocarcinoma histology that harbor a sensitizing mutation in *EGFR* or an *ALK* or *ROS1* gene rearrangement, it is preferable that those patients receive erlotinib or crizotinib (or a similar targeted agent) upfront as they lead to better responses and time to progression than platinum-based doublet chemotherapy, respectively. Rash, diarrhea, and fatigue, versus fatigue, visual disturbances, nausea, and hepatitis may be more pronounced with use of erlotinib and crizotinib, respectively, among older adults. However, it is important to note that

older adults may require dose reductions even for such oral therapies. Therefore, it may be prudent in more vulnerable older adults to start a reduced dose and gradually dose-escalate depending on their tolerability of the drug.

For second-line therapy or beyond for NSCLC, approved treatment options usually include docetaxel, erlotinib, vinorelbine, and, based on histology, pemetrexed and gemcitabine if not already employed in the first-line therapy. Docetaxel's superiority over erlotinib in terms of efficacy has been controversial and recent studies are looking at ways to help utilize biomarkers to aid in decision making regarding selection of therapy. Erlotinib in this setting is of interest for older adults with NSCLC because of its generally more manageable toxicity profile and its oral formulation. Ramucirumab, an antibody directed against vascular endothelial growth factor receptor 2, has recently been approved in combination with docetaxel based on a phase III trial. However, the combination's survival advantage over docetaxel monotherapy is relatively small. It is important to note that less than half of patients enrolled on this trial were greater than or equal to 65 years, and patients with an ECOG PS of 2 were excluded. Based on subset analysis, there was no survival benefit over docetaxel monotherapy seen in the few patients age greater than or equal to 70, which adds a tale of caution to interpreting clinical trial data within a geriatric oncology context. Furthermore, second-line-therapy or beyond trials specifically in older or functionally vulnerable patients with metastatic NSCLC remain elusive. Goals-of-care discussions within the context of the patient and caregivers' preferences regarding relative risks and benefits are even of more significance at the time of disease progression for metastatic lung cancer.

Maintenance chemotherapy is an evolving treatment strategy for select patients with stage IV NSCLC with a good response to initial platinum-based doublet chemotherapy. Pemetrexed-based maintenance therapy for patients with adenocarcinoma histology has been shown in several studies to improve progression-free survival and, in at least one major study (PARAMOUNT), demonstrated an overall survival benefit over placebo. However, many of these patients were relatively younger (early 60s) with good performance status. How maintenance chemotherapy strategies versus "drug holidays" should be employed in older and/or frailer patients with NSCLC remains unclear. For those with squamous cell carcinoma, the evidence for gemcitabine- or erlotinib-based maintenance chemotherapy is less robust.

Looking forward, it is important to note that novel agents may change the therapeutic landscape, particularly in the area of immunotherapy. Inhibitors targeting the PD1 receptor on peripheral T cells or targeting the PDL1 (ligand) on tumor cells may boost the immune system's response against cancer. Initial data for anti-PD1 antibodies used in NSCLC and SCLC appear promising and confer substantially less toxicity than that seen with traditional chemotherapy. How these drugs will be employed (alone or in combination with other agents), sequencing (first-line vs second-line therapy or beyond, localized vs metastatic disease), and how well they are tolerated by older adults with lung cancer remain important questions that will need to be addressed in the near future. However, two such agents (pembrolizumab and nivolumab) have recently been approved for metastatic melanoma.

SMALL-CELL LUNG CANCER

SCLC is less common than NSCLC (< 20% of all lung cancer cases), but it is more intimately associated with smoking exposure and duration. SCLC has a rapid growth and, unlike NSCLC, patients with SCLC tend to be symptomatic at the time of diagnosis, with common symptoms including chest pain, dyspnea, hemoptysis, SVC syndrome, hyponatremia/the syndrome of inappropriate antidiuretic hormone (ADH) (SIADH), or symptoms related to brain metastases. Although the same tumor, node, metastasis (TNM) staging system for NSCLC is applied to SCLC, cancer providers frequently still utilize the older clinical staging of limited-stage (LS) (ie, disease that can be confined to a radiation port, ie, up to stage IIIB) versus extensive-stage (ES) disease (ie, stage IVA–B). Because of SCLC's higher penchant for central nervous system (CNS) involvement, all patients with SCLC should undergo brain imaging as part of their initial staging evaluation. Due to SCLC's chemo- and radiosensitivity, objective response rates are common, which can lead to rapid symptomatic relief in first-line therapy. Median overall survival rates associated with treatment for LS- and ES-SCLC range from 12 to 18 months and 8 to 12 months, respectively.

Treatment for limited-stage disease is approached utilizing concurrent chemoradiation utilizing a platinum-based doublet, frequently with etoposide. Based on a large meta-analysis, carboplatin can be incorporated in lieu of cisplatin for older adults or other patients in whom cisplatin may not be well tolerated for either limited- or extensive-stage SCLC. Extensive-stage disease treatment is combination chemotherapy and even older and poor-performance-status patients may derive benefit from such an approach.

Because of the risk of CNS involvement and as a site of relapse in patients with limited- or extensive-stage SCLC, PCI has been evaluated in patients with SCLC who have exhibited a clinical response to initial cancer therapy and remain free of obvious brain metastases. PCI involves the use of WBI for up to a total dose of 25 to 30 Gy. Although

there is current controversy as to the extent of clinical benefit of PCI in adults with ES-SCLC, multiple studies in LS-SCLC have demonstrated its benefit in lowering the risk and time of development of brain metastases, thereby improving overall survival in the majority of studies. Older adults (ie, 70–80 years) with LS-SCLC may still derive a survival advantage with PCI but are at increased risk of treatment-related adverse events. Any form of WBI may confer risk of later-term neurocognitive effects, which may particularly be of concern for LS-SCLC patients whose prognosis is generally better than that of those with ES-SCLC. Data for older adults with LS-SCLC who may have subclinical mild cognitive impairment at baseline may be at higher risk for these complications. Hippocampal-sparing radiation therapy planning techniques and the use of neuroprotectants such as memantine have shown some initial promise in patients undergoing WBI for known brain metastases that may help reduce this risk in patients undergoing PCI in the future.

Although SCLC is a chemo- and radiosensitive disease as mentioned above, relapses are common, with second-line or beyond chemotherapy options remaining less optimally defined and of generally limited clinical benefit. Second-line options have included agents such as camptothecins (ie, topotecan, irinotecan) and taxanes (ie, paclitaxel, docetaxel), with response rates ranging from 15% to 30% and median overall survival ranging from 4 to 8 months (depending on platinum-sensitivity status to initial treatment). Patients with platinum-refractory SCLC whose disease progresses on or fails to respond to additional therapy are unlikely to benefit from further therapy. Novel therapeutic agents currently remain elusive for these patients but immunotherapies such as anti-PD1 inhibitors similar to those being studied for NSLC with minimal toxicities may be potentially efficacious options in the near future.

THE ROLE OF PALLIATIVE CARE

A recent prospective, randomized controlled study evaluated the effect of early palliative care after a new diagnosis of metastatic NSCLC on patient-reported outcomes and end-of-life care among ambulatory patients. Of the 151 patients who underwent randomization, 27 died by 12 weeks and 107 (86% of the remaining patients) completed assessments. Patients assigned to early palliative care had a better quality of life than did patients assigned to standard care (mean score on the Functional Assessment of Cancer Therapy-Lung [FACT-L] scale [in which scores range from 0–136, with higher scores indicating better quality of life] 98.0 vs 91.5; $p = 0.03$). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs 38%, $p = 0.01$). Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs 54%, $p = 0.05$), median overall survival was longer (11.6 vs 8.9 months, $p = 0.02$).

Older patients may have goals or expectations different from those of younger patients and this may be particularly relevant in the setting of a disease as lethal as lung cancer. In a multi-institutional, prospective, observational cohort study that included among others, 710 patients with advanced lung cancer treated with palliative-intent chemotherapy, 69% gave answers that were not consistent with understanding that chemotherapy was very unlikely to cure their cancer. In multivariable logistic regression, factors that were associated with a greater likelihood of this apparent misunderstanding were nonwhite race or ethnic group as compared with white race (odds ratio [OR] for Hispanic patients, 2.82; 95% CI, 1.51–5.27; OR for black patients, 2.93; 95% CI, 1.80–4.78). Educational level, functional status, and the patient's role in decision making were not associated with such inaccurate beliefs about chemotherapy. However, there was a strong trend of worse understanding with increasing age (OR 1.68 for patients in the age group 70–79; 95% CI, 1.10–2.59). Thus, goals of chemotherapy need to be conveyed clearly to patients as there is a high prevalence of misconceptions about the role of chemotherapy with minority ethnic groups and older patients being at greater risk for such misunderstanding. Furthermore, in the above-cited prospective study evaluating the role of early integration of palliative care, participants completed baseline and longitudinal assessments of their perceptions of prognosis and the goals of cancer therapy over a 6-month period. Despite having terminal cancer, a third of patients reported that their cancer was curable at baseline, and a majority (69%) endorsed eradicating the cancer as a goal of therapy. A greater proportion of patients who were assigned to early palliative care in this study developed an accurate assessment of their prognosis over time (83% vs 60%; $p = 0.02$) compared with those receiving standard oncology care. Patients receiving early palliative care who reported an accurate perception of their prognosis were less likely to receive intravenous chemotherapy near the end of life (9.4% vs 50%; $p = 0.02$).

GERIATRIC ASSESSMENT

Identifying appropriate treatment for a potentially vulnerable patient population is not straightforward in the absence of evidence-based guidelines. Moreover, chronological age does not capture the physiologic and functional status in older patient with advanced lung cancer. There has been a great reliance on ECOG performance status as a measure of physical function in lung cancer clinical trials. However, this test may represent an oversimplification for assessment of function in older adults with lung cancer. Comorbidity, polypharmacy, nutrition, cognitive function, and psychosocial factors should be taken into account when caring for older adults with lung cancer (**Table 99-2**). The recently reported ESOGIA trial recently was a phase III, randomized, multicenter study comparing older patients (≥ 70 years) with stage IV NSCLC a standard strategy of treatment allocation (carboplatin based bitherapy or monotherapy with docetaxel) based on performance status and age with an experimental strategy allocating the same regimen or BSC according to a comprehensive geriatric assessment (CGA). There was no significant difference in overall survival between the two treatment arms but decreased toxicity and adverse events in the CGA-directed arm. In the United States, the CALGB has set a precedent and completed a feasibility study of incorporating CGA into cancer treatment trials. Patients age greater than 65 with cancer, who enrolled on cooperative group cancer treatment trials, were eligible to enroll on CALGB 360401. They completed the CGA tool prior to initiation of protocol therapy, consisting of valid and reliable GA measures which are primarily self-administered and require minimal resources and time by health care providers. This brief, primarily self-administered CGA large prospective study across several tumor types of over 500 patients using the same CGA process, predicted toxicity of chemotherapy in adults receiving chemotherapy better than MD-rated performance status. Currently in clinical practice, physicians use age, performance status, and an overall "gestalt" of how fit an older patient is, which can lead to both under- and overtreatment in this patient population. CGA would serve as a uniform and reproducible instrument to guide therapy and optimize treatment decisions. Future studies across tumor types are needed; however, CGA use in lung cancer is particularly relevant due to the median age of 70 at diagnosis. Geriatric oncologists use the CGA and other chemotherapy toxicity tools to try to address the multimorbidity and underlying heterogeneity of an aging oncology population.

TABLE 99-2 TEN MOST COMMON CO-OCCURRING CHRONIC CONDITIONS AMONG MEDICARE BENEFICIARIES WITH LUNG CANCER (*N* = 331,992), 2011

BENEFICIARIES < 65 YEARS (*N* = 30,260)			BENEFICIARIES 65 YEARS AND OLDER (*N* = 301,732)		
	N	%		N	%
Lung cancer prevalence		0.6	Lung cancer prevalence		1.2
Top 10 comorbidities			*Top 10 comorbidities*		
Hypertension	18,035	59.6	Hypertension	221,714	73.4
COPD	17,973	59.4	COPD	172,252	57.1
Anemia	14,368	47.5	Hyperlipidemia	163,444	54.2
Hyperlipidemia	12,289	40.6	Ischemic heart disease	159,387	52.8
Ischemic heart disease	12,121	40.1	Anemia	155,927	51.7
Depression	11,348	37.5	Arthritis	101,777	33.7
Diabetes	9579	31.7	Diabetes	96,350	31.9
Arthritis	8811	29.1	Heart failure	94,639	31.4
Heart failure	7309	24.2	Chronic kidney disease	89,542	29.7
Chronic kidney disease	7146	23.6	Depression	62,776	20.8

COPD, chronic obstructive pulmonary disease.

Data from *CMS administrative claims data, January 2011–December 2011, from the Chronic Condition Warehouse (CCW), ccwdata.org*.

MULTIPLE CHRONIC CONDITIONS

Multiple chronic conditions or MCCs are increasing among geriatric oncology patients and are defined as having two or more chronic conditions in addition to cancer. In 2010, among Medicare Fee-for-Service (FFS) beneficiaries with

cancer, fewer than 10% had only one condition, 25% had one to two conditions, 35% had three to four chronic conditions, and 30% had more than five other chronic conditions. This heterogeneous patient population is underrepresented in clinical trials, suggesting standard management and routine care recommendations may not be applicable. Cancer treatment can exacerbate MCCs, or MCCs can worsen anticipated adverse effects requiring modification of routine care offered and/or comanagement. MCCs should be reviewed and considered not only in shared treatment decision making but also during follow-up among survivors. For example, patients with diabetes, HIV, nonalcoholic steatohepatitis (NASH), or peripheral vascular disease (PVD) have a higher risk of chemotherapy-induced peripheral neuropathy. MCC management guidelines in geriatric oncology are under development for implementation across cancer treatment health care settings.

SUPPORTIVE CARE

Every lung cancer patient whether they are receiving treatment or not, should receive full supportive care or BSC. Among treatment patients, supportive care includes but is not limited to transfusions of blood and blood products, nutritional support, growth factor support (eg, granulocyte colony-stimulating factor [G-CSF]), antibiotics, antiemetics, and antidiarrheal agents.

Myelosuppression, including neutropenia and anemia, is among the most common and potentially dangerous adverse effects of chemotherapy. Radiation is more likely to cause fatigue as well as pneumonitis, pericarditis, and/or esophagitis depending on its location. If directed at a bone metastasis, it can also cause myelosuppression. The American Society of Clinical Oncology now supports the use of G-CSF in older patients who are high risk for the development of neutropenic fever. Education regarding neutropenic fever is standard and requires close temperature monitoring with early hospitalization and antibiotic use. Although routinely used, use of G-CSF should not be a surrogate for proper dose reduction or adjustment in older, more frail patients or those treated with palliative intent. However, the use of recombinant erythropoietin (EPO) is no longer routinely used in this setting.

Nausea, vomiting, and diarrhea are the typical nonhematologic adverse side effects of many chemotherapeutic agents; however, antiemetics have significantly improved. Extreme caution and aggressive management is undertaken with both oral and intravenous medications, particularly with the use of cisplatin (highly emetogenic). Prophylactic use of dexamethasone, 5-HT_3 antagonists (ondansetron and granisetron), and NK1 receptor antagonists (fosaprepitant, IV, or aprepitant, oral) are commonly used. Both acute and delayed nausea and vomiting are more easily prevented and controlled with the use of these combinations.

Mucositis and esophagitis are particularly common in chemoradiation regimens for curative intent. Several topical and oral medications are available for use; however, nutritional support becomes of utmost importance, particularly with combined modality use. Anorexia, weight loss, and dysgeusia are also very common, requiring close weight monitoring and often IV hydration. Comanagement with a nutritionist/dietician is often advised.

Fatigue, pain control, and stress also require supportive care. Steroids have been found to be more effective for fatigue than usual care or methylphenidate. Pain control often requires long- and short-acting narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), or gabapentin for neuropathic pain. Neuropathic pain is often associated with taxane-containing chemotherapy regimens used in both curative- and palliative-intent regimens. Bisphosphonates are also used for bony metastatic disease. Cancer diagnosis and treatment cause psychological, financial, and caregiver burden. Many cancer centers now include clinical support staff to address all of these issues.

PERSONALIZED MEDICINE

Patients and providers will often hear term “personalized medicine” or “targeted therapy” for the treatment of their lung cancer. This largely applies to advanced disease; however, may soon have a role in earlier-stage diseases as well. Researchers and clinicians are beginning to better understand the complex molecular biology of lung cancer that includes largely the activation of oncogenes by mutation, amplification, or translocation. Although tumor molecular profiling has become standard of care for EGFR and ALK, for which treatments are available, testing for PD1, PDL1, ROS1, RET, KRAS, BRAF, HER2, MET, PIK3CA, FGFR1, and DDR2 are all under investigation either in vitro or clinical trials. Understanding tumor heterogeneity in the genetic makeup of lung cancer is evolving and becoming increasingly complex in regards to targeted treatment options. Many clinical trials are currently focusing on multiple tissue biopsies and high throughput sequencing to track mutations and their evolution during treatment. Other targeted

therapies use immunotherapy to use the patient's immune system to directly attack lung cancer cells. Despite these advances, in most cases, cytotoxic chemotherapy still remains the standard of care either alone or in combination with surgery or radiation.

COST OF CARE

In the United States, we spend over $125 billion annually on cancer care, the majority of which is on advanced disease. This is projected to increase to $158 billion annually by the year 2020 if the incidence, survival, and cost remain constant. It could rise to as high as $173 billion annually based on a 2% annual increase in initial and end-of-life cost increases based on the aging US population and a lung cancer prevalence of 457,000 people in 2020. For lung cancer costs, this could be an increase from $12 billion annually in 2010 to $15 to $18 billion by 2020. This does not account for the new preliminary decision by Centers for Medicare and Medicaid Services (CMS) to cover the cost of LDCT scans projected to cost anywhere from $22 to $37 million. In cancer care, one recent study has cited acute hospital cancer care as the driver of regional spending variation in advanced disease. For lung cancer, several cost-effectiveness studies have been done for different chemotherapy agents both in first-line and second-line treatment, different surgical procedures, and among radiation treatments including newer modalities such as SBRT. Retrospective and prospective data are lacking directly comparing cost-effectiveness between surgical and radiation procedures. So how do we "bend the cost curve of cancer care"? Issues arise with direct therapeutic cost and the extent of care due to prolonged survival particularly in prostate and breast cancer treatments. For older lung cancer patients, new molecular-targeted oral treatments or newer cytotoxic chemotherapeutic agents pose unsustainable monthly costs both for the individual and the Medicare payment system. Several solutions target both oncologists' testing and prescribing behavior and patients' attitudes and expectations of their cancer care. More comparative effectiveness studies are needed to inform and help contain cancer health care costs in lung cancer, particularly in advanced disease.

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Chapter 100

Gastrointestinal Malignancies

Ryan Nipp, Nadine J. McCleary

Learning Objectives

- Identify effective methods of colorectal cancer screening.
- Integrate appropriate colorectal cancer screening recommendations into health maintenance models of care for older adults, including potential discontinuation of screening when expected lifespan is fewer than 5 to 10 years.
- Recognize the overwhelming need to enroll older adult patients with gastrointestinal (GI) cancers in clinical trials.

Key Clinical Points

1. **Colorectal cancer accounts for approximately 10% of all cancer-related deaths in the United States; it causes more deaths than prostate cancer in men 60 to 79 years and falls just short of breast cancer in women 80 years or older. Noncancer deaths account for a sizeable percentage of deaths in older adults with colorectal cancer; congestive heart failure, chronic obstructive pulmonary disease, and diabetes account for 9.4%, 5.3%, and 3.9% of deaths, respectively, in older patients with localized disease.**
2. **Medicare covers surveillance fecal occult blood testing plus sigmoidoscopy or barium enema or colonoscopy for all beneficiaries; it may be reasonable to discontinue screening when life expectancy is shorter than the time a polyp progresses to a cancer, that is, 5 to 10 years.**
3. **Men who were curatively treated with radiation for localized prostate cancer have a 70% increased risk of developing cancer in previously irradiated portions of the bowel and could potentially benefit from more frequent colorectal cancer screening.**
4. **Perioperative mortality is lower for colorectal cancer surgery in high-volume centers versus low-volume centers. Further, less aggressive surgical intervention is more likely in low-volume centers and in older patients, and increases the risk of recurrence and cancer-related death. Finally, laparoscopic procedures have lower mortality and equivalent outcomes in older adults.**
5. **Morbidity and mortality for surgery to treat resectable pancreatic or gastric cancer are similar in young and older adults.**
6. **A large number of expanded options in chemotherapy (eg, targeted antibodies, kinase inhibitors) that are generally tolerated by older adults are now available and should prompt clinicians caring for older adults to seek medical oncology consultation even in those with advanced GI cancer.**
7. **In those with esophageal cancer, African-American patients 65 years and older were noted to have a lower rate of surgical consultation and half the rate of curative surgery as their older adult Caucasian counterparts—very likely contributing to worse outcomes in minorities with esophageal cancer.**

INTRODUCTION

Gastrointestinal cancers are primarily diseases of persons in their sixth, seventh, and eighth decades of life. Both

incidence and mortality of gastrointestinal cancers increase with advancing age (**Figures 100-1, 100-2,** and **100-3**). Many older persons, however, have additional medical problems that almost certainly contribute to inferior outcomes. This chapter will explore the epidemiology, presentation, treatment options, and disparities in the care of older persons with gastrointestinal malignancies.

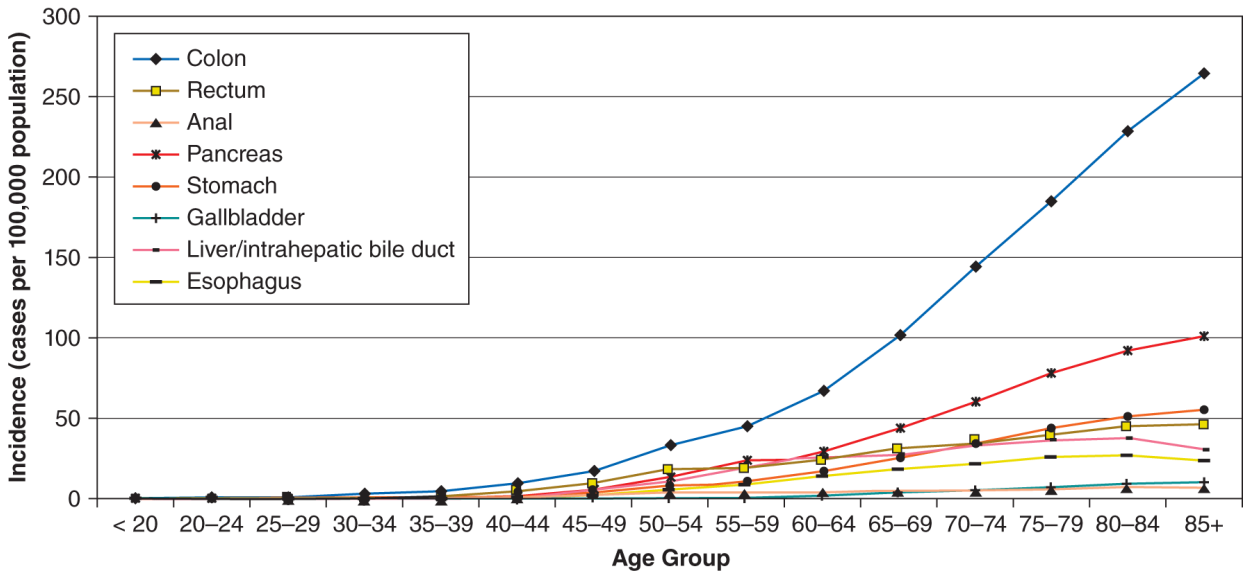


FIGURE 100-1. Percentage of incident cases by age group for gastrointestinal (GI) malignancies (2007–2011).

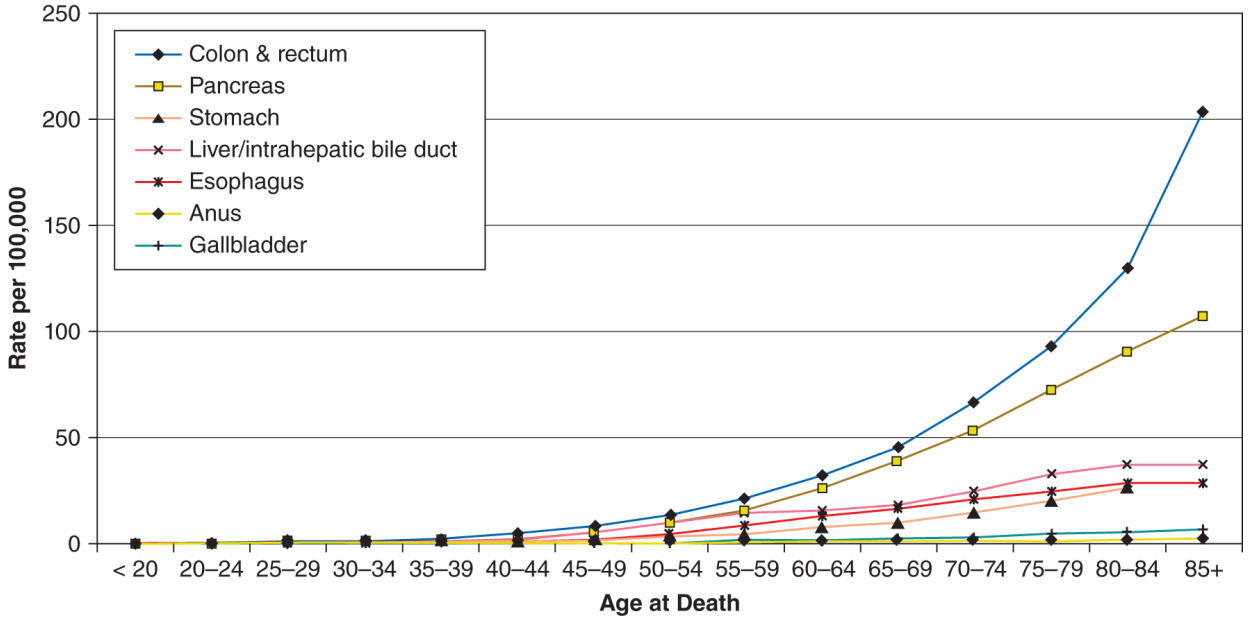


FIGURE 100-2. Mortality rates for gastrointestinal malignancies (2007–2011) by age at death.

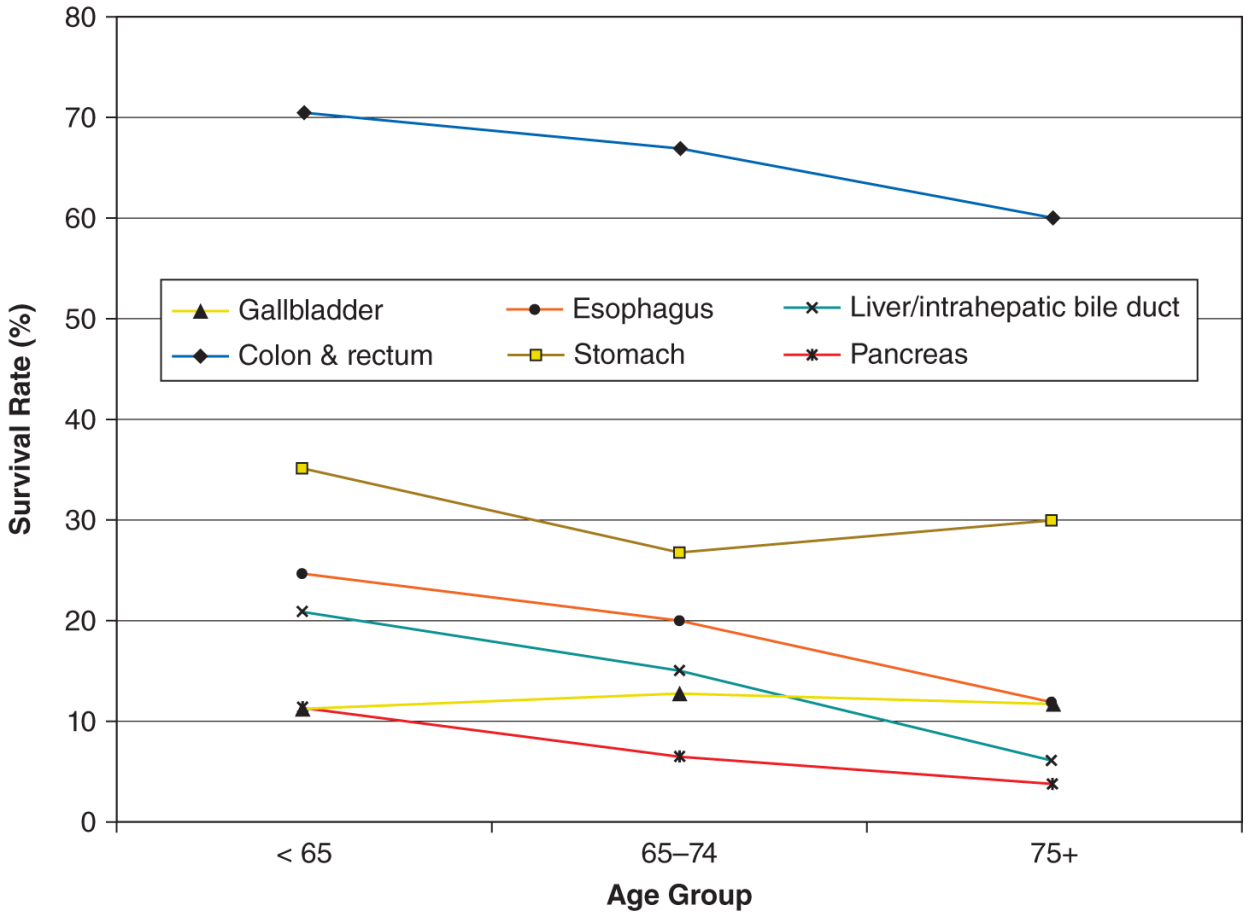


FIGURE 100-3. Five-year survival rates for gastrointestinal malignancies by age group.

In general, the symptoms and presentation of gastrointestinal cancers in older individuals appear similar to those of persons of younger age. Although treatments for these cancers have been developed primarily in younger patients, greater expertise over time has permitted similarly safe and efficacious therapy to be extended to older age groups. Since the greatest percentage of gastrointestinal cancers are located in the colon and rectum, most of the information regarding older persons focuses on colorectal cancer. Unfortunately, there is a paucity of information concerning the treatment of older patients with other gastrointestinal malignancies. Where we lack data specific to older adults for individual therapies, attention should be paid to the toxicities of the treatments, with consideration of patients' concurrent medical conditions and social support. Additionally, early referral to an oncologist to facilitate decision making is advised. In this chapter, gastrointestinal malignancies are ordered by incidence in the US population.

COLORECTAL CANCER

Colorectal cancer accounts for approximately 10% of all new cancer cases and 10% of all cancer-related deaths in the United States. In fact, colorectal cancer causes more deaths than prostate cancer in men 60 to 79 years and falls just short of breast cancer in women 80 years or older. In 2014, 96,830 new cases of colon cancer and 40,000 new cases of rectal cancer will be diagnosed, accounting for approximately 50,310 deaths. The probability of developing colorectal cancer increases from 0.6% in the first four decades of life to 3.7% for females and to 4.0% for males in the seventh decade of life. Median age at diagnosis of colorectal cancer is 72 years. The overall 5-year relative survival is 65% with this cancer. It is 69% for persons under the age of 65 and declines to 61% for persons over age 65 (**Figure 100-4**).

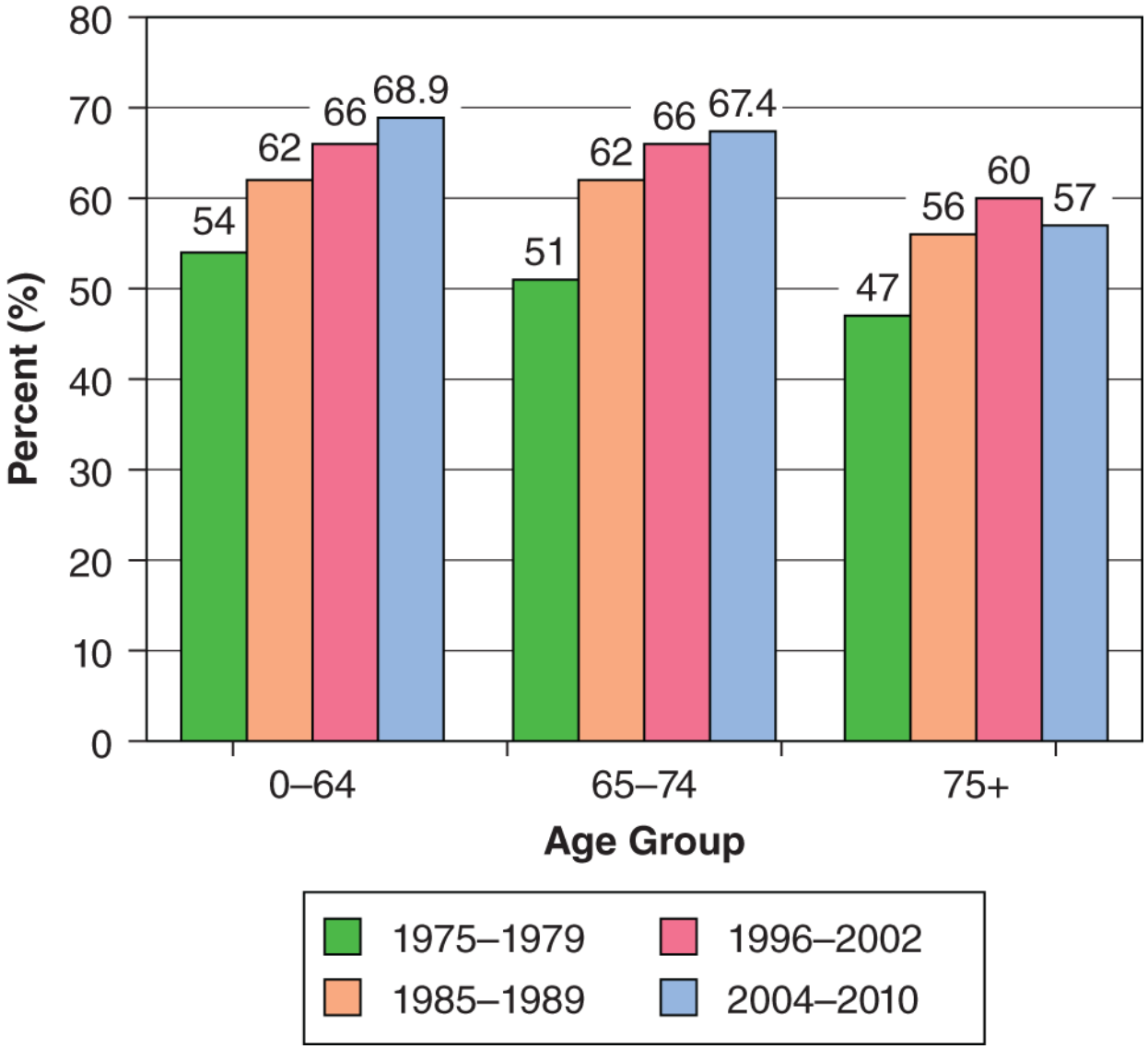


FIGURE 100-4. All-stage 5-year survival by age group for colon and rectal cancer.

Studies suggest that older patients present at the time of diagnosis with the same probabilities of having localized and advanced colon cancer as younger patients. In randomized studies, older patients are reported to have the same performance status and incidence of tumor-related symptoms as younger patients but tend to have more disease-related weight loss. Older patients also appear to have a greater incidence of right-sided (proximal) tumors, and higher rates of obstruction and perforation. This in turn results in a greater likelihood of acute presentations, leading to a higher perioperative mortality rate in this older age group.

While some investigators have noted that overall survival is shorter in older patients, this difference is not significant if noncancer deaths are excluded. In fact, comorbid illnesses account for a substantial number of deaths among older patients with colorectal cancer. In one study of 29,733 patients 67 years and older with localized colorectal cancer in the Surveillance, Epidemiology, and End Results (SEER)/Medicare database, congestive heart failure, chronic obstructive pulmonary disease, and diabetes accounted for 9.4%, 5.3%, and 3.9% of deaths, respectively.

Risk Factors of Colorectal Cancer

As in younger individuals, most older persons have no clearly defined risk factors for the development of their colorectal cancer. Hereditary syndromes, such as familial adenomatosis polyposis or hereditary nonpolyposis colorectal cancer, have less impact in this older age group, since the majority of cases are diagnosed before the age of 65. There is one risk factor specific to men who were curatively treated with radiation for localized prostate cancer. These men have a 70% increased risk of developing cancer in previously irradiated portions of the bowel and could potentially benefit from more frequent colorectal cancer screening.

Chemoprevention of Colorectal Cancer

Various dietary supplements and drugs have been proposed as chemopreventive agents for colorectal neoplasia. Of these, aspirin has been the most widely studied; the regular use of this drug appears to confer a significant risk reduction (relative risk 0.56–0.68).

In at least two prospective cohort studies, the use of postmenopausal estrogens has been shown to reduce the risk of colorectal cancer by approximately 30%. Estrogen supplementation, however, has been associated with an increased risk for coronary heart disease, breast cancer, thromboembolic events, and early mortality in at least one large randomized study of postmenopausal women, thereby limiting its use as a chemopreventive agent in older women.

Additionally, it has been reported that cholesterol-lowering statins can significantly reduce the risk of colorectal cancer. As compared to individuals who did not use statins, individuals who used these agents for at least 5 years were able to reduce their relative risk of colorectal cancer by one-half.

Screening of Colorectal Cancer

Approximately one in two persons will have an adenomatous polyp in their colon by the age of 70. The risk of sporadic colorectal cancer can be reduced by 50% to 90% if adenomatous polyps are implicated by fecal occult blood testing or are visualized by barium enema, sigmoidoscopy, or colonoscopy and are then removed before they transform into a malignancy over a 5- to 10-year period. Randomized trials have demonstrated that routine fecal occult blood testing can diminish colon cancer mortality by 15% to 20% during an 8- to 18-year follow-up period. The mortality benefit for older patients was slightly lower (10%–16%) than for younger patients (19%–23%).

Case-control studies suggest that lower endoscopy and removal of polyps may decrease the incidence and mortality of colorectal carcinoma by 50% to 80%. However, screening extends life to a lesser degree with advancing age. Although colonoscopy appears to be particularly beneficial in older patients who have a higher incidence of proximal neoplasms, which are beyond the view of a flexible sigmoidoscopy, the risk of perforation from colonoscopy is higher than from sigmoidoscopy (OR 1.8). This risk increases with advancing age and number of comorbidities. Therefore, screening decisions must be individualized for every older patient.

Guidelines from the American Cancer Society, US Multisociety Task Force on Colorectal Cancer, and the American Radiological Society suggest the following regarding the screening of average risk men and women beginning at age 50: flexible sigmoidoscopy to 40 cm or splenic flexure every 5 years, colonoscopy every 10 years, double-contrast barium enema every 5 years, or computed tomography colonography every 5 years. These guidelines also review screening and surveillance for colorectal cancer in increased-risk and high-risk persons, with accompanying recommendations. Those at increased risk include those individuals with a personal history of adenomatous polyps or colorectal cancer and patients with a family history of colon neoplasias.

Since only a small percentage of persons at risk for colorectal neoplasia undergo routine screening in the United States, Medicare now provides reimbursement for surveillance fecal occult blood testing plus sigmoidoscopy or barium enema or colonoscopy for all beneficiaries. This has increased the prevalence of “screening within 1 year” for fecal occult blood testing from 20% in persons under 65 years to 26% in persons 65 years and older and the prevalence of “endoscopy within 5 years” from 37% in persons under 65 years to 48% in persons 65 years or older.

Most older persons have a stated preference to continue colorectal cancer screening, feeling that their own life expectancy does not factor into this decision. Since the risk of advanced neoplasia and colorectal cancer is highest in the oldest individuals, it seems doubtful that screening should be arbitrarily discontinued after a certain age. In the United States, an individual who reaches the age of 80 has an average life expectancy of an additional 9.7 years for women and 8.1 years for men. At age 85, average survival is 7 years for women and 5.8 years for men. This estimate must be adjusted for the number and severity of chronic diseases affecting the individual, as well as his or her functional status. It may be reasonable to discontinue screening when life expectancy is shorter than the time a polyp progresses to a cancer, that is, 5 to 10 years.

Localized Colorectal Cancer

Surgery—localized colon cancer Cancers of the colon are typically resected with a hemicolectomy. Whether older age is an adverse prognostic factor in resection of localized colon cancer is controversial. Data on 20,862 patients undergoing surgery in 1997 for colon cancer from the Nationwide Inpatient Sample, a claims-based database, suggested that perioperative mortality increases gradually with advancing age until the age of 80, after which a

substantial increase in mortality is seen (6.9% for patients older than 80 years). In Australia, patients 70 years and older had a worse prognosis for early-stage colon cancer treated with surgery alone. A European study also showed increased 30-day morbidity and mortality rates for patients 80 years and older compared to their younger counterparts.

Older patients in the Nationwide Inpatient Sample from 1997 had lower mortality rates at high-volume hospitals than at low-volume institutions: 3.1% versus 4.5% for patients older than 65 years ($p = 0.03$). This effect was even more pronounced for patients older than 80 years, where 4.6% of patients died at high-volume centers compared to 7.3% at smaller institutions ($p = 0.04$). Therefore, it may be preferable to send the very oldest patients with colon cancer to high-volume hospitals for their resections.

A tendency to perform less aggressive surgery in older patients may be evident from an analysis of 116,995 adults with localized colorectal cancer in the SEER database (1988–2001). This retrospective study revealed that patients 71 years or older were half as likely to receive adequate lymph node evaluation (examination of at least 12 lymph nodes) as younger patients. Multiple studies have now demonstrated that inadequate lymph node evaluation correlates with inferior survival. These data would suggest that less aggressive surgical intervention predisposes older patients to a higher risk of recurrence and cancer-related death.

Increasingly, laparoscopic-assisted colectomies are being performed in the United States and elsewhere. Randomized studies indicate that patients undergoing this procedure have a similar outcome to patients undergoing an "open" colectomy, with slightly less postoperative pain and a one-day shorter hospital stay. Persons 75 years or older tolerate laparoscopic-assisted colectomy equally as well as younger individuals. One study compared 51 patients 70 years or older who underwent laparscopic colectomy to 102 age-matched patients who underwent open colectomy. Older patients had less overall morbidity with laproscopic colectomy (17.6%) than with open surgery (37.3%), suggesting that laparoscopic surgery may lessen surgical morbidity for frail, older individuals ($p = 0.013$).

Surgery—localized rectal cancer A radical resection with anastomosis or ostomy is the standard surgical procedure for cancers of the rectum. A Veteran's Administration study of 7243 patients who underwent surgery for their rectal cancer during the period of 1990 to 2000 revealed that 30-day mortality following resection for rectal cancer was 2.1% for patients younger than 65 years compared with 4.9% for patients 65 years or older ($p < 0.0001$). Five-year survival was 60% versus 48%, respectively ($p < 0.0001$). French investigators reviewed the records of 92 surgical patients who were 80 years or older and matched these to records of 276 younger patients who underwent resection during the same time interval. Although not statistically significant, older patients had a higher operative mortality than younger patients (8% vs 4%, respectively). Among elective surgeries, the operative mortality was nearly identical (3%–4%). Although 5-year overall survival was greater for younger patients, 5-year cancer-specific survival was comparable for the two groups.

Adjuvant therapy—localized colon cancer Since the publication of a National Institutes of Health (NIH) consensus statement in 1990, 5-fluorouracil (5-FU)-based adjuvant therapy has represented the standard of care for patients in the United States following the complete resection of colon cancer that has spread to regional lymph nodes (stage III disease). A benefit for postoperative chemotherapy has not been prospectively demonstrated in patients with fully resected, muscle-invasive, lymph node–negative (stage II) colon cancer. However, stage II cancers with high-risk features for recurrence (eg, presentation with obstruction, perforation, or invasion into adjacent organs—stage IIB) are often treated by medical oncologists and are included in many randomized adjuvant trials.

For stage III colon cancer, single-agent 5-FU (with leucovorin [LV]) adjuvant chemotherapy became the standard of care after the publication of multiple studies in the 1990s highlighting its superior survival benefits compared to observation alone. The benefit of adding oxaliplatin to 5-FU/LV was first suggested in the MOSAIC trial, which randomly assigned 2246 patients with resected stage II (40%) or III colon cancer to a 6-month course of 5-FU/LV plus oxaliplatin compared to 5-FU/LV. Patients receiving FOLFOX experienced improved survival. The data are less clear concerning the optimal adjuvant treatment of stage II disease. For patients with stage II tumors with mismatch repair enzyme deficiency (dMMR), microsatellite instability (MSI-H), an oxaliplatin-based regimen should be considered superior to a fluoropyrimidine-alone regimen.

In 2013, an updated analysis of the Adjuvant CC End Points (ACCENT) database (including seven randomized trials of newer adjuvant chemotherapy, such as MOSAIC, National Surgical Adjuvant Breast and Bowel Project [NSABP] C-07, and NO16968) showed no DFS or OS benefit among older patients receiving oxaliplatin-based adjuvant chemotherapy. In 2012, Sanoff et al. published an updated SEER-Medicare analysis of receipt and effectiveness of adjuvant chemotherapy which looked at the differences based on age for colon cancer patients. The data showed trend toward a marginal survival benefit with oxaliplatin use in patients age greater than or equal to 75. Another study performed a subpopulation analysis of 315 patients age 70 to 75 enrolled onto the MOSAIC trial. This

study demonstrated that age did not alter the impact of treatment on survival outcome. Although the previously observed survival benefit of fluoropyrimidine persisted in the older subgroup, there was no survival advantage with the addition of oxaliplatin to fluoropyrimidine chemotherapy. Additionally, a subgroup analysis of patients greater than or equal to 70 years from the phase III RCT NSABP C-07 trial showed no benefit to the addition of oxaliplatin to fluoropyrimidine chemotherapy, despite the risk of added toxicity. There are other studies that also question the use of oxaliplatin in the postoperative setting for older adults, but prospective studies are needed. Until then, the current data need to be considered when planning treatment, and caution taken when considering the addition of oxaliplatin for older patients. Currently, oxaliplatin can be considered for fit patients with minimal comorbidities.

Data have shown that the receipt of oxaliplatin is inversely related to advancing age, and older patients are more likely to prematurely discontinue this therapy. The addition of oxaliplatin to fluoropyrimidine adjuvant therapy in some older patients may also exacerbate underlying comorbidities and unmask frailty. For example, oxaliplatin-induced peripheral neuropathy may increase the risk of falls and limit functional status in some older patients with colon cancer. Falls and impaired functional status are both associated with a poorer prognosis in this population.

Older patients receive adjuvant chemotherapy less often than their younger counterparts. A retrospective cohort study from 2012 utilized multiple data sets, including the SEER database, to identify 5489 patients 75 years or older with resected stage III colon cancer from 2004 to 2007. Overall, over 40% of patients received adjuvant chemotherapy. The likelihood of receiving treatment declined steeply with increasing age (**Figure 100-5**). Similar results were noted in an Italian study of 1014 patients with resected stage II/III colon cancer.

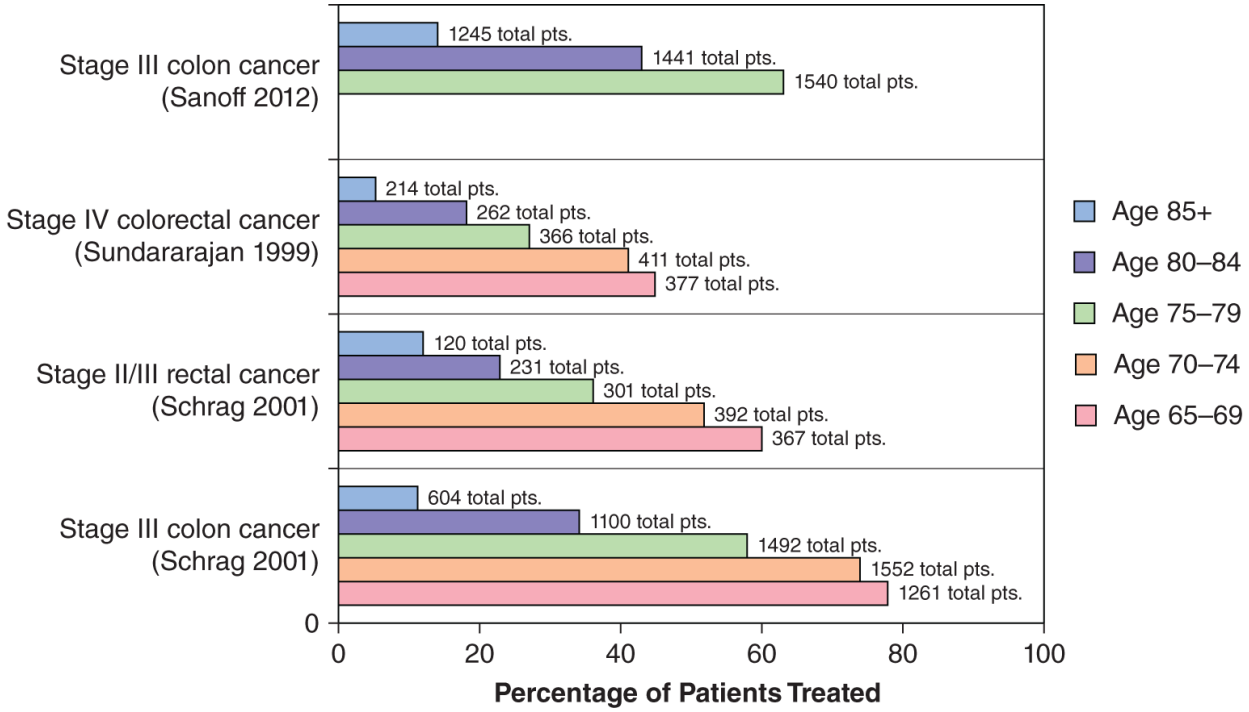


FIGURE 100-5. Use of chemotherapy for colorectal cancer by age.

The reason for this age-related disparity in management is not entirely clear. In one study utilizing the California Cancer Registry, oncologists cited patient refusal, comorbid illness, or advanced age as the most common reasons for not providing chemotherapy to older patients with resected colon cancer. Financial considerations and logistical problems may also prevent some older adults from seeking care. Additionally, treatment for older patients is more frequently discontinued, suggesting reluctance by physicians to treat older patients who have experienced some degree of side effects to chemotherapy.

A pooled analysis of 3351 patients in the United States, stratified by decade of life, from seven randomized trials evaluated the benefit of adjuvant chemotherapy in older persons with stage II or III colon cancer. The primary conclusion of this pooled analysis was that older patients derive the same clinical benefit from postoperative chemotherapy as younger patients. Treatment-related toxicity was somewhat higher for older patients, yet not statistically significant. Another US study, however, could not extend this observation to patients 75 years and older, given limitations in the data.

Adjuvant chemotherapy appeared to be slightly more toxic for older patients in a SEER-derived retrospective

cohort study (**Table 100-1**). Hospitalizations for various chemotherapy-related toxicities increased steadily with advancing age. Prospective data from the Royal Marsden Hospital in London confirmed this trend toward higher rates of severe toxicity in patients 70 years or older.

TABLE 100-1 TOXICITY TO TREATMENT FOR PATIENTS WITH ADVANCED COLORECTAL CANCER

	AGE			*P* VALUE
NORTH CENTRAL CANCER TREATMENT GROUP—5-FLUOROURACIL-BASED THERAPY (NCI CTC GRADE > 3)	**< 66**	**66–70**	**> 70**	
Any	46%	53%	53%	0.01
Diarrhea	16%	23%	21%	0.01
Leukopenia	14%	18%	17%	0.23
Nausea/vomiting	9%	9%	9%	0.95
Stomatitis	13%	18%	17%	0.03
Infection	2%	5%	4%	0.02
	TREATMENT GROUP (AGES FOR PERSONS ON STUDY, 35–87)			
FOCUS2 OPEN LABEL, RANDOMIZED TRIAL (NCI CTC GRADE > 3)	**FLUOROURACIL (FU)**	**OXALIPLATIN PLUS FU**	**CAPECITABINE (CAP)**	**OXALIPLATIN PLUS CAP**
Any	27%	33%	37%	43%
Diarrhea	5%	6%	9%	18%
Neutropenia	3%	6%	2%	2%
Nausea	1%	2%	5%	5%
Stomatitis	2%	3%	1%	2%
Neurosensory	0%	1%	0%	4%
Lethargy	7%	9%	13%	15%
BRiTE OBSERVATIONAL COHORT STUDY—THERAPY CONTAINING BEVACIZUMAB (RATES PER 100 PATIENT-YEARS)	**AGE**			
	< 65	**65–< 75**	**75–< 80**	**≥ 80**
Gastrointestinal perforations	1.9	0.9	1.4	0.7
Arterial thromboembolic events	1.4	1.4	4.8	4.0
Grade 3/4 bleeding events	1.8	2.0	2.4	1.3
New or worsening hypertension	1.4	3.4	1.5	3.1
Post-op wound bleeding/healing complication	4.7	4.1	8.5	6.7

In conclusion, it appears that postoperative chemotherapy in stage III colon cancer is as beneficial in older patients, as it is in younger individuals. A slight increase in toxicity should not prevent the clinician from treating these older patients, although increased vigilance during chemotherapy is warranted.

Adjuvant therapy—localized rectal cancer Chemoradiation before or after surgery reduces the local recurrence rate and increases disease-free survival in patients with deeply invasive (T_3–T_4) or lymph node–positive rectal cancer. Although there are few data to suggest that older patients respond any differently to chemoradiotherapy than younger patients, they are less frequently referred to oncologists for this treatment. Analysis of the SEER database identified patients 65 years or older with stage II or III rectal cancer who underwent surgical resection between 1992 and 1996. Increasing age corresponded inversely with the percentage of patients who received adjuvant therapy (see **Table 100-1**). Overall, chemoradiation therapy was associated with a 17% reduced risk of death among all cases, with a 29% reduced risk of death in stage III patients, but no statistically significant improvement in stage II cases, similar to the results reported in younger patients.

Postoperative surveillance—localized colorectal cancer There is general agreement that all patients with resected

colorectal cancer should undergo regular surveillance screening with colonoscopy, carcinoembryonic antigen (CEA) testing, and possibly an annual computed tomography (CT) scan. Analysis of 52,283 Medicare beneficiaries treated for locoregional colorectal cancer between 1986 and 1996 suggested that younger patients are more likely to undergo periodic surveillance endoscopies and that the median time to first follow-up endoscopy is significantly shorter ($p < 0.0001$) for patients at younger ages.

Advanced Colorectal Cancer

Surgery—advanced colorectal cancer Removal of the primary cancer is indicated in patients who have an (impending) obstruction, uncontrollable bleeding, or oligometastatic disease that may potentially be cured with aggressive therapy. In spite of these restrictive criteria, a recent pattern of care study, utilizing the SEER database, revealed that the majority of patients 65 years or older with stage IV colorectal cancer undergo resection of their primary tumor. Overall, 72% of patients underwent this primary cancer–directed surgery. The percentage of patients undergoing surgery declined gradually from 76% in patients 65 to 69 years old, to 70% in patients 80 to 84 years old, and then dropped to 62% in patients 85 years or older.

In this pattern of care study, the 30-day mortality was 10% for all patients. However, higher perioperative mortality rates for older adults with advanced colorectal cancer have been reported elsewhere. In patients 70 to 79 years, the mortality may be as high as 21% and in octogenarians it may reach 38%. Overall, improvements in surgical technique and postoperative care have led to a decrease in operative mortality particularly in older patients, so that current operative survival figures for older patients now approach those reported for younger patients a decade ago.

Older patients with oligometastatic disease or isolated recurrences of their colorectal cancer may be candidates for a “curative-intent” resection. In a series from the Memorial Sloan Kettering Cancer Center, 128 patients 70 years or older underwent liver resection for metastatic colorectal cancer between 1985 and 1994. While these patients experienced a 4% perioperative mortality rate and a 42% complication rate, their median survival was 40 months and 5-year survival rate was 35%. These older patients had a similar outcome to 449 patients less than 70 years old who underwent comparable liver resections during the same time period. In a retrospective analysis of patients age 65 and older in the SEER database, only 6.1% of the 13,599 patients identified with colorectal metastases limited to the liver underwent hepatic resection. The 30-day mortality rate was 4.3%. Five-year survival for resected patients was superior to those who did not undergo resection (32.8% vs 10.5%; $p < 0.0001$). Additionally, investigators have reported that appropriately selected older patients can tolerate resection of colorectal lung metastases with similar outcome as younger patients, with acceptable morbidity and mortality.

Chemotherapy—advanced colorectal cancer

5-Fluorouracil Until the early 1990s, the only active treatment for advanced colorectal cancer was 5-FU, a thymidylate synthase inhibitor. Multiple studies have now demonstrated that this agent, given as a bolus with leucovorin or as an infusion with or without leucovorin, is effective and well tolerated in older adult population, with similar response rates and overall survival compared to younger cohorts.

Folprecht and colleagues carried out a pooled analysis of 22 randomized European trials in which patients received palliative 5-FU-based therapy. In this retrospective analysis, overall survival (10.8 months for younger patients vs 11.3 months for older patients; $p = 0.31$) and response rate (20.8% for younger patients vs 17.6% for older patients; $p = 0.14$) were nearly identical in younger and older patients. Infusional 5-FU proved to be superior to bolus 5-FU in all age groups. Similar results were obtained in a meta-analysis of four large trials of 5-FU-based therapy to examine the efficacy and toxicity of 5-FU in patients 70 years and older ($n = 303$) compared to younger individuals ($n = 1181$). While severe neutropenia (40.4% vs 33.6%) and stomatitis (10% vs 4.6%) were significantly increased in older patients, overall response rate (39.5% vs 33.1%) and overall survival (15.9 vs 15.4 months) were similar to that of younger patients.

The North Central Cancer Treatment Group (NCCTG) conducted another pooled analysis of 1748 patients with advanced colorectal cancer treated with 5-FU-based therapy. No significant differences in response rate ($p = 0.90$) or overall survival ($p = 0.42$) were observed between patients younger than 56 years and older than 70 years. Patients 65 years or older had more overall severe toxicity than their younger counterparts (53% vs 46%; $p = 0.01$). Statistically significant differences in severe diarrhea and stomatitis were reported. Other studies have also noted higher rates of 5-FU-related palmar-plantar erythrodysesthesia in older patients.

Capecitabine The oral 5-FU prodrug, capecitabine, has similar efficacy to monthly intravenous 5-FU and leucovorin (Mayo Clinic Regimen) in the metastatic and adjuvant setting. In patients 70 years or older with metastatic colorectal

cancer, the overall response rate with capecitabine was 24% and the overall survival time was 11 months. In patients 70 years and older with resected colon cancer, capecitabine offered the same disease-free survival advantage as standard 5-FU and leucovorin. In this adjuvant trial, severe capecitabine-related toxicity was noted in only 12% of patients. Overall, the results with capecitabine in older patients appear similar to those seen in younger individuals.

Irinotecan Irinotecan, a topoisomerase I inhibitor, is another active drug in metastatic colorectal cancer. A multi-institutional phase II study found similar rates of severe toxicity in patients 65 years or older and those younger than 65 years receiving a weekly schedule of this agent. In a trial comparing the weekly and the triweekly dosing regimens of this drug as second-line therapy for metastatic disease, more than one-third of 291 patients were at least of 70 years. Age greater than 70 did not affect survival or time to progression, but was associated with an increased risk of severe neutropenia and diarrhea compared to patients younger than 70 years.

Various trials have evaluated irinotecan-based chemotherapies in older patients with metastatic colorectal cancer. These have included combinations of irinotecan, bolus 5-FU and leucovorin (IFL), irinotecan, infusional 5-FU and leucovorin (FOLFIRI), irinotecan and capecitabine (CAPIRI), and irinotecan and oxaliplatin (IROX). These trials uniformly revealed that response to chemotherapy, median survival times, and degree of toxicity in these older adults appear to be similar to those observed in younger patients.

Oxaliplatin Oxaliplatin is a third-generation platinum analogue, which induces platinum-DNA adducts, inhibiting the replication of DNA. Although it has limited activity as a single agent in colorectal cancer, oxaliplatin has notable synergy with 5-FU and leucovorin (FOLFOX). In metastatic colorectal cancer, the toxicity following treatment with FOLFOX was evaluated for patients 70 years and older in a pooled analysis of four randomized clinical trials. Although severe hematologic toxicity was increased in older patients, there was no difference in other severe toxicities or 60-day mortality.

For patients with resected colon cancer, a randomized adjuvant trial, in which 35% of patients were 65 years or older, has suggested that disease-free survival can be enhanced if oxaliplatin is added to 5-FU and leucovorin. Subgroup analysis suggested a similar benefit for older patients as for the group as a whole. For those older patients with resectable liver metastases, preoperative FOLFOX therapy may be superior to 5-FU therapy. In this study, 2-year overall survival was prolonged in the “FOLFOX group” compared to the “5-FU group” or to the “no chemotherapy group” (84% vs 60% vs 23%).

The combination of capecitabine and oxaliplatin (CAPOX) has been evaluated in 76 patients 70 years and older with metastatic colorectal cancer. Overall response was 41%, median progression-free survival was 8.5 months and median overall survival was 14.4 months with little severe toxicity (3% peripheral neuropathy and 13% palmar-plantar erythrodysesthesia). A recent randomized study has suggested that the FOLFOX and CAPOX regimens have similar efficacy and rates of toxicity.

The FOCUS2 trial investigated reduced-dose chemotherapy for frail and older patients. A total of 459 patients were randomized to treatment with 5-FU, FOLFOX, capecitabine, or CAPOX all starting at 80% of standard doses with discretionary adjustment as appropriate. Median survival for the groups ranged from 10 to 12 months. The addition of oxaliplatin showed nonsignificant improvement in progression-free survival (PFS) (5.8 vs 4.5 months). Capecitabine did not improve quality of life compared with 5-FU.

Bevacizumab The humanized monoclonal antibody, bevacizumab, binds to the vascular epidermal growth factor (VEGF), reducing the vascularity of tumors, leading to hypoxia and necrosis. It also appears to lower interstitial fluid pressure in cancer nodules, promoting diffusion of other chemotherapeutic agents into these tumors. Three pivotal studies in patients with advanced colorectal cancer have established that this agent consistently enhances the efficacy of 5-FU-based therapy with either irinotecan or oxaliplatin for patients of all age groups. A fourth study compared bolus 5-FU and leucovorin alone or in combination with bevacizumab in patients 65 years and older or in patients of poor performance status. This study demonstrated that bevacizumab could significantly improve survival by 4 months in “suboptimal” patients without significantly increasing toxicity.

Bevacizumab may increase the risk of arterial thrombosis, that is, myocardial infarction, stroke, or peripheral arterial thrombotic event. In multivariate analysis, persons 65 years or older increased their risk of arterial thrombosis from 2.3% with chemotherapy alone to 7.1% with chemotherapy plus bevacizumab. This risk increased further to 17.9% if the patient had a history of prior arterial thrombosis. However, progression-free and overall survival was better for those receiving the bevacizumab combination than for those receiving chemotherapy alone. Therefore, bevacizumab was felt to potentially provide a benefit in carefully selected older patients with a history of atherosclerosis-related disease.

Prospective studies evaluating the clinical benefit of combining bevacizumab with 5-FU or capecitabine as first-line therapy for older patients with metastatic colon cancer have been promising. A phase II study evaluating treatment with 5-FU with or without bevacizumab among patients age greater than 65 demonstrated a statistically significant increase in PFS and a nonsignificant improvement in OS. The prospective, randomized phase III Avastin in Elderly With Xeloda (AVEX) study was recently published, comparing capecitabine alone or in combination with bevacizumab. PFS was longer in the combination arm, and a trend was seen toward improved OS. The NCCTG attempted a prospective study evaluating the benefit of oxaliplatin added to 5-FU/capecitabine and bevacizumab among untreated older patients with metastatic colon cancer (N0949). This study was terminated early due to poor accrual, which may be related to the concern oncologists have about the use of oxaliplatin in older patients.

Cetuximab/panitumumab Cetuximab and panitumumab are monoclonal antibodies to the epidermal growth factor receptor (EGFR). Blockade of this receptor in colorectal cancer cells induces apoptosis and cell death. In individuals with extensively treated metastatic colorectal cancer, these agents can induce significant tumor regressions in 8% to 11% of patients; cetuximab in combination with irinotecan has a response rate of 23%. The most common severe toxicities of these agents include dyspnea, asthenia, and an acneiform rash. Cetuximab may also cause a hypersensitivity reaction. In one phase II study of 114 patients 65 years and older with metastatic colorectal cancer refractory to irinotecan, oxaliplatin and 5-FU, cetuximab achieved a response rate of 9.6% compared to a 12.5% response rate in 232 patients younger than 65 years ($p > 0.05$). In a randomized trial for patients with chemotherapy-refractory metastatic colorectal cancer, panitumumab resulted in partial response rate of 8% and a 46% reduction in risk of tumor progression compared to best supportive care (BSC). Similar to cetuximab, rash is the predominant adverse effect of panitumumab therapy. A severe rash early in the treatment course is predictive of enhanced response and survival with either agent. Based on systematic reviews of the relevant literature, the American Society of Clinical Oncology (ASCO) released a provisional clinical opinion in 2009 stating that all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for KRAS mutations. For patients with metastatic colorectal carcinoma, if KRAS mutation in codon 12 or 13 is found, they should not receive anti-EGFR antibody therapy as part of their treatment.

Cetuximab and bevacizumab along with FOLFOX or FOLFIRI were compared in a phase III Cancer and Leukemia Group B (CALGB)/Southwest Oncology Group (SWOG) 80405 trial presented at the 2014 ASCO Annual Meeting. The targeted agents had comparable benefits as first-line treatment with chemotherapy for metastatic colorectal cancer, suggesting that the selection of the targeted agent does not impact the outcomes, as long as 5-FU is used and the biomarkers are appropriately considered. Biomarker data are likely to be increasingly used to help guide treatment decisions for colorectal cancer patients. Recent papers, including an analysis of ARCAD data showed that the distribution of age and the prognostic effect of age did not differ according to KRAS or BRAF mutational status. The data regarding use of biomarkers in routine clinical practice is likely to evolve and further relationships between age and these biomarkers will be explored.

Regorafenib Regorafenib is an oral multikinase inhibitor that blocks the activity of several protein kinases, including kinases involved in the regulation of tumor angiogenesis, oncogenesis, and the tumour microenvironment. In the phase III international CORRECT trial, patients with metastatic colorectal cancer who had progressed on previous therapies were randomized to regorafenib or BSC. The patients receiving regorafenib had a median survival of 6.4 months, compared to a 5-month median survival for those who received BSC.

Aflibercept Aflibercept is a recombinant fusion protein containing VEGF-binding portions from the extracellular domains of human VEGF receptors that blocks the activity of VEGF. A phase III trial published in 2012 demonstrated that aflibercept in combination with FOLFIRI showed a survival benefit over FOLFIRI combined with placebo in patients with metastatic colorectal cancer previously treated with oxaliplatin.

PANCREATIC CANCER

In the United States, the number of expected new cases and the number of anticipated deaths for pancreas cancer in 2014 are almost identical (46,420 and 39,590, respectively). Overall, the probability of 5-year survival for this cancer is less than 10%. The median age at presentation is 71 years and thus a significant proportion of patients are older adults. A tissue confirmation of pancreas cancer is established less frequently in older individuals. Thus, a disproportionate number of older patients may be misdiagnosed with this malignancy and may be incorrectly given a

poor prognosis in an attempt to spare them the discomfort of an accurate pathologic diagnosis.

Treatment—Localized Pancreas Cancer

Older patients are more likely than younger patients to present with early-stage pancreas cancer. Pancreaticoduodenectomy (the Whipple procedure) is the only potentially curative therapy for this malignancy. There is ample evidence that this procedure can be performed safely in geriatric patients. For example, in 206 patients over age 70 who underwent surgery at the Mayo Clinic between 1982 and 1987, operative morbidity and mortality rates were 28% and 9%, respectively. Overall median survival was 19 months and 5-year survival was 4%. Similarly, the operative mortality in 138 patients older than 70 years who underwent pancreatic resection at Memorial Sloan Kettering Cancer Center was 6% and the major complication rate was 45%. These results are virtually identical to those of younger patients. However, the probability of 5-year survival was slightly lower in this group of older patients (21% vs 29%; $p = 0.03$), possibly because of an enhanced risk from comorbid diseases.

Patients with grossly resected pancreas cancer or locally unresectable pancreas cancer may benefit from chemoradiation therapy. Alternatively, a prospective study evaluating the benefit of gemcitabine, a nucleoside analogue, after complete resection of pancreatic cancer demonstrated a disease-free but not an overall survival benefit in comparison to the observation arm. Although patients up to 82 years were included in this study, there was no specific evaluation of the effect of adjuvant gemcitabine in older patients.

Treatment—Advanced Pancreas Cancer

Gemcitabine has typically been considered the standard initial therapy for patients with metastatic pancreas cancer who are not candidates for a more intensive first-line chemotherapy regimen. Patients treated with gemcitabine have a median survival time of 5 to 7 months and a 1-year survival rate of 20%. In the pivotal trial of this agent, median age was 62 and individuals as old as 79 years were enrolled, indicating tolerance of such treatment in older adults. Although the addition of erlotinib, an epidermal growth factor receptor inhibitor, to gemcitabine demonstrated a small survival benefit in younger patients, no such advantage was demonstrated in the 268 patients 65 years or older.

In 2013, a phase III trial (the ACCORD 11 trial) enrolled 342 patients who were chemotherapy-naïve with metastatic pancreatic cancer (10% of patients were age ≥ 75). Patients were randomly assigned to gemcitabine alone versus FOLFIRINOX. The response rate was significantly higher with FOLFIRINOX (32% vs 9%). Median PFS (6.4 vs 3.3 months) and overall survival (11.1 vs 6.8 months) were both better in the FOLFIRINOX arm. A multivariate analysis of this data revealed that age greater than 65 correlated with worse overall survival. The side effects of FOLFIRINOX include febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy, whereas gemcitabine can cause liver enzyme elevations and rarely hemolytic uremic syndrome (HUS).

An alternative to FOLFIRINOX for metastatic pancreatic cancer would be gemcitabine plus nanoparticle albumin bound (nab)-paclitaxel. Phase III trial data from 2013 showed significant improvements in nab-paclitaxel-gemcitabine as compared with gemcitabine alone. Median overall survival was 8.5 months in the nab-paclitaxel-gemcitabine group as compared with 6.7 months in the gemcitabine. Median PFS was 5.5 months in the nab-paclitaxel-gemcitabine group, as compared with 3.7 months in the gemcitabine group; the response rate was 23% versus 7% in the two groups. Over 40% of the patients in this trial were over age 65. The added toxicity of nab-paclitaxel includes peripheral neuropathy, nausea, and cytopenias.

Palliative Care

Pancreatic cancer patients may require treatment of biliary and gastric outlet obstruction, pain, depression, cachexia, and malnutrition. Stents or percutaneous biliary drainage may be necessary to alleviate patients' symptoms from biliary obstruction. Cachexia, anorexia, and weight loss occur in up to 80% of pancreatic cancer patients and pancreatic insufficiency can contribute to this problem. Microencapsulated lipase supplements can alleviate these symptoms. For pain management, celiac plexus neurolysis may help.

GASTRIC CANCER

Gastric cancer is the third leading cause of cancer death (after lung and liver cancer) in the world. The median age at diagnosis is 69. Over 60% of new cases are diagnosed in patients over the age of 65. In the United States, the predicted number of new cases for 2014 is 22,220, with 10,990 deaths expected. The results of a German study have suggested

that cancers with diffuse histology are more common in younger patients than in patients 70 years or older. In Japan, patients 80 years or older are found to have more advanced disease than younger patients, perhaps because of a later time to diagnosis.

Treatment—Localized Gastric Cancer

Gastrectomy is the only curative treatment for gastric cancer. In patients who undergo the resection of all macroscopic and microscopic disease, the long-term survival is approximately 35%. A prospective review of 310 older patients with gastric cancer found that surgery in this group was reasonably well tolerated and led to a survival duration comparable to the results obtained in younger patients. Most, but not all, studies suggest a similar perioperative morbidity and mortality risk for gastrectomy in older and younger patients. For instance, a British multicenter prospective cohort study showed that surgical morbidity and mortality did not differ significantly by age. Of the 955 patients who underwent esophagectomy or gastrectomy, morbidity for patients younger than 70 years and older than 70 years was 50% and 48%, respectively. Mortality was also similar at 10% and 14%, respectively for those two age groups. In Italy, age was found to be an independent predictor of recurrence in 536 patients following gastric cancer resection.

Although data specific to older patients are not currently available, it is generally recommended that patients with localized gastric cancer be considered for perioperative chemotherapy or postoperative chemoradiation. In a randomized controlled trial of perioperative chemotherapy for resectable esophageal, gastroesophageal junction and gastric cancers, two cycles of combination chemotherapy administered before and after surgical resection provided a 4-month improvement in median survival compared with surgical resection alone. In another study of 556 patients with resected gastric or gastroesophageal junction cancer, individuals who received adjuvant chemoradiotherapy had a 9-month increase in overall survival compared to those who underwent surgery alone. It is currently uncertain which one of these two approaches is better tolerated and offers a superior survival advantage.

Treatment—Advanced Gastric Cancer

The efficacy of chemotherapy programs for gastric cancer has not been specifically analyzed by patient's age. Single-agent therapy generally results in less toxicity than is observed with platinum-based combinations and may be better suited for older individuals. Platinum analogues must be carefully dosed, since renal platinum clearance declines with increasing age. Single agents commonly used in gastric cancer include 5-fluorouracil, capecitabine, the taxanes, and irinotecan. Trials, including combinations of 5-FU, leucovorin, and oxaliplatin, capecitabine and oxaliplatin, irinotecan and cisplatin, and 5-FU, leucovorin, and irinotecan have included patients 65 years or older. However, subgroup analyses evaluating response and toxicity in these older patients have not been performed. Thus, it is unclear how older patients fare with more aggressive regimens. Small, single-institution trials have shown a benefit for combination therapy in selected, fit older patients. One such study of cisplatin, leucovorin, and fluorouracil in 58 patients 65 years and older with metastatic gastric cancer noted significant responses in 43% of patients. Investigators noted that the therapy was well tolerated. Another study comparing epirubicin, cisplatin, and fluorouracil (ECF), irinotecan and cisplatin (IC), and FOLFOX found that ECF and FOLFOX both had similar response rates and overall survival (better than IC), but that FOLFOX was less toxic. Given the paucity of data about the older patients in studies of gastric cancer, this may represent an appropriate time to weigh the toxicities of the chemotherapy regimens when selecting the treatment of older patients with gastric cancer.

Human epidermal growth factor receptor 2 Human epidermal growth factor receptor 2 (HER2; also known as ERBB2), a member of a family of receptors associated with tumor cell proliferation, apoptosis, adhesion, migration, and differentiation is a biomarker in gastric cancer showing amplification or overexpression in 7% to 34% of tumors. In 2010, the phase III ToGA trial demonstrated that trastuzumab, a monoclonal antibody against HER2, in addition to chemotherapy benefits patients with gastric cancer (median survival of 13.8 months in those assigned to trastuzumab plus chemotherapy compared to 11.1 months to the control group).

Ramucirumab Published in 2014, the phase III REGARD trial demonstrated significant improvements in overall survival (5.2 vs 3.8 months) in patients receiving ramucirumab, a human immunoglobulin G1 (IgG1) receptor targeted antibody. In this trial, 36% of the patients were over age 65. Ramucirumab resulted in similar improvements for overall survival and progression-free survival between patients under 65 years and those age 65 and over. Adverse effect profiles were also similar between age groups.

Also in 2014, results were released from the RAINBOW trial, an international phase III, randomized, double-blind study of ramucirumab plus paclitaxel versus placebo plus paclitaxel in the treatment of metastatic gastroesophageal

junction and gastric adenocarcinoma following disease progression on first-line platinum- and fluoropyrimidine-containing combination therapy. The authors found a statistically significant and clinically meaningful OS benefit of more than 2 months for the patients treated with ramucirumab plus paclitaxel versus placebo plus paclitaxel. There is currently no documented data regarding the outcomes of the older patients from this trial.

PRIMARY LIVER CANCER

Primary liver cancer—hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC)—is the second most common cause of cancer death in the world, leading to over half a million deaths annually. In contrast, the annual incidence in the United States has been relatively low, with 33,190 new cases and 23,000 deaths expected in 2014. In the United States, the incidence of HCC levels off at older age in males (70 years for Caucasian males and 55 years for African-American males) whereas the incidence of ICC continues to climb with increasing age for both genders. The risk factors for primary liver cancer do not vary by age, but Japanese investigators suggest that the presence of portal vein thrombosis is a more important prognostic factor than tumor size or the number tumors for patients 80 years and older.

Treatment—Primary Liver Cancer

Treatment options for older patients with hepatocellular carcinoma restricted to the liver include operative resection, transarterial hepatic chemoembolization, nonsurgical tumor ablation, and liver tranplantation. Surgery and chemoembolization in the geriatric population have been found to be tolerable in some but not all experiences. In one Italian study, the operative mortality was 8% in patients 65 years or older, with 1-, 3-, and 5-year survival probabilities of 89%, 61%, and 45%, respectively. These percentages were nearly identical to those of patients younger than 65 years. Localized tumor ablation with ethanol, cryotherapy, or radiofrequency has been increasingly utilized to eradicate small tumors and may be particularly appropriate for older patients, who are frequently considered poor candidates for surgery.

In a review of the 2696 Medicare patients with HCC between 1992 and 1999, 13% had procedures with curative intent (0.9% transplant, 8.2% resection, 4.1% local ablation), 4% underwent transarterial chemoembolization, 57% received palliative therapy, and 26% did not get treatment. Only 34% of patients with solitary lesions or lesions less than 3 cm in diameter received therapy with curative intent, suggesting underutilization of curative interventions in eligible older patients. Three-year survival for transarterial chemoembolization or local ablation was less than 10%.

Surgical resection of liver tumors is well tolerated in older patients. In a European study, cirrhotic patients with HCC over 70 years were compared to patients under 70. The operative morbidity and liver failure rates were lower in the subset of older patients (23.4% vs 42.4%; and 1.6% vs 12.9%, respectively). Operative mortality and 5-year survival rates were not significantly different between the two groups. Although smaller tumor size was predictive of better outcome for younger patients, this was not noted for older patients. Similar findings were reported by investigators in Taiwan.

The use of cytotoxic chemotherapy has shown modest benefits for patients with hepatocellular carcinoma, and the durations of these benefits are commonly short. No single regimen has proven superior to any other. Molecularly targeted agents, particularly sorafenib, offer the potential for improved survival for advanced HCC. The phase III multicenter European SHARP trial randomly assigned 602 patients with inoperable HCC and Child-Pugh A cirrhosis to sorafenib versus placebo. Overall survival was significantly longer in the sorafenib-treated patients (10.7 vs 7.9 months), as was time to radiologic progression (5.5 vs 2.8 months). The average age for patients on this trial was approximately 65.

Orthotopic liver transplantation among older patients is controversial, yet studies have shown that even though older age may be a negative risk factor for transplantation outcomes due to increased rates of long-term complications (malignancy, cardiovascular disease), age alone should not exclude a patient from liver transplantation. A study comparing patients greater than or equal to 65 years found that overall survival, retransplantation rates, and disease-free survival were comparable to their younger counterparts.

ESOPHAGEAL CANCER

Squamous cell carcinomas and adenocarcinomas of the esophagus are the sixth leading cause of cancer death

worldwide. In the United States, esophageal cancer is less common, with 18,170 new cases and 15,450 deaths anticipated in 2014. Between 1974 and 1994, the appearance of adenocarcinomas of the esophagus has increased substantially, particularly in white men between 65 and 74 years, while the incidence of squamous cell carcinomas has declined slightly. The epidemiologic pattern of esophageal carcinoma does not appear different in older patients. Most studies report similar clinical symptoms at the time of presentation, as well as similar distribution of histology, stage, and location of tumors for patients older and younger than 70 years. In these series, approximately 50% to 75% of the older patients were found to have adenocarcinoma and 25% to 50% had squamous cell carcinoma.

It is unclear if the incidence of Barrett-associated adenocarcinoma increases with advanced age. Although one study has suggested a higher incidence in older patients, another study suggested this incidence is not age dependent. The location of tumors in the esophagus does not differ between older and younger patients—distal esophageal tumors predominate in all groups. A similar distribution in early- and late-stage cancers has also been reported.

Treatment—Localized Esophageal Cancer

Most, but not all, studies suggest that age is not a limiting factor in surgery of the esophagus. Although older patients tend to have a higher incidence of respiratory and cardiovascular complications than younger patients, this does not appear to have a significant effect on operative mortality or survival. In one series, 50 patients older than 70 years were compared to 89 patients younger than 70 years; postoperative complications and in-hospital mortality occurred in 38% and 3% of younger patients and in 44% and 0% of older patients. The mean duration of hospitalization was 17.9 days for younger patients and 18.6 days for older patients. The severity of postoperative dysphagia and weight loss were similar for both groups. The likelihood of survival after 8 years was identical at 20%.

In a second study of 60 patients 70 years and older, no difference was observed in the rate of resection with curative intent, surgical complications or hospital mortality rate in comparison to a younger population. This was confirmed in another study, demonstrating equivalent surgical morbidity and mortality for older patients stratified by performance status and overall fitness in comparison to younger patients. A contradictory study suggested that age was predictive of morbidity and mortality following esophagectomy in multivariate analysis ($p = 0.002$). Age and comorbidity were also noted to be significant predictors of outcome in a simple risk score developed to predict surgical mortality for esophageal cancer.

Although the rate of surgical complications may not be significantly increased in older adults, the presence of such complications significantly worsens survival. This was the conclusion in a review of 510 patients who underwent resection of esophageal or gastroesophageal junction carcinoma at the Memorial Sloan Kettering Cancer Center from 1996 to 2001. Surgical complications occurred in 31.8% of the 173 patients 65 to 74 years and in 34.8% of the 66 patients 75 years and older. Although survival at 30 days did not differ significantly between patient groups who did and did not experience surgical complications, there was a notable decline in 1-year survival for patients 65 years and older who had suffered a perioperative complication. In a separate study at the same institution, octogenarians were noted to have more than a threefold higher mortality rate than patients 50 to 79 years, although they experienced similar rates of operative complications (blood loss, cardiopulmonary complications, infection, and anastomotic leak).

A review of 945 patients in the Veterans' Administration National Surgical Quality Improvement Program found no difference in 30-day surgical mortality and morbidity between transthoracic and transhiatal esophagectomies. Age did significantly impact the overall mortality rate for both surgical techniques, with increasing age associated with an increased risk of surgical mortality. The same age-related surgical mortality risk was also noted in a French study of gastroesophageal junction adenocarcinomas.

Although age may not be a significant factor in the rate of curative resection, curative surgery is still underutilized in older racial minority patients. African-American patients 65 years and older were noted to have a lower rate of surgical consultation and half the rate of curative surgery as their older adult Caucasian counterparts (70% vs 78%; $p < 0.001$ and 25% vs 46%; $p < 0.001$, respectively).

Chemoradiation therapy appears equally effective in patients 70 years and older as in younger individuals. Furthermore, there appears to be no association between age and toxicity in patients of good performance status. At Memorial Sloan Kettering Cancer Center, 24 older patients (median age 77) with locally advanced esophageal cancer were treated with 5040 cGy of radiation and infusional 5-fluorouracil plus mitomycin C over a 6-week period. Nine of these individuals (38%) required hospitalization for toxicity and three required dose reductions. Sixteen patients achieved a clinical remission and 10 remained without evidence of disease after a median follow-up of 1.2 years, suggesting that selected chemoradiation therapy is a feasible and well-tolerated alternative to esophagectomy in older patients.

The CROSS trial, published in 2012, compared surgery alone to neoadjuvant carboplatin and paclitaxel and concurrent radiotherapy followed by surgery. The chemoradiotherapy group had higher rates of complete resection (92% vs 69%) and overall survival (49.4 vs 24 months). The median age of patients on this trial was 60.

Treatment—Advanced Esophageal Cancer

Single agents, such as the taxanes, irinotecan, 5-fluorouracil, capecitabine, and vinorelbine, have some efficacy in palliating metastatic esophageal cancer and represent management options for older patients, particularly for those with lower performance status or significant comorbidities. Combination chemotherapy regimens tend to have more side effects and have not been systematically evaluated in older patients with esophageal cancer. Preliminary results of one study in patients 70 years or older suggested that the combination of weekly docetaxel and infusional 5-FU is well tolerated in this age group. Toxicities were primarily neutropenia and mucositis. The advances in gastric cancer frequently apply to the esophageal population; thus the promising results from the REGARD trial and the RAINBOW trial discussed in gastric cancer may also extend to this population.

GALLBLADDER CANCER

Cancers of the gallbladder occur infrequently in the United States. The incidence increases with age and reaches its peak in the seventh decade of life. In 2014, 10,650 new cases and 3630 deaths are expected. The presentation and clinical features of this cancer do not appear to differ appreciably between older and younger patients. Endoscopic retrograde cholangiopancreatography (ERCP) is often used in the diagnosis of gallbladder cancer and is well tolerated in older patients—even the very old. In a study of 126 patients 90 years and older who underwent a total of 147 ERCP procedures, 9.5% were noted to have malignant stenosis. The overall morbidity and mortality rates were low at 2.5% and 0.7%, respectively.

Treatment—Gallbladder Cancer

Surgery is the only potentially curative treatment for this disease. A retrospective single institution study from Japan reviewed the cases of 54 patients who were 75 years or older and compared them to 152 patients less than 75 years. Approximately 58% of patients in both age groups underwent a radical resection (rather than a simple cholecystectomy). Operative mortality and survival rates were similar between the two age groups. The investigators noted that the likelihood of 5-year survival was better for those older patients who had undergone a radical resection, compared to those who had undergone a simple cholecystectomy (61% vs 14%; $p = 0.0098$). These uncontrolled results have not been validated through a randomized trial.

Although advanced gallbladder cancer is highly resistant to chemotherapy, single agents such as gemcitabine, 5-FU, and capecitabine are generally well tolerated in older patients and may offer some palliation in this disease. Trial data to date suggest that gemcitabine and gemcitabine-based platinum regimens offer a slight advantage over other regimens for gallbladder cancer. Studies have shown that adding fluoropyrimidines, cisplatin, oxaliplatin, and irinotecan to gemcitabine can yield similar results, but the toxicity and tolerability data tend to favor gemcitabine-oxaliplatin combinations. Thus, while several combinations have been tried, single agents appear to be better for older adults. In a small study of advanced biliary tract cancers and gallbladder cancer, treated with the combination of gemcitabine and cisplatin, no difference in response rate was noted between 10 patients 60 years and older and 30 younger patients, although the older patients had higher rates of hematologic toxicity.

ANAL CANCER

Squamous cell carcinoma of the anal canal is the least common but most treatable of the gastrointestinal malignancies. In 2014, 7210 new cases but only 950 deaths are expected for this malignancy. The risk factors for anal cancer and genital malignancies are similar. The risk of human papillomavirus (HPV)-related anal cancer in men who have sex with men increases with age. Older age at first receptive intercourse was associated with increased prevalence of both low- and high-grade squamous dysplasia, the precursor lesions to anal cancer. The higher incidence of anal cancer is more pronounced in patients 65 years and older than in younger age groups. Five-year survival does not differ significantly by gender or age.

Treatment—Anal Cancer

Since the 1970s, the standard treatment for anal cancer has been the combination of 5-FU, mitomycin, and radiation therapy. With this technique, 60% to 73% of patients will remain free of disease recurrence and a colostomy at 4 years. Age has not been associated with either tumor-related or therapy-related rates of colostomy. A small study evaluating this nonsurgical strategy in patients 75 years or older demonstrated similar complication rates to those seen in younger patients, suggesting that sphincter-conserving treatment is feasible in older patients with anal carcinoma. In an Australian study of 62 patients, treated with chemoradiation (mitomycin C and 5-FU) and anal sphincter preservation surgery, the local control rate was 86% and the colostomy-free survival at 2 years was 83%. This study included 38 patients 60 years and older.

Radiation used in the treatment of anal cancer in women 65 years or older can lead to a threefold increased risk of pelvic fracture. These women are at greater risk for fracture than women treated with radiation therapy for cervical or rectal cancer. Therefore, older women treated with chemotherapy and radiation therapy for anal cancer should undergo regular bone densitometry screening and bisphosphonate therapy.

CLINICAL TRIALS

Whereas 70% to 75% of colorectal cancers are diagnosed in patients older than 65 years, only 40% to 48% of patients enrolled in NCI-sponsored or cooperative group trials are drawn from this age group, and cancer is the leading cause of death among men and women aged 60 to 79. This underrepresentation of older patients with colorectal cancer has not improved in the past several years. During the 2000 to 2002 time period, only 2% of colorectal cancer patients 65 to 74 years and 0.5% of colorectal cancer patients 75 years or older enrolled in NCI-sponsored trials, substantially fewer than the 4% enrollment recorded for patients 30 to 64 years. Similar data are not available for the less common gastrointestinal malignancies.

A possible explanation for this discrepancy may be financial, although a similarly low rate of enrollment for older patients has been documented in Canada, where the national health care program provides reimbursement for all health care costs. More plausible explanations for the lack of participation of older patients in clinical trials may include lack of social and home care support, physician reluctance to offer research protocols to older individuals, difficulties with access to clinics and hospitals, potential noncoverage of investigational treatments by Medicare, patient refusal, increasing concomitant medication usage and comorbidities with advancing age, and fewer trials specifically aimed at older patients. The NCCTG attempted a prospective study in collaboration with CALGB (now combined with other clinical trial groups as the ALLIANCE) evaluating the benefit of oxaliplatin added to 5-FU/capecitabine and bevacizumab among untreated older patients with metastatic colon cancer (N0949). This study was terminated early due to poor accrual, which may be related to the concern oncologists have about the use of oxaliplatin in older patients.

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Chapter 101

Intracranial Neoplasms

Clayton L. Haldeman, Robert J. Dempsey

Learning Objectives

- Learn the epidemiology, natural history, clinical presentations, diagnosis, and treatment of common brain neoplasms in older adults.
- Recognize the benefits, adverse effects, and limitations of common treatment modalities, including surgery, radiation therapy (RT), and chemotherapy for common brain tumors in older patients.
- Understand the determinants of prognosis and factors driving treatment decisions for intracranial neoplasms in the older population.
- Learn the significance and indications of symptomatic treatments for brain tumors in older adults.

Key Clinical Points

1. **Metastases are the most common intracranial neoplasms in older adults.**
2. **It is important to differentiate metastases from primary brain tumors. In many patients the primary source of metastases remains unknown.**
3. **Glioblastoma multiforme (GBM) is the most common primary tumor of the brain and is uniformly fatal.**
4. **Patients with vestibular schwannoma (VS), also known as acoustic neuroma, require follow-up for throughout their entire life.**
5. **Symptomatic treatment of brain tumors includes corticosteroids to reduce or prevent cerebral edema, antiepileptics to control seizures, and antidepressants to manage depression, commonly seen in patients with brain tumors.**

INTRODUCTION

Despite making up 13% of the US population, people aged 65 and older make up 61% of new cancer diagnoses each year, and 37% of new central nervous system (CNS) cancer diagnoses. Regardless of tumor type, nearly all brain tumors present one of four ways: elevated intracranial pressure, seizures, focal neurologic deficits, or cognitive dysfunction. While these symptoms raise red flags that trigger extensive work-ups in younger patients, in older adults, they can be masked by dementia, depression, or sometimes just attributed to “getting old,” and can delay diagnosis significantly. CNS tumors in older adults present unique diagnostic, treatment, ethical, and social challenges. We review here the various CNS neoplastic diseases and their treatment in the older population.

METASTATIC DISEASE

Metastatic tumors to the brain are by far the most common intracranial neoplasm in adults (**Figure 101-1A** and **B**). They occur in 20% to 30% of all patients with systemic cancer. Though intracranial metastases are still an ominous

portent, advances in surgery and systemic therapy for specific cancer types have shown that long-term survival is possible. Karnofsky Performance Scale (KPS) is crucially important when deciding upon treatment and prognosticating outcome. KPS greater than or equal to 70, that is, the patient is able to care for himself, seems to be the most significant factor for improved outcome—age less than 65 and controlled systemic disease are also important. In this case advanced age may affect survival by affecting the patient's ability to tolerate treatments.

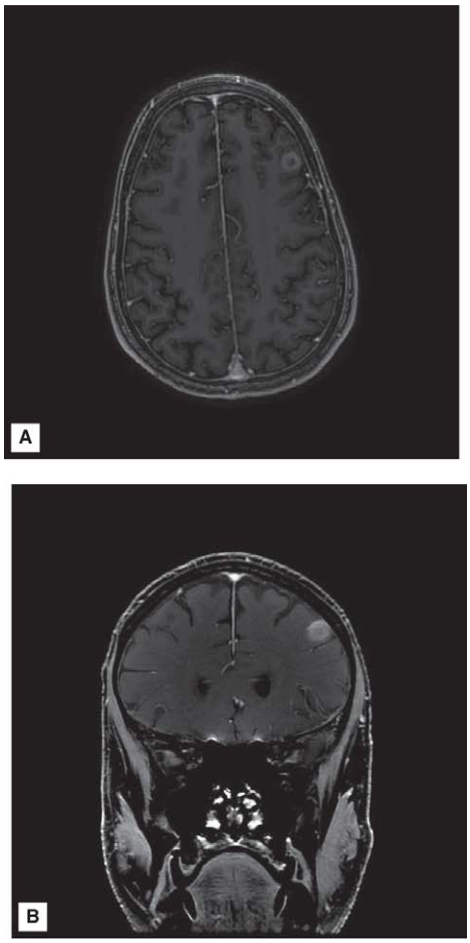


FIGURE 101-1. (**A**) Axial and (**B**) coronal contrast magnetic resonance sequences of metastatic squamous cell carcinoma. Note the lesion is round and well circumscribed, and occurs at the junction of the gray matter and white matter typical of metastatic lesions.

The route of metastatic spread to the brain is typically hematogenous. The distribution of lesions, therefore, follows the distribution of blood flow with most lesions occurring in the cerebral hemispheres (with a preference for the gray-white junction), and less commonly involving the leptomeninges (20%) or posterior fossa (16%), though metastatic disease is still the most common posterior fossa tumor in adults. Lung and breast cancer account for the lion's share of metastatic disease to the brain, greater than 50% in most series. Renal cell cancer, gastrointestinal (GI) tumors, and melanoma each account for about 5% of lesions. Up to a quarter of the time, the primary site is never identified.

Clinically, it is impossible to differentiate a metastatic lesion from a primary brain tumor, and most patients present with the slowly progressive symptoms mentioned above; acute presentations are usually due to hemorrhage into metastases resulting in seizures. Often, due to availability or convenience, the metastases are found on computed tomography (CT) as round, well-circumscribed lesions, sometimes associated with hemorrhage. Magnetic resonance imaging (MRI), however, is the preferred imaging modality and is more sensitive. Up to 20% of the time, a single lesion is seen on CT; MRI will detect multiple lesions.

With a history of treated cancer, about 90% of solitary lesions in the brain turn out to be metastatic in origin. In patients without a known history of cancer and suspected intracranial metastases, chest x-ray, CT of the chest, abdomen, and pelvis, fecal smear for occult blood, along with mammogram in women, and prostate-specific antigen (PSA) in men should be undertaken to evaluate for a primary source. Positron emission tomography (PET) scan and radionuclide bone scan should be considered for patients on an individual clinical basis. If all of the above are negative, approximately 85% turn out to be primary brain tumors, about 7% of lesions are metastatic, and 6% are nonneoplastic. Biopsy or resection of the lesion would then be diagnostic.

The natural history of metastases to the brain is dismal, and by the time neurologic findings develop, survival is about 1 month without treatment. The goal when treating brain metastasis is control of the disease to the extent that quality of life and survival will be determined by the primary malignancy and not the brain lesion. General medical strategies for temporizing disease should include an anticonvulsant for supratentorial lesions, corticosteroids for edema, and proton pump inhibitor (PPI) or H_2 antagonist for gastrointestinal prophylaxis while on steroids.

Radiation

Whole-brain radiation therapy (WBXRT) is the traditional treatment of choice for patients with multiple brain metastases. The thought being that by the time macroscopic metastases are found, the entire brain is likely to be microscopically seeded. In addition, nearly 70% of patients with metastatic lesions have multiple intracranial lesions at the time of diagnosis, making purely focal treatments, such as surgery, difficult or incomplete. The standard dose for WBXRT is 30 gray (Gy) divided into 10 fractions, regardless of tumor histology, and variations in timing and intensity of this regimen have not been shown to be beneficial. WBXRT in addition to steroids extends life expectancy to between 3 and 6 months.

Stereotactic radiosurgery (SRS) is a focused technique of delivering radiation where higher doses can be given to more targeted areas. There have been no randomized controlled trials comparing SRS to WBXRT, however there is level I evidence that a single dose of SRS in addition to WBXRT leads to longer survival times in patients with a single metastatic lesion and KPS greater than or equal to 70.

Surgery

In a landmark randomized controlled trial from 1990, Patchell et al. showed that resection of a single brain metastasis in addition to radiation therapy provides a better quality of life and longer survival than radiation therapy alone. For patients where total removal of the lesion was achievable, no recurrence or new parenchymal mets appeared for 6 months, and the most common cause of death was uncontrolled primary disease, thus achieving the primary goal of treatment of the brain metastasis. Surgery can be considered for patients with multiple metastases if all lesions are readily surgically accessible. Outcomes in these cases appear to be similar to those with single mets that are removed. Surgical intervention or resection may also be indicated in patients with multiple mets if a single lesion is life threatening, for example, a posterior fossa mass causing acute hydrocephalus. The median survival of patients with a single metastatic lesion undergoing resection followed by WBXRT is 8 months, and 44% of patients survived longer than 1 year. The patients who receive the most benefit are patients with KPS greater than or equal to 70, age less than 60, and absent or controlled primary disease. In patients with low performance status and high burden of extracranial disease, strong consideration should be given to palliative care alone, due to both an inability to tolerate treatment and age-related decline in immune function.

GLIOMA

Glial cells are various nonneuronal cells that support and protect neurons. Glioma is a term used for any neoplasm arising from these cells. Unfortunately these neoplasms are devastating in older adults. Gliomas are increasingly being recognized as a molecularly heterogeneous disease. The first hint of this came in 1998, when it was noticed that patients with anaplastic oligodendroglioma whose tumor had loss of chromosomal element 1p had a better response to chemotherapy than those whose 1p element was intact. Furthermore, those who had codeletion of 1p/19q had improved survival times, though the biological mechanism for this is not currently known.

Methylation of the DNA repair enzyme O(6)-methylguanine-DNA methyltransferase (MGMT) (ie, downregulation) also results in improved prognosis. Temozolomide (TMZ), the alkylating drug patients with glioblastoma take, works by methylating guanine leading to cell death. MGMT reverses this action and renders TMZ much less effective, therefore MGMT methylation (downregulation) predicts improved TMZ sensitivity and improved outcome. Patients without MGMT methylation, however, also benefit from alkylating agents, though not to the degree of those with methylation. In older patients who tolerate chemotherapy less well, it may make sense to forgo TMZ for those with unmethylated tumors. Importantly, MGMT methylation has also been shown to be an independent predictor of improved outcome in older patients with newly diagnosed glioblastoma. MGMT methylation is also associated with higher incidence of radiographic pseudoprogression in the period after initial treatment, so knowledge of MGMT methylation status can help assess the likelihood of pseudo-progression versus recurrence.

Mutations in *IDH1* and *IDH2* have also been associated with improved survival. Interestingly, these mutations are most often found in so-called "secondary" GBM, that is, those who have progressed from lower-grade astrocytoma, and rarely in primary GBM, which appears to arise de novo as a grade IV astrocytoma. Secondary GBM is seen most often in younger patients, however, even when age is controlled for, patients do better when IDH is mutated. A 2009 study by Yan et al. showed that IDH mutations increased the median survival from 15 months to 31 months in those with GBM, and from 20 months to 60 months in patients with anapestic astrocytoma. The decreased presence of these markers in older adults may help explain the biology of their worse outcomes.

GLIOBLASTOMA MULTIFORME

GBM (World Health Organization [WHO] grade IV astrocytoma) is the most common and malignant primary brain tumor (**Figures 101-2A, B** and **101-3**). The overall incidence in adults is about 3.2 in 100,000; however, among those aged greater than or equal to 65, it is as high as 10.6 per 100,000. The median age at diagnosis in 2006 was 64. Though GBM is a uniformly fatal disease, patients aged greater than or equal to 65 do considerably less well than their younger counterparts, with a population-based median survival of about 6 months. Patient age and performance status are the two most important factors predicting outcome in multiple population-based studies. Advanced age predicts a more aggressive biology of the tumor as well as a decreased ability to tolerate aggressive treatment. The disease appears to be sporadic. Known risk factors are few. Men are more likely to be affected, and there has been some association with certain viruses including cytomegalovirus and human herpesvirus 6 (HHV-6); however, no genetic risk factors have been identified.

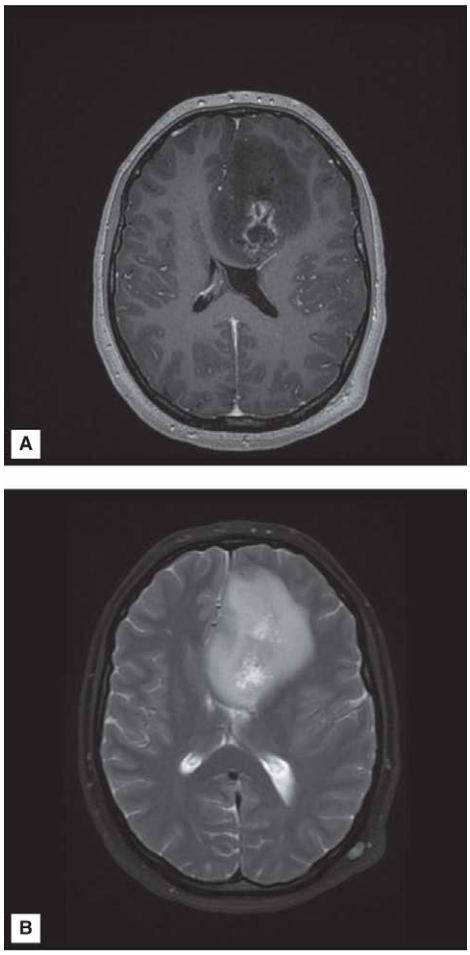


FIGURE 101-2. (**A**) T1 with contrast and (**B**) T2 MRI images of a left frontal grade IV astrocytoma (glioblastoma multiforme [GBM]). The lesion is large, effacing the frontal horn of the left lateral ventricle, causing significant mass effect. The T1 with contrast images show an irregular cystic enhancement typical of GBM, with a hypointense center representative of necrosis. The T2 sequence shows the surrounding vasogenic edema.

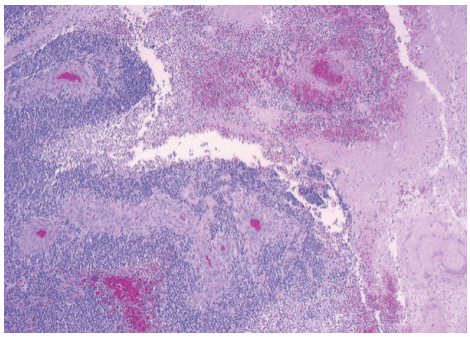


FIGURE 101-3. Hematoxylin and eosin (H&E) stain of resected grade IV astrocytoma shows diffuse infiltration with increased cellularity and pallid areas representing necrosis.

Radiation Therapy

Most practitioners give abbreviated courses of RT to the older population due to concern for toxicity and impact on quality of life. Because many clinical trials have poor representation of patients aged greater than 70, the scientific basis of such a stance is not clear. In 2005 the French oncologist group ANOCEF found superiority of RT in addition to supportive care following surgery versus supportive care (steroids, antiepileptic drugs [AEDs], physical therapy [PT], etc) alone following surgery in a randomized trial of 85 patients aged greater than 70. The radiation group received 50.4 Gy in addition to supportive care. They found a median survival of 7.3 months compared to 4.2 months in the non-RT arm, and significantly, no differences in quality-of-life outcome measures at 4.5 months. Villa et al. treated patients with a mean age of 70 with 54 to 66 Gy of external beam radiation and found a median survival of 18.1 weeks for all patients and 45 weeks for those who started RT. Pierga et al. treated 30 patients with a median age 73 with 45 Gy for more than 5 weeks after maximal resection and found a median survival of 36 weeks. With evidence accumulating that RT does extend survival in older adults, and can be done without significantly impacting quality of life, there is now some emphasis on sorting out whether abbreviated dosing may be beneficial. There is an ongoing phase III study by the Radiation Therapy Oncology Group to examine whether concurrent TMZ chemotherapy is beneficial with reduced dose radiation therapy in patients 65 and older.

Surgery

A significant survival advantage has been shown for patients with GBM who undergo gross total resection. A study in 2010 based at M.D. Anderson found an increase in median survival from 8.8 months to 13 months when 98% or more of tumor volume was removed. Inability to achieve complete resection, however, is also associated with more aggressive tumors, as they infiltrate disparate areas. More recently there have been studies looking at molecular markers and how they impact prognosis. Cahill et al. have shown that IDH1 mutant astrocytomas are associated with improved survival if gross total resection is achievable. MGMT, mentioned earlier, is associated with better response to chemotherapy. However, other favorable molecular markers, such as IDH1, are less common in older adults, and may contribute to worse outcomes.

Chemotherapy

TMZ is the only therapeutic agent that has been shown to result in improved survival in patients with GBM. Stupp, in 2002, reported results of the use of daily TMZ (75 mg orally per square meter body surface area) during radiation (approximately 6–7 weeks), followed by 6 months of adjuvant therapy at 150 to 200 PO mg/m^2 on days 1 through 5 of a 28-day cycle. The median survival in this phase II study was 16 months. The rationale for this approach included the possibility of radiosensitization. The concept of daily dosing was an attempt to overcome TMZ drug resistance. The background for this related to observations demonstrating that the repeated administration of TMZ depletes the DNA-repair enzyme 0^6-methylquanine-DNA methyltransferase (MGMT). MGMT is a resistance mechanism for TMZ. Thus, it is termed a “suicide enzyme.” After MGMT removes a methyl group from DNA (deposited by TMZ), TMZ is no longer active and the tumor cell surveys the treatment attempt. The use of adjuvant TMZ starting 1 month postradiotherapy was predicated on the inherent antitumor activity of the drug. As the study by Stupp et al. demonstrated a promising 2-year survival rate of 31%, the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) launched a phase III trial comparing this phase

II regimen to radiotherapy alone. In a 2005 randomized phase III study, also from Stupp, it was shown that the combination of RT and TMZ followed by 6 months of TMZ was better than RT alone in terms of overall survival and disease control. This has become the standard of care for GBM. Patients treated with chemotherapy and radiation had a progression-free survival of 6.9 months compared to 5 months, a median survival of 14.6 months compared to 12.1 months, and a 2-year survival of 27% compared to 10%.

GBM is an aggressive disease that is universally fatal. Despite the data available, the best approach for the older patient is not known. For patients with a good performance status and no significant comorbidities, maximal resection followed by RT (60 Gy) plus TMZ followed by TMZ for 6 months should probably be the approach to use. It has become a convention in the United States to treat patients with TMZ for 1 year post-RT, but there is no level I data to support this practice. A 2013 paper looking at hospitalization burden and survival in the US patients aged greater than 65 found that 22% of patients spent at least 25% of their time since diagnosis as an inpatient. With a median survival of only 6 months, it is crucial to have frank discussion with the patient and his family about treatment options, quality of life, and prognosis.

ANAPLASTIC GLIOMAS

Grade III astrocytomas, as well as anaplastic oligodendroglioma, are less common in older patients. The mainstay of therapy is surgery and RT. The definitive role for chemotherapy is yet to be defined in these diseases. By extrapolation from the success of TMZ chemotherapy in the treatment of newly diagnosed grade IV astrocytoma (ie, GBM, discussed earlier), some oncologists feel there is a role for TMZ chemotherapy in treating these patients at the time of diagnosis. There are, however, no level I data to support this therapeutic approach currently.

LOW-GRADE GLIOMAS

Low-grade gliomas (ie, astrocytomas and oligodendrogliomas) are relatively uncommon in patients older than 65 years (**Figure 101-3**). In a Minnesota cohort study, patients older than 65 years accounted for only 7% of all low-grade glioma patients and 3% of all oligodendroglioma patients. Therapy usually involves maximally feasible resection. RT may be reserved for symptomatic patients, or patients with recurrent disease. In a randomized European trial, RT did not improve overall survival, but did improve progression-free survival. Another indication for RT relates to a patient for whom minimal disease progression might result in significant neurologic deterioration. It should be noted that low-grade oligodendrogliomas with chromosomal deletions in the 1p and 19q loci are very sensitive to both radiation and chemotherapy. This enhanced sensitivity to therapy is also true for anaplastic oligodendroglioma (discussed above). A thorough understanding of the genetic markers of these tumors has greatly expanded our knowledge of the influence of age on outcomes.

MENINGIOMA

Meningiomas are slow growing, extra-axial tumors that arise from the arachnoid and are typically benign. On imaging they are enhancing lesions attached to the dura, often seen with a dural tail of tumor spread along the adjacent dura (**Figure 101-4A–C**). They may be associated with increased bone growth in the adjacent skull. Atypical, malignant, and invasive variations of meningiomas are all possible, though less common than the typical benign lesion. Patient age may play an important role in the development and presentation of these tumors. The peak age of incidence is 45 years, though in one study, 3% of patients age greater than 60 who underwent autopsy were found to have a meningioma. Many meningiomas are found incidentally. For small, asymptomatic lesions in older adults, it makes sense to follow them with serial imaging. In a small case series of 63 patients, 68% showed no increase in size in a follow-up of 36 months.



FIGURE 101-4. (**A**) Axial, (**B**) coronal, and (**C**) sagittal contrast MR images of a right-sided parasagittal meningioma. Note the lesion is homogeneously enhancing and well circumscribed and appears to arise from the dura. The dural tail, characteristic of these lesions, is best seen on the coronal image (**B**).

The female sex steroids progesterone and estrogen also play a role in meningioma proliferation. This was initially suspected due to sex distribution of these tumors—two-thirds of meningiomas occur in women—and confirmed with molecular assays. As a result, these tumors tend to proliferate during pregnancy, and their growth can slow remarkably after menopause. Therefore, small (< 1 cm), asymptomatic lesions are common in postmenopausal women and should only be treated if they are increasing in size or become symptomatic.

When these lesions are symptomatic, they typically present with seizures or mass effect on the adjacent brain. Skull base tumors may compress cranial nerves or vessels, leading to ischemia. Surgery is the treatment of choice for symptomatic lesions, and extent of resection is the most important factor in preventing recurrence. While the majority

of meningiomas are benign, those with increased mitotic activity or cortical invasion are termed atypical and anaplastic, with higher recurrence rates, respectively. If pathology is found to be atypical or anaplastic, post-op external radiation therapy (XRT) with 55 to 60 Gy is recommended. Overall, however, the prognosis for meningiomas is excellent with a 5-year survival of more than 90%. A recent retrospective, multi-institutional cohort study examining the Charlson comorbidity index as a predictor of postoperative outcomes looked at 5717 patients and showed that resection of meningiomas can be done safely through the ninth decade of life as long as patients are medically fit.

PRIMARY CNS LYMPHOMA

Primary CNS lymphoma (PCNSL) is a form of extranodal non-Hodgkin lymphoma that affects the brain, spinal cord, leptomeninges, and eyes. It accounts for about 3% of all primary intracranial neoplasms. The biggest risk factor for acquiring the disease is immunosupression, which is thought to allow the reactivation of latent Epstein-Barr virus. The incidence of PCNSL increases with age as well, though this may not be a second risk factor and may just represent decreased immune functioning in older adults—so-called "immunosenescence." As a result, patients aged 60 or greater are at highest risk for the disease, and the incidence of PCNSL seems to be increasing in the population out of proportion to what would be expected, which may be related to improved imaging and longer increased life expectancy. There are approximately 1200 cases per year in the United States, nearly half are in patients greater than 60, and 20% occur in those 80 or older.

Diagnosis

Presentation can be variable. In a study of 248 immunocompetent patients with PCNSL, 70% had a focal neurologic deficit and over 40% had neuropsychiatric symptoms at the time of presentation—patients typically do not present with B symptoms (fever, night sweats, etc). MRI with contrast typically shows a vivid, homogeneously enhancing lesion that is T1 hypointense and T2 isointense, which, due to its hypercellularity, restricts diffusion. Patients with suspected disease should undergo contrast MRI of the brain and entire spine. A lumbar puncture (LP) should be performed for cytologic studies and flow cytometry once increased intracranial pressure and cerebrospinal fluid (CSF) flow obstruction is ruled out. Slightly less than one-third of patients will have intraocular lymphoma, therefore slit-lamp examination by an ophthalmologist is recommended. In addition, contrast CT of the chest, abdomen, and pelvis is recommended, as 5% to 10% of patient will have disease outside of the CNS.

It is important to consider PCNSL in the differential diagnosis of an intracranial mass due to the difference in treatment compared with other brain tumors. Stereotactic biopsy is indicated for diagnosis in patients with suspected disease, however surgery for debunking or gross total resection results in increased morbidity without improving outcome. One caveat is that PCNSL is initially extremely sensitive to steroids. Initiation of high-dose steroids prior to biopsy can result in transient near-complete regression of the lesion making definitive tissue diagnosis difficult. Unfortunately, this regression is temporary.

Treatment

Survival with PCNSL is poor, averaging 14.7 months. Whole-brain radiation has traditionally been the mainstay of treatment for patients. Recently, however, WBXRT alone has been abandoned, and some practitioners question its role at all. A major focus of recent research has been on chemotherapy alone, usually based on high-dose methotrexate (HD-MTX). A German study (G-PCNSL-GS1) published in 2010 showed that omission of WBXRT in patients with newly diagnosed PCNSL had no effect on overall survival. This study was parsed further in 2012 by Roth et al. where patients greater than or equal to 70 years (n = 126) were analyzed as a subgroup to evaluate toxicity, response, and survival. Overall survival was again unchanged with the omission of WBXRT. Older patients do respond less well than their younger counterparts to HD-MTX–based regimens (44% in older adults vs 57% in the younger cohort). They also found that older patients were treated less often and less aggressively at relapse, further contributing to poorer outcomes. In addition, retrospective experience published by Memorial Sloan Kettering Cancer Center has suggested improved median survival in older patients treated with chemotherapy alone. A median survival of 29 months was observed in the patients greater than or equal to 60 years, which is significantly improved in comparison with historical data in older patients receiving WBXRT alone (median survival 7–12 months). As with other primary CNS tumors there has been considerable effort recently to search for molecular markers that may portend outcomes or provide treatment specificity. Improved outcomes have been associated with patients whose tumors overexpress B-cell

lymphoma 6 (BCL-6)–101 versus 14.7 months median survival in a study of 33 patients. Further research is needed to delineate the best treatment course and predict outcomes more precisely; however, due to the rarity of PCNSL, progress has been slow.

VESTIBULAR SCHWANNOMA

Vestibular schwannomas (VSs), also known by their misnomer, acoustic neuromas (as they arise from neither neurons nor the acoustic nerve), are benign tumors arising from the Schwann cells surrounding the vestibular portion of the eighth cranial nerve. The incidence is estimated to be about 1.5 per 100,000 people. Due to their attachment to the eighth nerve, they cause sensorineural hearing loss. Unilateral hearing loss is the most common presenting symptom, followed closely by tinnitus and balance problems. They are typically found at the cerebropontine angle of the brain stem and most have an intracanalicular component, extending along the nerve into the skull. The vast majority of unilateral tumors are nonsyndromic. Bilateral VS are pathognomonic for neurofibromatosis type 2. They are usually slow growing 1 to 2 mm/year, and displace tissue rather than invade it. Surgical resection is the treatment of choice for most patients with this lesion. However, in older adults, due to slow growth, many surgeons advocate watchful waiting for lesions less than 2.5 cm in patients older than 65 years as long as symptoms are minimal and there is not brainstem compression. Newly diagnosed patients should also undergo audiogram speech discrimination testing. We recommend an MRI every 6 months after the initial diagnosis, followed by yearly MRIs thereafter. Observation should continue as long as significant growth is not seen, symptoms are minimal or stable, and no brainstem compression occurs.

Treatment

The goals of treatment are stabilization of hearing symptoms and avoidance of future brain compression. It is not expected to reverse any hearing loss noted at presentation. Radiation, surgery, or a combination of both are options for patients who fail observation. Radiation has the appeal of being noninvasive. However, long-term follow-up documenting high cure rates are currently not available for radiation. Patients need continued yearly follow-up for life. Patients that receive high doses are at risk for developing brain edema or trigeminal neuralgia. Surgery offers a very high cure rate. In the hands of experienced surgeons, rates of hearing preservation and facial nerve preservation are similar to those of radiation for tumors less than 10 mm. CSF leak is the most common complication after surgery. In a large series from 2001, CSF leak was seen in about 9% of patients, however, only 2% required surgical repair of the leak, and the remainder healed spontaneously.

OTHER CONSIDERATIONS FOR ALL BRAIN TUMORS

Corticosteroids (most commonly dexamethasone) are commonly used in the setting of CNS neoplasms to reduce or prevent edema. Although this may be of great benefit for symptoms, including headache, the long-term use of these drugs is accompanied by predictable severe side effects. The dose of steroid may be tapered after several weeks of treatment if symptoms have stabilized. The lowest possible dose to control symptoms should be used. Common or serious side effects with this medication include oral thrush, hyperglycemia and steroid-induced diabetes, insomnia, weight gain, agitation, and delirium, all of which may complicate use in older patients. It is our practice to start empiric antithrush prophylaxis at the time of starting corticosteroids. We also check blood glucoses while on higher doses of steroids. Patients and their caregivers should be counseled about the side effects of corticosteroids prior to administration.

Antiepileptics are commonly used to treat seizures associated with brain tumors or the accompanying edema. They are not required without a history of seizures except perhaps for prophylaxis around the time of surgery. The provider should recall that most antiepileptic agents interact with several medications metabolized by liver, including dexamethasone, some chemotherapeutic drugs and anticoagulants, such as warfarin. There are a few antiepileptics (such as gabapentin and levetiracetam) that are not hepatically processed, and have fewer drug interactions.

The majority of patients with CNS neoplasms have some degree of a reactive depression, which should be treated in all but the minority of cases. This depression appears to be more severe in the older patients. Although the discussion regarding which antidepressant should be used is beyond the scope of this chapter, it is notable that the tricyclic and monoamine oxidase inhibitors should be avoided in patients on procarbazine chemotherapy.

CONCLUSION

Aging is the biggest risk factor for cancer. The passage of time leads to the accumulation of cell damage, and the aging of the immune system, so-called "immunosenescence," leaves the host less well equipped to battle altered cells that ultimately become malignant. The complex relationship between tumorigenesis, immunity, and aging is not fully understood; however, data show that patients aged 65 or older make up 61% of new cancer diagnoses. Despite this, older patients are often underrepresented in clinical trials. As a result, the best course of treatment is not always known. Although prognosis declines with increasing age, treatment is not futile in this group. The patients' functional status and comorbidities are often more important than chronological age. Recent literature has shown that advanced age, a priori, should not exclude patients from treatment and that prolonging life does not always mean impairment in quality of life.

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Chapter 102

Skin Cancer

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Learning Objectives

- Recognize different types of skin cancer including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), melanoma, and Merkel cell carcinoma (MCC). Understand various treatment modalities.
- Determine when referral to a dermatology specialist is indicated.

Key Clinical Points

1. **Skin cancers are common in older adults, and the vast majority of skin cancers in this population represent basal and SCC.**
2. **Malignant melanoma and MCC are more aggressive and carry a higher risk of lymph node and distant metastasis.**
3. **Overall, definitive treatment of these skin cancers is well tolerated by older adults.**

INTRODUCTION

Nearly 5 million adults in the United States are treated each year for skin cancer, as compared to 10.3 million for all other cancer diagnoses. Approximately 10,000 people die annually of skin cancer in the United States; one an hour from melanoma and one every 4 hours from nonmelanoma skin cancer (NMSC). There are three common types of skin cancer: basal cell carcinoma (BCC) (79% of skin cancers), squamous cell carcinoma (SCC) (14%), and melanoma (5%). Other skin cancer types comprise the remaining 2%. While melanoma accounts for only 5% of skin cancer diagnoses, it accounts for 75% of skin cancer deaths. Basal and SCCs are considerably less lethal, but these tumors are associated with significant morbidity. As with most malignancies, the incidence of skin cancer increases with age. Owing to their sheer numbers, the public health burden from skin cancer is great.

One in five people in the United States and one in three Caucasians will develop skin cancer during their lifetime. Treatment of NMSC has increased in the Medicare fee for service population by nearly 77% from 1992 to 2006. The incidence of skin cancer continues to rise faster than any other cancer, and skin cancer has been labeled as “today’s epidemic” in the lay press. In addition, data on the incidence and prevalence of basal and SCCs are likely underestimated as these cancers are not reported in state or national cancer registries. Importantly, a significant proportion of skin cancer diagnoses are made in patients of advanced age.

ETIOLOGY

Both genetic and environmental risk factors are implicated in the development of skin cancer. The most common known environmental risk factor is chronic and/or acute intense intermittent ultraviolet light exposure in the form of sunlight, artificial tanning devices (tanning booths), and sunburns. The Centers for Disease Control and Prevention Behavior Risk Factor Surveillance System data estimate that nearly 34% of all adults and 69% of adolescents in the United States develop at least one sunburn annually. Sunburns are most common in Caucasian men, young adults, and

high-income groups in national surveys. About 30% of adults routinely practiced sun-protection behaviors, most common in women and older adults. Approximately 60% of parents apply sunscreen to their children. Substantial proportions of adolescents, young adults, and females use indoor tanning, about one-third of women from high school through age 25. Ultraviolet B (UVB), at wavelengths between 290 and 320 nm, causes most of what we see as sun tanning and sunburns, and is responsible for much of the actinic skin damage caused by sunlight. Ultraviolet A (UVA), 320 to 400 nm, penetrates more deeply into the skin and is also an important factor in photoaging and skin cancers. UVB radiation induces skin cancer by a variety of mechanisms including direct DNA damage, damage to DNA repair systems, and alteration of the local cutaneous immune system. Some of the strongest evidence that implicates ultraviolet light as important in the etiology of skin cancer comes from epidemiologic and experimental data correlating the incidence of tumors with the degree of pigmentary protection. Fair-skinned individuals with blue or green eyes and red, blonde, or light brown hair are at highest risk. These patients also typically tan poorly and sunburn and freckle easily. The risk of skin cancer varies with race and ethnic group with Caucasians having the highest incidence rates. Skin cancer is less common in African Americans, Asians, and Hispanics, but a rise in the Hispanic and Asian population is occurring. Other epidemiologic data correlate an increased incidence of skin cancer with residence at lower latitudes with associated higher levels of ambient UVB radiation. And finally, conclusive data demonstrate sunscreen use prevents melanoma and other skin cancers.

The changes that most persons equate with aging of the skin are a result of chronic solar damage. Prolonged exposure to ultraviolet light leads to cutaneous atrophy, alterations in pigmentation, wrinkling, dryness, telangiectasia, and solar elastosis. Ultraviolet light from the sun or artificial tanning devices is believed to be the most common cause of skin cancer. Most NMSCs occur on sun-exposed sites such as the face, head, neck, or extensor arms and hands. Other environmental/exposure factors associated primarily with SCC include chronic exposure to chemicals such as hydrocarbons (coal tars, soot, cutting oils, and asphalt). Chronic exposure to arsenic is associated with NMSC on both sun-exposed and sun-protected sites. Psoralen in combination with UVA (PUVA) used in the treatment of psoriasis and other inflammatory dermatoses produces a dose-dependent increase in SCC and melanoma. Cigarette smoking is linked to SCC of the lip and mouth. The human papilloma virus has been associated with cutaneous SCC in the genital and acral/periungual areas. The carcinogenic effect of ionizing radiation inducing NMSC is documented in human and animal models. Other conditions associated with NMSC include burn and vaccination scars, chronic inflammatory processes and ulcers, and immunosuppression.

A number of genetic syndromes are associated with an increased risk of developing NMSC. Nevoid BCC syndrome (Gorlin syndrome) is an autosomal dominant or mosaic disorder associated with the occurrence of hundreds to thousands of lifetime BCCs beginning in childhood or young adulthood. Jaw cysts, palmoplantar pits, abnormal ribs and vertebrae, frontal bossing, and hypertelorism are also found. Albinism, which can occur owing to one of several causal genetic defects, is associated with an increased risk of all skin cancer types. It is characterized by partial or complete failure to produce or distribute ocular, hair, and/or cutaneous UV protective melanin pigment. Xeroderma pigmentosum is a rare autosomal recessive disorder that results in the inability to repair UV-induced DNA damage. It is characterized by hypersensitivity to UV light and the relentless development of skin cancer, especially SCC and melanoma. Individuals with xeroderma pigmentosum are usually diagnosed with their first cancer prior to the age of 10.

Many genes are associated with melanoma development currently known in a minority of patients such as *CDKN2A* (p16). The hereditary nature of melanoma is also noted in families with more than 100 normal nevi or any number of atypical-appearing (dysplastic) nevi. Atypical nevi are not “premelanoma” *per se* but represent a marker for an increased risk of melanoma. A positive family history of melanoma is present in 5% to 15% of melanoma patients. Five to ten percent of individuals with a prior melanoma develop a second primary melanoma. The genetic associations of melanoma continue to evolve.

Congenital nevi (CN) are present at birth or appear within the first 6 months of life. The risk of melanoma developing in CN less than 20 cm in diameter is similar to that of any other area of skin. Melanoma arising within CN usually occurs after childhood and arises at the dermoepidermal junction making early detection possible. Thus, in the absence of warning signs or symptoms, routine prophylactic removal of CN less than 20 cm in diameter is rarely indicated. Large (≥ 20 cm) CN are at increased risk for developing melanoma (5%–20%), tend to progress to melanoma prior to age 10 (70%), and may originate deep in the lesion resulting in later detection.

NONMELANOMA SKIN CANCER

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common type of skin cancer; it is typically seen in older adults, and has no known precursor lesion. Approximately 80% of BCCs occur on the head and neck. BCCs are classified by clinical appearance and histologic pattern most commonly as nodular, superficial, aggressive growth, and pigmented subtypes. BCCs rarely metastasize and grow slowly for years prior to developing a more rapid growth rate. BCCs grow relentlessly and, if left untreated, can cause extensive local destruction and disfigurement. Occult local invasion may be deep and asymmetric with root-like extensions sometimes several centimeters beyond their clinically apparent borders. Metastatic BCC is a rare event (0.03% of all BCCs), most often spreading to the regional lymph nodes followed by the lungs, bones, and skin. The overall survival rate for patients with metastatic BCC is poor.

The most common BCC subtype is the well circumscribed or nodular variant. This typically begins as a small, translucent or waxy flesh-colored or pink, pearly papule or nodule with small telangiectasias on the surface and a translucent, sometimes rolled border (**Figure 102-1**). Symptoms include itching or bleeding. With time, the nodule increases in size and undergoes central ulceration. Most nodular BCCs present as small (< 1 cm) papules, however, patients still present with large, disfiguring lesions that have been neglected for many years. Classic histologic features of the nodular BCC include the presence of well circumscribed, basaloid tumor lobules of various sizes in the dermis. The basal cells at the tumor periphery appear to line up, a phenomenon known as peripheral palisading. Areas of separation or retraction artifact between tumor nodules and the adjacent connective tissue embedded in a pale mucinous stroma are also seen.

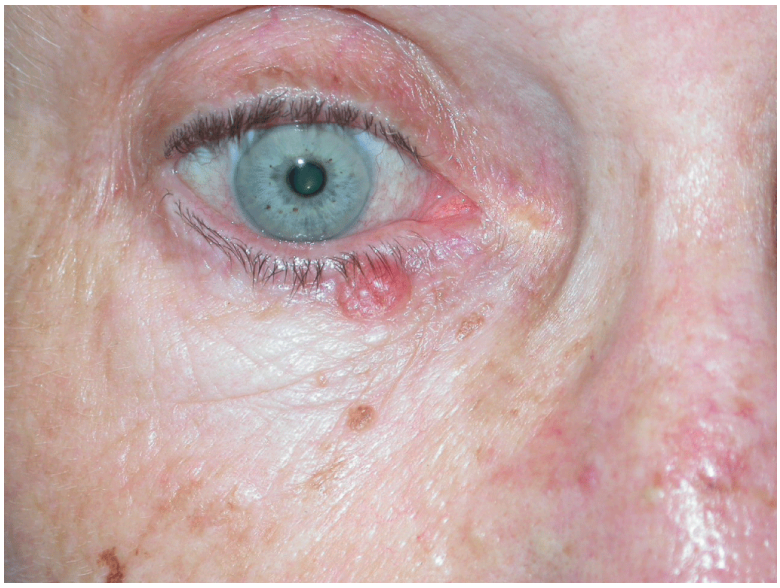


FIGURE 102-1. Nodular BCC on the lower eyelid. Small pearly papule with telangiectatic blood vessel visible at superior aspect of lesion.

Superficial BCCs present as a pink to red, flat, scaly lesion, sometimes with a fine, thread-like translucent border (**Figure 102-2**). They are sometimes confused with scaly skin conditions such as psoriasis or other eczematous dermatoses, and may closely resemble actinic keratosis or Bowen disease. Significant and sometimes extensive superficial subclinical involvement is common as they grow by peripheral extension. Histologic features of the superficial BCC include numerous, multifocal small buds of basaloid tumor cells that arise in the epidermis and extend into the superficial dermis and down and around hair follicles.



FIGURE 102-2. Superficial BCC occurring on the chest. Pink, flat lesion with slightly raised scaly borders.

The aggressive growth pattern BCC subtype usually presents as a flat, firm, indurated, pale, white-to-yellow papule or plaque with harder to detect clinical borders and a "scar-like" appearance. This subtype is also known as infiltrating, morpheaform, sclerosing, sclerotic, and fibrotic BCC. Clinically, aggressive growth pattern BCCs may exhibit subclinical extension widely beyond (> 1 cm) their apparent borders, and can also ulcerate (**Figure 102-3**). They have a higher rate of recurrence following standard treatment modalities because of distant, small finger-like projections of tumor cells that may deeply invade into the dermis, subcutis, and muscle and skate along fascial planes, cartilage, and bone. These small, finger-like islands are often missed with standard histologic margin control. Histologic features of aggressive growth pattern BCC include small islands and spiky finger-like linear strands and cords of basaloid tumor cells embedded in a dense, fibrous sometimes sclerotic connective tissue stroma. Peripheral palisading and stromal retraction is often subtle or absent and perineural invasion is more common. Micronodular BCC, similar to aggressive growth pattern BCC, may exhibit significant subclinical extension through the dermis, subcutis, and muscle. Histologically, small tumor islands characterize micronodular BCC. BCC may also have histologic features of squamous metaplasia and keratinization. These tumors have basosquamous differentiation and may become more aggressive and develop regional lymphatic spread. It is important for the pathologist to convey the BCC histologic subtype pattern to the clinician, which helps form the basis for treatment and treatment options. Multiple histologic patterns may be present in up to 35% to 50% of BCC with the most aggressive pattern correlating with biological behavior. Pigmentation from melanin can be seen in all BCC subtypes, but is most commonly seen in nodular BCCs. Some lesions categorized as pigmented BCC are heavily pigmented and can bear a striking resemblance to melanoma.



FIGURE 102-3. Aggressive BCC on the nose. Note the indurated plaque central ulceration. This lesion is likely to have wide subclinical extension present.

BCC is thought to originate from tumor progenitor cells within the epidermis and hair follicle, and may develop in both hereditary and sporadic fashions. Patients with hereditary nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin syndrome develop hundreds of BCCs in their lifetime. At the molecular level, uncontrolled hedgehog (Hh) signaling is associated with both hereditary and sporadic BCC. Inactivating mutations on the tumor-suppressor patched (*PTCH*) gene and activating mutations in the proto-oncogene smoothened (*SMO*) are causative of NBCCS as well as sporadic BCCs. These mutations result in the unregulated activation of the Hh pathway which is associated with growth promotion and cancer development in tumor progenitor cells within the epidermis and hair follicle. Mutations that inactivate the tumor-suppressor gene *p53* have also been identified in more than half of BCCs, but a causal role for *p53* mutations in BCC development or progression has not been demonstrated. Patients with Li-Fraumeni syndrome, characterized by a germline inactivating mutation in the *p53* gene, have an increased incidence of a number of malignancies, but an increase in NMSC has not been reported.

Squamous Cell Carcinoma

SCC is the second most common skin cancer type. It possesses the potential to metastasize, the risk of which depends on various factors. The most common first site of metastasis is the regional lymph nodes, which occurs in approximately 85% to 90% of metastatic cases. Approximately 10% to 15% of metastases involve distant sites such as the lungs, liver, brain, bone, and skin. The prognosis for patients with metastatic SCC is poor with 10-year survival rates of less than 20% for patients with advanced regional lymph node involvement and less than 10% for patients with distant metastases. Fortunately, the majority of cutaneous SCCs are low-risk lesions that are treated with high cure rates.

SCC has a precursor “premalignant” lesion termed actinic keratosis (AK). AKs are extremely common in fair-skinned older Caucasian individuals who have had significant chronic sun exposure. AKs usually occur in areas damaged by sun exposure, such as the bald scalp, face, and extensor forearms/hands. AKs occur as well-demarcated, scaly, rough patches or plaques on chronic sun-exposed skin surfaces. Their color can vary from skin-colored, erythematous, pink, or to brown, and they are often more easily palpated than seen. The majority of cutaneous SCCs arise in AKs. However, the incidence of progression of an individual lesion from AK to SCC in situ (Bowen disease) and then to invasive SCC remains low, ranging from 0.025% to 20%, and occurs slowly over years in immunocompetent individuals. The cumulative risk depends on the number of lesions and the length of time they persist. AKs are easily treatable with cryotherapy or topical agents such as 5-fluorouracil (5-FU) for more numerous lesions. Other conditions predisposing to SCC include radiation exposure; scarring from a previous injury such as a burn, chronic inflammatory processes such as chronic wounds or ulcers, osteomyelitis, sinuses, or discoid lupus; human papilloma virus particularly in acral and genital sites; and chronic arsenic or hydrocarbon exposure.

Patients who are immunosuppressed such as following organ transplant deserve special consideration and attention. SCC is the most common skin cancer in immunosuppressed organ transplant recipients, occurring 65 to 250 times

more frequently than in the general population. Large numbers of premalignant AKs can rapidly develop and progress in fair-skinned, immunosuppressed individuals with a history of significant sun exposure. Moreover, these AKs behave more aggressively and tend to transform into invasive, rapidly growing SCCs with a more aggressive behavior and increased risk of metastasis. Frequent clinical surveillance and early intervention and prevention are thus essential in these patients. Almost half of the malignancies that arise in patients with impaired immune surveillance occur in the skin. The great majority of these are squamous cell cancers, occur in sun-exposed areas, and almost 50% of patients have multiple tumors.

Ultraviolet-induced mutations of the *p53* tumor-suppressor gene interfere with apoptosis of the damaged cells, permitting damaged cells to proliferate. More than half of cutaneous SCCs and AKs have *p53* gene mutations. Nucleotide sequence analysis demonstrates that these mutations are specifically associated with exposure to UVB light.

Clinically, cutaneous SCCs (80%) most commonly develop on chronically sun-exposed areas on the head and neck and extremities, followed by the trunk. Clinical presentation varies, but most often occurs as a 0.5 to 1.5 cm firm, sometimes tender, hyperkeratotic pink to red papule, nodule, or plaque (**Figures 102-4** and **102-5**). Ulceration and easy bleeding is a relatively common finding. Rapid and deep local invasion may occur. In darker skinned patients, SCC may present in non–sun-exposed areas and is most commonly associated with chronic inflammatory or scarring processes.



FIGURE 102-4. Invasive SCC on the cheek. Large ulcerated nodule with central core filled with hyperkeratotic material.



FIGURE 102-5. Invasive SCC on the dorsal hand. Crusted lesion on the hand with surrounding actinic damage.

Histologically, several subtypes of SCC exist, but the conventional subtype is the most common. Other subtypes include adenoid/acantholytic, bowenoid, spindle/pleomorphic, small cell, verrucous, and keratoacanthoma. The conventional subtype is associated with irregular masses of epidermal cells proliferating downward and invading the dermis. The invading tumor masses are composed of varying proportions of normal squamous cells and atypical cells. These atypical cells demonstrate variations in the size and shape of the cells, hyperchromasia and hyperplasia of the nuclei, absence of intracellular bridges, keratinization of individual cells, and the presence of atypical mitotic figures. In SCC, differentiation is toward keratinization. Horn pearls, which are concentric layers of squamous cells with gradually increasing keratinization toward the center, can also be seen. The dermis often shows a marked inflammatory reaction. Histologic grading of SCC depends on the percentage of keratinizing cells, percentage of atypical cells, number of mitotic figures, and depth of invasion. The Broder classification system is based on the degree of dedifferentiation of the cells: in grade 1, fewer than 25% (well-differentiated); in grade 2, fewer than 50%; in grade 3, fewer than 75%; and in grade 4, greater than 75% of the cells are undifferentiated (poorly differentiated).

Treatment for BCC and SCC

Prior to any treatment, a biopsy confirming the diagnosis is mandatory. Numerous surgical and nonsurgical modalities are effective in treating BCC and SCC. Despite the enormous amount of literature pertaining to the treatment of BCC and SCC, there is relatively little high-level evidence-based research on the efficacy of the treatment modalities used. Based on the best available cumulative evidence, the selection of therapy is based on several clinical and histologic risk factors noted in **Table 102-1**. The majority of lesions are relatively low risk and can be treated effectively with standard techniques such as destructive electrodessication and curettage, standard surgical excision, or radiation with 92% to 98% local control rates for low-risk tumors. As the lesions develop additional risk factors, noted in **Table 102-1**, the control (cure) rate begins to drop precipitously. For higher-risk lesions, Mohs surgery or surgical excision with comprehensive margin control or wide margins still results in 95% to 99% local control rates in the majority of cases.

TABLE 102-1 BASAL CELL CARCINOMA (BCC) AND SQUAMOUS CELL CARCINOMA (SCC) HIGH-RISK FACTORS FOR OCCULT SUBCLINICAL INVASION AND RECURRENCE

Recurrent tumor
Location
High risk: mask areas of face (eyelid, eyebrow, periorbital, nose, lip, chin, mandible, temple, ear, in front or behind the ear), genitalia, hands, and feet
Size
Lesions > 5 mm on high-risk areas: mask areas of face, genitalia, hands, and feet
Lesions > 9 mm on medium-risk areas: cheeks, forehead, scalp, and neck
Lesions > 19 mm on low-risk areas: trunk and extremities (excluding pretibial, hands, feet, and ankles)
Histology
BCC: aggressive growth (morpheaform, fibrosing, sclerosing, infiltrating, micronodular)
SCC: poorly differentiated, adenoid, adenosquamous, or desmoplastic subtypes
Ill-defined clinical borders
Perineural invasion or vascular involvement
Immunosuppression
Etiology: development in site of prior radiation, scar, chronic inflammatory process
SCC depth of invasion ≥ 2 mm or Clark level IV or V
SCC rapid growth
SCC neurologic symptoms

Electrodessication and curettage Electrodessication and curettage (ED&C) is a common, effective, operator-dependent treatment option for low-risk tumors in low-risk areas. ED&C causes local tissue destruction and is quickly performed with local anesthesia in the office. First, a curette is used to remove the gross tumor, which is soft and friable. This is followed by electrodessication of the periphery and base of the wound to destroy residual tumor cells.

This process is repeated for two to four cycles depending on the size and feel of the lesion. The experienced operator can provide similar high cure rates with curettage alone, omitting electrodessication. The resulting wound heals by granulation with a hypopigmented, atrophic, and sometimes a depressed scar. If the curette extends into the subcutis or a sclerotic "feel" is noted, ED&C should be discontinued and excision of the site should be performed.

Topical chemotherapy Topical chemotherapy can be an effective treatment modality for AKs and has been used for select very low-risk BCC. The two main agents available are topical 5-FU and imiquimod. Topical 5-FU is particularly useful for treating larger areas of AKs, when more localized treatment such as cryosurgery becomes impractical. Local inflammation and irritation are the main complications of therapy. Topical imiquimod is another treatment for AKs and in the 5% cream is also used for select low-risk superficial BCC. Imiquimod is an immune response modifier and exerts its effect via toll-like receptors to increase inflammatory cytokine production. Similar to topical 5-FU, local inflammatory reactions are common, and some patients of all ages can also develop systemic flu-like symptoms.

Radiotherapy Fractionated radiation therapy (RT) may be used for both BCC and SCC and is usually performed in 15 to 25 daily treatments over 3 to 5 weeks. Experience and a clinical understanding of NMSC are vitally important to achieve good results with high cure rates. Contraindications for RT include genodermatoses predisposing to skin cancer (nevoid BCC syndrome and xeroderma pigmentosum) and potentially connective tissue disease which may flare (lupus and scleroderma). Local recurrences following RT may be more aggressive.

Surgical excision Surgical excision is an effective treatment modality for all types of NMSC and possesses the advantage of a tissue specimen for histologic assessment of margins. Excisions heal more rapidly often with superior cosmetic results when compared with destructive techniques. Recommended margins for excision of NMSC generally range from 4 to 10 mm. Surgical excision is more invasive, more expensive for low-risk lesions, and requires training and experience. Many cases can be performed in a treatment room with local anesthesia, but larger cases may require general anesthesia or intravenous sedation in the operating room. High-risk lesions require more comprehensive histologic processing and evaluation or widely clear margins with standard tissue processing to achieve high control rates. Standard histopathologic (bread loaf) processing of excision specimens examines less than 1% of the true surgical margin. This may be problematic for higher-risk NMSC such as those with greater asymmetric subclinical extension. Following an incompletely excised NMSC, except in the situation of excision for palliation, observation is usually not appropriate. Rather, re-excision by either Mohs surgery or additional therapeutic intervention should be performed. The cure rate of low-risk lesions by excisional surgery is similar to those of destructive techniques and RT.

Mohs surgery Mohs micrographic surgery is a highly effective treatment for NMSC when done by experienced, appropriately trained Mohs surgeons and results in the highest local control (cure) rates with maximal sparing of normal tissue for appropriate select cases. The technique involves serially excising cancerous tissue with 1- to 3-mm margins per stage, and examining the entire undersurface and edges of the specimen (the entire true margin). By definition, the Mohs surgeon performs a dual role as both surgeon and pathologist. Through advanced postgraduate ACGME fellowship training, the Mohs surgeon is adept at microscopic interpretation of horizontally cut frozen sections as well as local flap and graft soft tissue reconstruction techniques to repair the resulting wounds.

Mohs surgery is usually performed under local anesthesia in an office-based setting. First, all gross tumor is removed by curettage. The surgeon then excises a layer of tissue in the shape of a saucer with 1 to 3 mm deep and peripheral margins around and under the curettage defect. The specimen is divided into sections, color coded with dyes, and a schematic map is made for precise anatomic orientation. The tissue is processed with horizontal frozen sections that incorporate the entire deep and peripheral margin for interpretation.

The Mohs surgeon examines the sections under the microscope for evidence of remaining cancer. If residual cancer cells are noted at a margin, the precise location on the map is identified on the patient and another layer of tissue at the corresponding site of residual tumor is excised. This layer is again examined microscopically for additional cancer cells. The process continues layer by layer in stages until no detectable cancer cells at the margin remain. Maximal normal tissue conservation is preserved, and nearly 100% of the margin is examined resulting in exceedingly high local control rates. Reconstruction is performed without delay after margins are free. In cases involving extensive defects or very large or complex tumors, a collaborative multidisciplinary team approach is important. Adjunctive RT may be indicated in cases of extensive perineural spread and cases with a higher risk of local recurrence.

Mohs surgery is a labor-intensive technique and requires an experienced team. Mohs surgical training, and thus technique and results, is highly variable, ranging from no postgraduate training to weekend courses to postgraduate ACGME-approved fellowship training. Mohs surgery when performed optimally is considered the "gold standard" for removal of higher-risk NMSC. However, for small lower-risk lesions, the cure rates for the treatment of NMSC with

Mohs versus standard therapies are comparable.

Treatment of nodal disease with SCC Metastasis with SCC most commonly occurs in the regional lymph nodes. Nodal disease is treated with completion lymph node dissection and when indicated, based on number of involved nodes and status of extranodal extension, adjuvant local radiation therapy.

Systemic therapy The occurrence of locally advanced and metastatic BCC is uncommon. Vismodegib is a hedgehog pathway inhibitor approved by the Food and Drug Administration (FDA) for the treatment of metastatic and locally advanced inoperable BCC in patients also not candidates for radiation therapy. Objective response rates approaching 30% for metastatic and 43% for locally advanced BCC are reported. Partial response rates of 30% for metastatic and 22% for locally advanced BCC are reported. Unfortunately, tumors may recur while on treatment or after discontinuation of the drug with a median duration of response about 8 months in both metastatic and locally advanced cohorts. Adverse events occur in over 30% of patients (25% serious) and include most often muscle spasms, taste disturbances, alopecia, weight loss, and fatigue. Basset-Seguin et al. recently reported an interim analysis of the STEVIE trial, which was designed to analyze safety of vismodegib. In this interim analysis, 62% of the 499 patients were greater than or equal to 65 years. In the cohort 80% discontinued the medication with 36% due to adverse effects. Distant metastasis with cutaneous SCC occurs more commonly than BCC however this is still a rare event. In these cases systemic chemotherapy may be used to control disease.

Follow-up Thirty to fifty percent of patients with NMSC will develop another within 5 years, and are at increased risk of developing melanoma. For this reason these patients should have regular skin examinations, and receive education on self-skin examinations and sun protection. In addition, with respect to SCC, recurrence most often happens within the first 2 years (70%–80% of the time). Closer follow-up within this time frame with attention to the primary site and to the regional primary draining nodal basins is indicated. These patients should be educated in self-examination of lymph nodes which should be performed with monthly skin self-examinations. Suspicious or palpable lymph nodes should be evaluated for metastatic disease.

MELANOMA

Epidemiology and Clinical Presentation

Melanoma results from the malignant transformation of melanocytes usually located at the dermal-epidermal junction. Melanoma confined to the epidermis is termed melanoma in situ. With time, melanoma invades vertically into the dermis where it can metastasize to the regional lymph nodes and other distant organ systems via the lymphatic or vascular systems. The deeper the melanoma invades, the greater the risk for metastasis and advanced systemic disease.

The incidence of melanoma continues to increase around the world, currently 2% to 3% annual increase in the United States, a 200% increase in the United States since 1973. In the United States alone, there will be an estimated 73,870 new invasive melanomas and 63,440 new cases of melanoma in situ diagnosed in 2015 resulting in 9940 deaths (> 65,000 worldwide). One in 50 Caucasians born in 2015 is projected to develop melanoma over their lifetime; 1:200 Hispanic, 1:350 Native American, 1:800 Asian, and 1:1100 African American. Melanoma is the fifth most common cancer in men and the seventh most common cancer in women. The average age at diagnosis is 62 but melanoma occurs in all age groups. Melanoma is the most common cancer type in young adults 25 to 29 years, second in adolescents and young adults 15 to 29 years, and second in women 30 to 35 years. The incidence of melanoma in Caucasian women younger than 44 has increased greater than 6% annually in part due to tanning bed use in this cohort. Melanoma is the leading cause of cancer death in women 25 to 30 years and second in women age 30 to 35. As such, melanoma represents one of the leading cancers in terms of average years of life lost due to death from disease.

Risk factors for the development of melanoma include blue or green eyes, blonde or red hair, fair complexion with a tendency to freckle, sunburn, and tan poorly, the presence of dysplastic nevi or more than 100 normal-appearing nevi, a personal or family history of melanoma, and a history of significant UV exposure or sunburns.

Primary care practitioners are often the patient's first contact with the healthcare system, and therefore play a vital role in the diagnosis of melanoma. Lives can be saved and healthcare costs reduced by early detection of this potentially fatal skin cancer. Although not all melanomas are detected by physicians and health care providers, provider-detected melanomas are significantly thinner, resulting in a better prognosis and lowered costs for treatment. Patients should be taught to examine their skin and of the importance of bringing suspicious skin lesions to the attention of their providers as these interventions lead to earlier detection by patients.

Melanoma can arise anywhere on the skin surface. Approximately one-third of melanomas arise from a melanocyte within a preexisting pigmented lesion. Two-thirds arise within scattered melanocytes, developing on clinically normal-appearing skin. The most frequent site for melanoma in men is the trunk, particularly the upper back and shoulders. The most frequent sites for melanoma in women are the legs followed by the trunk. Melanoma can occur in mucosal, genital, nail bed, and ocular sites, although this is rare.

The earliest clinical features of melanoma include a change in the size, shape, or color and occasionally persistent itching in a lesion. Later features include ulceration, bleeding, and tenderness. Classically an ABCD rule has been used to help recognize lesions suspicious for melanoma. "A" stands for asymmetry—one-half of the lesion does not match the other half as a mirror image when drawing an imaginary line through the center of the lesion. "B" stands for irregularity of the borders—the edges of the lesion are ragged, notched, jagged, scalloped, or fuzzy. "C" stands for color—the color is not homogeneous throughout the lesion. Varying and mottled shades of tan, dark brown to jet-black, or shades of red, white, and/or blue may be present. Historically, "D" stands for diameter greater than 6 mm, which has proven to be relatively insensitive as an independent factor. At our melanoma center and in many in the United States, "D" stands for difference whose meaning is twofold. The first application of "difference" describes any change or difference in an individual lesion, especially with respect to size, shape, color, or persistent itching. The second applies more to the evaluation of multiple nevi. In patients with multiple normal or slightly abnormal-appearing nevi, those nevi when viewed as a group should grossly appear similar to one another, or belong to the same family. An isolated lesion that does not appear similar to the patient's other nevi, or does not belong to the family, should be examined and possibly tested. This has also been called the ugly duckling sign. The ABCD rule and other diagnostic aids enhance early detection, but do not provide the ability to differentiate between benign and malignant in every setting. Some advocate adding an "E" to denote evolution and change.

Early melanomas can lack all of these classic ABCD features. Therefore, any changing pigmented lesion or new atypical lesion should be evaluated and considered for biopsy especially in a patient with risk factors for melanoma. Melanomas can completely lack pigmentation (amelanotic melanoma) in 3% to 4% of cases (**Figure 102-6**). Understandably, these are often associated with later detection. As previously mentioned, melanoma arises within a preexisting nevus in only 33% of cases, and therefore occurs *de novo* on clinically normal-appearing skin in 66% of cases. Although one's threshold for biopsy should be low and suspicion for melanoma high, prophylactic removal of preexisting nevi is therefore not indicated.



FIGURE 102-6. Amelanotic melanoma. Pink nodule on the lower leg.

Historically, melanomas are classified by histologic patterns and clinical characteristics into four major subtypes: superficial spreading melanoma, lentigo maligna melanoma, nodular melanoma, and acral lentiginous melanoma. These classifications are of little prognostic value as the biological behavior and risk of metastasis today are based mainly on several features, most important the thickness of the primary tumor measured in millimeters (Breslow depth).

Superficial spreading melanoma comprises approximately 60% to 70% of melanomas and represents the most

common melanoma subtype. Superficial spreading melanoma often arises in a preexisting nevus and typically develops as a spreading pigmented plaque with irregular borders and variation in color and surface contour. They often exhibit the classic clinical features of melanoma (**Figures 102-7** to **102-9**). Areas of regression may result in pink to white areas within the black or brown tumor.



FIGURE 102-7. Early superficial spreading melanoma. Note asymmetry and irregular border.



FIGURE 102-8. Superficial spreading melanoma showing all of the ABCD features. Breslow depth 3.5 mm.



FIGURE 102-9. Superficial spreading melanoma. Breslow depth 1.1 mm.

The lentigo maligna melanoma subtype comprises approximately 10% to 15% of all melanomas and usually begins as a pigmented macular lesion with variation in black and brown color (**Figures 102-10** and **102-11**). They are most common on chronically sun-exposed areas of the head and neck, most often in older individuals. Lentigo maligna represents the in situ phase and, with time, progresses to the invasive phase then termed lentigo maligna melanoma. These lesions have irregular outlines and may slowly enlarge over many years with progression to black and development of other classic melanoma features. The malignant cells may extend asymmetrically several centimeters beyond the clinical lesion and extend down hair follicles and other skin appendages. These characteristics can make lentigo maligna and lentigo maligna treatment result in higher recurrence rates with standard surgical margins. Amelanotic and desmoplastic melanoma with neurotropism may arise more frequently within the lentigo maligna pattern melanoma.

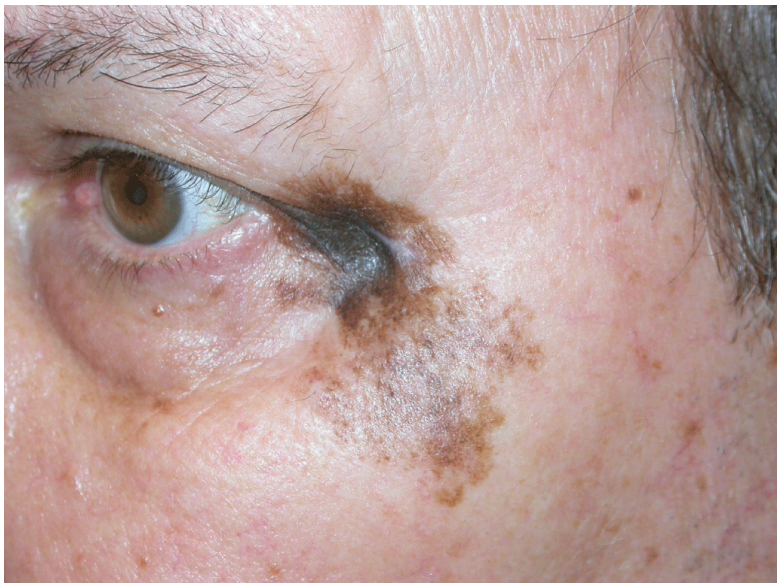


FIGURE 102-10. Lentigo melanoma (melanoma in situ) on the left lateral canthus and cheek. Large, asymmetric, irregularly pigmented flat patch.



FIGURE 102-11. Lentigo melanoma (melanoma in situ) on the dorsum of the nose. Irregularly pigmented flat macule that had been slowly enlarging over a number of years.

Nodular melanoma often arises without evidence of a preexisting lesion. This subtype constitutes approximately 15% to 30% of melanomas. Nodular melanoma has a minimal radial-lateral growth phase, instead growing vertically early on the disease course. Due to the early vertical growth phase, nodular melanoma is typically thicker at the time of detection, which leads to a worse prognosis. Nodular melanomas usually appear as a raised, nodular, or polypoid lesion with more uniform color and regular borders. They often present as less than 6 mm, may become ulcerated with rapid growth, and can lack the classic melanoma features (**Figure 102-12**). This subtype highlights the importance of lesion change and difference for early detection.



FIGURE 102-12. Large nodular melanoma. Breslow depth 11.5 mm with ulceration associated with 45% 5-year survival (stage IIc).

Acral lentiginous melanoma represents approximately 2% to 8% of melanomas in Caucasians, but 35% to 60% in people of color. They usually occur on acral sites, that is, the hands, feet, fingers, toes, and under the nails (**Figure 102-13**). Subungual melanomas can present as an irregular, tan-brown longitudinal streak in the nail (**Figure 102-14**). Approximately 75% of subungual melanomas involve the great toe or thumb and are often misdiagnosed as subungual hematoma.



FIGURE 102-13. Acral lentiginous melanoma. Black, irregularly shaped macule on the sole of the foot.



FIGURE 102-14. Subungual melanoma. Longitudinal dark brown streak along nail plate with associated brown pigmentation on the proximal nail fold and nail dystrophy. Suture identifies biopsy site of the nail matrix.

Staging and Prognosis

The American Joint Committee on Cancer (AJCC) uses a system that is based on classifying melanoma according to tumor thickness (T), nodal status (N), and metastatic disease (M). Five stages exist, which correlate with prognosis: stage 0 (in situ melanoma), stage I (local disease), stage II (local disease), stage III (regional nodal disease, satellitosis or in-transit metastases), and stage IV (distant metastases). Distant metastasis portends a poor prognosis. Melanoma metastasizes most frequently to the lymph nodes, skin, and subcutaneous tissue. Visceral metastases manifest most commonly in the lungs, liver, brain, bone, and intestines but may occur in any organ.

The most important histologic prognostic factors for melanoma staging are the Breslow depth of invasion, ulceration status, and for lesions less than 1 mm Breslow depth a mitotic rate greater than or equal to $1/mm^2$. Poorer prognosis correlates with deeper Breslow depth, the presence of ulceration, and a higher mitotic rate.

The status of the regional lymph node basin is the most powerful predictor of overall survival for patients with melanoma. For those with nodal metastasis, the tumor burden (both microscopic vs macroscopic disease and the number of involved lymph nodes) has an inverse correlation with survival. The 5-year survival rate for patients with involved lymph nodes ranges from 23% to 87% based primarily on tumor burden and ulceration status of the primary

lesion. Clinically node-negative patients with significant risk of regional nodal disease at the time of diagnosis are staged with sentinel lymph node biopsy (SLNB), ideally performed at the time of definitive treatment of the primary site. The lymph node status and nodal tumor burden (based on SLNB) are incorporated into the current AJCC staging system. A thorough description of prognosis based on Breslow depth and other prognostic factors is found in a seminal article by Balch et al.

Treatment of Melanoma

Biopsy Lesions clinically concerning for melanoma should ideally be biopsied with a full-thickness excision with narrow margins (2 mm) oriented parallel to the lines of lymphatic drainage or a deep saucerization shave biopsy of the entire lesion, with the goal being to remove the entire clinical lesion for complete histologic evaluation. A superficial shave biopsy is never recommended for a lesion suspicious for melanoma because if the melanoma is transected, the ability to obtain an accurate measurement of tumor thickness may be lost. For suspicious lesions too large for complete excision, a full-thickness incisional biopsy deep enough to avoid transecting the lesion at the deep margin may be performed using an ellipse, deep saucerization shave, or punch. Incisional biopsies of melanoma do not increase the risk of metastasis. Formalin-fixed, paraffin-embedded, permanent sections are required for accurate microstaging and diagnosis of the primary lesion. The biopsy should be interpreted by a dermatopathologist with experience in melanocytic lesions. Frozen sections and fine-needle aspiration (FNA) have no role in the diagnosis of primary cutaneous melanoma, but may be useful in the diagnosis of metastatic disease in palpable nodules found in the nodal basin or soft tissues.

In the case of recently diagnosed melanoma and in the presence of an unremarkable history and physical examination, the National Comprehensive Cancer Network (http://www.nccn.org/) recommends against routine imaging studies (computed tomography [CT], positron emission tomography [PET] scan, magnetic resonance imaging [MRI]) for patients with stage I melanoma. These imaging modalities may be used for symptom-directed work-up for patients with stage II disease. For clinically node-negative patients at significant risk for metastasis, SLNB is the gold standard for staging. Imaging for asymptomatic patients with stage III disease is generally felt to be low yield, but may be performed at the discretion of the treating physician. Stage IV metastatic disease should be confirmed by tissue biopsy (either FNA or open biopsy) when possible and additional staging with imaging and blood serum lactate dehydrogenase (LDH) recommended.

Surgical excision of the primary tumor Surgical excision of the primary tumor is the standard therapy for melanoma to prevent local recurrence caused by persistent disease. For melanoma in situ, excision margins of 0.5 to 1 cm are indicated. For invasive melanoma, excision with margins of 1 cm for melanoma less than or equal to 1 mm thick, 1 to 2 cm for those 1 to 2 mm thick, and 2 cm for those more than 2 mm thick is indicated for local control. For the clinically ill-defined lentigo maligna melanoma, these standard margin recommendations may be inadequate because of potentially extensive (up to several centimeters) subclinical extension. Histologic confirmation of negative margins is necessary for complete surgical resection of lentigo maligna melanoma, with permanent section processing the “gold standard.”

Regional node management

Sentinel Lymph Node Biopsy Melanoma may metastasize first to the regional nodal basin in an orderly fashion with metastasis to one lymph node [the sentinel node (SN)] as the first step in the process. The SN can be identified by use of radiolabeled colloid lymphatic tracers plus blue dye injected intradermally at the site of the primary lesion. These tracers and dye travel through the lymphatic vessels draining that area of skin and collect in the SN. This node (or nodes) is then removed for careful histologic evaluation with the aid of immunohistochemical stains. The technique of SLNB is most often performed in conjunction with the wide excision of the primary tumor and is routinely performed as an outpatient procedure. If the SLN is negative for melanoma, no further treatment is indicated. If the SLNB is positive for melanoma, regional therapeutic lymphadenectomy is indicated and patients may be eligible for adjuvant therapy.

Patients without clinical evidence of metastasis with primary melanoma greater than or equal to 1 mm Breslow depth should be counseled regarding the risks and benefits of staging with SLNB. For some patients with melanoma Breslow depth 0.75 to 1 mm, staging is also indicated if there are other high-risk features present. High-risk features for regional metastasis in thin melanoma include young patient age, presence of ulceration of the primary lesion, presence of angiolymphatic invasion, a mitotic rate of greater than or equal to 1 mitosis/mm^2, or a positive deep margin on the initial biopsy. Reasons not to perform SLNB include a low risk of regional nodal metastasis (typically

lesions Breslow depth < 0.75 mm), significant medical comorbidities, or the patient does not desire SLNB after an informed discussion. As the accuracy of SLNB requires injection of the tracers at the site of the primary lesion, ideally SLNB is performed at the time of the wide local excision (WLE) so that the tracers can be injected at the most appropriate site.

The status of the SN is the most powerful independent factor predicting survival and provides the highest sensitivity and specificity of any nodal staging test available. Additionally, SLNB allows for early identification of patients with nodal disease and allows for immediate intervention with completion lymph node dissection (CLND) which is the current standard of care in 2015. The impact of SLNB and early treatment of the nodal basin on patient survival was investigated in the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I). Ten-year follow-up data from this trial were published in early 2014. Subgroup analysis from this trial indicated that for patients with intermediate-thickness melanoma (defined as Breslow depth 1.2–3.5 mm) and nodal disease, early intervention with CLND after detection of a positive SN led to improved outcomes as compared to performing CLND upon the development of clinically apparent nodal disease (10-year melanoma-specific survival 56 ± 4.3% in SLNB arm vs 41.5 ± 5.6% in observation arm; $p = 0.04$). The utility of SLNB in older patients was investigated by the University of Michigan. In a study of 952 melanoma patients greater than or equal to 75 years, SLNB was associated with improved outcomes and was recommended to be strongly considered in this patient population.

Adjuvant Therapy After surgical resection of regional nodal disease in the absence of known distant metastasis, high-dose protocol interferon-α2b (IFN-α) is the only adjuvant treatment that has demonstrated a modest benefit in disease-free survival for patients with stage III melanoma. IFN-α is associated with significant side effects, and many patients are thus not good candidates. New emerging therapies are under investigation in clinical trials.

Treatment of stage IV melanoma For many years treatment options for patients with stage IV melanoma were limited to dacarbazine (single-agent chemotherapy) or high-dose systemic interleukin 2 (IL-2), neither of which had acceptable durable response rates. However, recently the FDA-approved several new classes of medications have shown to improve overall survival for patients with stage IV melanoma. These therapies broadly categorize into either targeted therapy or immunotherapy. Targeted therapies include BRAF inhibitors (vemurafenib or dabrafenib) typically given in combination with MEK inhibitors (trametinib). Immunotherapy options for patients with metastatic melanoma include ipilimumab (CTLA-4 inhibitor), nivolumab (PD1 inihibitor), and pembrolizumab (PD1 inhibitor). While limited data exist due to the relatively recent development of these medications, some reports indicate safe use within older patients. Within the University of Michigan Multidisciplinary Melanoma Clinics, several older patients (> 80 years) have been treated with excellent response. As with any systemic medication, the risks and benefits must be weighed against the performance status and comorbidities of the patient prior to initiation of therapy.

OTHER CUTANEOUS TUMORS

There are a number of less common cutaneous tumors that are beyond the scope of this chapter. We feel that MCC deserves discussion given the propensity to affect the geriatric population and the highly aggressive nature of MCC. The reader is referred to a standard dermatology text for discussion of other tumors including cutaneous T-cell and B-cell lymphoma, histiocytic tumors, mast cell tumors, malignant adnexal tumors, cutaneous sarcoma, and metastatic cancer to the skin.

Merkel Cell Carcinoma

MCC is a rare, highly aggressive cutaneous neuroendocrine carcinoma. Approximately 1400 cases are diagnosed annually in the United States. Upon diagnosis, 5-year overall survival estimates range from 40% to 62%. MCC most commonly occurs on sun-exposed skin of older adults. Patients often present with a red-to-purple bump or nodule that grows rapidly over 3 months (**Figure 102-15**). Initially, the clinical lesion may be misdiagnosed as an inflamed hair follicle, boil, or cyst. Rapid growth often prompts biopsy and accurate diagnosis.



FIGURE 102-15. Merkel cell carcinoma. Red-to-purple 2.3-cm nodule on the lower leg.

Histologically, the tumor is typically a dermal nodule of small round blue cells with powdery chromatin. MCC is distinguished from other small round blue cell tumors such as lymphoma and metastatic small cell lung carcinoma by morphology and immunophenotyping. The pathogenesis of MCC is an area of active investigation; evidence supports patient characteristics such as sun exposure and immunosuppression as well as molecular pathways.

In 2010, the AJCC introduced the first consensus staging system for MCC which utilizes characteristics of the primary tumor (T), nodal status (N), and distant metastases (M). Four stages exist, stage I (local disease with primary tumor < 2 cm), stage II (local disease with larger tumor size), stage III (regional nodal disease), and stage IV (distant metastatic disease). MCC commonly metastasizes to the regional nodal basin. Studies have shown that even the smallest clinical tumors have at least 15% to 20% risk for occult metastatic disease in the regional lymph node basin. Given the highly aggressive nature, rarity, and evolving and changing clinical practice guidelines, optimal treatment and management of patients with MCC is optimized through a multidisciplinary approach.

PALLIATIVE TREATMENT OF SKIN CANCERS

Skin cancers often present in the older adult. When a patient of advanced age presents with multiple skin lesions, the role of the geriatrician is to determine which skin lesions need further pathologic evaluation and possible treatment, which lesions may be clinically monitored, when to refer to a dermatologist, and perhaps when active nonintervention is preferred. The first assessment is that of risk. What is the clinical assessment of the lesion? Does the lesion represent a benign, but premalignant actinic keratosis or a malignant squamous cell carcinoma? Does the lesion represent a small slow-growing basal cell carcinoma or lesion with high metastatic risk such as an amelanotic melanoma or a MCC? Lesions concerning for high-risk skin cancers such as SCC, melanoma, or MCC should be biopsied in all cases with some exceptions. Methods of definitive treatment for these tumors are discussed earlier. However, treatment recommendations do vary when the tumors present at the end of life (eg, life expectancy of 6 months due to known stage IV metastatic cancer) or when patients have multiple medical comorbidities and the morbidity of treatment is too high. In these cases, we recommend clear discussion of treatment goals with the patient and the patient's family to arrive at a consensus plan. When the clinical assessment of risk is lower, then next assessment is that of the patient and the symptoms of the lesion. For example, compare these two scenarios: an active older adult develops an asymptomatic 1-cm basal cell carcinoma on the left cheek versus a stable older adult with a 6-month life expectancy who develops a painful bleeding 1-cm basal cell carcinoma on the left cheek. Given the clinical scenario, we would recommend diagnosing and treating the low-risk skin cancer in both of these patients. Treatment is often well tolerated, eliminates symptoms, and improves the quality of life. However, when our patients are at the end of life, whether due to stage IV cancer or other debilitating illness, active nonintervention is often the best course of action. At the end of life, palliation of symptomatic lesions may be recommended or discussed and nonintervention of asymptomatic lesions may simply be preferred. In these cases, it is important to discuss the treatment or active surveillance plan with the patient and the patient's family.

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Chapter 103

Aging of the Hematopoietic System

William Tse, Maxwell M. Krem, Jino Park, Nathan A. Berger, Scot C. Remick

INTRODUCTION

As with nearly all tissues, the hematopoietic system suffers the consequences of aging, manifested by the emergence of chronic anemia, immune dysfunction, increased incidence of myeloproliferative syndromes, and overt chronic and acute myeloid malignancies. Although hematopoietic stem cells (HSCs) can sustain blood production throughout life, recent studies demonstrate that with aging they undergo dramatic phenotypic and functional changes. This notion is supported by a meta-analysis conducted by the National Marrow Donor Program (NMDP) that assessed multiple donor traits, including donor age, cytomegalovirus serology, ABO blood group compatibility, race, and sex. This study found that advanced donor age is a major negative prognostic factor in clinical outcomes of allogeneic HSC transplant recipients. This is manifested clinically by delayed engraftment; further, molecular HSC microarray studies have revealed that myeloid-specific and chromatin remodeling genes change expression over time. In mouse models, several hallmark age-dependent changes in the HSC compartment have been identified, including an increase in HSC numbers, a decrease in homing capacity, and a myeloid skewing of differentiation potential. Age-related epigenetic dysregulation leads to aberrant gene expression that may contribute to malignant transformation and emergence of myeloid leukemia, which is commonly associated with aging. These results indicate that HSC senescence is not the product of a few programmed genes, but of a large number of genetic changes that affect the entire biological system.

MECHANISMS OF AGING IN THE HEMATOPOIETIC SYSTEM

The hematopoietic system is dependent on a small pool of HSCs (see **Figure 103-1**), their surrounding microenvironment, and regulatory molecules (ie, hematopoietic growth factors) that dictate cell turnover and maturation. Most studies suggest that alterations in the HSC compartment with age arise at the level of individual HSCs. Hence, fundamental changes in the epigenetic program and signal transduction within these individual cells have been proposed as a mechanism driving functional alterations. Emerging evidence demonstrates that interactions between HSCs and the marrow microenvironment may reveal novel insights of the aging process of the hematopoietic system as outlined below.

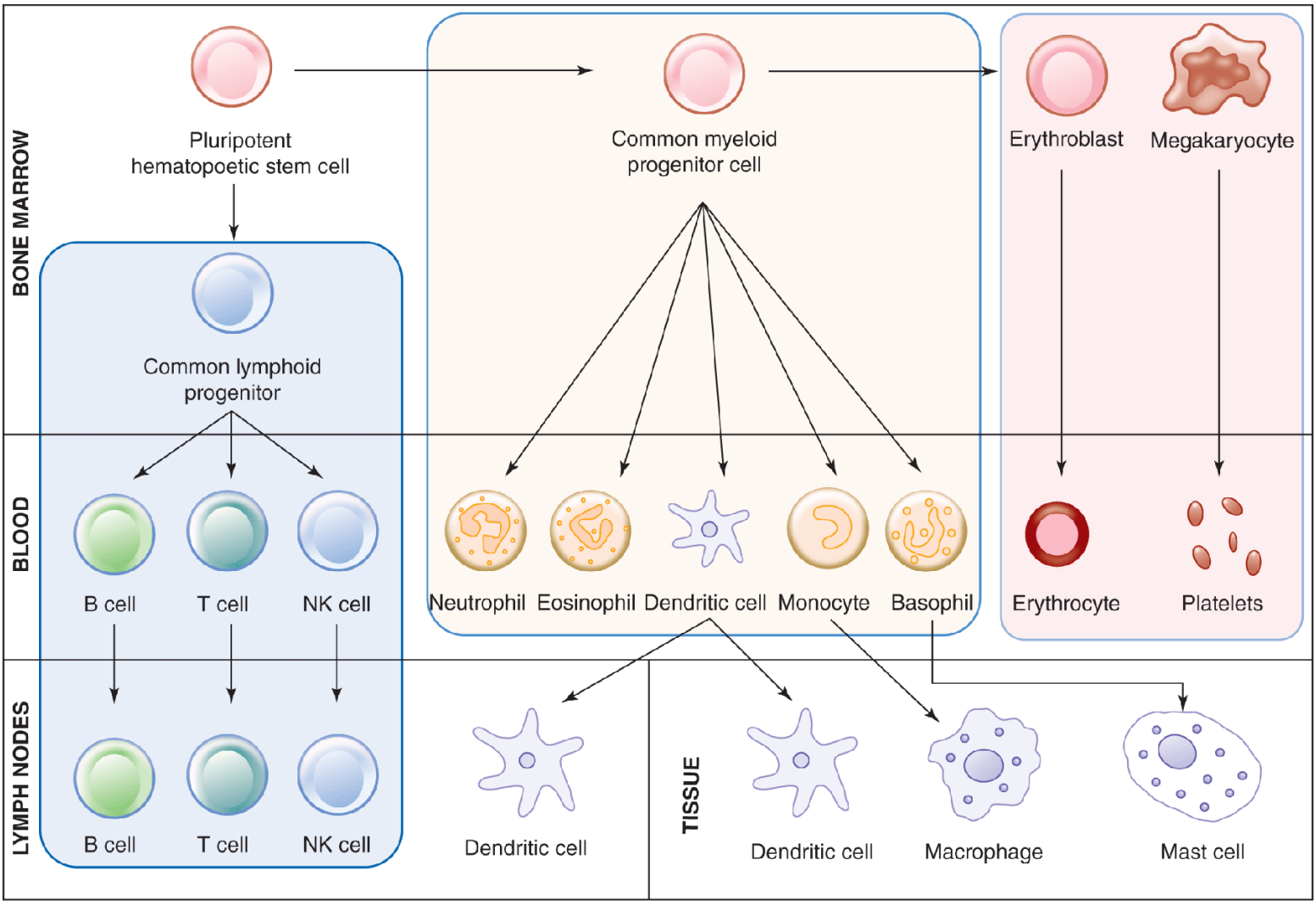


FIGURE 103-1. Schematic representation of hematopoiesis. Hematopoietic stem cells (HSCs) differentiate into lymphoid proin the bone marrow that give rise to T cells (which develop in the thymus) and B cells, and myeloid progenitors that differentiate to monocytes, dendritic cells, neutrophils, basophils, eosinophils, as well as erythroid and megakaryocytic lineages. Aging is associated with impaired HSC differentiation and repopulation function, and with a bias toward myeloid at the expense of lymphoid progenitors.

Aging Processes in HSCs

Studies conducted in mice more than 20 years ago showed that aged marrow donors can repopulate blood cells in serial hematopoietic transplantation experiments spanning multiple lifetimes, prompting the hypothesis that the HSCs are "effectively ageless." Clinical observations and recent studies suggest that the ability of human HSCs to produce hematopoietic progenitors declines substantially during the ontological transitions from fetal liver to umbilical cord blood and ultimately to adult marrow, which is indicative of progressive loss of intrinsic stem cell function with age.

The functional phenotype of aged HSCs Hematopoietic reconstitution from aged HSCs in older mice is skewed from lymphopoiesis toward myeloid-biased hematopoiesis when compared to HSCs from younger mice. On a per cell basis, aged HSCs are inferior to young HSCs in their capacity to reconstitute lethally irradiated recipients and to self-renew. Furthermore, homing and in vitro proliferation in stromal cocultures are reduced, although reconstitution of the HSC compartment by aged HSCs is normal. Intravital microscopy suggests that early progenitors from aged mice localize farther from the osteoblastic niche and show reduced polarization of the microtubule cytoskeleton compared with cells from young mice. Several lymphoid precursors such as common lymphoid progenitors (CLPs) and pre–B cells are depleted in the bone marrow of old mice. Cumulatively, these studies suggest two clinically important pathobiological features of the aged hematopoietic system: (1) impaired constitution of the immune system and (2) increased propensity toward the evolution of myelopro liferative diseases. Accordingly, myeloproliferative disorders are appropriately considered conditions of aging.

Molecular phenotype of the aged HSCs Genome-wide expression profiling of HSCs from young and old mice shows that expression of myeloid development- and inflammatory-associated genes are significantly increased, whereas expression of lymphoid development-associated genes markedly diminished in older mice when compared to young mice. Aged mouse HSCs show general hypermethylation, while most other aged tissue compartments are characterized by hypomethylation. Hypermethylated genes are more commonly associated with committed progenitors of erythropoietic and lymphopoietic lineages instead of HSCs themselves. A fraction of aged HSCs display lower histone H4 lysine acetylation (AcH4K16), providing further evidence of epigenetic regulatory changes. Although aging of HSCs has been for a long thought to be an irreversible process imprinted on stem cells, this hypothesis has been recently challenged. Geiger and Zhang's group have found that aging is associated with elevated activity of the Rho GTPase Cdc42 in HSCs that is causative for the loss of polarity, altered epigenetic modifications, and functional deficits of aged HSCs. Their mouse models suggest that inhibition of Cdc42 activity in aged HSCs may reverse a number of phenotypes associated with HSC aging. Aged HSCs express higher levels of the Rho GTPase and Cdc42 that are associated with decreased polarity and AcH4K, and the altered epigenetic modification compared with young HSC counterparts. Furthermore, accumulated DNA damage is suggested by increased γH2AX foci in aged HSCs. This accumulation of DNA damage, coupled with downregulation of genes associated with the preservation of genomic integrity (eg, telomere maintenance) is one possible mechanism for altered HSC regenerative functional capacity with age.

Physiologic phenotypes of aged HSCs HSC niches comprise cell types that promote HSC maintenance by regulating HSC self-renewal, quiescence, mobilization, and differentiation. Young and aged HSCs have distinct locations within the niche relative to the endosteum and differ with respect to adhesive properties in vivo. The recruitment of HSCs to the blood in response to stimuli (eg, cytotoxic chemotherapy agents or cytokines) is increased in aged HSCs compared with young HSCs. These observations highlight differences in either the intrinsic adhesive properties of the aged HSC compartment or in the properties of the niche cell compartment that interacts with HSCs in the aged marrow. Better characterization of the expression pattern of adhesion molecules on aged HSCs may help to explain how the cross talk between HSCs and their niche changes upon aging.

The criteria used to identify HSC aging include an increased number of cells with an HSC-associated cell surface phenotype; a reduced capacity of HSCs for self-renewal; myeloid-biased lineage skewing upon transplantation of HSCs in vivo; enhanced mobilization of HSCs from the marrow into the blood; and reduced homing of HSCs back to the marrow. In addition to HSC-intrinsic phenotypes, HSC-niche interactions change with aging, and these criteria may help to distinguish the "physiologic aging phenotype" of HSC.

Most available evidence suggests that the HSC compartment is maintained through attempted repair at the cost of retaining damaged HSC rather than replacing them by enhancing self-renewal. Aged HSCs may lose such natural protective functions. One of the major hallmarks of aged HSCs is increasing intrinsic production of reactive oxygen species (ROS) by mitochondria that can result in HSC loss of specific protective functions.

Developmental programming of aged HSCs Benz and colleagues introduced the nomenclature of balanced, or β-HSCs, and myeloid-biased, or α-HSCs. They demonstrated that β-HSCs predominate in the fetal liver, while the frequency of α-HSCs increases as hematopoietic development proceeds. Common lymphopoietic precursors (CLPs) derived from developed and myeloid-biased α-HSCs share similar defective and lower levels of B-lineage-specific genes with aged CLPs. The adoptive immune system starts to develop early in life so that the body can respond to the multitude of antigens encountered after birth. However, this natural and defensive HSC developmental programming comes with the "first" risk of malignancy in early life, such as acute lymphoblastic leukemia (ALL) due to the iterative recombination of T- and B-cell receptor loci accompanied by massive proliferation and deletion of the majority of lymphoid precursors. After the immune repertoire is mature, cessation of recombination and establishment of vigorous and rapid memory responses likely benefits "myelo-health" fitness.

It has been demonstrated that most HSCs reside in the perivascular bone marrow niche, whereas very early lymphoid progenitors reside in the osteoblastic (peritrabecular) niche. It is unknown if α-HSCs and β-HSCs occupy distinct niches. However, it is possible that the localization of aged early progenitors farther away from the osteoblasts reflects a shift toward myelopoiesis.

The Hematopoietic Microenvironment and Aging

The functional phenotype of the aged hematopoietic microenvironment In 1978, Schofield proposed the "niche" hypothesis to describe the physiologically limited microenvironment that supports stem cells. In recent years

the effect of niche “aging” on altered phenotypes associated with aged HSC has been appreciated. This central question is critically important with respect to therapeutic interventions in light of reversion/rejuvenation.

Transplantation of young HSCs into an aged niche elicits at least some of the phenotypes associated with aged HSCs, like myeloid skewing, which has been attributed molecularly to elevated expression of RANTES by stroma cells in aged mice. In vivo experiments using aged animals transplanted with AML1-ETO positive leukemic HSCs show a significant increase in the frequency of AML-ETO positive early progenitor cells in the bone marrow as well as an increased immature myeloid cell load in blood compared to young recipients suggesting an aged bone marrow microenvironment allows better expansion of preleukemic stem and immature myeloid cells.

Molecular phenotype of the aged hematopoietic microenvironment Within the marrow niche, mesenchymal stem cells (MSC) are responsive to metabolic factors and their products, such as oxidative stress and ROS. Paracrine and signaling factors such as Notch, transforming growth factor (TGF)-β, mitogen-activated protein kinase (MAPK), Wnt, and NF-κB are known to be age-dysregulated in the stem cell niche. Physical and environmental factors such as space constraints, and cell-cell interactions between bone marrow–MSC and other stem and non–stem cells resident in the bone marrow, and between bone marrow–MSCs and the local extracellular matrix may undergo age-associated changes. In response to these changes, MSCs are likely to undergo molecular level changes, such as increased levels of proaging factors, DNA damage, telomerase attrition, and transcription factor changes. The direct consequence of these changes is diminished bone marrow–MSC function, self-renewal, and differentiation capacity manifested by the emergence of peripheral cytopenia.

Signaling Pathways Associated with Aging of the Hematopoietic System

Aging in several tissue types involves a progressive decline in cell replacement and repair processes, resulting in reduced bone mass and dysregulation of hematopoiesis.

Mayack and colleagues used complementary in vivo and in vitro heterochronic models and showed that age-associated changes in stem cell–supportive niche cells alter normal hematopoiesis by causing hematopoietic stem cell dysfunction. They found that age-dependent defects in niche cells are regulated by circulating factors and can be reversed by exposure to a young circulatory system in heterochronic parabiosis experiments or by neutralization of the conserved longevity regulator insulin-like growth factor 1in the marrow microenvironment. These interesting results demonstrate a critical role for local and systemic factors in signaling age-related hematopoietic decline and highlight a new model in which blood-borne factors in aged animals act through local niche cells to induce age-dependent disruption of stem cell function (**Figure 103-2**).

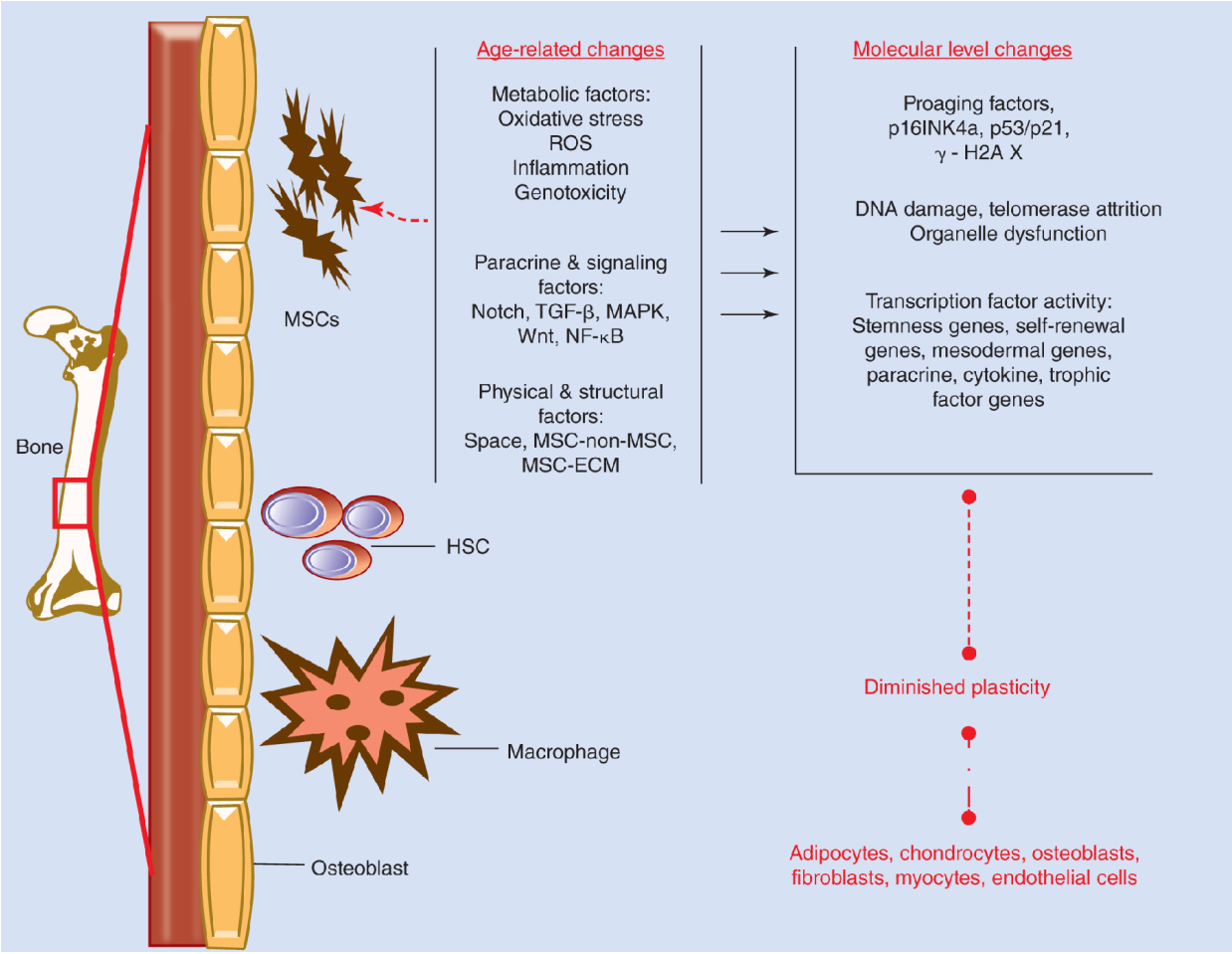


FIGURE 103-2. Diagrammatic illustration of potential factors that feed into the bone marrow–derived mesenchymal stem cell (BM-MSC) niche. (From Asumda FZ. *Stem Cell Res Ther*. 2013;4[3]:47.)

Florian and colleagues described a new role of the Wnt cascade in HSCs. They demonstrated that the balance between canonical and noncanonical Wnt ligand expression, and therefore Wnt signaling, underlies the HSC aging process. The levels of Wnt5a are significantly elevated in aged long-term HSCs (LT-HSCs), whereas expression of canonical Wnt ligands remains unaltered during aging (**Figure 103-3**). Increasing or decreasing Wnt5a levels leads to induction or reversal of age-related HSC phenotypes, respectively. Exposure of HSCs to Wnt5a induced lymphoid to myeloid skewing of donor cells in blood after transplantation, while conversely, Wnt5a downregulation increased lymphoid chimerism from aged HSCs. Moreover, the age-related increase in the fraction of phenotypically defined LT-HSCs was attenuated in aged Wnt5a+/– mice, and a similar effect was observed in recipients of aged Wnt5a shRNA-transduced bone marrow cells. Their data provide additional exciting support for the notion that aging-related HSC changes can be attenuated by alteration of signaling.

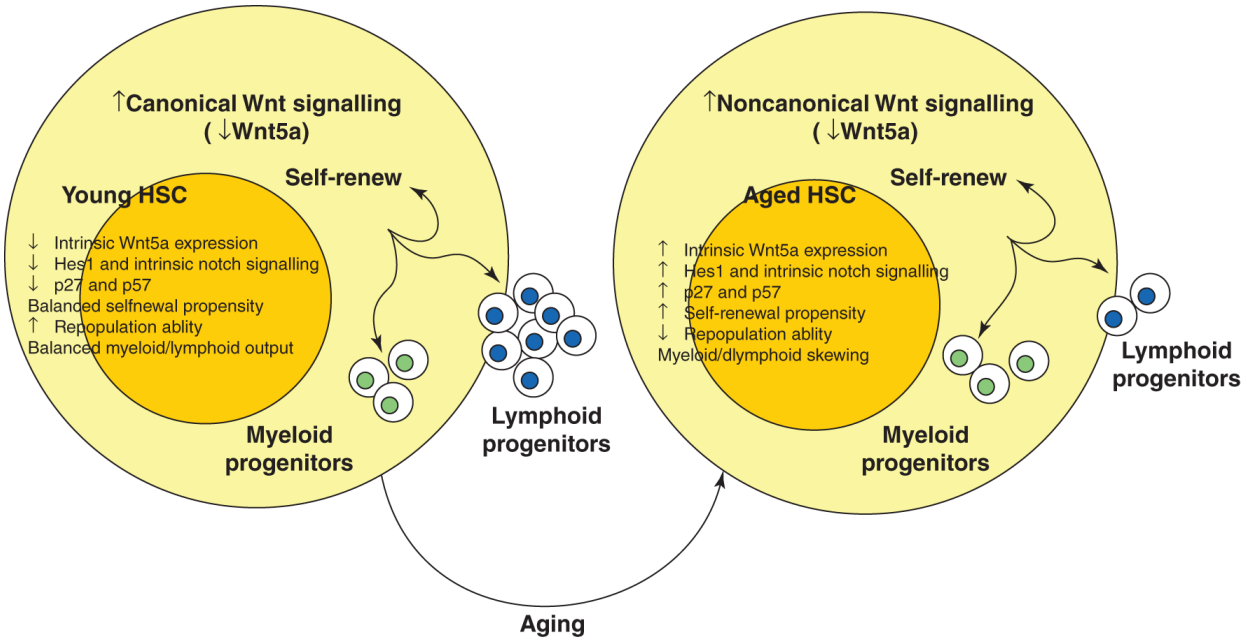


FIGURE 103-3. Mechanisms of hematopoietic stem cell aging: balancing act between canonical and noncanonical signaling pathways in hematopoietic stem cell aging process. (From Florian MC, Nattamai KJ, Dörr K, et al. A canonical to non-canonical Wnt signalling switch in haematopoietic stem-cell ageing. *Nature*. 2013;503:392–396.)

Tse's group recently found that a very small acidic protein, AF1q, which was originally discovered in acute myeloid leukemia (AML) patients whose blasts carried the chromosomal abnormality t(1;11) (q21;q23), is a critical cofactor for the Wnt signaling pathway. The AF1q expression pattern in the hematopoietic stem cell compartment is a "bell-shaped" curve. Robustly upregulated AF1q expression is seen largely during the early development of the hematopoietic stem cell compartment (Tse laboratory observations). Activation of the cofactor AF1q simultaneously enhances multiple signaling pathways that are closely associated with stem cell aging, including Notch. Interestingly, the Cdc42-binding protein, SPEC1, shares the same bidirectional transcriptional promoter as AF1q. Our hypothesis is that one of the important mechanisms of the hematopoietic stem cell aging process is associated with the transcriptional direction of the bidirectional promoter balancing transcription of SPEC1 and AF1q (**Figure 103-4**).

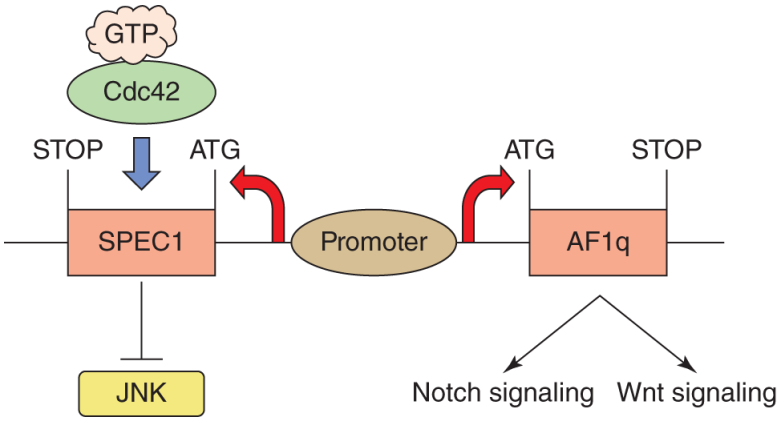


FIGURE 103-4. Illustration of the bidirectional promoter. A bidirectional promoter regulates AF1q and SPEC1, which are actively involved in Wnt and Cdc42 signaling pathways for the hematopoietic stem cell aging process.

CONSEQUENCES OF THE AGED HSC COMPARTMENT

Advancing age is accompanied by a number of clinically significant conditions arising in the hematopoietic system, including diminution and decreased competence of the adaptive immune system, elevated incidence of certain autoimmune diseases, increased incidence of hematologic malignancies, and elevated incidence of age-associated anemia.

Aging Negatively Affects the HSC Intrinsic Stemness Features

Aging of HSCs results in increased differentiation biased toward the production of common myeloid progenitors and a decreased ability to produce common lymphoid progenitors and erythroid cells. These changes lead to hematopoietic stem cell exhaustion, decreased repopulation capacity, and reduced survival rates. The cell adhesion molecules α4, α5, and VCAM on aged HSCs are downregulated, leading to increased mobilization in aged mice. TGF-β1 enhances myeloid-biased HSC differentiation while inhibiting lymphoid-biased HSC differentiation. A helix-loop-helix transcription factor, the aryl hydrocarbon receptor (AhR), has been shown to have a role in HSC regulation in aging. AhR depletion leads to premature HSC exhaustion, downregulated self-renewal potential in competitive repopulation and serial transplantation, and development of myeloproliferative disorders.

The deletion of Ott1 (Rbm15), a protein that is associated with hematopoiesis, pre–B-cell development, and competitive reconstitution, induced a phenotype similar to that observed in age-associated physiologic changes, including loss of quiescence during stress, increased bias toward myeloid cell production, elevated ROS levels, increased mitochondrial mass, DNA damage, and increased activation of NF-κB and p38 MAPK151. On the other hand, HSCs without activated leukocyte cell adhesion molecule (ALCAM) also displayed a phenotype that was consistent with aging, with a diminished capacity for long-term repopulation.

The chromatin regulator Satb1, important for differentiation from HSCs to lymphoid lineage cells, is characterized by decreased expression levels in aged HSCs. There are increased levels of Cdc42, a Rho GTPase associated with cell-cell contact, cell-ECM adhesion and cell polarity in aged mice, resulting in the onset of an aging phenotype that includes lineage skewing, decreased regenerative capacity, impaired homing, loss of cell polarity, and increased mortality. As previously mentioned, HSC aging was recently demonstrated due to the shift from canonical to noncanonical Wnt signaling through increasing Wnt5a expression resulting in the activation of Cdc42 in aged HSCs. Inhibition of Wnt5a in LT-HSCs using shRNA in aged mice led to a phenotype that was characteristic of young HSCs; this finding could form the basis for rejuvenation therapy, and is in agreement with our hypothesis regarding Spec1-Cdc42 and the AF1q-Wnt regulatory axis.

In oxidative stress, increased ROS levels seem to associate with decreased levels of thioredoxin-interacting protein (TXNIP), FOXO depletion, p38-mTOR activation, and telomere shortening that leads to DNA damage. DNA damage also induces a phenotype similar to premature HSC aging that is characterized by anemia, lymphopenia, and myeloid lineage skewing. Thus, although mitochondrial DNA mutations might be a contributing factor in physiologic aging, they may not be the primary driver of somatic stem cell aging. The overlapping HSC phenotype between irradiation stress and age-induced cellular changes (derived from ROS activation and subsequent DNA damage) indicates that irradiation may induce premature aging. Irradiation is capable of generating chromosomal aberrations, primarily translocations and inversions that are clonally transmitted in HSCs. This concept, however, needs further validation.

In summary, several aspects of HSC function such as self-renewal, cell polarity, homing capacity, and myeloid lineage differentiation are negatively affected and become the hallmarks of the aged HSC. Additional consequences of the intrinsic HSC changes include increased ROS levels leading to DNA damage, replicative senescence, exhaustion, and reduced survival rates (**Figure 103-5**).

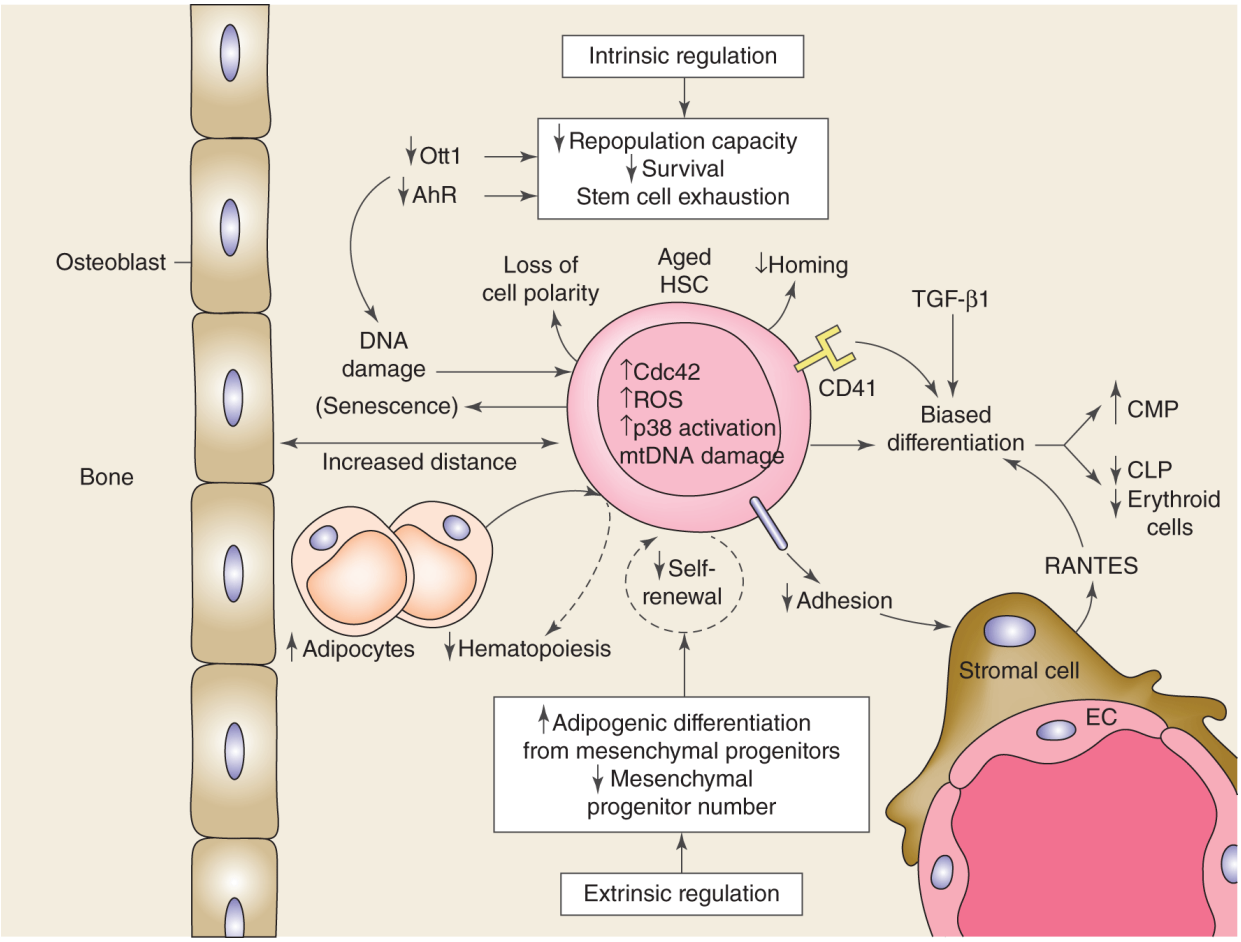


FIGURE 103-5. The effects of aging on hematopoietic stem cell (HSC) behavior. CLP, common lymphoid progenitor; CMP, common myeloid progenitor; mtDNA, mitochondrial DNA. (From Mendelson A, Frenette PS. *Nat Med*. Hematopoietic stem cell niche maintenance during homeostasis and regeneration. 2014;20:833–846.)

Aging Negatively Affects the HSCE Microenvironment Functions

Extrinsic regulation mediated by the microenvironment induces a common myeloid progenitor bias rather than the effects caused by age-specific intrinsic HSC changes. HSCs have also been demonstrated to change location relative to the bone surface in aged mice compared with HSCs of young animals and localize farther away from the endosteum. Given that bone marrow endothelial cells have been shown to promote HSC regeneration in part through upregulation of adhesion proteins, the reduction in HSC adhesion to bone marrow stromal cells with aging could account for the decrease in self-renewal ability among aged HSC. Aged mice also had a decreased number of mesenchymal progenitor cells located near the endostea surface compared with young mice, potentially hampering the ability of HSCs to remain quiescent. The proinflammatory cytokine CCL5 may be another important factor promoting extrinsic stem cell regulation that induces myeloid lineage-skewing in aged HSCs, as it is associated with a decrease in lymphoid progeny. Adipocytes are increasingly present in the bone marrow microenvironment with age; adipocytes negatively regulate hematopoiesis and delay engraftment.

In summary, intrinsic changes often yield phenotypes that are complementary to extrinsic aging effects, indicating that the HSC aging phenotype involves a complex array of factors and a line of communication between the HSC and its niche. Observed HSC-extrinsic changes include decreased adhesion to bone marrow stromal cells and increased adipocyte numbers with aging, leading to reduced hematopoietic activity. Additionally, HSCs localize farther from the bone surface and other key structures with age, potentially affecting their ability to remain quiescent (see **Figure 103-5**). Intrinsic changes often yield HSC phenotypes similar to those from extrinsic effects, and their interplay awaits further resolution. Further investigations into the interplay between the intrinsic and extrinsic mechanisms involved in regulating HSC aging could provide a therapeutic rationale for promoting stem cell rejuvenation.

NEOPLASIA-PREDISPOSING FEATURES OF HSC AGING

Age is the primary risk factor for a number of hematologic malignancies. This phenomenon is traceable to features of the aging HSC compartment, including decreased ability to repair DNA damage, accumulation of double-strand breaks (DSBs) in DNA, telomerase dysfunction and shortening, development of chromosomal instability, and the emergence of clonal dominance. Clinically, those biological features translate into adverse disease biology and worse prognoses when HSC-derived malignancies afflict older patients.

Aging Negatively Impacts Maintenance of Genomic Integrity

The yin and yang of quiescence Stem cell quiescence plays a crucial but incompletely understood role in regulating HSC aging processes. Quiescence appears to play a protective role in preserving the stem cell pool against DNA damage, oxidative stress, and telomere shortening during aging. Exiting from dormancy leads to DNA damage-induced stem cell attrition; function of the Fanconi anemia DNA repair pathway, suggested by murine models, may be essential for the protective effect of HSC quiescence. On the other hand, DNA repair pathways are downregulated during quiescence; HSCs repair DNA damage upon their exit from quiescence. Quiescent HSCs restrict DNA damage but are not impervious to it. Additional molecules implicated in the regulation of quiescence are the transcription factor Nrf2, ATM, and CEBP/a.

Correlates of chromosomal instability DSB repair pathways are essential to protecting against hematologic malignancies, as well as the development of the lymphocytopenic phenotype of aging HSCs. DSBs increase with age in HSCs, perhaps due to impaired DSB repair capacity of aged HSCs. In mice, crippling the nonhomologous end-joining (NHEJ) pathway through deficiency of Nhej1 (XLF) produces the recapitulation of age-dependent lymphocytopenia and the premature aging of HSCs. Strand breaks accumulate in murine HSCs during aging and are seen with higher frequency in the HSCs of middle-aged and older adults. Telomere dysfunction and shortening lead to loss of lymphoid-based HSCs; murine HSCs with shortened telomeres may be unable to enter the cell cycle. Telomere dysfunction also predisposes to clonal dominance.

Chromosomal instability (CIN) triggered by telomere dysfunction or DSBs may lead to negative downstream consequences. CIN provokes cell cycle dysregulation, stem cell dysfunction, and lymphoid neoplasia; a cyclin E knock-in HSC model led to CIN and impaired cell cycle exit. Aneuploidy, a manifestation of CIN, triggers the unfolded protein response and may thus exacerbate aging phenotypes. Increased protein folding stress in mitochondria leads to HSC aging and decreased regenerative capacity. Increased replication stress, another contributor to CIN, drives functional decline in aging HSCs. Old or stressed HSCs may survive until faced with potent replication challenges, such as stem cell transplantation. The findings of that study may account for the NMDP study results suggesting that stem cells from older donors experience delayed engraftment.

Clonal Dominance of HSCs Increases With Aging

Clonal dominance is a cardinal feature of leukemic stem cells, and aging is associated with an increase in clonal hematopoiesis. In a fascinating case report involving phylogenetic analysis of the white blood cells from a healthy 115-year-old patient, the majority of the leukocytes were derived from only two clones. Clonal hematopoiesis is markedly increased in those older than 65 and produces more than a 10-fold increased risk of hematologic cancers by generating mutations that target a recurrent set of genes. Clonal tendencies may also be seen downstream of the HSC progenitor compartment; enhanced predisposition to B-cell malignancies may result from lifelong immunologic pressure to select more potent B-cell receptor clonotypes, resulting in clonality of B-cell populations.

Aged HSCs Contribute to Poor Disease Outcomes

AML is the malignancy most closely associated with the HSC compartment. As aging alters nearly all aspects of the biology of HSCs, aging has a profound effect on the biology of the malignant cells derived from HSCs and a strong negative impact on AML outcomes. Older patients have a propensity toward the following adverse features: unfavorable, myelodysplasia-associated cytogenetic alterations; increased multidrug resistance due to MDR expression; and reduced response rates and remission durations. Those factors are hypothesized to result from the phenomenon of older leukemic stem cells (LSCs) having greater genetic instability and more clonal diversity. Thus, the phenotype of the aging HSC poses unique challenges that will require therapeutic approaches that address its unique features in order to yield satisfying outcomes in HSC disorders.

CONCLUSION

There are clearly biological features and properties that distinguish young and aged HSCs (**Table 103-1**) and provide insight to fundamental disease pathogenic mechanisms and especially the inherent evolution and increased risk of immunologic, hematologic (eg, chronic anemias), myelodysplastic, and HSC-proliferative disorders that so frequently accompany aging. Aging affects not only the cellular, HSC compartment, but also the bone marrow microenvironment. With improved understanding of the fundamental molecular events contributing to these pathogenic changes, there are prospects to develop mechanism-based therapeutic interventions to preserve and maintain both hemato- and lymphopoietic homeostasis. This may provide opportunities for prevention of these diseases and further identify, in a more rational manner, novel therapeutic approaches in treating these disorders in older patients.

TABLE 103-1 BIOLOGICAL FEATURE(S) AND PROPERTIES OF YOUNG AND AGED HEMATOPOIETIC STEM CELLS (HSCs)

BIOLOGICAL FEATURE(S)/PROPERTIES	YOUNG HSCS	AGED HSCS
Hematopoietic skewing	Lymphopoiesis-skewed	Myelopoiesis-skewed
Self-renewal	Brisk	Restricted
Molecular profile		
DNA damage	Less damage	Accumulates over time
Epigenetic modification	Hypomethylation pattern	Hypermethylation pattern
Bone marrow microenvironment and niche localization		
Cellular adhesion	Intact	Impaired
Location	Perivascular marrow niche	Peritrabecular marrow niche
Mobilization from marrow	Restricted from marrow to blood	Enhanced from marrow to blood
Homing to bone marrow	Intact	Reduced
Maintenance of HSC compartment	Renewal mechanisms predominate	Repair mechanisms predominate

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Chapter 104

White Cell Disorders

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Learning Objectives

- Identify the most likely causes of leukopenia and leukocytosis and initiate evaluation of the most likely causes of altered white blood cell (WBC) counts in older adults.
- Assess malignant versus nonmalignant causes of WBC elevation in older adults.
- Recognize the value of geriatric assessment in determining outcomes for older adults with malignant WBC disorders.

Key Clinical Points

1. **Age is not associated with changes in WBC counts, so elevated or depressed WBC count should be evaluated as possible illness.**
2. **Drugs and infections are common causes of both increased and decreased WBC counts and should be considered when evaluating new-onset leukopenia or leukocytosis in seniors.**
3. **Older adults make up a large proportion of incident and prevalent cases of malignant WBC diseases, as well as those dying from these conditions.**
4. **The response rates and cure rates for older patients with malignant WBC diseases have lagged behind those of young adults for a number of reasons: more resistant tumor biology, presence of multiple chronic conditions, and functional impairments which decrease treatment tolerance. Underrepresentation of older adults in clinical trials remains a limitation as well.**
5. **Disease characteristics alone do not fully explain age-related outcome disparity in acute myelogenous leukemia (AML). Even among older adults with favorable disease biology, outcomes remain worse for older adults than young adults. Increased comorbidity, age-associated physiologic changes, polypharmacy, and functional and cognitive impairment complicate therapy in older adults and likely contribute to decreased treatment tolerance and shorter survival. Several small trials suggest geriatric assessment is feasible in the context of AML therapy and may better predict survival and treatment tolerance than standard clinical assessment.**
6. **Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western Hemisphere and may be expected to be encountered in a geriatric practice; median age at diagnosis is approximately 70.**

White blood cells (WBCs) provide major host defense mechanisms against invading pathogens through phagocytosis and triggering immune responses. In addition, lymphocytes provide immune surveillance against viral infections and the development of cancer, and are important mediators of disorders of the immune system. White cell disorders are usually the result of overproduction or underproduction of one or more of the WBC series, which include the granulocytes—neutrophils, basophils, and eosinophils—and/or mononuclear cells—lymphocytes and monocytes. Less frequently, WBC disorders result from WBC dysfunction despite normal number of cells. The acuity and severity of these disorders are related to the number of white cells, the subset(s) of WBC involved, their degree of maturity, and their functional capacity.

Initial clinical manifestations of WBC disorders can vary widely but often include signs and symptoms of infection. Disorders of WBC, benign or malignant, frequently also involve abnormalities of the red blood cells (RBCs) and platelets. In these situations, the signs and symptoms of disease at presentation may include those related to anemia (ie, weakness and easy fatigability) and/or thrombocytopenia (ie, easy bruisability, mucosal or gastrointestinal bleeding, and hematuria). A careful history and physical examination with evaluation of the peripheral blood, and bone marrow when needed, will establish a diagnosis in many cases.

Aging is not associated with significant changes in the peripheral WBC count or WBC differential. Therefore, abnormalities in white cell numbers should be evaluated as a probable sign of an active disease process. Most white cell disorders are more common with increased age and the most common WBC disorders in the older adults are neoplastic diseases. **Table 104-1** lists a spectrum of white cell disorders encountered in clinical practice. Full descriptions of these processes are available in textbooks of hematology and oncology. This chapter focuses on these disorders as related to geriatric medicine.

TABLE 104-1 DISORDERS OF WHITE BLOOD CELLS

I. Lack of production
   - A. Drug or toxin suppression, which may be temporary or permanent
   - B. Ineffective myelopoiesis secondary to B_{12} or folate deficiency
   - C. Bone marrow failure (aplastic anemia)
   - D. Neoplastic causes of decreased WBC (eg, MDS, acute leukemia, LGL leukemia)

II. Increased destruction
   - Immune neutropenia secondary to rheumatologic disorders, Felty syndrome, and lymphoproliferative malignancies

III. Increased splenic sequestration
   - Congestive splenomegaly with cirrhosis, Gaucher disease, etc

IV. Nonneoplastic increases in WBC
   - A. Response to stress (eg, infection)
   - B. Response to drug (eg, corticosteroids, granulocyte colony-stimulating factor)
   - C. Other reactive increases (eg, inflammation)

V. Neoplastic diseases
   - A. Primary hematologic
     1. Myelodysplastic syndromes (MDS)
     2. Acute leukemias
        a. Acute myelogenous leukemia (AML)
        b. Acute lymphocytic leukemia (ALL)
     3. Chronic leukemias
        a. Chronic lymphocytic leukemia (CLL)
        b. Chronic myelogenous leukemia (CML)
        c. Hairy cell leukemia
        d. Large granular lymphocytic leukemia (LGL leukemia)
     4. Other myeloproliferative diseases
     5. Non-Hodgkin lymphoma (with circulating lymphoma cells)
   - B. Cancers metastatic to bone marrow
     - Most commonly breast, lung, prostate, and lymphomas

VI. Normal count with impaired function
   - A. Diabetes mellitus: impaired polymorphonuclear neutrophil function

B. Chronic renal failure: impaired polymorphonuclear neutrophil and lymphocyte function

C. Drugs (eg, corticosteroids)

The most common assessment of white cells is quantitative evaluation of their numbers. Careful attention should also be paid to the distribution of the different types of white cells (WBC differential). Equally important is the microscopic examination of the peripheral blood smear (and bone marrow when needed) for morphologic changes in the WBC as well as the red cells and platelets. Specific quantitation of WBC subsets by immunophenotyping and genomic techniques can aid in the diagnosis of many neoplastic WBC disorders. Qualitative or functional defects are more difficult to establish with laboratory techniques and are usually strongly suggested by the medical history.

DECREASED WHITE BLOOD CELLS

Leukopenia may occur with a broad array of medical problems. Leukopenia can range from a mild suppression of the WBC to clinically significant neutropenia (**Table 104-2**). Most intrinsic (hereditary/familial) disorders and syndromes are typically detected during infancy or childhood. Benign ethnic neutropenia (an inherited mild neutropenia that typically occurs in individuals of African descent) may occasionally be first noted in an older aged person when coming in contact with the health care system. Most often, leukopenia in older adults is the result of acquired or secondary disorders, either reactive (drugs, nutritional, infections, immune) or malignant. **Table 104-3** presents key components in the clinical work-up of neutropenia.

TABLE 104-2 NEUTROPENIA

ANC[a]	INFECTION RISK
≥ 1000	Essentially normal
500–1000	Slight ↑ risk
< 500	"Significant" risk
< 100	Severe risk

[a]Absolute neutrophil count (ANC) = WBC × %(seg + bands).

TABLE 104-3 KEY COMPONENTS IN THE EVALUATION OF NEUTROPENIA

1. Clinical history	Duration (acute vs chronic) History of infection History of bleeding/bruising/fatigue Medication history Presence of comorbidities (rheumatologic disease, cirrhosis, malabsorption)
2. Examination	Evaluate for signs of infection including careful skin and mucosal examination Evidence of bleeding/bruising Splenomegaly
3. Complete blood count	Severity of neutropenia Presence of anemia or thrombocytopenia Macrocytosis Immature granulocytes on differential
4. Peripheral smear	Toxic granulation/vacuolation of neutrophils Presence of dysplastic features Immature granulocytes

	Nucleated red cells Megaloblastic changes (hypersegmentation of neutrophils)
5. Bone marrow biopsy	Indicated for severe neutropenia, pancytopenia, evidence of dysplasia or granulocytic immaturity on peripheral smear

Drug/Toxin Effects

Older patients commonly consume many prescribed and over-the-counter medications and are at higher risk for developing drug-related neutropenia or pancytopenia. The bone marrow is one of the more rapidly proliferating organs of the body; therefore, it is not surprising that exposure to noxious agents may temporarily or permanently inhibit production of one or more elements of the blood. The list of possible offenders is extensive and constantly evolving with new drug development. **Table 104-4** lists some of the more commonly reported offenders. In a situation of neutropenia, leukopenia, or pancytopenia, the physician should thoroughly review the patient's medications and the duration of the medication exposure. Short duration of exposure does not remove the possibility of a drug-induced cytopenia; it could be an idiosyncratic reaction. Diagnosis involves identification of a possible offending agent and exclusion of alternative etiologies for the leukopenia. A bone marrow biopsy is often indicated as part of the work-up if the leukopenia is severe.

TABLE 104-4 DRUGS ASSOCIATED WITH AGRANULOCYTOSIS/NEUTROPENIA

1. Cancer chemotherapeutic agents
2. Psychotropic drugs:
   - Clozapine
   - Risperidone
   - Olanzapine
   - Haloperidol
   - Phenothiazine
   - Tricyclic antidepressants
   - Meprobamate
3. Anti-inflammatory/antiarthritic drugs:
   - Sulfasalazine
   - Nonsteroidal anti-inflammatory agents
   - Colchicine
   - Immunosuppressive agents
   - Penicillamine
   - Gold salts
   - Allopurinoly
   - Immunosuppressants
4. Thyroid suppressants:
   - Propylthiouracil
   - Carbimazole
   - Methimazole
5. Cardiovascular drugs:
   - Antiarrhythmic agents (procainamide, quinidine, amiodarone)
   - ACE inhibitors (captopril, enalapril)
   - Nifedipine
   - Hydralazine
   - Propranolol

Methyldopa
Ticlopidine
Dipyridamole
Digoxin

6. Antibiotics:
   Sulfa drugs
   Semisynthetic penicillins
   Cephalosporins
   Macrolides
   Vancomycin
   Rifampin
   Clindamycin
   Gentamicin
   Linezolid
7. Anticonvulsants:
   Phenytoin and derivatives
   Carbamazepine
   Valproate
8. Diuretics:
   Thiazides
   Acetazolamide
   Furosemide
   Spironolactone
9. Antihistamines—H_2 blockers
10. Oral hypoglycemia drugs

ACE, angiotensin-converting enzyme.

Drug effects on the bone marrow range from mild neutropenia (more common) to agranulocytosis; lymphocytopenia occurs less frequently. The RBC and platelets may or may not be affected. Drug-induced reduction of the granulocytic series may be a direct toxic effect, as with many cancer chemotherapeutic drugs or may be the result of an immunologic phenomenon wherein a drug-antibody complex reacts with mature neutrophils and/or their precursors in the peripheral blood or bone marrow. Treatment usually consists of supportive care, with administration of antibiotics for febrile patients. Upon withdrawal of the offending agent, there may be a relatively brisk marrow recovery within 14 to 21 days. A bone marrow examination during this recovery period may reveal an increased number of immature elements, which can be confused with a malignant process such as an acute leukemia or myelodysplasia. If this is a possibility, close follow-up for an additional 2 to 3 weeks will usually provide the answer. The recovering marrow will go on to differentiate, but the malignant marrow will either stay the same or worsen. Other marrow toxins include a variety of household and industrial chemicals, especially organic solvents, naphthalenes, insecticides, and herbicides. Inquiries about chemical exposure from hobbies or occupations must therefore be part of history-taking. While the hematologic effects of drug and chemical exposure are frequently reversible, some may result in myelodysplastic syndromes (MDS) or aplastic anemia which, in turn, may evolve into AML.

Nutritional Deficiency

Mild neutropenia may be associated with nutritional anemias secondary to folate or B_{12} deficiency. The associated anemia is typically macrocytic. Older individuals, especially those living alone, may not be attentive to their diet for various socioeconomic, psychological, or medical reasons. The main sources of folates are fresh green vegetables, many fruits, and beans. Cooking and canning destroys folates. The body’s folate stores can be depleted after 4 to 5 months of poor dietary intake. Thus, a dietary history may provide an important clue to the diagnosis of the

hematologic problem. Dietary folate deficiency may be aggravated by alcoholism and chronic hemolysis. Additional hematologic findings of folate deficiency include macrocytic anemia and hypersegmented neutrophils. Potential folate deficiency is best evaluated by measuring RBC folate.

In contrast, body stores of vitamin B_{12} are not readily depleted by poor dietary habits alone. It takes 3 to 5 years to deplete the body stores of vitamin B_{12}. However, gastric atrophy is more common with increasing age, and this may lead to failure of gastric secretion of intrinsic factor, which binds to dietary cobalamin—a necessary step in the absorption of vitamin B_{12} in the ileum. Other conditions that cause a B_{12} deficiency include gastrectomy or subtotal small bowel (ileal) resection. It should be noted that neurologic signs and symptoms of B_{12} deficiency may be confused with other neurologic problems in older adult patients. These include peripheral paresthesias, loss of balance (posterior column damage), spasticity (lateral column damage), and impaired cognitive function. Any of these neurologic signs and symptoms may be mistakenly attributed to "old age," but if caused by B_{12} deficiency may be corrected with vitamin B_{12} replacement therapy. Low serum cobalamin levels (< 200 ng/L) are diagnostic of deficiency and will be found in the majority of patients who are symptomatic. Subclinical cobalamin deficiency can be detected by measuring serum methylmalonic acid. Subclinical cobalamin deficiency is characterized by low normal serum cobalamin level (200–350 ng/L) and an elevated methylmalonic acid level. It should be noted that homocysteine will be elevated in both folate and cobalamin deficiency.

Copper deficiency is an uncommon cause of neutropenia. The neutropenia is typically associated with anemia and may be confused with early MDS, particularly in an older adult. Copper deficiency is most commonly associated with malabsorption, malnutrition, use of total parenteral nutrition, or excess oral zinc supplementation. The diagnosis is suggested by the appropriate clinical setting and a low serum copper level. Hematologic changes are potentially reversible with oral copper supplementation.

Infections

A number of infections can be associated with neutropenia and/or leukopenia in older adults. These infections include viral (eg, influenza, varicella, hepatitis A, B, or C, cytomegalovirus, human immunodeficiency virus, parvovirus B19), and bacterial (eg, *Staphylococcus aureus*, brucellosis, tularemia, rickettsia, and tuberculosis) etiologies. Neutropenia associated with most viral illnesses is self-limited and of minimal clinical consequence. A few viruses (hepatitis B, Epstein-Barr, and human immunodeficiency virus) can cause protracted, clinically significant neutropenia. Bacterial septicemia, particularly with gram-negative organisms, is a serious cause of acquired neutropenia and confers a poor prognosis. The mechanism of leukopenia is usually bone marrow suppression, but in the case of overwhelming bacterial sepsis, can result from exhaustion of bone marrow reserves. Treatment focuses on supportive care including use of antibiotics for infection; the role of myeloid growth factors in this setting is unproven.

Bone Marrow Failure

Severe and prolonged bone marrow failure may occur in association with drugs, toxins, or infections, but is frequently idiopathic. Aplastic anemia is characterized by severe pancytopenia and bone marrow hypoplasia. Clinical signs and symptoms reflect the cytopenias: infection, bleeding, and/or the signs/symptoms of anemia. Pure white cell aplasia occurs rarely. Treatments for this life-threatening disease include supportive care (transfusion, antibiotics), immunosuppression (antithymocyte globulin, cyclosporine, steroids), and stem cell transplant (limited application in older adult populations).

Increased Destruction

Immune neutropenia may be associated with various rheumatologic conditions such as systemic lupus erythematosus, rheumatoid arthritis, polyserositis, and lymphoproliferative malignancies. In these situations, neutropenia is caused by the elimination of immunoglobulin-coated granulocytes by the reticuloendothelial system. Immune-mediated neutropenia is often clinically significant with absolute neutrophil count (ANC) less than 500 cells/mm^3, predisposing to increased infection risk. In general, the bone marrow is hypercellular or normocellular and lacking in mature neutrophils. Neutropenia of Felty syndrome (rheumatoid arthritis, splenomegaly, and neutropenia) has a complex etiology that includes immune destruction and suppression as well as splenic sequestration. These neutropenias frequently respond to granulocyte colony-stimulating factors (GCSF) or granulocyte-macrophage colony-stimulating factors (GM-CSF).

Splenic Sequestration

Any condition causing splenomegaly (eg, hepatic cirrhosis) may lead to sequestration of sufficient neutrophils to cause mild-to-moderate neutropenia as a component of the pancytopenia of hypersplenism. The mild-to-moderate neutropenia usually does not predispose to increased infections and often occurs in association with anemia and/or thrombocytopenia.

Neoplastic Causes of Decreased WBC

Malignancies (hematologic and nonhematologic) can present with neutropenia and need to be considered in the evaluation of this finding. Details of the presentation and work-up of many of these disorders will be presented later in this chapter.

INCREASED WBC

Benign Causes of Leukocytosis

The most common causes of sustained increases in WBC are neoplastic diseases. However, there are a number of nonneoplastic etiologies for increases in one or more white cell forms. The most common among these is a leukocytosis, specifically neutrophilia, in response to infection. This is associated with a "left shift" in the differential, with increases in bands and other less-mature granulocytes, including metamyelocytes and myelocytes. Such a normal granulocytosis can also be seen in response to an exogenous steroid. Increases in specific subsets of white cells (eg, eosinophils or basophils) can occur in response to a number of exposures or illnesses. Hereditary and familial (eg, Down syndrome) causes of leukocytosis are rare and usually detected early in life.

Infection

Infection stimulates the acute release of neutrophils from the marginated storage pools of the bone marrow. Neutrophilia commonly occurs with acute bacterial infections, and is less predictably seen with viruses. An increase in band neutrophils and metamyelocytes is most common. Toxic granules in those cells are frequently present on review of the peripheral blood smear. A dramatic "leukemoid reaction," characterized by a WBC greater than 50,000/μL, a marked left shift with increased immature granulocytes including myelocytes, promyelocytes, and even blasts, may be confused with malignant disorders, especially chronic myelogenous leukemia (CML). Leukemoid reactions are characterized by a high-leukocyte alkaline phosphatase (LAP [low in CML]) and absence of the Philadelphia (Ph) chromosome. Leukemoid reactions are uncommon and the probability of an underlying bone marrow disorder should always be suspected in this setting.

Drug-Induced Leukocytosis

Corticosteroids are the most common medications associated with increases in WBC, primarily neutrophilia. The mechanism includes reduced neutrophil adhesion and release from marrow stores. The hematopoietic colony-stimulating factors (eg, GCSF, GM-CSF) are designed to stimulate neutrophilia, and lithium can induce neutrophilia through similar CSF pathways. β-Adrenergic agonists also frequently stimulate acute release of neutrophils from marginated pools.

Other Reactive Leukocytosis

Mild neutrophilia (WBC 12,000–20,000/μL) can occur after a stress, resulting from release of neutrophils from marginated pools into the bloodstream. Stressful stimuli include exercise, seizures, anesthesia, and surgery. Acute inflammation and tissue necrosis are also associated with neutrophilia. Examples include burns, electric shock, trauma, and infarction. Asplenia can be associated with moderate leukocytosis. Chronic inflammatory conditions such as colitis, rheumatoid arthritis, and vasculitis may stimulate a modest increase in bone marrow production and release of neutrophils. Mild-to-moderate leukocytosis (WBC < 30,000/μL) may also occur in association with a variety of malignancies without bone marrow involvement.

Isolated increases in WBC subsets occur with or without increase in total WBC. Monocytosis may be associated with inflammatory diseases, specifically infections, autoimmune and granulomatous diseases, and numerous

malignancies. Eosinophilia (> 600/μL) usually represents a reaction to drugs, infection (eg, fungi, parasites), allergic disorders, vasculitis, or malignancies. Lymphocytosis, though frequently representing malignancy, may occur in response to infection.

MALIGNANT DISEASE OF THE HEMATOPOIETIC SYSTEM

Hematologic malignancies, although most frequently characterized by elevated WBC, can be associated with low, normal, or high WBC. The WBC differential, as well as the red cell and platelet counts, are usually abnormal.

Malignant diseases of the WBCs include the four major subtypes of leukemia—AML, acute lymphocytic leukemia (ALL), CML, and CLL; as well as the MDS; the myeloproliferative disorders other than CML; hairy cell leukemia; large granular lymphocytic leukemia; metastatic cancers to the bone marrow; and circulating non-Hodgkin lymphoma cells. Older adults make up a large proportion of incident and prevalent cases of these diseases as well as those dying from these conditions (**Figures 104-1** and **104-2**). As the population ages, the burden of these diseases will rise affecting older adults disproportionately.

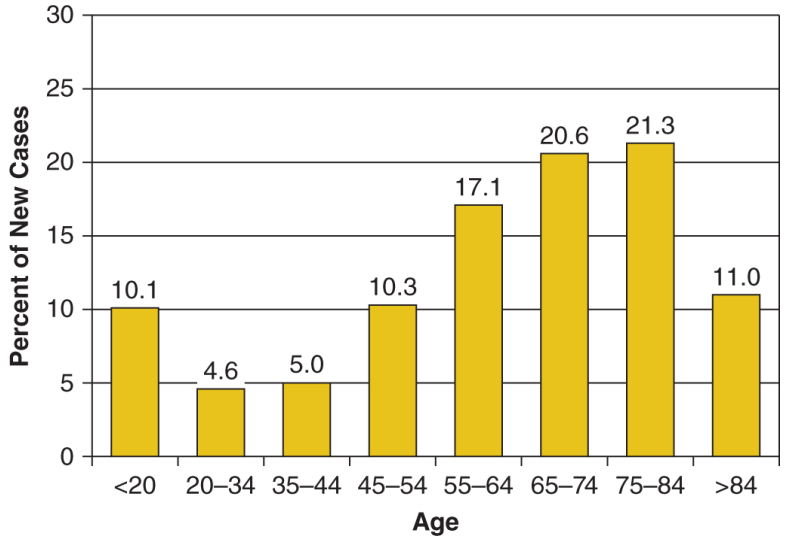


FIGURE 104-1. Percentage of new cases of leukemia by age group from Surveillance, Epidemiology, and End Results (SEER) data 2007–2011. (Source: National Cancer Institute Surveillance, Epidemiology, and End Results Program. http://seer.cancer.gov/statfacts/html/leuks.html.)

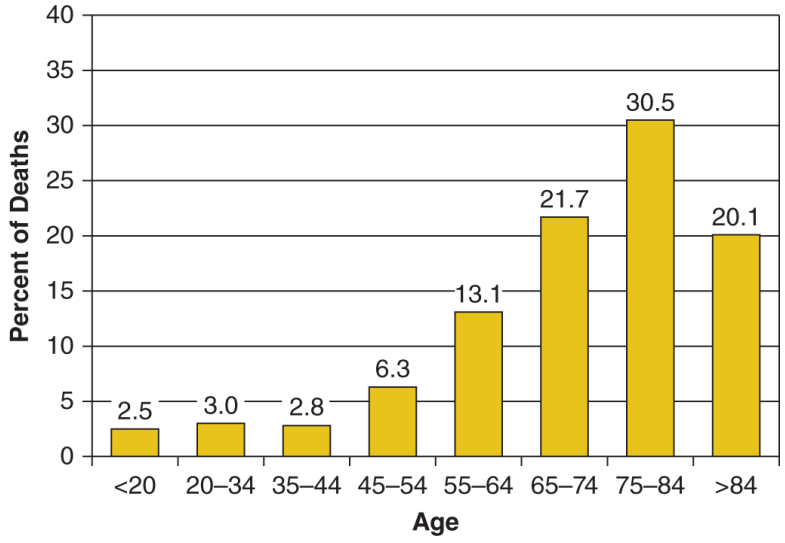


FIGURE 104-2. Percentage of deaths for people diagnosed with leukemia by age group from Surveillance, Epidemiology, and End Results (SEER) data 2007–2011. (Source: National Cancer Institute Surveillance, Epidemiology, and End Results Program.

http://seer.cancer.gov/statfacts/html/leuks.html.)

The effectiveness of treatments has improved substantially over recent decades for most hematologic malignancies. Unfortunately, the response rates and cure rates for older patients have lagged behind for a number of reasons, including in some cases more resistant tumor biology, presence of multiple chronic conditions, and functional impairments which decrease treatment tolerance. Underrepresentation of older adults in clinical trials remains a limitation. With the increased focus on clinical trials designed specifically for older adults and the ongoing development of less toxic, targeted therapies, opportunities for effective treatment of older adults with malignant WBC disorders continue to improve.

Myelodysplastic Syndromes

MDS are a heterogenous group of clonal hematopoietic disorders characterized by ineffective hematopoiesis and peripheral blood cytopenias. In these diseases, cells of the affected lineage are unable to undergo maturation and differentiation, resulting in cytopenias. MDS can be indolent or progress rapidly to bone marrow failure. The major clinical significance of these disorders is the morbidity associated with profound cytopenias and the potential to evolve into AML. MDS is associated with impaired quality of life and high health care utilization with an estimated 3-year survival rate of 45%. Approximately 15,000 to 20,000 new cases per year are diagnosed annually in the United States and about 80% of these are among adults over age 70.

Diagnosis and work-up Diagnosis of MDS relies mainly on peripheral blood and bone marrow findings. The diagnosis should be suspected in individuals presenting with cytopenia. In clinical studies, the majority of patients have a hemoglobin of less than 11, platelet count less than 100,000, and an ANC less than 1000 at the time of diagnosis. However, careful attention should be paid to consistent decreases in blood counts over time in an older adult, which may signify early developing MDS. A frequent presentation is progressive macrocytic anemia in an older adult followed by developing pancytopenia. Many patients are asymptomatic at the time of diagnosis. However, careful history-taking should include questions regarding recurrent infections, bruising, and bleeding. The differential diagnosis for suspected MDS includes AML, aplastic anemia, megaloblastic anemia (B_{12} and folate deficiency), copper deficiency, viral infections (HIV), large granular lymphocytic leukemia, and heavy metal poisoning.

The initial serologic work-up includes a complete blood count (CBC) with differential, reticulocyte count, RBC folate, serum B_{12}, iron studies, and review of the peripheral smear. Classic peripheral blood findings associated with MDS include macrocytosis and hypogranular, hypolobated (dysplastic) neutrophils. A bone marrow biopsy with cytogenetic analysis is required to confirm the diagnosis. The bone marrow is typically hypercellular and demonstrates evidence of dysplasia. Cytogenetic abnormalities play a critical role in the diagnosis and natural history of MDS. Common cytogenetic abnormalities involve chromosomes 5, 7, 8, 17, or 20.

Risk stratification A classification scheme proposed by the World Health Organization (WHO), which incorporates evolving knowledge of the biology of disease including the significance of cytogenetic abnormalities, is presented in **Table 104-5**. This table highlights the heterogeneity of MDS which has historically complicated accurate prognostication. The International Prognostic Scoring System (IPSS) was developed to risk stratify patients at the time of diagnosis based on cytogenetic, morphologic, and clinical data. The IPSS for MDS was derived from an analysis of 816 patients, 75% of whom were greater than 60 years. The IPSS incorporates specific cytogenetic abnormalities, the percentage of marrow blasts in the bone marrow, and the number of hematopoietic lineages involved in the cytopenia. Risk scores are determined based on these variables, and a categorization of low risk, intermediate-1, intermediate-2, and high risk is assigned. These categories can differentiate patients with median survival of more than 5 years at diagnosis (low risk) from those with less than 1-year survival (high risk). Another risk stratification system proposed by the WHO includes additional variables shown to add prognostic information including multilineage dysplasia, severe anemia, or transfusion dependency. This system can be used both at diagnosis and after progression to predict survival. A five-category revised IPSS was developed using over 7000 patients (median age 71) which differs by further subdividing cytogenetic abnormalities and increasing the weight of higher blast percentages. In the development cohort, age was a prognostic factor for survival but not for progression to AML, having more impact in lower- versus higher-risk disease. The revised IPSS is commonly used and represented in **Tables 104-6** and **104-7**.

TABLE 104-5 PERIPHERAL BLOOD AND BONE MARROW FINDINGS IN MYELODYSPLASTIC SYNDROMES

DISEASE	BLOOD FINDINGS	BONE MARROW FINDINGS

Refractory cytopenias with unilineage dysplasia (RCUD) Refractory anemia Refractory neutropenia Refractory thrombocytopenia	Unicytopenia or bicytopenia No or rare blasts	Dysplasia in ≤ 10% of cells in one myeloid lineage < 5% blasts < 15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	≥ 15% ringed sideroblasts Erythroid dysplasia only < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias No or rare blasts (< 1%) No Auer rods < 1×10^9/L monocytes	Dysplasia in ≥ 10% of the cells of two or more myeloid cell lines < 5% blasts in marrow No Auer rods ± 15% ringed sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias < 5% blasts No Auer rods < 1×10^9/L monocytes	Unilineage or multilineage dysplasia 5%–9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias 5%–19% blasts Auer rods ± < 1×10^9/L monocytes	Unilineage or multilineage dysplasia 10%–19% blasts Auer rods ±
Myelodysplastic syndrome–unclassified (MDS-U)	Cytopenias ≤ 1% blasts	Dysplasia < 10% of cells in one or more myeloid cell lines accompanied by a cytogenetic abnormality that is characteristic for MDS < 5% blasts
MDS associated with isolated del (5q)	Anemia Usually normal or increased platelet count < 1% blasts	Normal-to-increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

Adapted from Brunning R, et al. Tumours of Hematopoietic and Lymphoid Tissues. Geneva, Switzerland: World Health Organization; 2008.

TABLE 104-6 REVISED INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS) FOR MDS

PROGNOSTIC VARIABLE	SCORE						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blasts (%)	< 2		> 2 to < 5		5–10	< 10	
Hemoglobin (g/dL)	> 10		8 to < 10	< 8			
Platelets (cells/μL)	≥ 100	50–100	< 50				
Absolute neutrophil count (cells/μL)	≥ 0.8	< 0.8					

Very good, –Y, del(11q); good, normal, del(5q), del(12p), double including del(5q); intermediate, del(7q), +8, +19, i(17q), and other single or double independent clones; poor, –7, inv(3)/del(3q), double including –7/del(7q), complex: 3 abnormalities; very poor: complex: > 3 abnormalities.

Data from Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system (IPSS-R) for myelodysplastic syndromes. Blood. 2012; 120(12):2454–2465. Copyright © American Society of Hematology.

TABLE 104-7 OVERALL SURVIVAL AND RISK OF AML EVOLUTION BY REVISED IPSS SCORE

RISK GROUP	IPSS-R SCORE	MEDIAN OVERALLSURVIVAL (YEARS)	MEDIAN TIME TO 25% AML EVOLUTION (YEARS)
Very low	< 1.5	8.8	> 14.5
Low	< 1.5–to 3	5.3	10.8
Intermediate	> 3–4.5	3.0	3.2
High	> 4.5–6	1.6	1.4
Very high	> 6	0.8	0.7

Data from Greenberg PL et al. Revised International Prognostic Scoring System (IPSS-R) for myelodysplastic syndromes. Blood. 2012;120(12):2454–2465.
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Selection of treatment for patients with MDS depends not only on disease risk stratification but on assessment of a patient's overall fitness and competing comorbid conditions. Most patients with MDS have additional comorbidity and higher comorbidity burden has been associated with shorter survival independent of age or disease risk. A prospective study investigating the predictive utility of a geriatric assessment among older adults treated nonintensively for MDS (N = 51) and AML (N = 69) found that requiring assistance with activities of daily living (ADLs) and high fatigue rating were independently associated with survival These characteristics and others detected by geriatric assessment may also identify those who are vulnerable to the toxicities of therapies and can inform decisions related to the intensity and chronicity of treatment.

Treatment Treatment strategies have been evolving in recent years to target higher-risk MDS and subgroups defined by specific cytogenetic abnormalities. Current treatment recommendations involve a risk-adapted therapeutic approach (outlined in **Table 104-8**). Supportive care, aimed at controlling symptoms related to cytopenias, is indicated for all patients and is the mainstay of treatment for lower-risk patients or frail patients. Supportive care often includes red cell and platelet transfusions and antibiotics for infection. Hematopoietic growth factors such as erythropoietin are used to try to minimize transfusion requirements in responding patients. Those most likely to benefit have lower risk R-IPSS scores, serum erythropoietin level less than 200 mU/mL, low transfusion requirement, and shorter interval between diagnosis and treatment. Over time, most patients become transfusion dependent, increasing the risk of iron overload. Guidelines suggest iron chelation therapy should be initiated for those with lower-risk MDS, ongoing transfusion dependence, and expected survival greater than 1 year.

TABLE 104-8 ■ TREATMENT OPTIONS FOR OLDER ADULTS WITH MDS BASED ON DISEASE AND PATIENT CHARACTERISTICS

DISEASE CHARACTERISTICS (REVISED IPSS)	GOAL OF THERAPY	PATIENT CHARACTERISTICS	TREATMENT CONSIDERATIONS
Very low/low risk asymptomatic	Improve QOL	Any	Observation
Very low/low/intermediate symptomatic 5q deletion	Improve QOL	Any	Lenalidomide
Absence of 5q with erythropoietin level < 500	Improve QOL	Any	Erythropoietin +/– GCSF Consider lenalidomide
	Improve QOL	Good performance status/minimal comorbidity	Consider hypomethylating agents
Intermediate/high/very high	Delay progression, extend life	Any age, good performance status, absence of major comorbidity	Hypomethylating agents
	Cure	Age 60–75, excellent performance status, absence of major	Consider referral for RIC HSCT versus hypomethylating agents Comprehensive geriatric assessment

		comorbidity	may help inform “fitness”
	Delay progression, extend life	Poor performance status and/or major comorbidity	Consider hypomethylating agents versus supportive care

GCSF, granulocyte colony-stimulating factor; HSCT, hematopoietic stem cell transplantation; QOL, quality of life; RCT, randomized controlled trial; RIC, reduced-intensity conditioning.

Adapted from Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. J Clin Oncol. 2014;32(24):2541–2552.

Patients in the higher-risk IPSS categories are more likely to experience morbidity related to cytopenias and to progress to acute leukemia in a shorter time interval from diagnosis. Hypomethylating agents which inhibit DNA methyltransferases (azacitidine and decitabine) represent the mainstay of treatment for most patients. Randomized studies with azacitidine compared to placebo have shown improvements in survival, quality of life, and a longer time to progression to acute leukemia, in patients with MDS. A survival advantage exists even for those greater than 75 years. The Food and Drug Administration (FDA) also approved decitabine for the treatment of higher-risk MDS. Decitabine decreases transfusion requirements and symptoms although has not yet shown a definitive survival benefit in randomized trials. Challenges for older adults using hypomethylating agents include a 7-day scheduling for azacitidine and myelosuppression which often worsens for several months before response is detectable. The duration of treatment can be challenging as well with most clinical trials treating for more than 6 months for all patients and more than 12 months for responders.

Treatment options have expanded for patients with the 5q– syndrome. This subset of MDS is defined by a deletion of the long arm of chromosome 5 as the sole abnormality. The 5q– syndrome typically manifests as refractory, severe anemia, and a relatively normal platelet count. It is considered a more favorable MDS subset because a large percentage of patients do not progress to acute leukemia. In clinical trials and population-based studies lenalidomide, an oral immunomodulatory drug, significantly decreases transfusion requirements and demonstrates reversal of cytogenetic abnormalities in patients with 5q– syndrome which may translate into improved quality of life. The primary toxicity is myelosuppression which resulted in dose reductions and dose delays in a substantial proportion of patients treated on clinical trial. Careful attention to dosing is required with adjustments needed for mild impairment in renal function which is common among older adults. This drug has become the standard of care for treatment of transfusion-dependent, patients with 5q– syndrome and reinforces the clinical and therapeutic importance of cytogenetic evaluation in MDS. Studies suggest it also has efficacy in patients with low-risk MDS without 5q deletion and may be considered for these patients as well if they are transfusion dependent.

Higher-intensity therapy such as allogeneic stem cell transplantation, to date the only curative therapy for MDS, is generally restricted to younger adults with acceptable donors because of the high morbidity and mortality associated with therapy. However, with use of reduced-intensity conditioning regimens (RIC), stem cell transplantation is increasingly considered for selected adults between ages 60 to 80 with good functional status and minimal comorbidity. Hematopoietic stem cell transplantation can result in appreciable survival rates among patients with high-risk disease. However, most older adults in this context are age less than 70 with minimal data for those greater than 75. The real-world applicability of transplantation for most older adults with high-risk MDS will require refined definitions of “fitness” and collection of outcomes such as quality of life, functional independence, and health care utilization to inform treatment decisions.

Acute Myelogenous Leukemia

AML refers to a group of clonal hematopoietic disorders that are characterized by proliferation of immature myeloid cells in the bone marrow. Accumulation of leukemic cells impairs the normal hematopoietic function of the bone marrow, resulting in cytopenias with or without leukocytosis.

AML is a disease of older adults, with a median age at diagnosis between 68 and 72; approximately one-third of whom are greater than or equal to 75 years. The American Cancer Society estimated that 18,860 patients would be diagnosed with AML in 2014 with an anticipated 10,460 dying of disease.

Risk factors for the development of AML include a history of preceding MDS, exposure to certain chemotherapy drugs (alkylating agents, topoisomerase 2 inhibitors, and nitrosoureas), radiation or benzene exposure, and a history of Down syndrome. The majority of diagnosed cases of AML, however, are not linked to any known risk factor.

The clinical signs and symptoms of AML can be varied and nonspecific. Patients usually present with evidence of

bone marrow failure: anemia, thrombocytopenia, granulocytopenia. Fatigue, dyspnea, bleeding, fever, and infection are common upon presentation. Leukemic infiltration of tissues outside the bone marrow such as liver, spleen, skin, lymph nodes, and central nervous system (CNS) can produce a variety of other symptoms specific to the site of involvement. Some patients present with severe leukocytosis, which can produce symptoms of leukostasis as a result of a large blast fraction in the peripheral blood. Peripheral blood findings range from pancytopenia with or without circulating blasts cells to severe leukocytosis with circulating blasts typically with anemia and thrombocytopenia.

Diagnosis The diagnosis of AML depends primarily on detection of leukemic blasts of myeloid lineage (≥ 20%) in the bone marrow. Morphologic evaluation can be aided by immunohistochemical and flow cytometry techniques to confirm myeloid versus lymphoid origin. The WHO classification of AML incorporates morphologic, immunophenotypic, genetic, and clinical features. There are four major categories, each with two or more subtypes. The main categories of AML are as follows: (1) AML with recurrent genetic abnormalities; (2) AML with myelodysplasia-related features; (3) therapy-related AML and MDS; and (4) AML not otherwise specified. Identification of genetic and molecular abnormalities have highlighted the heterogeneity of AML and identified subsets associated with better or worse prognosis. For example, the core binding factor leukemias [inv 16, t(8;21), t(16;16)], and acute promyelocytic leukemia [t(15;17)] are associated with better prognosis. The presence of mutations in *FLT-3* in tumors with normal karyotype is associated with worse overall survival. Risk-adapted treatment strategies have been developed to maximize clinical outcomes and minimize toxicity based on cytogenetic classification. In addition, molecular abnormalities are increasingly identified as treatment targets in clinical trials.

Treatment If untreated or unresponsive to chemotherapy, AML may be rapidly fatal (median survival < 2 months). The major causes of death are overwhelming infection and hemorrhage related to the disease-associated cytopenias. AML is one of the most dramatic examples of age-related outcome disparity in oncology (**Figure 104-3**). There is no consensus regarding optimal therapy for older adults with AML in part due to the higher morbidity and mortality rates seen in clinical trials and population-based data for older persons. Concerns regarding the efficacy and toxicity of therapies have resulted in fewer than 40% of older adults in the United States receiving any therapy. However, it is clear from both clinical trial and population-based data that chemotherapy can provide a survival benefit over supportive care for selected older adults.

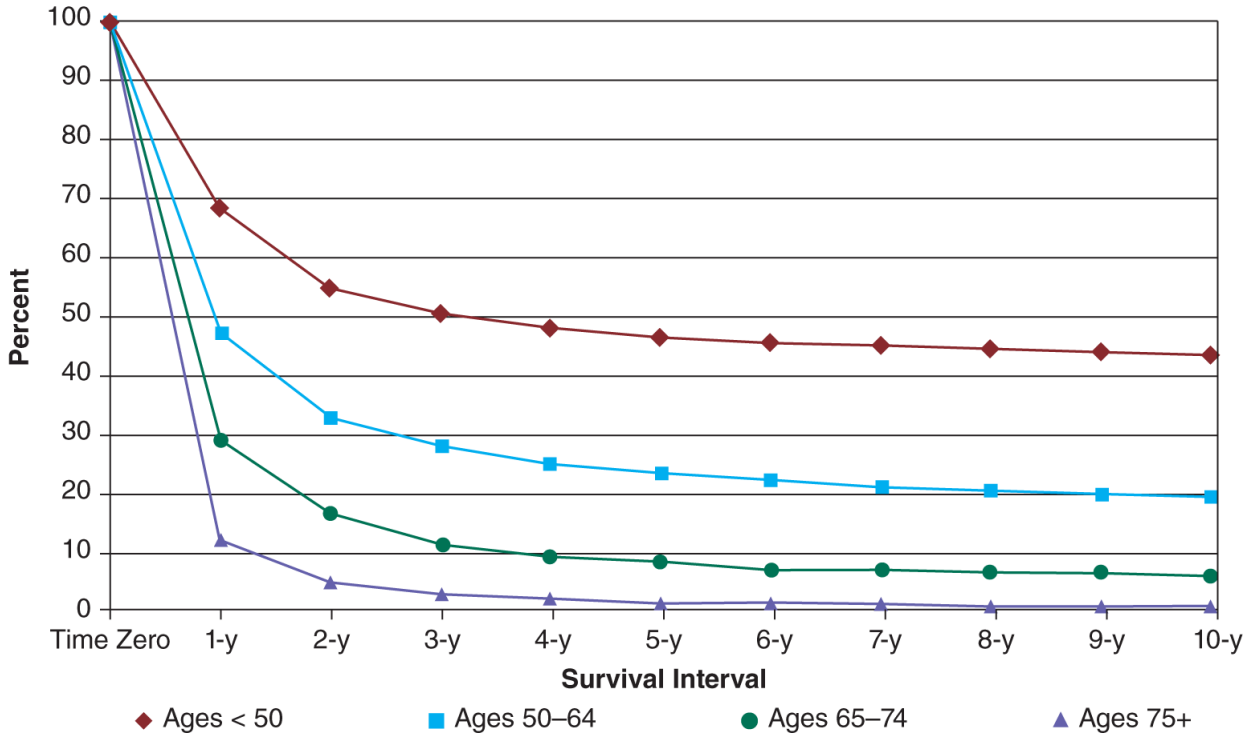


FIGURE 104-3. Relative survival by time and age for acute myeloid leukemia (AML) based on Surveillance, Epidemiology, and End Results data. (Source: National Cancer Institute Surveillance, Epidemiology, and End Results Program. http://seer.cancer.gov.)

Most clinical trials in AML have enrolled patients aged 60 to 80. Median survival in clinical trials has historically been less than 1 year with improvements seen in more recent trials. In general, older adults are less likely to achieve

complete remission (CR) (although rates vary from 30% to 80% in trials), are more likely to relapse, and their 30-day mortality rates range from 10% to 30%.

Standard induction therapy for AML is combination chemotherapy that includes cytosine arabinoside (ara-C) and an anthracycline such as daunorubicin. These drugs yield CRs in 50% to 80% of patients, depending on various prognostic factors. Increased age is an important negative prognostic factor. The poorer prognosis associated with increased age is related to both a higher frequency of fatal infections and hemorrhage during the period of disease and treatment-related marrow hypoplasia (induction deaths) and to chemotherapy failure (residual or resistant leukemia). A landmark randomized study by Lowenberg et al. demonstrated improved survival in selected patients aged 65 and older treated with standard induction chemotherapy versus supportive care alone. This study demonstrated a potential benefit to aggressive treatment for selected older adults. However, outcomes remain suboptimal in this population. Attempts to improve response rates in older patients with AML have included dose attenuation, anthracycline substitution, use of growth factors, and modulation of multidrug resistance. Overall improvements have been incremental without a clear practice changing regimen identified. Two studies have shown improvement in overall survival with addition of low-dose gemtuzumab ozogamicin to intensive induction for patients greater than age 50 but this therapy is currently unavailable in the United States.

The role of lower-intensity therapies including the DNA hypomethylating agents (eg, azacitidine and decitabine) is an area of active investigation. These agents have shown some efficacy for older adults with AML and may improve outcomes compared to supportive care alone for selected patients. In practice, hypomethylating agents are frequently used to treat older adults with comorbidity or poor functional status. To date, no therapy has been shown to be superior to intensive induction in randomized trials.

The median duration of complete remission when achieved is approximately 1 year, and a small percentage (≤ 15%) of older (60 years and older) patients will be cured of their leukemia. Patients who achieve remission should be considered for therapy after remission in an attempt to prevent or delay relapse. However, the exact role and optimal type of such postremission therapy in older patients remain poorly defined. An increasing number of older adults who achieve remission are being referred for reduced-intensity allogeneic transplantation in an effort to improve longer-term disease-free survival and cure rates.

Treatment recommendations differ for patients with acute promyelocytic leukemia (APL). APL is characterized by a translocation between chromosomes 15 and 17 leading to the fusion of the promyelocytic leukemia (*PML*) gene with the retinoic acid receptor α (*RARα*) gene, resulting in disruption of normal cell differentiation. While less common among older adults, this disease has a very high response and cure rate with current therapies that include use of all-*trans* retinoic acid (ATRA) which overcomes the differentiation block. A unique clinical feature of APL is presentation with bleeding secondary to disseminated intravascular coagulation and requires emergent treatment. Hemorrhage is a frequent cause of early mortality, particularly if untreated. When suspected, treatment with ATRA should begin immediately. Curative treatment includes induction with ATRA with either arsenic trioxide (ATO) for patients with WBC less than 10×10^9/L, or plus an anthracycline for patients with WBC greater than 10×10^9/L. Induction therapy is followed by consolidation with ATRA plus ATO-based therapy, with remission and disease-free survival rates of approximately 90%. In addition, relapsed patients may respond to arsenic trioxide, with a high proportion achieving a second remission. This subtype of AML should be treated aggressively in older adults given the high probability of response.

Risk stratification The biology of AML differs among older adults compared to younger patients and contributes to worse prognosis in older adults with AML. Cytogenetic abnormalities are the most important prognostic factor in AML. As a group, older patients with AML have a higher percentage of unfavorable cytogenetic abnormalities and a lower percentage of favorable cytogenetic abnormalities compared to younger patients. Unfavorable cytogenetic abnormalities are associated with decreased rates of remission and shortened overall survival. Expression of MDR1, which confers resistance to chemotherapeutic agents, is more common in older AML patients. Older patients are more likely to have a secondary AML arising from underlying myelodysplastic syndromes, which is less responsive to standard therapy. Patients with preceding MDS may also have some impairment in functional status related to prior therapies and symptoms related to chronic myelosuppression. Finally, age-related changes in the bone marrow microenvironment influence outcomes for older adults. Overall, AML in older patients is more resistant to available therapies resulting in lower remission rates and higher chance of relapse after achieving remission.

There are several well-validated prognostic models developed from clinical trial data that are used to predict outcomes for older adults treated with induction chemotherapy (**Table 104-9**). Each is useful to help individualize a treatment decision for an older patient. These models are heavily weighted toward characterization of tumor biology

and rely on chronological age as the primary patient characteristic measured. Disease characteristics alone do not fully explain age-related outcome disparity in AML. Even among older adults with favorable disease biology, outcomes remain worse for older adults. Clinical characteristics including increased comorbidity, age-associated physiologic changes, polypharmacy, and functional and cognitive impairment complicate therapy in older adults and likely also contribute to decreased treatment tolerance and shorter survival. Several small trials have suggested the value of performing geriatric assessment in the context of AML therapy to better predict survival and treatment tolerance (see **Table 104-9**). Geriatric assessment can be feasibly performed in the setting of AML therapy and it adds information to standard clinical assessment. For example, in a prospective study of adults age greater than or equal to 60 who received intensive therapy, pretreatment geriatric assessment detected significant impairments: cognitive impairment, 24%; depression, 26%; distress, 50%; ADL impairment, 34%; impaired physical performance, 31%; and comorbidity, 40%. Importantly, most patients on study were impaired in one (92.6%) or more (63%) measured characteristics. Impaired cognition (modified Mini Mental Status Examination < 77) and physical performance (short physical performance battery < 9) were independently associated with worse survival. The utility of geriatric assessment is currently under investigation in multisite treatment trials. Ultimately, understanding specific patient vulnerabilities may help to predict tolerance and response to standard therapies, inform adaptive clinical trial design for specific patient subgroups, and identify targets for intervention to improve treatment tolerance such as exercise for physical impairment.

TABLE 104-9 FACTORS ASSOCIATED WITH SURVIVAL AMONG OLDER ADULTS RECEIVING CHEMOTHERAPY FOR AML

AUTHOR (N)	TREATMENT	TUMOR CHARACTERISTICS	CLINICAL VARIABLES	PATIENT CHARACTERISTICS	OUTCOMES
Predictive models derived from clinical trials					
Kantarjian et al. (2010) (*N* = 446)	Intensive	Complex karyotype	Creatinine > 1.3 mg/dL	Age > 80 ECOG PS > 1	8-wk mortality
Krug et al. (*N* = 1406)	Intensive	Secondary AML/ or prior hematologic disease Molecular/cytogenetic risk	Body temperature Hemoglobin Platelets LDH Fibrinogen	Age	60-d mortality CR
Rollig et al. (*N* = 909)	Intensive	Karyotype *NPM1* mutated CD34 expression > 10%	White cell count > 20/μL LDH > 700 U/L	Age > 65	Survival
Wheatley et al. (*N* = 2208)	Intensive	Cytogenetic risk group Secondary AML	White cell count	Age ECOG PS	Survival (1 y)
Geriatric assessment studies					
Deschler et al. (*N* = 107)	Nonintensive	Bone marrow blast % Cytogenetic risk group		Impaired ADLs KPS < 80 High fatigue score HCT-CI ≥ 3	Survival
Klepin et al. (2011) (*N* = 74)	Intensive	Cytogenetic risk group Prior MDS	Hemoglobin	Cognitive impairment (3MS < 77) Impaired physical performance (SPPB < 9)	Survival
Sherman et al. (*N* = 101)	Mixed	Adverse cytogenetics Secondary AML		HCT-CI > 1 Difficulty with strenuous activity Pain (more often vs less) ECOG PS > 1	Survival

3MS, modified Mini Mental Status Examination; ADLs, activities of daily living; CR, complete remission; ECOG, Eastern Cooperative Group; HCT-CI, hematopoietic cell transplantation–comorbidity index; LDH, lactate dehydrogenase; PS, performance status; SPPB, short physical performance battery.

Adapted from Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults.. J Clin Oncol. 2014;32(24):2541–2552.

Treatment decisions for older adults with AML should be individualized. Decisions should include risk stratification based on tumor biology and an estimate of physiologic reserve based on clinical characteristics such as comorbidity and functional status. Older adults with favorable cytogenetics and good functional status should be considered for aggressive curative treatment. Poor-risk patients based on tumor biology or clinical characteristics could be considered for novel treatments on clinical trials, lower-intensity therapies, or supportive care in an effort to maximize quality of life. Proposed treatment considerations based on risk stratification is presented in **Table 104-10**.

TABLE 104-10 ■ PROPOSED RISK STRATIFICATION AND TREATMENT CONSIDERATIONS FOR OLDER ADULTS WITH AML

PATIENT RISK CATEGORY	CHARACTERISTICS	TREATMENT CONSIDERATIONS (CLINICAL TRIALS PREFERRED)
Frail	Poor oncology performance status (ECOG PS score ≥ 3) Major comorbidity (ie, HCT-CI > 2) Impairment in ADLs	High treatment-related mortality (particularly for adults > 75 y). *Favorable tumor biology*[a]: Consider lower-intensity therapy (HMAs, low-dose ara-C). Patients with poor PS (particularly aged 60–75) but without end-stage comorbidity may consider intensive treatment if risks/benefits are consistent with goals of care. *Intermediate/unfavorable:* Consider best supportive care including palliative care consultation if available versus lower intensity therapy (HMAs, low-dose ara-C). *Clinical trials targeting frail patients are needed.*
Vulnerable	ECOG performance status score 0–2 Absence of major comorbidity (HCT-CI ≤ 2) Presence of: Impairment in IADLs Impaired physical performance (SPPB < 9) Impaired cognition (3MS score < 77) High symptom burden (fatigue, pain)	Outcomes for this subgroup are poorly defined in clinical trials. In nonrandomized studies, this group is at risk for shorter survival compared to fit patients. *Favorable tumor biology:* Consider intensive therapy. *Intermediate/unfavorable:* Consider intensive therapy if risks and benefits are consistent with goals of care versus lower-intensity therapies (HMAs, low-dose ara-C). Consider enhanced supportive care targeting vulnerabilities such as early physical therapy for impaired mobility. *Clinical trials are needed to validate definitions of vulnerability and to test treatment and supportive care strategies to improve outcomes in this group.*
Fit	ECOG performance status score 0–1 Minimal comorbidity (ie, HCT-CI < 1) Absence of any above-mentioned risk factors	Best evidence suggests fit older adults derive benefit from aggressive therapy. *Favorable tumor biology*: Intensive therapy should be offered. *Intermediate/unfavorable*: Consider intensive treatment with possible RIC allogeneic HSCT if risks/benefits consistent with goals of care versus lower-intensity therapies (HMAs, low-dose ara-C). *Future clinical trials should compare investigational therapies to standard intensive treatment among fit older adults.*

3MS, modified Mini Mental Status Examination; ADLs, activities of daily living; ara-C, cytarabine; ECOG, Eastern Cooperative Oncology Group; HCT-CI, hematopoietic cell transplantation–comorbidity index; HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplant; IADLs, instrumental activities of daily living; PS, performance status; RIC, reduced-intensity conditioning; SPPB, short physical performance battery; TRM, treatment-related mortality.

[a]Favorable tumor biology: inv(16), t(16;16), t(8;21), t(15;17); intermediate risk: normal cytogenetics, +8 alone, t(9;11), other nondefined: unfavorable: complex (≥ 3 clonal abnormalities), –5, 5q–, –7, 7q–, abnormalities of 11q, inv(3), t(3;3), t(6;9). In the normal cytogenetic category, NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation confers better risk versus presence of FLT3-ITD which confers worse risk.

Adapted from Klepin HD, Rao AV, Pardee TS. Acute myeloid leukemia and myelodysplastic syndromes in older adults. J Clin Oncol. 2014;32(24):2541–2552.

Acute Lymphoblastic Leukemia

ALL is primarily a disease of children, but in adults, age-adjusted incidence increases in older adults. There are approximately 6250 new cases of adult ALL in the United States annually. With available therapy today, childhood ALL is curable in the majority of patients. ALL in adults is not the same as the childhood disease. First, the frequency of complete response is lower—70% to 75% in adults as opposed to more than 90% in children. Second, the remission duration and curability using the same therapy is considerably less. Important prognostic features for outcome in the treatment of ALL include age, cytogenetics, and immunophenotype. Poor prognosis is especially associated with the presence of chromosomal translocations such as Ph chromosome t(9;22), t(4,11), t(8;14), t(2;8), or t(8;22), and with a phenotype indicating mixed lymphoid-myeloid leukemia (also called biphenotypic leukemia).

The initial goal of therapy for adult ALL is to correct problems secondary to bone marrow failure; that is, to treat anemia with blood transfusions, treat documented or suspected infection, and control bleeding. Specific antileukemia treatment is then directed toward the achievement of a CR. Induction chemotherapy for ALL, very different from that for AML, usually includes the use of prednisone, vincristine, daunorubicin, and asparaginase. While these drugs are well-tolerated in children, increasing age is associated with poorer drug tolerance. Mortality, usually from infection and/or bleeding during the induction process, may occur in 10% to 20% of older adult patients.

In contrast to the treatment of AML, it is widely accepted that patients with ALL require therapy postremission. These phases of treatment once the patient is in CR have been referred to as intensification therapy and maintenance therapy. The optimal therapy after remission and the duration of such therapy in older patients are not clearly defined. Most programs use multiple drugs administered in a cyclic fashion over a 2-year period; the more intensive therapy is given over about 6 months after CR is achieved (intensification or consolidation), followed by a less-intensive outpatient maintenance regimen for approximately 18 months.

Directed treatment to the craniospinal axis (CNS prophylaxis) is standard practice in the treatment of childhood ALL. While the incidence of CNS leukemia is lower in adults than in children, treatment to the CNS is also part of ALL therapy in adults. This usually consists of intrathecal methotrexate in conjunction with high-dose systemic therapy such as high-dose methotrexate and ara-C, or cranial radiation.

With the above intensive treatment plan, the median duration of remission is approximately 2 years, with 35% to 45% of adult patients disease free at 5 years; however, prognosis is poorer for older adults. One contributing feature to this poorer response duration in adults as opposed to children is the inability to deliver optimal chemotherapy at maximal doses caused by comorbid diseases and increased susceptibility to toxicity.

Therapy for patients with Philadelphia chromosome–positive ALL also includes the addition of a BCR-ABL tyrosine kinase inhibitor such as imatinib or dasatinib. Addition of imatinib to standard chemotherapy increases rates of complete remission compared to historical controls with minimal increase in toxicity. For older adults with significant comorbidity or poor functional status, treatment with a tyrosine kinase inhibitor and steroids alone may offer an option for remission without the additional toxicity of cytotoxic chemotherapy.

Chronic Lymphocytic Leukemia

CLL is the most common leukemia in the Western Hemisphere and may be commonly encountered in a geriatric practice. CLL is a disorder of clonal proliferation of mature lymphoid cells in the peripheral blood, bone marrow, and lymphoid organs. CLL occurs predominantly in older adults, with median age at diagnosis of approximately 70. About 14,620 new cases were estimated in the United States for 2015 by the American Cancer Society. This may be an underestimate because many patients are asymptomatic for years. There is no racial difference in the United States between blacks and whites, and a slight male predominance. Current diagnostic studies, especially immunophenotyping, allow for differentiation of the chronic lymphoid malignancies: B-cell CLL, T-cell CLL, prolymphocytic, circulating non-Hodgkin lymphomas, and hairy cell leukemia.

B-cell CLL B-cell CLL accounts for over 95% of all CLL. Approximately 25% of such patients are identified with asymptomatic lymphocytosis during evaluation for other medical problems. Symptomatic patients may present with weight loss, fatigue, recurrent infections, fevers, or pain associated with hepatosplenomegaly or bulky lymphadenopathy. In most patients, the disease has a gradual progression spanning several years and the extent of the lymphoid burden at diagnosis correlates well with length of preexisting disease. In some patients, the disease has a more aggressive course and progression to advanced clinical stages may occur within a few months of diagnosis. Identification of molecular and protein markers are beginning to explain the heterogenous natural history observed in this disease.

The diagnosis of CLL requires presence of monoclonal B lymphocytes greater than or equal to 5×10^9/L with a specific immunophenotyping pattern (coexpression of CD5 and CD20/23 with weak expression of surface immunoglobulin) by flow cytometry. Diagnosis and staging of CLL can usually be established by history, physical examination (careful evaluation for lymphadenopathy and splenomegaly), CBC with review of the blood smear, and immunophenotyping of the peripheral blood using flow cytometry. Classic findings on the peripheral smear include increased mature-appearing lymphocytes and smudge cells (peripheral smear artifact reflecting the fragility of the B-CLL cells to mechanical manipulation). Bone marrow studies are usually not needed for diagnosis.

The differential diagnosis for B-CLL includes other mature B-lymphoproliferative disorders such as mantle cell lymphoma, prolymphocytic leukemia, hairy cell leukemia, and splenic lymphoma with villous lymphocytes. The clinical course and treatments differ widely for these disorders, particularly mantle cell lymphoma. Evaluation of

clinical presentation, morphology, and immunophenotype are necessary to arrive at the correct diagnosis (**Table 104-11**). Inclusion of flow cytometric evaluation for cyclin D1 or fluorescent in situ hybridization (FISH) analysis for t(11:14) is essential to rule out mantle cell lymphoma.

TABLE 104-11 IMMUNOPHENOTYPE OF MATURE B-CELL NEOPLASMS

DIAGNOSIS	SIG[a]	CD5	CD10	CD23	CD43	CD103
B-CLL	+/–	+	–	+	+	–
Mantle cell lymphoma	+	+	–	–	+	–
B-cell prolymphocytic leukemia	++	+/–	–	–	–	–
Splenic marginal zone lymphoma	+	–	–	–	–	–
Hairy cell leukemia	+	–	–	–	–	++

[a]SIG, surface immunoglobulin.

The original Rai classification (**Table 104-12**) implied an orderly progression from lymphocytosis alone to the successive development of adenopathy, organomegaly, and, eventually, anemia and thrombocytopenia. The prognostic importance of these variables has been confirmed although survival patterns differ primarily by the low-, intermediate-, and high-risk categories. Specific cytogenetic abnormalities correlate with prognosis. A 13q deletion is associated with a better prognosis, compared to deletions of 11q and 17p, which confer a worse prognosis.

TABLE 104-12 CLL RAI CLINICAL CLASSIFICATION

STAGE	RISK[a]	CLINICAL FINDINGS
0	Low	Lymphocytosis only
1	Intermediate	↑ Lymphs plus ↑ nodes
2	Intermediate	↑ Lymphs plus ↑ spleen and/or liver ± ↑ Nodes
3	High	↑ Lymphs plus ↓ Hgb (< 11 g/dL) ± ↑ Nodes, ↑ liver, ↑ spleen
4	High	↑ Lymphs plus ↓ platelets (< 100, 000/μL) ± ↑ Nodes, ↑ liver, ↑ spleen, ↓ Hgb

Hgb, hemoglobin.
[a]Data from Rai classification.

Therapy for B-cell CLL has been considered palliative and therefore has been reserved for patients who are symptomatic or who progress to develop cytopenias (Rai stages 3 or 4). The mainstays of therapy for many years were oral alkylating agents (chlorambucil or cyclophosphamide) for control of lymphoid proliferation and steroids for autoimmune complications. Leukocytosis alone (stage 0) does not require therapy, because the prognosis of these patients is excellent in the absence of the other poor prognostic factors. The rate of increase of leukocytosis is a better indicator of disease activity than the absolute count. Leukostasis, associated with high circulating blast counts in acute leukemias, does not generally occur in this condition because most of the lymphocytes are mature, small cells.

Treatment with chemotherapy or local radiation can be used to control symptoms in patients with stage I or II disease; however, symptomatic improvement does not appear to prolong survival. In contrast, when treated with combination chemotherapy, patients with stage III or IV CLL have an improved median survival, which ranges from 1.5 years to more than 4 years.

Treatment options for older adults have expanded significantly in the past several years. Regimens including use of nucleoside analogs (eg, fludarabine) have shown improved response rates and a survival benefit which may be extrapolated to fit older adults with minimal comorbidity. For many older adults, however, especially those with comorbidity or functional impairments, use of fludarabine-based regimens may result in significant toxicity. A randomized trial of older adults greater than 65 years comparing fludarabine to oral chlorambucil showed no difference

in progression-free or overall survival despite an improved response rate with fludarabine. Another option for older adults is use of chemoimmunotherapy. Rituximab (an anti-CD20 antibody) alone or in combination with chlorambucil has shown efficacy among older adults without significant increased toxicity. A randomized trial is underway testing the benefit of adding rituximab to chlorambucil for older adults. A phase 3 randomized trial compared the efficacy of adding obinutuzumab (a humanized glycoengineered type 2 antibody to CD20) to chlorambucil versus rituximab specifically in patients with comorbidity. This study population was designed to better reflect those seen in practice with median age 73 and required a meaningful comorbidity burden (cumulative illness rating scale > 6) for eligibility. The median progression-free survival was improved from 11.1 months to 26.7 months when comparing the anti-CD20 combination therapy arms with chlorambucil alone. Treatment with the obinutuzumab combination resulted in improved overall survival compared to chemotherapy alone and was superior to Rituxan combination therapy for progression-free survival and response. This study was a landmark trial by both demonstrating efficacy of a novel therapeutic combination but also doing so in an older patient population with comorbidity. Several additional treatment options are available for older adults in practice with additional agents under investigation that may be considered in an effort to control symptoms of disease and maintain quality of life and independence.

Autoimmune manifestations of CLL are common and include development of antibodies to platelets and red cells (IgG and C3 on direct antiglobulin test) and to erythroid precursors, resulting in red cell aplasia. For anemic patients, reticulocyte counts and direct Coombs testing should be obtained to help differentiate hemolysis from decreased bone marrow production. All of the autoimmune complications are indications for therapy with steroids or intravenous gamma globulin for refractory cases of red cell aplasia.

Recurrent infections are the most common complications leading to death in CLL. Patients with stage 0 CLL have minimal increased risk of infection. In anticipation of gradual deterioration in immune response, however, pneumococcal vaccine and boosters should be administered while the potential for response is still intact. All other patients have higher risks for infection. As the disease advances clinically, immune function becomes progressively compromised, with increased susceptibility to viral, bacterial, and fungal infection. Patients should avoid direct contact with the body fluids of children who have received live virus vaccines (oral polio, measles-mumps-rubella) for the duration of viral shedding. The subset of patients presenting with recurrent bacterial infections may benefit from administration of intravenous gamma globulin.

B-cell prolymphocytic leukemia This rare subtype of lymphoid leukemia is characterized by marked lymphocytosis (often > 100,000 lymphocytes/μL), extensive bone marrow infiltration, massive splenomegaly, and minimal-to-absent adenopathy. Prolymphocytes comprise the majority of circulating WBC (> 55%; often > 90%). The prolymphocyte is about twice the size of a normal lymphocyte, with a characteristic dense border outlining a prominent nucleolus. B-cell prolymphocytic leukemia (B-PLL) cells usually express CD19, CD20, CD22, CD79a, FMC7, and strong surface IgM; CD23 is usually negative.

Most patients with B-PLL have advanced clinical disease at presentation, with a prognosis similar to that of patients with stage III and IV B-cell CLL. Therapy for these patients has included multiagent chemotherapy to control the splenomegaly and leukocytosis, and radiation therapy to palliate splenic engorgement. Patients become increasingly refractory to therapy, with an expected survival of 1.5 years and death caused by uncontrolled disease. Incorporation of alemtuzumab (anti-CD52 antibody) is suggested for patients with *TP53* deletions or mutations which are resistant to purine analog-/alkylator-based therapy.

T-cell prolymphocytic leukemia T-cell PLL is a rare T-cell neoplasm composed of lymphoid cells which typically involve the peripheral blood, bone marrow, lymph nodes, and spleen. Clinical manifestations include lymphocytosis, hepatosplenomegaly, generalized lymphadenopathy, skin infiltration (20%), and bone marrow involvement. Immunophenotyping in the peripheral blood shows a clonal proliferation of the malignant T cells—CD2, CD3, CD7 positive with weak CD3; in approximately 60% of patients, the cells are CD4+/CD8–, 25% are CD4+/CD8+, and 15% are CD4–/CD8+. Therapy is reserved for symptomatic patients; treatment goals are palliative with available therapies. Prognosis is generally poor, with limited responsiveness to therapy. Alemtuzumab, if available, has been the initial treatment of choice for most patients.

Hairy cell leukemia Hairy cell leukemia is rare and almost exclusively seen in men older than age 60. The clinical features include massive splenomegaly, absence of adenopathy, and peripheral pancytopenia. The diagnosis is made by the morphologic characteristics of the circulating lymphocytes, which are small and have cytoplasmic projections (“hairs”). Diagnosis, previously made histochemically with the tartrate-resistant acid phosphatase (TRAP) stain, is now made with immunophenotyping that shows positive sIgM, CD19, CD20, CD22, CD79a, CD11c, CD25, and CD103;

negative CD5, CD10, and CD23. Bone marrow aspiration usually yields little material (dry tap) and bone marrow biopsy shows increased cellularity with diffuse infiltration by the hairy cells. The spleen is infiltrated with the same clone of cells. Infections with gram-negative and staphylococcal species are the predominant complication.

This is a highly treatable disease even for older adults with comorbidity or impaired functional status. Historically, splenectomy was the treatment of choice with improvement of neutropenia in about 50% of patients for 8 to 10 years. Interferon (IFN)-α was also used and produced partial and CRs in more than 50% of patients, sparing many patients a surgical procedure and the effects of the splenectomy on the immune system. Interferon has now been replaced by the nucleoside analogs, especially cladribine (2-CdA), which is very well tolerated. This 5-day treatment yields high durable remission rates, frequently after only one course of therapy.

T-Cell Large Granular Lymphocytic Leukemia

T-cell large granular lymphocytic (T-LGL) leukemia is a rare clonal disorder of cytotoxic T lymphocytes, which typically presents with chronic neutropenia. T-LGL leukemia represents approximately 4% of lymphoproliferative disorders. Patients tend to be older, with a median age of 60. Many patients are asymptomatic and will have chronic neutropenia, mild lymphocytosis with or without anemia. Symptoms are typically related to recurrent infections particularly of the skin, oropharynx, and perirectal regions. Splenomegaly is common but lymphadenopathy is uncharacteristic. The peripheral blood demonstrates a proliferation of large granular lymphocytes. These can also be seen in reactive disorders such as viral infections. The diagnosis depends on establishing a clonal T-cell receptor gene rearrangement within the population of large granular lymphocytes using polymerase chain reaction (PCR) or flow cytometry techniques on the peripheral blood. The diagnosis is supported by the characteristic immunophenotype of CD3+, CD8+, CD16+, and CD57+. T-LGL leukemia is a relatively indolent disease with median survival of more than 10 years. Indications for treatment include severe neutropenia (ANC < 500), recurrent infections, and transfusion-dependent anemia. Treatment involves immunosuppression with agents such as methotrexate, cyclosporine, or steroids.

Chronic Myelogenous Leukemia

CML is a myeloproliferative disorder characterized by excess production of mature granulocytes that eventually progresses to a clinical picture similar to acute leukemia with an overgrowth of immature cells (blast crisis). CML is associated with the fusion of two genes: *BCR* (on chromosome 22) and *ALB1* (on chromosome 9). It accounts for a little over 10% of all leukemias according to the American Cancer Society, with 1 in approximately 555 persons getting the disease in their lifetime. The incidence increases with age and the average age at diagnosis is approximately 65.

Diagnosis is suspected by the demonstration of granulocytosis in the peripheral blood with a predominance of segmented neutrophils and myelocytes, increased basophils and eosinophils, and increased bone marrow cellularity. The presence of the Philadelphia chromosome t(9;22) and/or its products (*BCR/ABL* fusion mRNA, Bcr/Abl protein) are required to confirm the diagnosis. Diagnosis can be made on peripheral blood using PCR or FISH techniques. Bone marrow biopsy is still required for complete cytogenetic evaluation.

The disease characteristically proceeds through three phases: chronic (present in ~ 85% at diagnosis), accelerated, and terminal (blastic) phase (**Table 104-13**). The length of the chronic phase is highly variable. In the chronic phase, the disease is easily controlled without aggressive therapy. Many patients are asymptomatic (diagnosis prompted by leukocytosis), common symptoms include fatigue, weight loss, and abdominal fullness or pain related to splenomegaly. The accelerated phase begins with gradual increases in white cells, platelets, and spleen size. Initially good maturation persists, but eventually more blasts are seen in the peripheral blood. The terminal phase of the disease is indistinguishable from acute leukemia. The blasts have myeloid surface markers in 85% of the patients and lymphoid markers in the remaining 15%.

TABLE 104-13 CML CLASSIFICATION

CHRONIC PHASE	ACCELERATED PHASE	BLAST PHASE
< 10% blasts	Any of the following: 10%–19% blasts Thrombocytopenia < 100,000/cmm Thrombocytosis > 1,000,000 unresponsive to	Any of the following: ≥ 20% blasts Extramedullary blasts or large foci/clusters of blasts in the bone marrow

	therapy Peripheral basophilia > 20% Appearance of additional cytogenetic abnormality Increasing spleen size or progressive leukocytosis on therapy	

Treatment for CML has changed dramatically in the past decades, altering the natural history of this disease. IFN-α was the first drug to change the natural history of CML, decreasing the percentage of cells exhibiting the Ph chromosome and prolonging the chronic phase by 1 to 2 years. Imatinib mesylate (Gleevec; STI-571), a targeted tyrosine kinase inhibitor (TKI), designed specifically for the treatment of CML (in oral formulation), proved to have significant activity in the blast phase and accelerated phase of CML. In chronic phase CML, imatinib mesylate yielded marked improvements in clinical and cytogenetic responses, rates of disease progression, and treatment-related toxicity compared to IFN-α plus low-dose ara-C in a randomized clinical trial. Based on these results, imatinib mesylate replaced interferon regimens as the standard of care for patients with chronic phase CML. Imatinib is very well tolerated, which is particularly relevant for the older adult population. Many patients who would not have been good candidates for cytotoxic therapy or interferon can be effectively treated with imatinib. Responses are durable with many patients maintaining response now after well over a decade of therapy. More potent, second-generation, tyrosine kinase inhibitors (ie, dasatinib and nilotinib) have been tested and have been shown to produce more rapid and better responses than imatinib in first-line treatment. These drugs are also active in patients who have progressed on imatinib providing sequential treatment options prior to consideration of cytotoxic therapy.

Allogeneic stem cell transplantation in the chronic phase remains a consideration for curative treatment for younger patients, primarily those with suboptimal response to TKIs. It has a limited role in older patients because of the morbidity and mortality of this treatment and availability of therapies to control disease. TKIs should be the initial treatment for both the accelerated and blastic phases of CML if not already used during the chronic phase of the disease. Treatment of the blastic transformation (after TKI therapy) depends on the cell origin of the blasts. Myeloid blastic states respond poorly to standard AML therapies, and no standard therapy is available. Lymphoid blastic states can be controlled for 6 to 12 months, with standard combination regimens as used for de novo ALL.

Myeloproliferative Diseases

Myeloproliferative diseases include CML (described earlier), polycythemia vera, myelofibrosis, and essential thrombocytosis. Both polycythemia vera and myelofibrosis can be associated with increased WBC. Polycythemia vera is usually associated with mild increases in white count with a relatively normal differential, while myelofibrosis is frequently associated with immature WBCs in addition to nucleated RBCs. The leukocytosis associated with polycythemia vera is usually of little consequence and treatment is directed toward the control of the increased red cells. Myelofibrosis can be associated with variable abnormalities in WBC numbers, either increased WBC with circulating immature precursors or decreased WBCs, especially in the presence of massive splenomegaly.

Cancers Metastatic to Bone Marrow

Many of the common malignancies have a propensity for metastasis to the bone and bone marrow. These include carcinomas of the breast, lung, and prostate and the lymphomas. Space-occupying lesions in the bone marrow, which crowd out normal hematopoietic elements, are termed myelophthisis. Manifestations of myelophthisis in the peripheral blood include pancytopenia and leukoerythroblastosis. Pancytopenias may be aggravated by nutritional deficiencies, especially folate deficiency.

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Chapter 105

Non-Hodgkin and Hodgkin Lymphomas

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Learning Objectives

- The majority of lymphomas occur in older adults.
- Modern classification systems for lymphomas are evolving rapidly and incorporate immunophenotyping and genetics.
- Comorbidity and frailty are strong modifiers of prognosis and must be incorporated into treatment planning.
- Immunotherapies play an increasing role in treatment of some lymphomas; consider life expectancy when planning treatment.

NON-HODGKIN AND HODGKIN LYMPHOMA: INTRODUCTION

The intimate interplay between the aging process and the development of malignancy in many ways ensures that cancer is a disease of older individuals and the lymphoid malignancies are no exception. The lymphoid malignancies comprise over 60 heterogeneous and complex entities as identified in the World Health Organization (WHO) classification 2008. The median age at diagnosis of representative entities such as diffuse large B-cell lymphoma (DLBCL), multiple myeloma (MM), and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) are 64, 71, and 72 years, respectively. Consequently, the care of this patient population frequently requires the care of the older patient. In this chapter we focus on Non-Hodgkin lymphomas (NHLs) and Hodgkin lymphomas (HLs); acute leukemia and CLL/SLL are addressed in Chapter 104.

NHLs are the most common lymphoid malignancy, representing a heterogeneous group of lymphoproliferative disorders that originate from cells of the immune system, including B lymphocytes, T lymphocytes, or natural killer (NK) cells. In the United States, the B-cell lymphomas predominate, making up 80% to 85% of lymphoma diagnoses, with T-cell histologies representing 15% to 20% of the balance; NK-cell lymphomas are rare at less than 1%.

The spectrum of clinical presentations for lymphoma can be quite protean, dependent on the type of lymphoma, the disease subtype, each with variable disease courses, and the presence of nodal or extranodal involvement. Broadly speaking, lymphomas can be characterized as either indolent behaving with median survivals measured in decades or aggressive behaving, with life-threatening consequences in a matter of weeks or months if left untreated.

Indolent lymphomas are more often identified incidentally during routine physical examination or laboratory evaluation, particularly with increased reliance on routine blood testing and imaging in the modern era. Often, these entities present with slowly progressive lymphadenopathy, splenomegaly, and potential cytopenias from bone marrow involvement. Examples include the prototypic follicular lymphoma (FL), marginal zone lymphomas, and CLL/SLL.

In contrast, aggressive lymphomas are more likely to present with acute or subacute symptoms including a rapidly growing mass, systemic B symptoms (fevers, night sweats, weight loss), elevated serum lactate dehydrogenase, hypercalcemia, and hyperuricemia. Examples include DLBCL, peripheral T-cell lymphomas (PTCL), and Burkitt lymphoma (BL).

Clinical characteristics of NHLs include “B” symptoms, defined as fever greater than 38°C, unexplained weight loss greater than 10% of body weight over the past 6 months, and drenching night sweats. Up to 40% of patients with NHL may have B symptoms; more commonly evident in aggressive or biologically transformed disease (approaching 50%) than in low-grade lymphomas (< 25%). Less common presenting features can include skin rash, pruritus, fatigue, fever of unknown origin, effusions, and hypersensitivity to insect bites. Extranodal presentations occur in 10% to 35% of patients at initial diagnosis, with extranodal sites developing in approximately 50% of patients over the course of

their disease. As lymphocytes naturally transit through blood and can be found in any tissue compartment, lymphomas have been reported in essentially all conceivable sites. Gastrointestinal involvement can be associated with anorexia, weight loss, nausea and vomiting, early satiety, abdominal pain, obstruction, and, rarely, perforation. The central nervous system can be involved primarily or secondarily, presenting with headache, lethargy, focal neurologic symptoms, seizures, paralysis, cranial neuropathies, and lymphomatous meningitis. Monoclonal serum proteins (M spike) can be associated with some lymphoma entities, more commonly marginal zone lymphomas, lymphoplasmacytic lymphomas, and Waldenström macroglobulinemia. Paraneoplastic phenomenon can also rarely be present and, at times, precede the diagnosis of lymphoma. Examples include hemolytic anemia, cryoglobulinemia, and idiopathic thrombocytopenia.

EPIDEMIOLOGY

Based on the American Cancer Society data, in 2016, an estimated 81,080 individuals will be diagnosed with lymphoma in the United States, 72,580 NHL and 8,500 HL with 212270 individuals dying from a lymphoid malignancy (predominately NHLs, 20,150). To put this in perspective, NHL and HL together account for 5% and 4% of all new cancer diagnoses and 4% and 3% of all cancer deaths, in men and women, respectively.

Age-Related Incidence in the United States

From 2007 to 2011, incidence rates for HL were stable in both men and women, while rates for NHL slightly increased among men (0.3% per year) and were stable among women. Death rates for HL, however, have been decreasing for the past four decades; from 2007 to 2011, rates decreased by 2.2% per year among men and by 2.7% per year among women. Death rates for NHL began decreasing in the late 1990s with the advent of monoclonal antibody treatments, particularly rituximab, a chimeric anti-CD20 monoclonal antibody; from 2007 to 2011, rates decreased by 1.8% per year among men and by 2.9% per year among women. Declines in lymphoma death rates have reflected improvements in both supportive care and treatments over the decades.

The incidence of NHL in the United States had been increasing significantly from 1970 to 1995 with a slowing of the rise from the mid-1990s onward. Although a proportion of this increase is attributable to the human immunodeficiency virus (HIV) epidemic and the consequent increase in AIDS-related NHL, this does not account for the full picture. Rather, much of the increase in incidence is a likely consequence of the aging of the population, with the greatest increases noted in patients in their sixth and seventh decades. Increases in life-expectancy, baby-boomers entering late life, and decreases in mortality from other causes are all implicated. Attendant with this change in demographics, the United States is projected to witness increases in incidence of NHL by 67% and HL by 70% in older adults by the year 2030. This fact is evidenced as well by the increasing median age of individuals with NHL over the last two decades. Consequently, the interplay between aging biology, comorbidity and competing risks is ever more prevalent for the treating oncologist.

NHL CLASSIFICATION SYSTEM—WORLD HEALTH ORGANIZATION 2008

Increased Biological Basis

Historically, lymphoma classifications were based on the morphologic patterns of cell growth, including size and shape of tumor cells (Rappaport classification, 1956). However, with the discovery of distinct types of lymphocytes (B, T, and NK), this classification was replaced by the Kiel classification, dividing lymphomas into low and high grades on the basis of histologic features. These evolving concepts were further refined and unified in the International Working Formulation (IWF), which created three useful major categories of low, intermediate and high grade lymphomas, relying on both morphology and clinical behavior. Lack of reproducibility and of immunophenotyping hampered the IWF system.

Although lymphoma classification has remained a complicated endeavor, since the advent of the Revised European American Classification (REAL) classification in 1994 and the subsequent update by the World Health Organization (WHO) classification in 2001, lymphoma diagnosis has increasingly integrated cell of origin (B, T, NK), morphology, immunophenotype, genetic and clinical features to define disease. The REAL classification cohort comprised 1403 cases of NHL, identifying the 13 most common histologic subtypes in 90% of the cases in the United States. These

included DLBCL, 31%; follicular lymphoma (FL), 22%; SLL/CLL, 6%; mantle cell lymphoma (MCL), 6%; peripheral T-cell lymphoma (PTCL), 6%; and mucosa-associated lymphoid tissue (MALT) lymphoma, 5%. Notably, in the United States over 50% of cases are classified as either DLBCL or FL, two entities that are paradigmatic in many ways of treatment approaches for the aggressive and indolent lymphomas, respectively.

Importantly, in 2008 the WHO classification (**Table 105-1**) has undergone further refinements, with new updates and the International T-cell lymphoma Project's examination of 1314 cases of PTCL or NK/T-cell lymphomas lending greater clarity and complexity to these diagnoses. NK/T-cell lymphomas comprise 15% to 20% of all NHL diagnosis, with the most common subtypes being: PTCL not otherwise specified (NOS; 25.9%), angioimmunoblastic lymphoma (AILD; 18.5%), anaplastic large cell lymphoma (ALCL; 12.1%; ALK-positive 6.6% and ALK negative 5.5%), NKTCL (10.4%), and adult T-cell leukemia/lymphoma (ATLL; 9.6%). Furthermore, the 2008 updates more broadly integrated new diseases and subtypes identified in the past, affirmed the importance of detecting viral entities in some diagnoses (eg, EBV, HHV8, and HTLV1), as well as increased the use of genetic features in diagnosis, such as cytogenetics and fluorescent in situ hybridization (FISH) in defining specific NHL entities.

TABLE 105-1 2008 WORLD HEALTH ORGANIZATION (WHO) CLASSIFICATION

WHO Classification
Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma[*]
Hairy cell leukemia-variant[*]
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Heavy chain diseases
α Heavy chain disease
γ Heavy chain disease
μ Heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma (MZL)
Pediatric-type nodal MZL
Follicular lymphoma
Pediatric type follicular lymphoma
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
T-cell/histiocyte-rich large B-cell lymphoma
DLBCL associated with chronic inflammation
Epstein-Barr virus (EBV)$^{+}$ *DLBCL of older adults*
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type

ALK$^+$ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classic Hodgkin lymphoma
Hodgkin Lymphoma
Nodular lymphocyte-predominant Hodgkin lymphoma
Classic Hodgkin lymphoma
Nodular sclerosis classic Hodgkin lymphoma
Lymphocyte-rich classic Hodgkin lymphoma
Mixed cellularity classic Hodgkin lymphoma
Lymphocyte-depleted classic Hodgkin lymphoma

*Provisional entities for which there was thought to be insufficient evidence to classify as distinct entities.

ETIOLOGY OF NHL

For the majority of lymphomas, despite an increasing understanding of biology, the cause remains unknown. Stochastic mutational events inherent in the normal cell division process of lymphocytes are expected to result in a continuous random event rate. Epidemiologic studies have indicated increased incidences associated with a personal family history of lymphoma, past radiation or chemotherapy treatment, immunosuppressive agents, smoking, and obesity. Environmental exposures to agricultural pesticides accounted for an increased incidence of lymphoma in central United States, hair dyes (prior to the 1980s), agent orange and other dioxins. Dysregulation of the immune system may precede a lymphoma diagnosis, with increased risk associated with autoimmune diseases (eg, rheumatoid arthritis, lupus, Sjögren syndrome, Hashimoto thyroiditis), solid organ transplantation, and celiac sprue. A number of infections have also been implicated in the pathogenesis of lymphomas, either as a consequence of immune dysregulation or chronic antigenic drive. Associations clearly exist with human immunodeficiency virus (HIV), human T lymphoma atrophic virus type I (HTLV-I), Epstein-Barr virus (EBV), hepatitis C, hepatitis B virus, *Helicobacter pylori*, and human herpesvirus 8 (HHV8).

EBV in Lymphoma and Older Adults

In the most recent WHO classification iteration of 2008, a provisional entity termed EBV (+) DLBCL of older adults was defined, consisting of an EBV-positive monoclonal large B-cell proliferation in patients older than 50 years, median age approximately 70 years, with no known history of immunodeficiency. Most patients have an ABC phenotype, strong NF-κβ activation, increased extranodal distribution at diagnosis, and inferior survival. Optimal treatment strategies are not defined.

EBV has also been implicated in the pathogenesis and outcome of HL, with a negative impact on outcome in advanced age as distinct from younger patients. Nasal NK/T-cell NHL, primary CNS lymphoma, and EBV-associated PTLD.

Genetic Factors—Translocations

NHLs are frequently characterized by balanced translocations, resulting in functional fusions that confer a survival advantage for the affected cell population (**Table 105-2**). Such translocations often involve the immunoglobulin heavy chain region on chromosome 14, leading to constitutive activation of the translocated partner and consequently to increased signaling for the translocated gene, such as the antiapoptotic pathways (*BCL2*), cell cycle proteins (*CCND1*), and cellular proliferation (*cMYC*).

TABLE 105-2 LYMPHOMAS WITH KNOWN TRANSLOCATIONS

LYMPHOMA HISTOLOGY	COMMON TRANSLOCATION	GENE PARTNERS
Mucosa-associated lymphoid tissue lymphoma	T(11;18)(q21;q21)	*AP12/MALT, BCL-10*
Mantle cell lymphoma	T(11;14)(q13;q32)	*BCL-1, IgH*
Follicular lymphoma	T(14;18)(q32;q21)	*BCL-2, IgH*
Diffuse large-cell lymphoma	T(3;-)(q27;-) T(17;-)(p13-) T(14;18))(q32;q21) T(8;14)(q24;q32)	*BCL-6* *P53* *BCL-2* *C-MYC*
Burkitt lymphoma	T(8;14)(q24;32) T(8;22)	*C-MYC, IGH*
Anaplastic large-cell lymphoma	T(2;5)(p23;q35)	*ALK*
Lymphoplasmacytoid lymphoma	(9;14)(p13; q32)	*PAX5, IgH*

EVALUATION AND STAGING

Evaluation of a patient with suspected lymphoma includes a careful history and physical examination, with close attention to lymphatic sites including Waldeyer ring and the spleen. Extranodal sites of involvement to consider on examination include the skin, central nervous system abnormalities, testes, breasts, and bone. Standard blood work includes a CBC, comprehensive panel, calcium, uric acid, lactate dehydrogenase (LDH), serum protein electrophoresis, β_2 microglobulin (indolent lymphomas), serologic testing for HIV, and hepatitis B and C.

A biopsy is required for diagnosis and classification of NHL and HL. Generally, an excisional or incisional lymph node biopsy is preferred given the requirements for increasingly complex pathologic diagnostic evaluations. These regularly include need for adequate morphologic assessment, immunohistochemical (IHC) staining, flow cytometry, FISH testing, cytogenetics, polymerase chain reaction (PCR) studies for clonality (immunoglobulin gene rearrangement studies for B-cell clonality, T-cell receptor gene rearrangements for T-cell lymphomas), and increasingly gene expression profiling (GEP). Fine-needle aspiration is often helpful as an initial discriminator between reactive adenopathy, carcinoma, and lymphoma. However, more definitive biopsy is generally required, particularly for an initial diagnostic procedure. Core biopsy can occasionally render sufficient material when excisional biopsy is not feasible. The site of biopsy should be determined based on integration of available information such as safety of the procedure, likely diagnostic yield, and representative sampling. Functional imaging (eg, positron emission tomography [PET] scan) is often beneficial at directing the site of biopsy when discordant fluorodeoxyglucose (FDG) avidity is present, with the most metabolically active lesions generally representing the most aggressive biology.

Ann Arbor Staging System

Originally developed in 1974 for HL, the Ann Arbor staging system was the equivalent of the TNM (tumor-lymph node-metastasis) staging system for lymphoid malignancies. This staging system defines disease location and extent and prognostic information, permitting cross-study comparisons, and establishes baseline disease extent to allow for response comparison. Modified in 1988, the Cotswold classification formally included CT scans and designations for bulky disease (X), dividing HL patients in four stages, with A and B subclassifications based on the absence or presence of B symptoms. Universally accepted response criteria in NHL and HL were published in 1999 by the NCI Working Group and revised in 2007 by the International Working Group (IWG) to incorporate PET and bone marrow immunohistochemistry (IHC)/flow in response assessment. This has formed the foundation for staging and response evaluations for NHL and HL over the last decades, acknowledging certain histologies have warranted their own staging and response assessment given varied clinical course (eg, CLL/SLL, Waldenström macroglobulinemia, cutaneous T-cell lymphoma).

Of note, in contrast to many solid tumors, it is important to realize stage alone is often a poor arbiter of outcome in NHL. Clinical and biologic prognostic models, generally including stage as one of the risk factors, are better predictors of outcome. For instance, it is instructive that a substantial number of DLBCL patients with advanced-stage III/IV disease will be cured, and for indolent lymphoma patients, stage IV disease is the norm, but survival is measured in decades.

Updated Lugano Classification 2015

A workshop held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland in June 2011 sought to modernize recommendations for evaluation, staging, and response assessment for patients with HL and NHL. Comprising leading international hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, this effort led to a revision of the IWG guidelines of 2007 as the published Lugano classification in 2014 (**Table 105-3**). The most salient changes included formal integration of PET scanning into initial staging for FDG-avid lymphomas, modification of the Ann Arbor terminology eliminating A/B qualifiers except for HL, and departure from routine bone marrow biopsy in DLBCL and HL based on functional imaging. FDG-PET utilizing the Deauville 5-point scale was integrated into response assessment.

TABLE 105-3 REVISED STAGING SYSTEM FOR PRIMARY NODAL LYMPHOMAS

	STAGE	SITES	EXTRANODAL (E) STATUS
Limited stage	I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
	II[a]	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Advanced stage	III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
	IV	Additional noncontiguous extralymphatic involvement	Not applicable

Extent of disease determined by PET/CT for FDG-avid lymphomas and CT for nonavid lymphomas. Tonsils, Waldeyer ring, and spleen are considered nodal sites. Bulky disease is defined as 10 cm or greater on CT or greater than 1/3 transthoracic diameter at any level of thoracic vertebrae.

[a] Stage II bulky disease is considered limited or advanced based on histology and prognostic factors.

Bone Marrow Biopsy—Relevance to Staging, DLBCL/Hodgkin Versus Indolent NHL

Bone marrow aspirate and biopsy has historically been recommended as part of staging for both NHL and HL. Bone marrow involvement occurs in 30% to 50% of patients with NHL and is more frequent with indolent histologies. The Lugano revision of the staging criteria has suggested that bone marrow biopsy may not be necessary in DLBCL or HL if functional imaging fails to identify osseous lesions. One must acknowledge, however, that bone marrow involvement with indolent lymphoma is generally not evident on FDG-PET. A bone marrow biopsy should be performed if this knowledge alters clinical management (eg, identification of transformed biology).

Clinical Risk Prognostic Models

Impact of age across all prognostic models The lymphoma literature is replete with clinical risk models designed to prognosticate outcome in each of the lymphoma subtypes. The most frequently utilized model is the international prognostic index (IPI) that identifies five clinical factors as prognostic variables for PFS and OS in DLBCL both before and after the widespread use of rituximab (**Table 105-4**). Importantly, chronologic age remains an integral part of many lymphoma clinical risk predictors, including the IPI, the follicular lymphoma IPI (FLIPI), the mantle cell IPI (MIPI), and the HL international prognostic score (IPS). Although an age cutoff of 60 is often used to dichotomously segregate patients into younger and older, it is well appreciated that age is a continuous variable and that a more clinically relevant cutoff above which patients are likely to require treatment modifications exists between 70 and 75 years in the current era. A recently reported modification of the IPI in DLBCL patients specifically older than 60 suggested that age over 70 years conferred additional negative prognostic impact.

TABLE 105-4 VARIOUS PROGNOSTIC SCORES

PROGNOSTIC FACTOR					
IPI	**FLIPI**	**FLIPI2**	**MIPI**	**PIT**	**IPS**
Age > 60	Age > 60	Age > 60	Age	Age > 60 or (≤ 60)	Age > 45
Stage III/IV	Stage III/IV	BM involvement	Ki67	BM involvement	Stage IV
PS > 1	Hgb < 12 g/L	Hgb < 12 g/L	PS	PS	Hgb < 10.5 g/L
LDH > ULN	LDH > ULN	B2M > ULN	LDH compared ULN	LDH > ULN	Albumin < 4 g/dL
ENS > 2	> 4 nodal sites	LN diameter > 6 cm	WBC		WBC > 15 ALC < 600 or < 8% of total WBC count Male gender
Low (0–1) 2 y OS 84%, 5 y OS 73%	Low (0–1) 5 y OS 91%, 10 y OS 71%	Low (0) 3 y PFS 91%, 5 y PFS 80%	Low 5 y OS 81%	Low (0) 5 y OS 62.3%, 10 y OS 54.9%	0 factors 5 y FFP 84%, 5 y OS 89%
Low-Int (2) 2 y OS 66%, 5 y OS 51%	Int (1–2) 5 y OS 78%, 10 y OS 51%	Int (1–2) 3 y PFS 69%, 5 y PFS 51%	Int 5 y OS 63%	Low–Int (1) 5 y OS 52.9%, 10 y OS 38.8%	1 factor 5 y FFP 77%, 5 y OS 90%
High-Int (3) 2 y OS 54%, 5 y OS 43%	High ≥ 3, 5 y OS 53%, 10 y OS 36%	High (3–5), 3 y PFS 51%, 5 y PFS 19%	High 5 y OS 35%	High-Int (2) 5 y OS 32.9%, 10 y OS 18%	2 factors 5 y FFP 67%, 5 y OS 81%
High (4–5) 2 y OS 34%, 5 y OS 26%				High (≥ 3) 5 y OS 18.3%, 10 y OS 12.6%	3 factors 5 y FFP 60%, 5 y OS 78% 4 factors 5 y FFP 51%, 5 y OS 61% ≥ 5 factors 5 y FFP 42%, 5 y OS 56%

B2M, β_2-microglobulin; BM, bone marrow; FFP, failure free progression; FLIPI, follicular lymphoma international prognostic index; IPI, international prognostic index; IPS, international prognostic score; LDH, lactate dehydrogenase; MIPI mantle cell international prognostic index; PIT, prognostic index for T-cell lymphoma; OS, overall survival; PSF, progression-free survival; ULN, upper limit of normal; WBC, white blood cell.

From a clinical decision-making standpoint, distinctions in older population between "the young old" (65–74 years), "older old" (75–84 years), and "oldest old" (> 85 years) are somewhat arbitrary but have clinical utility in minimizing heterogeneity when devising treatment guidelines. Ultimately however, the variable nature of the aging process mandates that we think beyond chronologic age.

Biological Risk Factors

In addition to clinical risk predictors, biologic factors that are either prognostic or predictive, or both, are increasingly sought. In the modern era, with targeted therapies an increased reality, biomarkers to guide therapeutic decision making will be essential. The proliferative index, a measure of cellular division, as assessed by Ki67 percentage, has been demonstrated to have prognostic impact in DLBCL, MCL, and in predicting increased risk of indolent NHL transformation. As genetic and mutational profiling has become more approachable, the cell of origin signature in DLBCL and host immune signatures in FCL and DLBCL have been prognostic, as well as a proliferative signature in MCL.

In DLBCL, the putative cell of origin as identified on GEP is prognostic, with germinal center-derived DLBCL enjoying a better outcome than non-GC (ABC phenotype) with CHOP and RCHOP therapy. IHC models designed to approximate GEP exist (eg, the Hans model based on CD10, BCL6, and MUM1) and are implemented given their clinical utility and availability, but problems exist with sensitivity and specificity. Ultimately, newer molecular techniques will likely supplant IHC in this determination. Additionally, the concurrent presence of the antiapoptotic t(14;18) BCL2 translocation and a cMYC t(8;14) cellular proliferation signal (or less frequently BCL6 translocations)

has been termed a “double hit” biology (DH), borrowing a term from breast cancer. Roughly 10% of patients with DLBCL will have DH biology, a finding associated with very aggressive disease, older age, higher CNS risk, and no current standard of care recommendation. A larger population (~1/3) of DLBCL patients may have protein overexpression of BCL and MYC, termed double expressers, and have increased disease risk as well, but to a more variable degree.

CNS Risk Assessment

Central nervous system evaluation with lumbar puncture and analysis of cerebrospinal fluid (CSF) is important in patients with a clinical suspicion of nervous system involvement or those at high risk for CNS involvement at presentation. CSF investigation should include cell count, glucose, protein, cytology, as well as the more sensitive flow cytometry. This is generally a consideration in aggressive lymphomas and high-grade disease, with involvement rare in mantle cell or indolent lymphomas. Increased risk of CNS involvement historically has been associated with higher clinical risk factors, anatomic sites of involvement such as the testes, breast, multiple extranodal sites, and bone marrow.

Recently, a predictive model for DLBCL risk of CNS relapse was reported. This validated model is comprised of six factors (age, PS, LDH, stage, ENS, and kidney/adrenal involvement) with stratification of CNS relapse based on number of risk factors: low (0–1, 0.8% risk), intermediate (2–3, 3.9% risk), and high (4–6, 12% risk). Although the optimal method (intrathecal or high-dose methotrexate) and the actual magnitude of risk reduction in CNS prophylaxis remain debated, this predictive model is useful when considering the pros and cons in older adults.

Differences in Lymphoma Biology Between Older and Younger Patients

Regarding lymphoma biology, it is clear that in addition to host related factors accompanying the aging process, there are biologic differences in the underlying disease. Inflammatory levels, such as interleukin 6 (IL-6), are higher in older patients with lymphoma and correlate with the presence of B symptoms, increased LDH, advanced-stage, bulky disease, poor performance status, and are associated with poorer failure free and overall survival independent of traditional risk factors. Advancing age has been associated with increasing mutational and genetic heterogeneity and complexity which impact on outcome. GEP studies have confirmed older DLBCL patients more frequently are associated with a prognostically less favorable activated B-cell phenotype (ABC), associated with increased activation of the NF-KB pathway and inferior outcomes with RCHOP therapy. The EBV also has been connected to the inferior outcomes in both older adult DLBCL and HL patients. EBV-positive DLBCL of older adults is a clinical pathologic entity newly recognized by the WHO in the 2008 classification system. These patients are associated with more advanced disease, involvement of multiple extranodal sites, high-risk score, and inferior progression-free survival (PFS) and overall survival (OS).

TREATMENT OF OLDER PATIENTS WITH NON-HODGKIN LYMPHOMA

For the older patient, establishing clinical and disease-associated risk predictors is an essential part of the assessment, but this evaluation still represents an incomplete clinical picture of the individual for the treating oncologist. With increasing age, the physician is often confronted with significant host-related geriatric risk factors that may be equally or more profound than the aforementioned factors and ultimately define the palette of therapeutic options. The oncogeriatric factors of life expectancy, comorbidity, frailty, and geriatric syndromes independently predict treatment-associated morbidity and mortality, and consequently become essential considerations when deriving a treatment strategy. Ultimately, these clinical concerns are most weighty when there is an aggressive histology that is potentially curable, but therapy is associated with very real risks.

Life Expectancy

As a first step, age-related life expectancy assessment and comprehensive geriatric assessment are valuable tools in making therapeutic determinations. It is instructive to realize that an 80-year-old in average health has a predicted life expectancy of approximately 5 years absent a lymphoma diagnosis. As a result, even in advanced age, aggressive NHL will most frequently be the greatest risk to the patient in all but the most infirmed patients (eg, life expectancy < 1 year). Life expectancy tables are available from the National Comprehensive Cancer Network (NCCN) guidelines. The Lee and Schonberg 4- and 5-year estimates of mortality in older patients are practical web-based tools that can assist

in these estimations. Importantly, analysis of the SEER Medicare database suggests approximately 33% of patients with DLBCL age greater than 80 and older received no therapy at all. While at times this may be appropriate, curative and palliative therapy can generally be given to these patients and critical evaluation of factors such as ageism, physician and patient choice, and availability of adequate tools to predict toxicity is needed.

Comorbidity and Frailty Assessments

Although life expectancy evaluation can establish a general backdrop for treatment, the physician is further informed by comorbidity and frailty assessments. Comorbidity is prevalent in older patients, with 60% to 70% of older NHL patients older than 60 years possessing some comorbidity. Frequently used measures include the Charlson comorbidity score and the Cumulative Illness Rating Scale for Geriatrics, both of which capture information distinct from lymphoma-specific prognostic indexes and are independently associated with risk. The presence of comorbidity in NHL and HL patients has been associated with increased treatment-related mortality (TRM), treatment toxicity, lower dose intensity, and higher treatment failure.

Frailty is a distinct syndrome from comorbidity and has its own impact on outcomes. Frailty is often defined practically, with suggested criteria including age greater than 80 or 85, dependence in activities of daily living (ADL), exhaustion, slow gait speed, decreased hand grip, unintentional weight loss, and decreased physical activity. Frail patients have shorter life expectancies than nonfrail patient and have a higher likelihood of toxicity with interventions such as chemotherapy. Thus, frailty identifies a group of patients at greatest risk given lack of functional reserves and palliative chemotherapy approaches are generally recommended in this setting.

Comprehensive Geriatric Assessment

It is recognized that performance status and clinical judgment alone are insufficient when attempting to identify at risk older individuals and may misclassify a significant percent of patients, exposing them to harm or denying curative intent. In this vein, the NCCN, American Society of Clinical Oncology (ASCO), and International Society of Geriatric Oncology (SIOG) guidelines recommend performance of comprehensive geriatric assessment (CGA) in older patients, although the optimal integration of these interventions remains in evolution. A screening assessment (such as the VES-13) or at least ADL/instrumental activities of daily living (IADL) assessment should be performed on all patients. Those with impairments benefit from a more formal CGA analysis. The Cancer and Aging Group (CARG) and Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) CGA models are largely self-administered, time efficient, and predictive of serious hematologic and nonhematologic toxicities. Prospective trials integrating these tools into dose-adjustment or treatment choice algorithms are warranted, but in clinical practice, those at highest risk for toxicity should be considered for modifications or reduced-intensity regimens. Instructively, Tucci and colleagues demonstrated that a CGA applied in 173 DLBCL patients older than 69 years segregated fit (46%), unfit (16%), and frail (38%) patients with significantly different outcomes (OS 84% fit vs 47% nonfit, $p < .0001$) and a lack of clinical benefit from curative intent therapy in the frail category.

The Fondazione Italiana Linfomi (FIL) integrated a CGA tool into a trial treatment paradigm that stratified 334 DLBCL patients older than 65 years as either fit (68%) or frail (29%). Fit patients were randomized on a trial between RCHOP and R-mini-CEOP and had excellent and equivalent outcomes, while frail patients were treated per investigator choice. Frail patients were more frequently older (median age 78, range 65–93), with advanced stage (62%) and high risk (aaIPI 2/3 in 53%), and reported a 5-year estimated OS of 28% despite polychemotherapy administration in three-fourths of patients. TRM was 18% in this group compared with only 8% in the fit group. Prospective trials in the future will need to define therapeutic strategies for both the fit and frail categories based on the CGA to realize the true benefit of these tools.

Pharmacologic Considerations for the Older NHL Adult Patient

Neuropathic agents: Vinca alkaloids (vincristine, vinblastine), cisplatin, oxaliplatin, brentuximab vedotin, bortezomib It is worth noting that a number of approved agents for the treatment of NHL are associated with peripheral and autonomic neuropathy. In the older individual, although grade 3 neuropathy generally provokes drug modification orcessation, it is important to note that a painful grade 2 neuropathy may inhibit ADL/IADL and increase the risk of falls and impacting quality of life (QOL). Dose reductions and omissions need to be balanced against the potential benefit in a given scenario.

Anthracycline Doxorubicin has proven over the years to be one of the most active and essential agents in the

treatment of aggressive histologies such as DLBCL and HL. The anthracyclines are associated with a defined risk of anthracycline-induced cardiomyopathy that is related to cumulative dose (although rarely idiopathic), with risk increasing significantly with doxorubicin equivalents in excess of 400 mg/m^2 lifetime. Hypertension is an established risk factor. Infusional doxorubicin and liposomal doxorubicin may have an increased safety margin and a variety of non-anthracycline regimens exist when there is an absolute contraindication that may still preserve a curative intent. The cardioprotective agent Zinecard is not frequently utilized given a lack of data in NHL. It is worth noting a recent Veterans Affairs database analysis that has questioned the benefit of anthracyclines in older patients with DLBCL given associated toxicities.

Special Considerations With Small Molecule Inhibitors in the Older Patient

Ibrutinib is a small molecule inhibitor of Bruton tyrosine kinase (BTK) FDA approved for the treatment of CLL and MCL. Transient increases in lymphocytosis during the first weeks of therapy are likely in on target effects of the drug as lymphoma cell trafficking is modified and cells egressed from lymph nodes into the circulation. With longer follow-up, propensity toward bleeding has been identified with consideration for risk versus benefit in patients requiring antiplatelet her anticoagulation therapies necessary. Concurrent warfarin is generally contraindicated given interactions with CYP3A inhibitors and inducers. New-onset atrial fibrillation has also been reported in less than 5%.

Idelasilib is a small molecule inhibitor of PI3 kinase-δ that is FDA approved for patients with CLL/SLL and refractory FL. This drug has been associated with fatal and/or serious hepatotoxicity, severe diarrhea or colitis that may occur as a later complication, pneumonitis, and intestinal perforation. LFT abnormalities typically resolve with interruption of drug dosing patients can frequently resume therapy. Similar to ibrutinib, transient lymphocytosis is also a class effect with this agent.

DIFFUSE LARGE B-CELL LYMPHOMA

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL both in the United States and globally, representing roughly 30% of all new diagnosis. With a median age at diagnosis of 70 years, DLBCL is in many ways a disease of older individuals, a fact which will be magnified over the next decades as the population sees doubling and tripling of those older than 75 and older than 85 years, respectively. These projections indicate that over the same time, the number of NHL cases will increase by 67%. Hence, there is a pressing need to understand age-related host and disease factors, how they impact therapeutic choices and outcomes, and to develop specific strategies to address these factors.

Based on randomized controlled trials (RCTs), frontline therapy with anthracycline-based chemoimmunotherapy for DLBCL has resulted in overall survival rates of 60% to 70% and represents the best chance for cure, as the majority of relapsed or refractory patients will succumb to the disease. Without therapy, DLBCL is rapidly fatal in a matter of weeks. However, older patients frequently have comorbidities and functional impairment limiting feasibility of standard therapy. Hence, there are significant challenges facing the oncologist who must integrate disease, host, and patient factors with the goal of individualizing treatment decisions for the older DLBCL patient. In this context, oncogeriatric tools are essential to the initial assessment of these patients and augment the lymphoma-specific care plan.

From a practical standpoint, the initial assessment of the older patient with DLBCL is evolving to include parallel pretreatment disease staging, biologic and genetic risk assessment, and oncogeriatric risk assessment to inform decision making. Ideally, these assessments inform the oncologist and patient regarding the disease risk in the context of patient life expectancy, the likelihood of cure or disease control balanced against the likelihood of treatment related morbidity and mortality, and provide recommendations for treatment modification to mitigate these effects.

Biology: Effective Age, Germinal Center Versus Non-GC, and Methodology for Determining Cell of Origin

Definition of older age Chronologic age has factored prominently into the DLBCL landscape, as age is both associated with increased incidence of disease as well as poorer prognosis. Historically, a cutoff of 60 years was utilized in the IPI risk model, as high-dose therapy and stem cell rescue were generally limited above this age

category. However, when clinical prognostic models have been revisited in the era of chemoimmunotherapy (eg, RCHOP), this dichotomous cut point has often been revised to 70 to 72 years as a prognostic component. While binary cut points are useful in clinical models, it is recognized that chronologic age is a continuous variable with vast heterogeneity regarding biologic implications for any individual. Consequently, functional definitions of age are preferable and reflect individual physiology.

Biology in older patients It is readily acknowledged that DLBCL is a heterogeneous disease as evidenced by both varied clinical outcomes and increased understanding of the spectrum of underlying biology. Based on the WHO classification (WHO 2008), the majority of diagnoses in older patients will be classified as DLBCL, not otherwise specified (NOS); potentially adverse disease subsets such as T-cell–rich B-cell lymphoma, immunoblastic morphology, and EBV-associated DLBCL occur in greater frequency in older adults. Although associated with worse outcomes, specific treatment recommendations are lacking for these entities.

DLBCL expressing both cMyc t(8;14) and BCL2 t(14;18) by FISH are termed “double hit” lymphomas and have been associated with very poor prognosis. Double-hit lymphomas diagnosed by FISH may be present in 2% to 11% of new diagnoses. IHC can also identify DLBCL with dual expression of MYC and BCL2, coined double expressing DLBCL, which is also associated with inferior outcomes and may be present in one-third of patients. Optimal treatment is still undefined and increased treatment intensity is not a plausible strategy for most older patients.

Over the last decade, significant advances in molecular genetics have deepened our understanding of DLBCL biology. GEP of DLBCL, NOS has identified at least 2 distinct molecular subsets, namely a germinal center B-cell (GC) and an activated B-cell (ABC) phenotype, both reflecting the putative cell of origin biology. The ABC phenotype, with increased nuclear factor-κB (NF-κB) and chronic BCR receptor activation, is associated with worse outcomes under current standard of care therapy. Furthermore, both genetic complexity and the ABC phenotype increases with increasing age and account in part for worse outcomes independent of clinical predictors. The reality of DLBCL molecular changes, however, extends beyond merely assessing cell of origin, with significant genetic alterations identified in the microenvironment (stromal signals) as well as immune surveillance and antigen presentation aberrations, which are equally important.

In 2015, although increasingly cost-efficient, GEP remained impractical in daily practice and did not, as of yet, define therapy. As a result, surrogate IHC models of COO (eg, Hans, Tilly) have been implemented given ready availability and quick turnaround. Although prognostic value is maintained, the IHC models are fraught with misclassification and poorer reproducibility. Approaches using rapid assessment of predictive biology in paraffin-embedded samples, such as the nanostring predictors Lymph2Cx, are being validated currently and are promising technologies to anticipate in the near future. These discoveries have given us insight into the essential oncogenic pathways involved in the heterogeneity of DLBCL and offer the potential for targeted therapeutic agents.

Treatment of DLBCL

DLBCL is an aggressive entity with the natural history characterized by rapid progression and death in the absence of treatment. Consequently, chemotherapy is frequently used to extend survival, even among patients were curative intent cannot be achieved. Anthracycline-based chemotherapy has been associated with the greatest cure rates, with CHOP chemotherapy forming the backbone for modern-day therapy. The initial decision regarding the feasibility of anthracycline-based chemotherapy is consequently paramount. This decision must integrate assessments of organ function, clinical judgment, comorbidity, and performance status as previously discussed.

Early-Stage Treatment Paradigms

Therapeutic options for early-stage DLBCL (stage I/II without bulk) are distinct from advanced-stage disease with some overlap. Patients with age as their only risk factor have very good prognosis with combined modality therapy. Treatment approaches were initially defined by the SWOG 8736 which established CHOP × 3 cycles followed by IFRT as superior to CHOP × 8 cycles for PFS and OS at 5 years (PFS 77% vs 64%, OS 82% vs 72%); this difference, however, disappears after 8 years, a fact that should be considered in the context of life expectancy. The addition of rituximab to CHOP × 3 + IFRT was explored in SWOG 0014 in patients with one or more risk factors, with PFS of 88% at 5-year median follow-up. It is worth noting data from the GELA/LYSA group question the benefit of IFRT in older patients following four cycles of CHOP (LNH 93-4), and more recently following four cycles of RCHOP when in CR. Patients with bulky (> 10 cm) disease generally are treated with full course RCHOP ± IFRT for local control.

Whether or not to include radiation consolidation may be informed by disease location, associated RT toxicity,

comorbidity, and life expectancy. Radiation should be considered for definitive therapy in patients who cannot tolerate chemotherapy.

Advanced-Stage Treatment Paradigms

Anthracycline-based therapies The standard of care for initial treatment of DLBCL in both older and younger patients is chemoimmunotherapy comprised of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP 21) given every 21 days for six to eight cycles. The standard of care is based on the LNH 98–5 study, which included patients age 60–80 (median age of 69); 55% of patients were 70 years or older. This study has mature data, with 5-year progression-free and overall survival significantly longer for the rituximab-containing arms (54% and 58% RCHOP compared to 30% and 45% CHOP, respectively). Dedicated RCTs designed to improve upon RCHOP21 have explored upfront consolidative transplantation, dose-dense q14 day regimens, and maintenance rituximab without improvement in survival.

Ongoing efforts are exploring alternative regimens such as the dose-adjusted R-EPOCH regimen and cell-of-origin–directed trials. The DA-R-EPOCH regimen is an infusional chemotherapy regimen that may have improved efficacy in DLBCL, particularly in GC biology, and high proliferative rate tumors (eg, Myc +, high Ki67), and is potentially less cardiotoxic owing to infusional doxorubicin. Phase II data from the CALGB was associated with 5-year TTP and OS of 81% and 84% in all patients. A CALGB RCT comparing RCHOP21 versus DA-R-EPOCH was completed but not reported as of 2015. This regimen can be safely considered in older patients and may have an advantage in higher-risk scenarios (eg, double-hit biology). Cell-of-origin directed approaches are being explored in clinical trials and have taken into consideration differential activity of certain agents in the nongerminal center (ABC) phenotype. Agents such as bortezomib, ibrutinib, and lenalidomide all have phase I and II data supporting combination with RCHOP, with phase III studies ongoing globally.

Radiation consolidation to sites of bulk or residual masses may be beneficial in selected cases. IFRT has been associated with increased local control and PFS, but not OS. However, in older patients with competing nonlymphoma comorbidities for life expectancy and a lack of effective second-line options, this initial improvement in disease control may be worthwhile. Careful discussion of these pros and cons is often needed.

Patients who relapse following RCHOP chemotherapy have a poor prognosis, even when second-line therapy and subsequent high-dose therapy and autologous stem cell rescue can be utilized. For the vast majority of older individuals, this intensive strategy is not feasible due to age-related comorbidity and increased TRM associated with transplant approaches. In this setting, goals of care shift to disease control and palliation.

Prephase concept and reduced intensity Often at initial presentation, disease-related factors impair host performance status and are associated with treatment-associated morbidity and mortality. The German NHL high-grade study group has utilized a concept termed “prephase” to mitigate the impact of decreased functional status initially. Employing a week of corticosteroid and a single dose of vincristine before the initiation of therapy, the RICOVER60 study suggested there was a 50% reduction in cycle 1 and 2 TRM as a consequence of this maneuver. While dedicated validation of this approach is needed, other prospective studies have suggested there is clinical benefit to such a concept; clinicians frequently employ steroids to improve functional status in anticipation of starting definitive chemotherapy.

Reduced or nonanthracycline-based curative intent In clinical scenarios where RCHOP is not deemed feasible, there exist a variety of dose-reduced regimens, with relative dose intensities of 50% to 70% standard dosing, and a number nonanthracycline regimens that maintain curative potential. In general, the trade-off includes a reduction in efficacy with the advantage of reduced toxicity and TRM. Direct comparative data are frequently lacking in this area, with data more frequently culled from retrospective cohorts or phase II trials (**Table 105-5**).

TABLE 105-5 REDUCED DOSE OR NONANTHRACYCLINE THERAPY

REGIMEN	N	PLANNED RDI	AGE MEDIAN (RANGE)	ORR (CR/PR)	EFS	OS	TRM
RCHOP21 (Phase III)	N = 202	100%	69 y (60–80)	83% (75%/7%)	57% @ 2 y	70% @ 2 y	6%
RCHOP21 (retrospective)	N = 61	70%	76 y	87% (79%/8%)	57% @ 2 y	68% @ 3 y	NR
R-mini-CHOP (Phase II)	N = 149	~50%	83 y (80–95)	74% (63%/11%)	47% @ 2 y (PFS)	59% @ 2 y	8%
DRCOP (Phase II)	N = 80	NA	69 y (61–92)	86% (75%/11%)	60% @ 3 y	74% @ 3 y	5%
Nonanthracycline regimens							
R-miniCEOP (Phase III)	N = 114	100%	73 y (64–84)	81% (68%/13%)	54% @ 2 y	~74%@ 2 y	6%
R-GCVP (EF ≤ 55%) (Phase II)	N = 61	NA	76 y (52–90)	61% (39%/23%)	50% @ 2 y (PFS)	56% @ 2 y	NR
R-Bendamustine (Phase II)	N = 14	NA	85 y (80–95)	69% (54%/15%)	40% @ 2 y (PFS)	40% @ 2 y	0%

CR, complete response; EFS, event free survival; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PR, partial response; RDI, reduced dose intensity; TRM, treatment related mortality.

DLBCL patients characterized as very old adults, for example, over the age of 80 years, or with associated geriatric syndrome and/or frailty are under represented in clinical trials with a lack of evidenced-based guidelines. Typically, full-dose chemotherapy is not approachable, but often curative regimens can still be considered with modifications designed to mitigate serious toxicity. A phase II GELA study specifically in patients older than 80 years (n = 149) investigated a reduced intensity R-mini-CHOP protocol with 2-year PFS and OS of 47% and 59%, respectively, and maintained at 4 years. A variety of other nonanthracycline options also exist, such as CEPP, CDOP, CNOP, CEOP, and GCVP, all given with rituximab.

Response Assessment and Follow-Up

Interim restaging is performed to identify scenarios where disease is not responding or progressing despite therapy. This confirmation is particularly important in older adults where toxicity may be significant. Interim PET scans have been demonstrated to retain excellent negative predictive value, but questionable positive predictive value that has not allowed changes in therapy; consequently, interim PET scans are not recommended outside clinical trials. PET scans at the end of therapy, however, are now standard and remain very predictive of outcome.

Surveillance imaging as a routine post therapy has been called into question, with a lack of evidence supporting improved outcomes with screening CT scans and concern over false positives and exposure to medical radiation. For advanced-stage patients, CT scans every 6 months for 2 years are recommended currently, balancing the increased risk of relapse during this time interval with a desire to limit exposure.

High-Dose Therapy and Autologous Stem Cell Rescue in Older Patients

High-dose chemotherapy followed by autologous stem cell rescue (HDT/ASCR) was established in the PARMA study as the recommended second-line approach in chemosensitive transplant-eligible patients. In the absence of HDT/ASCR, relapsed DLBCL therapy is generally not curative. Unfortunately, there are limited data reporting the safety and efficacy of HDT/ASCR in the older patient. The Center for International Blood and Marrow Transplant Research (CIMBTR) has reported a 28% increase in the number of HDT/ASCR procedures in the United States when comparing 1994–1995 to 2004–2005. Commensurate with this increase, the proportion of patients 60 years or older undergoing HDT/ASCR during the same period went from less than 7% to 35%.

Given the significant potential for morbidity and mortality with HDT/ASCR, patient selection in the older patient is paramount. Factors considered include age, comorbidities, functional status, and psychosocial support systems. The second-line aaIPI (PS, LDH, stage) has been confirmed in a number of trials as predictive of PFS and OS with an intent to transplant; 3-year estimated event-free survival (EFS) for low/intermediate-risk versus high-risk patients was 40% versus 18% ($p < .001$). A Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) also exists and high-risk scores are associated with decreased likelihood of receiving transplant and OS. Despite age-related physiologic changes, in general age is not a limiting factor when considering the ability to mobilize and collect stem cells, although complete count recovery may be slower post transplant in older individuals. TRM in NHL patients older than 55 years in the CIBMTR database was 15% and increased 1.86 times compared to their younger counterparts. This may be as high as 18% to 19% for individuals older than 70 years at transplant.

The largest randomized study of second-line therapy followed by HDT/ASCR (Collaborative Trial in Relapsed

Aggressive Lymphoma [CORAL] study) included patients up to age 65, with a median age of 55. In this patient population, the intent to treat (ITT) EFS was 31% for all patients, with identified prognostic factors of relapse less than 12 months from prior therapy, prior rituximab, and the second-line age-adjusted IPI. For patients with early relapse following prior rituximab-based therapy, the ITT EFS was only 23%. Given these modest results in younger patients, one must be selective in recommending HDT/ASCR in the older individual. Early referral to a transplant center for evaluation, cardiac and pulmonary assessment, second-line aaIPI, and CGA should all likely precede initiation of intensive second-line regimens such as R-ICE or R-DHAP when transplant is the goal.

BURKITT LYMPHOMA AND HIGH-GRADE DLBCL WITH FEATURES INTERMEDIATE BETWEEN BL/DLBCL

Biology

Burkitt lymphoma (BL) is the prototypic high-grade lymphoma, and the history and treatment approaches of this disease have established many principles of lymphoma therapy. For instance, BL was the first malignancy associated with a virus (EBV), BL led to the identification of the tumor lysis syndrome, and treatment evolution defined intrathecal and CNS lymphoma therapy. BL has a propensity for CNS involvement. Endemic BL in Africa is associated with an interplay between EBV and malaria, prototypically presenting as a rapidly enlarging jaw mass in pediatric and adolescent patients. In the United States, BL more frequently is sporadic (or HIV associated) and less frequently associated with EBV (30%). Intra-abdominal presentation may dominate, with extranodal sites of involvement typical (CNS up to 40%, BM up to 70%).

The 2008 WHO classification recognizes it may not always be possible to distinguish between a high-grade DLBCL and BL, with treatment recommendations favoring the high-grade paradigms when feasible. The typical pathologic findings include a “starry sky” appearance caused by a monotonous population of medium- to large-size B lymphocytes with a near 100% proliferative rate and foamy macrophages engulfing apoptotic bodies. Flow and IHC typically reflect sIg(+), CD10(+), CD20(+), TdT(–), Ki67 ≥ 95%, BCL2(–), BCL6(+), and MYC [t(8;14) in 80% or t(8;22), t(2;8)] as a sole rearrangement. GEP may help distinguish between DLBCL with MYC and BL, but this is not common in clinical practice.

Treatment in the Older Adult With BL and Related High-Grade BL/DLBCL

Historically, standard of care regimens for BL require intensive therapy with non–cross-resistant agents that cross the blood-brain barrier. Initial therapy is generally rendered in the hospital, with tumor lysis prophylaxis mandatory. CHOP therapy has been insufficient to achieve cure. With current approaches evaluated in the SEER database (2002–2008), 5-year OS estimates are 56%. Roughly one-third of patients will be older than 60 years at diagnosis in the United States. The survival of older adults is less favorable compared with younger counterparts. Regimens associated with the best outcomes include CODOX-M-IVAC, hyperCVAD, and DA-R-EPOCH. Modifications of the CODOX-M-IVAC regimen have been published that decrease the associated toxicity and integrate rituximab; these modification may be more approachable in older patients. The hyperCVAD regimen is associated with increased toxicity in patients older than 65 years and often is not feasible. DA-R-EPOCH may be safest from a toxicity standpoint, and validation of this regimen in BL is under way. Cases of double-hit DLBCL and B-cell lymphoma, unclassifiable with features intermediate between DLBCL and BL, are often treated with BL regimens, acknowledging robust data are lacking and optimal management has yet to be defined.

MANTLE CELL LYMPHOMA

Clinical Presentation

Mantle cell lymphoma (MCL) is a rarer subtype of NHL with roughly 7000 new cases annually in the United States. Historically, this entity was associated with median OS of only 2 to 3 years and paradoxically shares the incurable features of indolent lymphoma with the behavior of an aggressive disease biology. In the modern era, MCL has been associated with significant advances in biologic understanding, therapeutic options, and increased median survivals of 5 to 7+ years. The median age of MCL patients at diagnosis is 65 years, with a male predominance and a propensity

for bone marrow and GI involvement. Advanced-stage disease is the norm, with localized stage I and II disease rarely present. Asymptomatic patients may be identified incidentally by screening colonoscopy, with a lymphomatoid polyposis presentation characterized by innumerable colonic polyps. It is now appreciated that more indolent presentations of MCL also exist, often with BM or GI only presentations. Although not sufficient for the development of MCL alone, dysregulation of cell cyclin D1 (rarely D2 or D3) due to translocation 11;14 is a hallmark of MCL.

Biology

MCL can generally be distinguished from similar morphologic appearing entities (eg, CLL/SLL, MZL, LPL) with IHC/flow and FISH. The typical immunophenotype consists of CD5(+), CD10(–), CD20(+), CD23(–/+), CD43(+), and cyclin D1(+) associated with a translocation of chromosomes 11 and 14. Nuclear overexpression of SOX11 is present frequently and is associated with prognosis. A blastic MCL variant, characterized by p53 derangement, myc, high proliferative rate, and a more aggressive disease course, is also recognized and poses a therapeutic challenge.

Upfront Transplant Versus Nontransplant Approaches

MCL remains an incurable entity with standard therapeutic approaches today. For the rare patients with limited-stage disease (I, II), a combined-modality approach with RCHOP and IFRT is favored based on retrospective data. In 2015, a dichotomy existed between upfront HDT/ASCR approaches and nontransplant approaches. HDT/ASCR is associated with increased PFS in randomized data but does not cure the disease, and consequently, a discussion of QOL and morbidity versus disease control is central to this discussion. In patients deemed eligible for HDT/ASCR, the cumulative data suggest that cytarabine-containing induction regimens such as hyperCVAD or the European MCL Network RCHOP/RDHAP regimen; randomized data comparing RCHOP/RDHAP versus RCHOP with HDT/ASCR consolidation (age $\leq$ 65 years) showed an improved TTF for the cytarabine-containing arm (88 vs 46 months, p = .038), with a survival advantage noted as well (not reached vs 82 months, p = .045). The hyperCVAD and upfront transplant approaches, however, are associated with increased toxicity in older patients and may not be feasible for the majority of MCL patients given median age at presentation. Consequently, for the older patient, nontransplant approaches are generally recommended.

Anthracycline-Based Induction RCHOP, VR-CAP, Versus BR

The majority of older patients presenting with MCL will best be served with a nontransplant approach. In early studies, the addition of rituximab to CHOP improved response rates, but unlike other NHL scenarios it did not translate into increased survival. Two randomized studies have defined anthracycline-based initial therapy, with a European MCL network phase III study dedicated to patients older than 60 and ineligible for HDT/ASCR randomizing patients first to RCHOP versus R-FC and secondarily to maintenance rituximab or interferon-α. This study established RCHOP induction followed by maintenance rituximab as superior to R-FC or interferon. OS was improved with maintenance in RCHOP-treated patients. Four-year OS rate for patients treated on this arm was 87%, with a median duration of response of 6+ years.

A second randomized phase III study evaluated the proteosome inhibitor bortezomib (FDA approved for relapsed/refractory MCL) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP, n = 243) versus RCHOP (n = 244); the median age of patients was 66 (range 26–88) with advanced stage in 95%. At 40-month follow-up, median PFS was double (24.7 vs 14.4 months) for VR-CAP without a survival advantage realized. Toxicity was comparable, although slightly higher for VR-CAP.

Taken together, the standard of care for older patients with MCL is chemoimmunotherapy with maintenance rituximab consolidation consideration (data are following RCHOP).

Other approaches have included initial treatment with rituximab and bendamustine based on the StiL (Study Group Indolent Lymphomas) phase II trial subgroup with MCL and supportive data from the US BRIGHT study. Overall response rates with this regimen are similar to RCHOP with longer PFS and less toxicity, although there was no impact on OS. This regimen may be preferable when comorbidity limits anthracycline approaches. The purine analogue cladribine has been evaluated in phase II studies with good outcomes in older patients as well.

Second-Line Regimens

Second-line therapy remains challenging, although increasing understanding of biology and recently approved agents such as bortezomib (targeting the proteasome), ibrutinib (targeting BTK), and the immunomodulatory agent

lenalidomide have increased therapeutic strategies beyond cytotoxic chemotherapy. Integration of these agents into initial treatment is the focus of current research.

FOLLICULAR LYMPHOMA/INDOLENT LYMPHOMAS

Introduction

Follicular lymphoma (FL) is the second most common NHL histology in the United States, accounting for roughly 30% of new cases. Prevalence of this disease is much greater than incidence, owing to a natural history with median survivals improving to greater than 15 years. FLs are the prototypical indolent or slow-growing lymphoma, characterized by systemic disease with a protracted disease course associated with waxing and waning adenopathy that is frequently asymptomatic and may not require therapy.

At presentation, the majority of patients with follicular lymphoma will have painless adenopathy, with B symptoms noted in less than 25% of patients, and systemic disease present with morphologic involvement of the bone marrow in up to 70%. Female gender is slightly more common than male gender. Median age is in the sixth decade. Although therapeutic advances have increased median survival, FCL remains a chronic illness that is characterized by the need for intermittent therapy with generally shorter and shorter response intervals. Marked heterogeneity does exist in disease course, with perhaps 10% to 15% of patients experiencing a more aggressive disease course with shorter survival, while many will have intermittent impact on their daily life.

Biology

FL is characterized morphologically by increased number and heterogeneity of lymphoid follicles with disruption of the normal nodal architecture and ablation of interfollicular space. As a result of this fairly consistent morphologic presentation, there is very high concordance between pathologists (> 90%) regarding an FCL diagnosis based on histology alone. A grading system (grades 1–3) based on increasing number of centroblasts per high-power field (hpf) is employed, with grade 3 divided into 3A and 3B subtypes. Concordance with this grading system is less reliable than the initial diagnosis, with distinction between grade 1 (< 5 centroblasts/hpf) and grade 2 (6–16 centroblasts/hpf) clinically insignificant. Grade 3 FCL may benefit from anthracycline-based therapy and DLBCL paradigms are often followed. Nuanced data suggest 3A may behave more indolently and that FCL 3B truly has a different biology and more aggressive behavior, although these distinctions remain challenging.

Immunophenotyping with IHC or flow cytometry is essential to establishing the diagnosis, with a characteristic pattern consisting of CD20(+), CD10(+), BCL2(+), CD23(±), CD43(–), CCND1(–), and BCL6(+). Rare cases may be CD10 or BCL2 negative. Ki67 immunostaining is helpful as higher proliferative rates are associated with more aggressive clinical behavior or overt transformation. GEP has identified the microenvironment milieu and attendant host immune response as a potentially important determinants of prognosis.

Genetically, over 90% of cases have a translocation involving the immunoglobulin heavy chain promoter on chromosome 14 and the antiapoptotic *BCL2* gene of chromosome 18 (t[14;18][q32:q21]). Although a hallmark of FCL, the t(14;18) translocation alone is not sufficient for the development of FCL and is not prognostic; in fact, a proportion of the general population will harbor this translocation in their peripheral blood and may never develop disease. This is perhaps not a surprise, given the dynamic nature of the normal germinal center B cell selection process as B lymphocytes undergo clonal expansion, somatic hypermutation, and class switch recombination by design. This inherent and necessary mutability increases the likelihood of genetic and epigenetic events involved in lymphomagenesis.

Expectant Monitoring

Many patients will present with advanced-stage disease but will not require immediate intervention. Asymptomatic patients with low burden of disease may be expectantly monitored with no detrimental effect on overall survival. This is supported by randomized studies over the last decades that have explored expectant monitoring at diagnosis versus both chemotherapy (chlorambucil) and immunotherapy alone (rituximab). In each instance, the early initiation of therapy did not improve long-term disease-specific or overall survival, supporting an expectant monitoring approach. Importantly, in the original UK study, up to 40% of patients older than 70 years never required treatment for their FCL. The median time to treatment in controlled settings has generally been about 3 years. Fascinatingly, spontaneous regression of adenopathy in FCL is well established and may occur in 10% to 15% of patients, further supporting a

contention that expectant monitoring in the absence of criteria for therapy is valid. Efforts to harness the presumed immune-mediated improvements in disease (eg, vaccine and checkpoint blockade approaches) have been a continual area of investigation with proof of concept demonstrated, but there is no widely validated approach.

Indications for Therapy

Currently accepted indications for therapy, generally chemoimmunotherapy in the modern era, are derived from clinical trial criteria established by the French in the context of clinical trials (termed the GELF criteria) and adopted by the NCCN guidelines. These criteria generally relate to tumor burden (**Table 105-6**).

TABLE 105-6 INDICATIONS FOR THERAPY IN FOLLICULAR LYMPHOMA

HIGH TUMOR BURDEN INDICATIONS FOR THERAPY: FCL
At least one of the following:
3 distinct nodal sites, each ≥ 3 cm
Single nodal site ≥ 7 cm
Symptomatic splenomegaly
Cytopenias (WBC < 1 and/or PLT < 100 × 10^9/L)
Leukemic disease (circulating cells > 5 × 10^9/L)
Pleural effusions, peritoneal ascites
B symptoms
LDH elevated or B2M ≥ 3 g/dL
PS ≥ 1

LDH, lactate dehydrogenase; PLT, platelet count; PS, performance status; WBC, white blood count.

Therapy—Localized Disease

Although the majority of patients will present with advanced-stage disease, roughly 5% to 10% will be diagnosed with localized disease. Patients with localized disease (stage I or II) may be treated with curative involved site radiotherapy (ISRT) of 24 to 30 Gy. In these instances, it is essential that complete staging with imaging (CT neck, CAP, ± PET) and bone marrow biopsy be accomplished to ensure there is no occult disease. When employed for localized disease, IFRT may result in roughly 50% of patients remaining long-term disease free. Patients with stage I disease and small volume (< 3 cm) may derive the greatest benefit. Despite this fact, practice patterns in the United States from the National Lymphocare study suggest a minority of early-stage FCL patients actually received RT; expectant monitoring is reasonable in some patients. Combined modality approaches may improve PFS but have not demonstrated increases in OS. Patients with bulky FCL are generally managed according to advanced-stage strategies.

Therapy—Advanced-Stage Disease

Chemoimmunotherapy Therapy for advanced-stage FCL is generally indicated when there are criteria indicating increased tumor burden and symptomatic disease. Current therapies are not curative, and consequently the goal is resolution of disease symptoms and maintenance of remission, with attention to toxicity. FL and lymphomas, in general, are very responsive to immunotherapy alone and in combination with chemotherapy, as well as radiation, with a rapid expansion of available agents in the current era. Current first-line strategies follow a number of broad themes based on outcomes for RCTs. In almost all instances, the addition of rituximab to a chemotherapy backbone has consistently resulted in improved response rates and increased PFS, as well as of evidence of increased OS. Alkylator-based regimens (eg, RCHOP and R-CVP), purine analogue regimens (eg, R-FCM), and rituximab-bendamustine have all been evaluated in the frontline treatment of symptomatic FCL. Overall response rates are generally in the 80% to 95% range, with expected median response durations over 2 years. The PRIMA study demonstrated a PFS benefit from maintenance rituximab (rituximab 375 mg/m^2 every 2 months for 2 years) compared with observation following chemoimmunotherapy induction, with a benefit maintained on long-term follow-up. Based on the FIT study, consolidative RIT is a consideration following chemotherapy induction.

Bendamustine is an alkylating agent with a purine-like benzimidazole ring component that is not cross-resistant with other alkylating agents. This agent has demonstrated significant activity (alone and with rituximab) with a favorable toxicity profile. Two randomized studies (StiL and BRIGHT) have compared RCHOP induction to R-bendamustine (BR) in indolent lymphoma, with demonstration of similar ORR (increased CR) and longer PFS with BR, with less frequent grade 3/4 toxicity (alopecia, neutropenia, infection) with BR.

In selected instances, such as older frail patients in whom systemic therapy will be poorly tolerated, low-dose ISRT (4 Gy) may be effective palliation. Single-agent rituximab monotherapy has proven activity in the initial and relapsed settings. Rituximab remains an initial option in frailer patients or those with low-risk profiles, with PFS of roughly 18 months in the upfront setting.

The choice of initial regimen The choice of initial regimen is based largely on the synthesis of both disease and host factors, integrating comorbidity concerns, side-effect profiles, and life expectancy considerations. Chemoimmunotherapy, incorporating rituximab with a chemotherapy approach, is the accepted standard of care, but which chemotherapy regimen to choose has not been determined by randomized trials. Studies from the Italian Lymphoma Group have suggested that long-term outcomes with alkylator-based therapy initially may be superior to purine analogues in terms of sequence, likely owing to long-term side effects of purine analogues. The favorable toxicity profile of rituximab-bendamustine has led to this being a very attractive initial approach. Biologic-based inductions, such a rituximab plus the immunomodulatory agent lenalidomide, are currently being compared to chemoimmunotherapy (RCHOP or R-bendamustine) in randomized trials.

Relapsed disease At relapse, the selection of salvage regimens depends on the efficacy and tolerability of prior therapies. Rituximab is generally included if the benefit from initial therapy was more than 6 months, and data support maintenance rituximab in the relapsed setting as well. Non-cross-resistant regimens are preferable generally. Radioimmunotherapy with ^{90}Y-ibritumumab tiuxetan and ^{131}I-tositumumab represents an effective approach and is a particular consideration in older patients with comorbidities not appropriate for chemotherapy. The oral phosphatidylinositol 3-kinase (PI3K) inhibitor idelesalib has proven safety and efficacy in relapsed indolent NHL refractory to rituximab and alkylators. HDT/ASCR is a consideration in select patients with short remission duration (< 2 years) from initial chemoimmunotherapy induction and physiology that allows this consideration.

Allogeneic stem cell transplantation is potentially curative in low-grade lymphomas; generally only a consideration in younger patients, the approachability of allogeneic stem cell transplant in older patients is increasing and may be considered in very select cases.

Risk of Transformation

Over the disease course of FCL, up to 40% to 50% of patients may experience transformation to a more aggressive biology that is overwhelmingly DLBCL in appearance. Clinically, transformation is often heralded by a rapidly growing nodal mass, new-onset B symptoms, hypercalcemia, elevated LDH, increased Ki 67%, and higher standardized uptake values (SUVs) on FDG-PET. The rate of transformation is roughly 1% to 3% per year, with a potential plateau of this risk around 12 to 15 years based on longitudinal retrospective studies. Patients with high FLIPI scores and grade 3 biology may be at increased risk of transformation, but to date, there is no convincing evidence that the risk of transformation is modified by either watchful waiting as an initial approach or earlier institution of anthracycline-based therapy. Genetic events associated with transformation include the accumulation of BCL6, p53, and cMyc abnormalities, with the FISH double-hit entity (t[14;18] and t[8;14]) often arising in this context.

Once transformation is documented, treatment generally follows DLBCL paradigms, with the goal of therapy to eradicate the aggressive life-threatening clone. Median survival following transformation is reported at less than 2 years, but patients with de novo transformed DLBCL and limited extent of transformation may have better outcomes. Some groups advocate for consolidative HDT/ASCR in first CR, but this is less often a consideration in older individuals. Of note, the vast majority of patients with FL who die have DLBCL as the cause of death.

MARGINAL ZONE LYMPHOMA: NODAL AND EXTRANODAL MALT LYMPHOMA

Introduction

Marginal zone and MALT lymphomas represent 8% to 10% of NHL. Marginal zone lymphomas comprise a number of clinical pathologic presentations with nodal, splenic, and extranodal presentations in which the malignant B cell is

thought to originate from a B lymphocyte derived from the marginal zone of the lymphoid follicle found in the spleen, lymph nodes, and mucosal lymphoid tissue sites. Typical immunophenotyping demonstrates a CD20(+), CD5(–), CD10(–), CD23(±), cyclin D1(–) pattern. MYD88 may be helpful in excluding Waldenström macroglobulinemia.

Nodal marginal zone lymphomas are similar in their behavior to FL, with generally parallel treatment paradigms applied. Splenic marginal zone lymphoma is characterized by splenomegaly, at times massive, and systemic bone marrow and peripheral blood involvement with splenic villous lymphocytes histologically.

The extranodal marginal zone lymphomas, MALT lymphomas, most commonly present in the stomach (50%), although alternatives extranodal sites include the orbit (7%–12%), intestine, thyroid, lung (8%–14%), skin (9%–12%), breast, salivary glands, urinary bladder, kidney, and, rarely, CNS. These presentations are often localized stage IE or IIE disease; systemic staging is required, however, when local therapy is being considered.

Patients with marginal zone lymphomas generally have good outcomes with prolonged disease courses measured in years. A SEER database analysis suggests 5-year relative survivals of 89% with MALT lymphomas, 80% with splenic marginal zone lymphomas, and 76.5% with nodal marginal zone lymphoma. Expectant monitoring is frequently employed as well as a variety of less intensive therapeutic options including monoclonal antibodies, chemoimmunotherapy, and radiation.

Biology

The biology related to MALT lymphoma has defined in many ways an established concept of lymphomagenesis dependent on chronic antigenic stimulation of B-cell population through chronic inflammation in an extranodal site. The most frequently involved organ is the stomach, where there is direct evidence that chronic gastritis induced by the microbial pathogen *Helicobacter pylori* leads to gastric MALT lymphoma. This antigenic drive model has been implicated in a number of settings, with both infectious (hepatitis C, *Borrelia burgdorferi*, *Chlamydia psittaci*) and autoimmune (Sjögren and Hashimoto thyroiditis) antigens associated with a risk of marginal zone lymphomas (**Table 105-7**). Early on in this antigenic cascade, elimination of the antigenic drive may be sufficient to cause regression of the lymphoma. This is most clearly evident with antibiotic eradication of *H pylori* and regression of clinically evident gastric MALT lymphoma. Gastric MALT lymphomas that harbor an API2/MALT1 translocation (t[11;18][q21;q21]) may be less likely to respond to antibiotics; in these instances, the MALT lymphoma may be driven by activation of NF-κB, acting as a row survival signaling pathway for malignant B cell.

TABLE 105-7 PRESUMPTIVE ANTIGENIC DRIVERS IN MARGINAL ZONE LYMPHOMA

EXTRANODAL SITE	PRESUMPTIVE ANTIGENIC-DRIVE	GENETICS
Gastric	*Helicobacter pylori*	t(11;18)(q21;q21) API2/MALT1; t(1;14) BCL10
Intestinal	*Campylobacter jejuni*	
Orbit	*Chlamydia psittaci*	t(14;18) MALT1/IgH; t(3;14) FOXP1
Parotid	Sjögren syndrome autoantibodies	t(14;18) MALT1/IgH
Thyroid	Hashimoto thyroiditis	t(3;14) FOXP1
Skin	*Borrelia burgdorferi*	t(1;14); t(14;18) MALT1/IgH; t(3;14) FOXP1
Splenic	Hepatitis C	
Lung		t(11;18)(q21;q21) API2/MALT1; t(1;14) BCL10

Treatment

Splenic marginal zone lymphoma historically was treated with splenectomy when therapy was indicated with excellent outcomes and treatment-free interval measured in years following surgical resection. There is an association with hepatitis C virus which may be causative in certain instances. With the advent of curative treatment for hepatitis C, treatment of the underlying virus is advised whenever possible and may lead to regression of lymphoma. Rituximab monoclonal antibody monotherapy has arisen as a very effective therapeutic strategy that can be repeated and has supplanted splenectomy as a first-line consideration, particularly in older individuals. More resistant disease has been addressed with purine analogs as well as alkylator-based therapy (CHOP-like). Vaccination against encapsulated organisms should be considered given the potential role for splenectomy.

Gastric MALT lymphomas associated with *H pylori* infection are initially treated with antibiotics to eradicate the

antigenic drive. Regression of the clinically evident lymphoma can occur with high frequency but may involve over months and require repeat EGD surveillance to ensure resolution. Interestingly, molecular evidence of the lymphoma clone may persist without clinically relevant disease in the absence of the antigenic drive. Predictors of a decreased likelihood of response with antibiotics include genetics, thickness of gastric wall involvement, and *H pylori* status.

Stage IE or IIE *Helicobacter*-negative gastric MALT lymphomas or antibiotic-resistant disease can be very effectively treated with involved field radiotherapy with estimated 10-year relapse-free rate and overall survival rate of 74% and 89%, respectively. Transformation to DLBCL does occur with gastric MALT lymphomas and generally requires chemoimmunotherapy ± radiation to eradicate. There are a few reports suggesting antibiotics may be considered in this scenario with institution of chemoimmunotherapy should antibiotics fail. Surgical resection is no longer a recommended modality for this entity.

In a similar vein, nongastric MALT lymphomas that are localized (stage IE or IIE) are frequently managed with expectant monitoring, involved site radiotherapy, or single-agent monoclonal antibody therapy. More advanced or disseminated disease is approached in a similar fashion to FL treatment paradigms.

T-CELL NHL

Peripheral (Mature) T-Cell Lymphoma

A detailed description of the peripheral (mature) T-cell lymphomas (PTCLs) is beyond the scope of this chapter. PTCLs are a heterogeneous group of lymphoproliferative disorders derived from postthymic T cells and make up 10% to 15% of all NHL diagnoses, generally with poor prognosis. They can clinically be divided into aggressive histologic subtypes predominated by: peripheral T-cell lymphoma NOS, angioimmunoblastic lymphadenopathy with dysproteinemia (AILD), NK/T cell lymphoma, and anaplastic large cell lymphoma divided into ALK-positive and -negative cases. Adult T-cell lymphoma/leukemia is an aggressive disease associated with HTLV-I infection with prolonged latency of over five decades. HTLV-I is endemic in Japan and in the Caribbean basin and remains a difficult disease to treatment. There is significant global variation in the frequency of T-cell lymphomas. Rare entities exist as well such as enteropathy associated T-cell lymphoma and gamma delta hepatosplenic T-cell lymphoma.

Older individuals have an age-associated increased risk of AILD as well as ALK-negative anaplastic large cell lymphoma when these subtypes are present. AILD usually presents with generalized adenopathy, frequently with associated hepatomegaly or splenomegaly, hypergammaglobulinemia, eosinophilia, rash, and fever. CHOP-based chemotherapy has been insufficient for the vast majority of patients in achieving curative outcome and new therapeutic strategies for T-cell lymphomas are a very active area of clinical investigation. When feasible, upfront transplantation following induction therapy may result in long-term disease-free survival of roughly 40% generally in younger individuals. Recent new agents specifically approved for treatment in T-cell lymphomas include Pralatrexate, Romidepsin, and Belinostat, all with a roughly 30% overall response rate. Brentuximab vedotin is an antibody drug conjugate targeted against the cell surface CD30 antigen with potent activity in anaplastic large cell lymphoma.

Mycosis fungoides is a cutaneous T-cell lymphoma that frequently confront the dermatologist and internist. Preexisting history of eczema-like lesions or psoriasis is often present for several years prior to a definitive diagnosis. Skin lesions progress from a patch to a plaque stage and ultimately to more systemic illness with tumor or Sézary syndrome characterized by erythroderma and circulating tumor cells. Early therapeutic interventions include topical therapy such as glucocorticosteroids, topical mustard, phototherapy including PUVA, retinoids, and electron beam radiotherapy.

HODGKIN LYMPHOMA

Hodgkin lymphoma (HL) is the most common lymphoid neoplasm in young patients, with a median age at diagnosis of 38 years. A bimodal age peak has been long reported and persists despite refinements in diagnostic approaches reclassifying some classic Hodgkin lymphomas (cHL) as T-cell-rich B-cell lymphoma. In population-based analyses, 15% to 35% of patients will present with disease over the age of 60 and pose a particularly difficult dynamic for the treating oncologist. If therapy can be given safely, these patients can be cured, but often, they have significant comorbidity that may limit curative regimens. Older patients are also less represented in clinical trials (< 5% of HL trial demographics are older) leaving less guidance and fewer advancements in the treatment of older patients. In the current era, more than 80% of younger patients will be cured with frontline therapy. Unfortunately there remains a

significant gap in curability for older patients due to multiple factors including disease biology, host biology, comorbidity, and less ability to effectively administer curative intent therapy.

Biology and Prognostic Models in Older Patients

HL is an uncommon malignancy characterized pathologically by the presence of malignant multinucleated giant cells, eponymously termed “Reed-Sternberg” cells after the defining pathologists, which have a typical IHC profile with expression of CD15 and CD30, while generally CD20 negative (< 40%), in the setting of an inflammatory microenvironment replete with a background milieu of eosinophils, plasma cells, and histiocytes. Four histologic subtypes are recognized: nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted cHL. Another subtype of HL, nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), is even rarer, both in terms of incidence (only 5% of all HL) and presentation at advanced age. NLPHD has a more indolent disease course, is typically CD20(+), while negative for CD15, and rarely expresses CD30.

A number of reports have implicated more aggressive disease biology in older patients with cHL compared with younger patients at presentation, including higher-risk scores, mixed cellularity histology, advanced stage, and EBV association. Staging is described above and includes PET imaging at baseline. In all HL patients, but particularly those who are older at diagnosis, assessment of LV function and pulmonary function testing with DLCO is essential prior to considering anthracycline-based therapy that includes bleomycin.

The definition of “older” in HL has often been at an earlier chronologic age (45 or 50) based on prognostic models, although clinically relevant age-related concerns impact care in those generally over 60 years. The IPS was developed by Hansenclever and colleagues in 1998 based on approximately 4600 patients, with seven predictive factors associated with adverse outcomes predicting freedom from progression (FFP) from 42% to 84% and overall survival (OS) from 56% to 89%. While still predictive of outcome in the modern era, survival results have improved, with the same model now associated with OS rates between 67% and 98% Importantly, there were only 5% of patients older than 60 years in this dataset. Retrospective assessments have suggested comorbidity and ADLs may be important predictors in older HL patients. More recently there has been a refinement of prognostication based on biology that has focused on tumor-associated macrophage markers (CD68 and CD163), as well as a 23-gene nanostring gene expression predictor.

Outcomes in Older Patients

Older patients with HL, typically defined as 60 years or older, have significantly inferior outcomes in comparison to younger patients in retrospective and population databases over the last decades. More recent reports from SEER have confirmed improvements in outcomes over time, but contemporary analysis from the randomized E2496 ABVD v Stanford V program continue to confirm this disparity.

One of the complex issues in this population is whether or not death is due to the underlying HL or due to competing factors. In the E2496 study, the cumulative incidence of death, including competing risks, was 23% and 30% for older patients compared to 7% and 10% for younger patients at 3 and 5 years, respectively. Death due to HL progression in older patients was 16% and 21% at 3 and 5 years, respectively. The reasons for differential outcomes in older patients are many, including disease biology, comorbidity, functional status, relative chemotherapy intensity, and toxicity.

Early-Stage Disease (Nonbulky Stage I-IIA)

Early-stage HL patients are typically younger and enjoy excellent survival, with approaches designed to minimize the long-term toxicities of associated therapy. Treatments are generally based on early-stage risk assignment as either favorable or unfavorable early-stage disease based on early-stage prognostic models. Age figures into two of the early-stage risk models as an adverse factor (EORTC age $\geq$ 50 and NCIC models age $\geq$ 40 years). Higher-dose and extended-field RT alone was historically a standard treatment option, and may be a consideration for older frail patients, but this has generally been supplanted by combined modality regimens (eg, ABVD + IFRT) in an effort to decrease the long-term toxicities of RT; these toxicities include increased heart disease, pulmonary dysfunction and secondary cancers. Latency periods for these late effects, generally 8 to 12+ years, should be a consideration in older individuals when chemotherapy is equally fraught with toxicity.

Patients With Early-Stage Favorable and Unfavorable Disease

ABVD (four cycles), developed as a less leukemogenic alternative to MOPP therapy, was established by Bonadonna and colleagues as the standard approach for early-stage disease in conjunction with IFRT (36 Gy). The HD10 German Hodgkin study group subsequently confirmed equal outcomes with ABVD × 2 cycles followed by 20 Gy IFRT for patients with no risk factors, with OS rates of 96.6% to 7.5%. MSKCC explored ABVD (six cycles) alone vs ABVD (six cycles) + IFRT/EFRT for patients with stage I, II, IIIA nonbulky disease and demonstrated comparable OS rates at 60 months of 97% versus 90% respectively (p = .08). The NCIC HD6 study demonstrated excellent outcomes for patients treated with ABVD alone if they were in CT CR following two cycles (total four cycles).

More recently, two trials in early-stage favorable patients have integrated interim PET into the treatment paradigm. The UK Rapid study explored ABVD × 3 cycles followed by functional imaging, with monitoring for patients who were PET negative (Deauville 1–2), or one additional cycle of ABVD followed by IFRT with excellent PFS (3-year PFS 93.8% for IFRT vs 90.7% with no further therapy; 3-year OS 97% vs 99.5%), sparing about 75% of patients from RT exposure. In contradistinction, the EORTC H10 trial concluded CMT resulted in fewer early progressions compared with ABVD alone, even in favorable disease with negative PET2, closing this arm early.

For patients with early-stage unfavorable disease, the HD11 trial from the GHSG established ABVD × 4 cycle followed by 30 Gy IFRT as an effective treatment option with less toxicity than BEACOPP, with 5-year PFS of 87%. The Stanford V regimen was initially developed to minimize anthracycline and bleomycin exposure and was heavily RT dependent. Subsequent investigations (E2496) comparing ABVD versus Stanford V in locally extensive and advanced-stage disease demonstrated Stanford V was not superior to ABVD and was associated in subgroup analysis with worse outcomes and more toxicity in older patients.

Advanced-Stage Disease (Stage III/IV)

For patients with advance stage HL, MOPP chemotherapy was the first successful regimen with DFS of 66% at greater than 10 years. The associated infertility and secondary malignancies (MDS and leukemia) led to a search for alternative regimens. A landmark CALGB study demonstrated ABVD alone (or alternating with MOPP), to be superior to MOPP as initial treatment for advanced-stage HL. This was confirmed in an Intergroup study, establishing ABVD as the standard of care for the last decades. Stanford V and BEACOPP are two regimens that have undergone randomized trials against ABVD with the goal of improving outcomes. The E2496 study showed no significant benefit for Stanford V versus ABVD and inferior outcomes with Stanford V for high-risk patients (IPS ≥ 3). This regimen is also associated with increased toxicity in older patients.

The intensive escalated BEACOPP regimen was compared with COPP-ABVD in the HD9 study with superior outcome for escalated BEACOPP at 1 year (OS 86% vs 75%). Importantly, a subgroup of HD9 for older patients demonstrated escalated BEACOPP to be too toxic in older patients (age > 60), and consequently, it is not recommended. Escalated BEACOPP for six cycles is currently considered an option based on the HD15 trial (rather than eight cycles or a dose intensified regimen), with OS of 95.3% but associated TRM of 4.6%. Ongoing studies have generally confirmed excellent disease outcomes with escalated BEACOPP, but improvements over ABVD are offset by secondary malignancy, toxicity, and a lack of OS benefit.

Consolidation with IFRT for patients following chemotherapy for advanced-stage disease is likely of small benefit in settings with PET negativity. Patients with PET-positive PR may benefit from additional RT, a particular consideration in older patients where salvage IFRT/ASCR may not be an option.

Relapsed/Refractory Disease

Second-line chemotherapy (ICE, GND) followed by HDT/ASCR for chemosensitive disease has been demonstrated to result in curative outcomes in more than 60% of patients, although this is modified by risk factors of B symptoms, extranodal sites of disease, and relapse less than 12 months from diagnosis at time of relapse. Patients with 0–1 risk factor have 5-year EFS and OS of 83% and 90%, while those with all three risk factors have EFS and OS of 10% and 25%, respectively.

Brentuximab vedotin (BV) is an antibody drug conjugate targeting CD30 with activity in relapsed and refractory CD30-positive lymphomas. Single-agent activity in relapsed disease post transplant results in ORR and CR of 75% and 34%, respectively. Maintenance BV posttransplant (AETHERA trial) improves PFS in a randomized study, without OS impact to date. Clinical trials are now incorporating BV earlier in the treatment paradigm to determine if it can improve outcomes and decrease toxicity. BV + ABVD was associated with pulmonary toxicity in a phase I trial, and consequently, ongoing efforts combine BV with AVD, eliminating bleomycin. This may be a desirable option for older patient in whom bleomycin is a frequent and, at times, fatal cause for significant pulmonary toxicity.

These outcomes must always be considered in the context of the life expectancy of patients at the time of diagnosis. In many instances, despite comorbidity, HL will represent the most immediate threat.

The CALGB 8251 trial was a prospective trial reporting outcomes with ABVD in older patients. In this analysis, patients 60 years or older had 5-year OS of 31% versus 63% for those aged 40 to 59, and 79% for those less than 40 years old.

The SHIELD study prospectively studied the VEPEMB (vinblastine, cyclophosphamide, procarbazine, etoposide, mitoxantrone, bleomycin, prednisolone) program in older patients, with phase II data demonstrating 3-year PFS and OS of 58% and 66%, respectively, for advanced-stage patients. For early-stage patients, 74% of patients achieved CR with PFS at 3 years of 87%.

For patients to whom anthracycline-based therapy cannot be given, regimens such as ChlVVP, MOPP, and C-MOPP can be considered.

FOLLOW-UP AND SURVIVORSHIP IN NHL AND HL

Based on the revised Lugano classification for response assessment, PET-CT scan should generally be utilized at the end of treatment to assess response based on a Deauville 5-point scale. This is generally performed 6 to 8 weeks following chemotherapy or chemo-immunotherapy. CT imaging is preferred in low or variable FDG-avid histologies. A complete metabolic response, even with persistent mass, is considered complete remission and has been associated with similar outcomes. Consequently, the term complete remission, unconfirmed (CRu), introduced in the IWF is no longer utilized.

Deauville score (5-point scale) (**Table 105-8**) utilizes the patient's FDG uptake in the mediastinal blood pool and liver as internal controls to assess disease response. Scores of 1-2 are generally consistent with a complete metabolic response. Scores of 3 require integration of the clinical context and whether or not the value is being used to change therapy in the setting of a clinical trial.

TABLE 105-8 DEAUVILLE 5-POINT SCALE

- 1—No uptake
- 2—Uptake ≤ mediastinal blood pool
- 3—Uptake > mediastinal blood pool but ≤ liver
- 4—Uptake moderately > liver uptake, at any site
- 5—Uptake markedly higher than liver (ie, two to three times the maximum SUV in the liver) and/or new lesions
- X—New areas of uptake unlikely to be related to lymphoma

Surveillance imaging in remission is increasingly discouraged, given the lack of evidence demonstrating improvement in survival and concerns over exposure to medical radiation. The clinical context is important to consider when making these decisions, as risk of relapse is greatest in the 1 to 2 years following completion of therapy for aggressive histologies. Given the long natural history of indolent lymphomas, judicious use of follow-up scans can be considered, particularly when intra-abdominal retroperitoneal disease is present. The risks of secondary malignancies for medical radiation exposure may have less impact in patients diagnosed at older age given the latency period.

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Chapter 106

Coagulation Disorders

Stacy A. Johnson, Matthew T. Rondina

Learning Objectives

- Understand the pathophysiology, diagnosis, and treatment of venous thromboembolism (VTE) in older patients.
- Understand the role of target-specific oral anticoagulants (TSOACs) in the management of older patients with VTE.
- Review current guidelines for the prevention of VTE in older adults.
- Understand how aging alters hemostatic pathways to increase the risk of both thrombosis and hemorrhage.
- Review the evaluation of older adults with hemorrhagic disorders.

Key Clinical Points

1. **Aging is associated with an increased risk of VTE.**
2. **The risk of hemorrhage also rises with age and is most commonly due to acquired bleeding disorders and disorders of platelet number or function.**
3. **TSOACs are safe and effective in carefully selected older adults for the prevention and treatment of thromboembolism.**
4. **A careful consideration of the net clinical benefit of anticoagulation in older adults is integral to the selection and management of oral anticoagulants in this high-risk population.**

INTRODUCTION

This updated chapter provides some new information on this topic. Due to space constraints, we are unfortunately unable to exhaustively cite the primary literature in this field. The reader is also referred to Chapters 45, 81, and 103, which contain additional information related to thrombotic and hemorrhagic disorders in older adults.

VENOUS THROMBOTIC DISORDERS

Definition and Brief Summary

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE) are common and, in many cases, preventable causes of in-hospital death in the United States. Age and accumulation of comorbidities markedly increase the risk of VTE in older adults increasing incidence, prevalence, morbidity, and mortality versus young adults. However, the diagnosis of VTE remains underrecognized in older adults. Clinical suspicion is essential to a prompt diagnosis in older adults who may have an atypical presentation; autopsy studies demonstrate PE is frequently not suspected, nor identified, despite being the cause of death in older persons. Despite this underrecognition in seniors, the diagnostic approach remains similar across all age groups. Antithrombotic agents are the mainstay of VTE treatment given their substantial risk reductions in VTE recurrence and mortality. However, the benefit of VTE treatment may be offset in older adults by an increased risk of major bleeding complications. Balancing the risks of recurrence with hemorrhage is important to guide treatment duration.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Incidence of VTE

In the general population the annual incidence of VTE approximates 1 in 1000 persons and appears to be increasing over time. Notably, incidence rates rise exponentially with age with an approximate 7- to 10-fold increase from less than 55 years to greater than 75 years.

Risk Factors

One or more clinical risk factors are usually identifiable at the time of VTE diagnosis in older adults. In patients presenting with a first episode of VTE, recent hospitalization is the most common risk factor. Additional known risk factors include recent surgical procedures, malignancy, acute infection, impaired mobility, heart failure exacerbation, chronic lung disease, central venous catheter placement, prior VTE, inflammatory bowel disease, and hormonal therapy. Major orthopedic procedures such as elective hip and knee arthroplasty, or surgical repair of a hip fracture, are additional major VTE risk factors in older adults. Less commonly occurring risk factors include antiphospholipid antibodies, heparin-induced thrombocytopenia (HIT), nephrotic syndrome, myeloproliferative disorders, and heritable thrombophilic disorders (factor V Leiden, prothrombin gene mutation, protein C/S deficiency, antithrombin deficiency).

Aging is considered as a nonmodifiable risk factor; as patients age they may accumulate VTE risk factors with additive risk. Impaired mobility, malignancy, and medical comorbidities (ie, heart failure and chronic lung disease) are common in seniors and highlight the importance of VTE awareness in older adults.

Venous Thrombosis Formation

Venous thrombi are comprised of red blood cells (RBCs), white blood cells, and platelets enmeshed in a fibrin lattice (**Figure 106-1**). The triad of vascular endothelial injury, stagnant blood flow, and hypercoagulability predisposes to thrombus formation. Typically venous thrombi form in an area of blood vessel injury or venous stasis. Endothelial injury activates the clotting cascade shifting the natural balance between blood coagulation and fibrinolysis toward thrombus formation. The sinuses behind venous valve cusps represent particularly vulnerable areas for thrombus formation due to disturbed blood flow and stasis. Venous stasis lengthens the time coagulation factors are exposed to sites of vascular injury, further propagating clot formation.

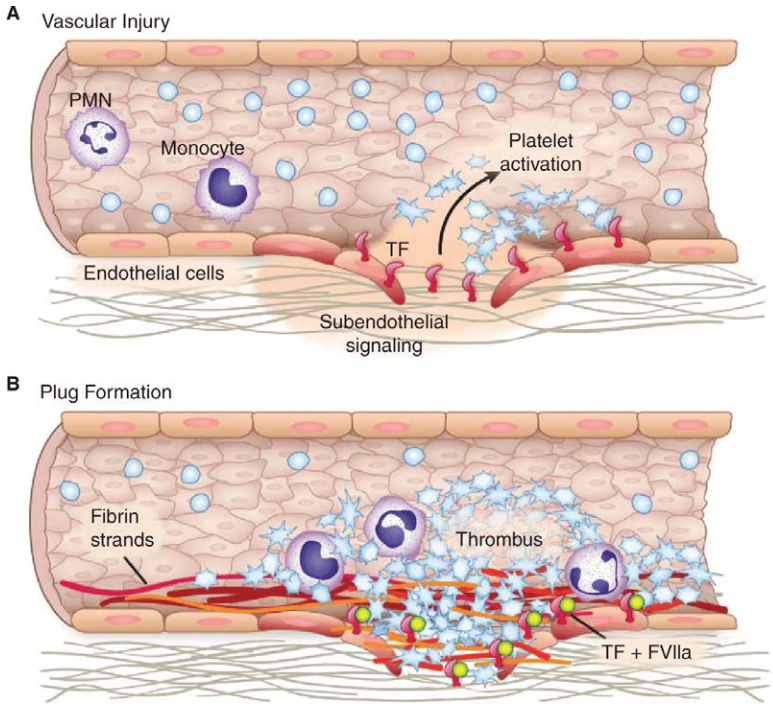


FIGURE 106-1. Thrombus formation may occur at areas of endothelial or vascular wall injury. Under normal physiologic conditions, this rapid, dynamic process is localized to the site of injury. **A.** Upon exposure of tissue factor (TF) in the exposed endothelium, there is initial platelet activation and adhesion with binding of platelets to the damaged vessel. **B.** As formation of the hemostatic plug continues, additional platelets, monocytes, polymorphonuclear cells (PMNs), and other cells migrate to and become incorporated within the hemostatic plug. Deposition of fibrin strands additionally helps seal the injured area.

Vessel injury from inflammation, surgery, trauma, or malignancy exposes subendothelial proteins, specifically tissue factor and collagen. Initial thrombin generation and subsequent coagulation cascade activation are precipitated by tissue factor (**Figure 106-2**). Exposed collagen acts as binding sites for platelet activation and aggregation. Inflammatory cytokine release increases plasminogen activator inhibitor 1 (PAI-1) levels, downregulating thrombomodulin production and its associated anticoagulant effect.

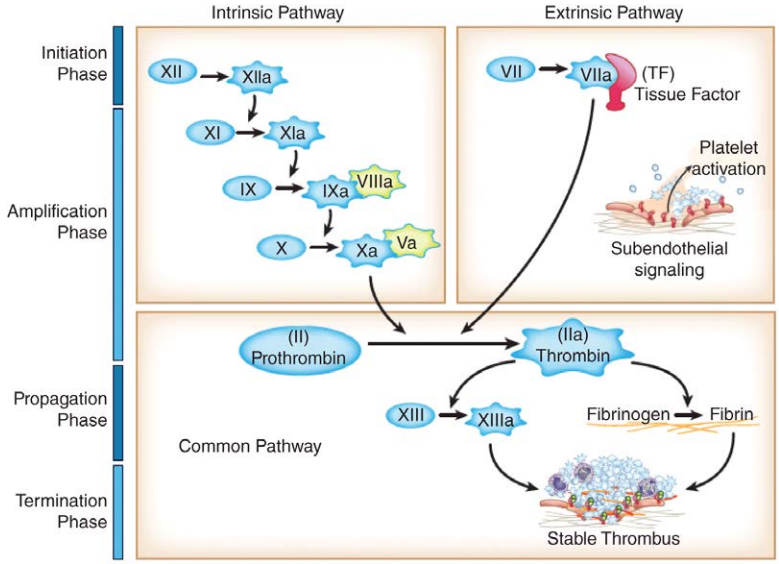


FIGURE 106-2. The clotting cascade is a complex series of pathways and key events. The coagulation cascade may be divided into the intrinsic and extrinsic pathways and, in parallel, also considered in the context of a cell-based model of coagulation that occurs on the cell surface in four sequential phases, as illustrated on the left side of this panel and described in Table 106-4: (1) initiation, (2) amplification, (3) propagation, and (4) termination. The primary event for initiation of the extrinsic pathway is the interaction between activated factor VII (FVIIa) and exposed tissue factor (TF), often at areas of endothelial or tissue injury. The intrinsic pathway begins with activation of factor XII, driving subsequent activation of factors XI, IX, and X. Both the intrinsic and extrinsic pathways result in the conversion of prothrombin (FII) to thrombin (FIIa), in the final common pathway. Thrombin then converts fibrinogen to fibrin, and overlapping fibrin strands are cross-linked and stabilized by activated factor XIII (FXIIIa), resulting in stable thrombus formation.

Impaired venous blood flow is attributable to several factors commonly found in older adults. Reduced mobility leads to venous pooling in the legs, development of venous varicosities, and associated venous valvular incompetence. Polycythemia from dehydration, chronic hypoxemia or a myeloproliferative disorder, or hypergammaglobulinemia related to chronic inflammation or multiple myeloma results in blood hyperviscosity, further altering blood flow and increasing thrombotic risk. Venous outflow obstruction from incompletely resolved DVT or extrinsic venous compression may worsen venous stasis and promote thrombosis.

Blood coagulation is carefully regulated by inhibitors of thrombin generation and subsequent fibrin formation and the fibrinolytic system. Disruptions in these counterregulatory systems may be inherited or acquired. The circulating antithrombotic proteins including proteins C and S and antithrombin are essential to prevent unabated fibrin formation. Proteins C and S and antithrombin deficiencies are uncommon, occurring in 0.02% to 0.3% of the population, usually presenting with a first episode of VTE between 20 and 50 years. The most common heritable thrombophilia is activated protein C (APC) resistance, accounting for 40% to 50% of cases in Caucasians. A point mutation in the factor V gene (substitution of arginine to glutamine) at amino acid 506, called factor V Leiden, renders it insensitive to degradation by APC and is the principle cause of APC resistance. Up to 20% of patients presenting with a first episode of VTE are carriers of the factor V Leiden mutation, the majority presenting before age 70. The *G20210A* prothrombin gene mutation is a point mutation resulting in a 30% increase in prothrombin levels. Heterozygous carriers account for roughly 6% of first-time VTE, equally distributed across age groups.

Acquired thrombophilic disorders in older adults include antiphospholipid syndrome, hyperhomocysteinemia, HIT, hormone replacement therapy, myeloproliferative disorders, and malignancy. The antiphospholipid syndrome is

defined by persistent circulating antiphospholipid antibodies (aPL) and the presence or history of thrombosis and/or pregnancy-related morbidity. Anticardiolipin antibodies, β_2-glycoprotein I antibodies, and the lupus anticoagulant are considered the clinically significant aPL, exhibiting widely variable thrombotic risk. These antibodies target multiple sites resulting in monocyte, platelet, complement, and endothelial cell activation; tissue factor production; and cytokine production, contributing to arterial and venous thrombotic events, thrombocytopenia, pregnancy morbidity, and cardiac valvular disease. aPL prevalence increases with age, yet many patients remain asymptomatic. Therefore the clinical significance of aPL in older adults remains uncertain, and routine screening is not recommended.

Similar to the antiphospholipid syndrome, hyperhomocysteinemia is associated with arterial and venous thromboembolic (TE) events. Increased homocysteine levels may be related to nutritional deficiencies of folic acid, vitamin B_6, and especially vitamin B_{12} (due to gastric atrophy), occurring more frequently in older adults. Hyperhomocysteinemia is implicated in multiple mechanisms of vascular injury: oxidative stress–induced endothelial injury; platelet accumulation; attenuation of tissue plasminogen activator binding sites; inhibition of protein C and heparin sulfate; and activation of coagulation factors V and VII. Despite the association of hyperhomocysteinemia with vitamin deficiency, vitamin therapy has not been shown to be an effective risk-reduction strategy for VTE.

HIT is a drug-induced immune-mediated thrombophilia that may develop after heparin exposure. Antibodies targeting platelet factor 4 increase platelet activation and consumption, activating the coagulation cascade, with resultant arterial and venous thrombi. Hormone replacement therapy to treat postmenopausal symptoms increases TE risk nearly threefold, especially in the first year of use. Myeloproliferative disorders including polycythemia vera, primary myelofibrosis, and essential thrombocytosis are frequently associated with thrombosis. Patients with polycythemia vera or essential thrombocytosis are particularly prone to thrombosis of the splanchnic veins (hepatic, portal, splenic, and mesenteric).

PRESENTATION

Venous thrombi may originate in superficial or deep veins anywhere in the body, most commonly developing in the leg veins. The deep and intramuscular calf veins are frequent sites of thrombus initiation. When the balance of the fibrin generation overwhelms the fibrinolytic system, thrombus extension into the proximal leg veins may occur. Calf vein extension into the proximal leg veins occurs in about 7% to 8% of cases, less frequently than previously suspected. Venous thrombi that are poorly adherent to the vessel wall may spontaneously embolize into the pulmonary circulation, occurring in up to 50% of cases. The majority of PE originates from lower extremity DVT, although with the increasing use of central venous catheters, PE associated with upper extremity DVT occurs in up to one-third of cases.

Acute Venous Thromboembolism

Symptoms of acute superficial venous thrombosis (SVT) are easily recognized by localized tenderness over the affected veins, swelling, erythema, warmth, and often a palpable thrombus within the vein. DVT may be asymptomatic or minimally symptomatic when confined to the calf veins. Proximal DVT involving the popliteal or femoral veins typically results in asymmetrical leg swelling, diffuse tenderness, erythema, and engorgement of collateral veins if the thrombus is occlusive. Pulmonary embolism can range from asymptomatic, to mild chest discomfort and dyspnea, to severe pleuritic pain and breathlessness, or sudden death with massive PE. Additional signs and symptoms include hemoptysis, cough, tachypnea, tachycardia, syncope, fatigue, and hypoxemia.

Chronic Venous Thromboembolism

Although acute VTE is associated with significant morbidity and mortality, chronic symptoms may develop following an acute event. The postthrombotic syndrome (PTS) develops in approximately 25% to 30% of all patients who experience a DVT due to chronic venous occlusion and incompetent venous valves, damaged by the acute DVT. Symptoms of PTS include chronic leg pain, swelling, hyperpigmentation, and leg ulcerations in severe cases (10%). PTS is associated with a large socioeconomic burden with an estimated 2 million lost workdays in the United States, and in 1999 an average cost of $10,000 per patient/year to treat leg ulcerations.

A devastating complication that may arise following PE is chronic thromboembolic pulmonary hypertension (CTEPH). Chronically occluded pulmonary arteries are responsible for CTEPH symptoms including chronic dyspnea and leg swelling from right-sided heart failure. The incidence of CTEPH ranges from 1% to 9% in reported series with

limited treatment options.

DIAGNOSIS

Deep Vein Thrombosis

Clinical prediction models Limb swelling, pain, erythema, and warmth should prompt evaluation for DVT. Clinical assessment alone cannot accurately identify DVT, and it is estimated that of all patients evaluated, only 20% have the disease. The integration of clinical prediction models with laboratory assays and noninvasive imaging allows for accurate DVT diagnosis in the majority of patients. Several scoring systems exist, however the Wells clinical prediction model remains the best validated and most utilized for DVT assessment. Early versions of the Wells model stratified patients into low, moderate, and high pretest probability. The current iteration stratifies patients into two pretest probability categories: DVT likely or DVT unlikely. Points are assigned based on clinical signs and symptoms, medical and surgical history, and clinician judgment regarding the likelihood of DVT (**Table 106-1**). The subjectivity involved with the clinician estimating likelihood is a major criticism of the Wells model. However several studies have shown that when pretest probability is objectively assessed, the accuracy of DVT diagnosis is enhanced, minimizing unnecessary testing.

TABLE 106-1 MODEL FOR DETERMINING CLINICAL SUSPICION OF DEEP VEIN THROMBOSIS

VARIABLES	POINTS[a]
Active cancer (treatment ongoing or within previous 6 mo or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden ≥ 3 d or major surgery within the past 4 wk	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Affected calf 3 cm greater than asymptomatic calf (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Dilated superficial veins (nonvaricose)	1
Previous deep vein thrombosis (DVT)/pulmonary embolism	1
Alternative diagnosis is at least as likely as that of deep vein thrombosis	–2
Total points	

[a]Total score < 2 indicates DVT unlikely; score ≥ 2 indicates DVT likely.

Laboratory testing D-Dimer is a cross-linked fibrin degradation product generated when mature thrombus is cleaved by plasmin. Levels of D-dimer are typically elevated in the presence of acute DVT. However, many other factors are associated with elevated D-dimer levels including advanced age, inflammation, infection, malignancy, and recent surgery, limiting the positive predictive value. Multiple D-dimer assays exist, with the high-sensitivity assays (ELISAs) demonstrating the best clinical utility and highest negative predictive values.

D-Dimer levels alone are insufficient to diagnose or exclude DVT and must be combined with a clinical prediction model (Wells score) and ultrasonography, if warranted. Low pretest probability combined with a negative D-dimer result safely excludes the presence of DVT. A positive D-dimer result in patients with low pretest probability necessitates further imaging to safely exclude DVT. Patients with a high pretest probability of DVT should initially undergo compression ultrasonography; if negative, then a D-dimer should be measured. If the D-dimer result is negative, then DVT is essentially ruled out, and if the D-dimer is positive, then repeat compression ultrasonography in 5 to 7 days is necessary to safely exclude DVT. Age-adjusted D-dimer levels have been proposed to improve the diagnostic accuracy in older patients, but require validation before their adoption into clinical practice.

Imaging

Compression Ultrasonography Noninvasive imaging with compression ultrasonography has essentially replaced

contrast venography as the standard method for DVT diagnosis. Whole-leg compression ultrasound involves imaging the entire venous network every 1 to 2 cm along its course with external pressure applied through the ultrasound transducer to visualize complete vessel collapse. Incompressibility or partial vessel collapse anywhere along the venous network is the hallmark of an intraluminal filling defect, representative of a thrombus. Supplementary imaging techniques including color Doppler and augmentation (manually squeezing the limb) allow visualization of venous blood flow, or the lack thereof, suggestive of thrombus. Benefits of whole-leg compression ultrasonography are the ability to image proximal and distal veins in a single study, eliminating the need for follow-up imaging. A simplified method, two-point compression ultrasound, relies solely on imaging the common femoral and popliteal veins. This method is easier and less time intensive to perform compared to whole-leg ultrasound, which is highly operator dependent and not widely available. Two-point ultrasound cannot exclude distal vein thrombus in a single study and therefore must be combined with pretest probability assessment and D-dimer testing. Patients with low pretest probability (DVT unlikely) and a positive D-dimer result can safely forego antithrombotic therapy following a negative two-point compression ultrasound. However, patients with higher pretest probability (DVT likely) and a positive D-dimer must undergo serial two-point compression ultrasound studies approximately 1 week apart to safely exclude DVT.

While whole-leg ultrasound is a more comprehensive examination and frequently identifies distal DVT, the majority will not extend proximally and will resolve spontaneously. The overdiagnosis and overtreatment of clinically insignificant findings may increase the risk of bleeding, especially in older patients.

Contrast Venography Contrast venography is the gold standard for DVT diagnosis, but has largely been replaced by noninvasive compression ultrasonography. It requires placement of an intravenous catheter into a distal vein and injection of contrast media followed by a series of radiographic images. These examinations are technically difficult to perform, painful to the patient, and are associated with risks of allergic reactions and contrast-induced nephropathy. In older adults, the age-associated decline in renal function significantly increases the likelihood of contrast-induced nephropathy; therefore the role of venography is generally limited to clarify discrepancies between high clinical probability and nondiagnostic ultrasonography.

Pulmonary Embolism

Clinical prediction models Presenting signs and symptoms of acute PE are nonspecific and often insufficient for diagnosis. The most common symptoms reported in older adults include dyspnea, tachypnea, tachycardia, and chest pain. Symptoms of DVT (leg pain and swelling) are present in more than 40% of patients with acute PE, and simultaneous DVT is identified in up to 60% of patients diagnosed with a PE. Clinical signs including rales, accentuated pulmonic second heart sound, and jugular venous distension may be identified at presentation. Similar to DVT, these signs and symptoms are not accurate enough to diagnose pulmonary emboli, but are useful to estimate pretest probability and guide additional testing.

Probability estimation of PE can be accomplished through several clinical prediction models, including the Geneva or Wells scores, or even clinical gestalt. The Wells score for PE is the best-validated scoring system and utilizes different clinical signs and symptoms than the DVT prediction model, although still incorporating the subjective assessment of PE likelihood, a potential weakness. The simplified version of the Wells score stratifies patients as "likely" or "unlikely" (**Table 106-2**) and, when combined with a D-dimer assay and computed tomographic pulmonary angiography (CTPA), provides an effective diagnostic strategy for PE.

TABLE 106-2 MODEL FOR DETERMINING A CLINICAL SUSPICION OF PULMONARY EMBOLISM

VARIABLES	POINTS[a]
Clinical signs and symptoms of deep vein thrombosis (minimum of leg swelling and pain with palpation of the deep veins)	3.0
An alternative diagnosis is less likely than pulmonary embolism (PE)	3.0
Heart rate > 100 beats/min	1.5
Immobilization or surgery in the previous 4 wk	1.5
Previous deep vein thrombosis/pulmonary embolism	1.5

Hemoptysis	1.0
Malignancy (treatment ongoing or within previous 6 mo or palliative)	1.0
Total points	

[a]Total score ≤ 4 indicates PE unlikely; score > 4 indicates PE likely.

Imaging

Chest Radiography The diagnostic utility of chest radiography in suspected PE is primarily to exclude other causes of dyspnea and hypoxemia (ie, pneumothorax or pneumonia), as most chest radiographs are normal with an acute PE. Identifiable signs of PE on chest radiography include oligemia (Westermark sign), a focal area of decreased perfusion of pulmonary vessels distal to the PE; wedge-shaped pleural-based opacity (Hampton hump) representative of a pulmonary infarct; and hilar enlargement, due to thrombus impaction and pulmonary artery engorgement.

Pulmonary Angiography Similar to contrast venography for DVT, pulmonary angiography was the reference standard for diagnosis of PE but has largely been replaced by noninvasive imaging due to its technical difficulty and invasiveness. Compared to modern CTPA, conventional pulmonary angiography was demonstrated to be less accurate than CTPA with more falsely abnormal studies. Given the lack of diagnostic superiority combined with potential complications of respiratory distress, angina, hematoma formation at catheter insertion sites, arrhythmia, and cardiac arrest, pulmonary angiography is now rarely performed.

Ventilation-Perfusion Lung Scanning Prior to widespread adoption of CTPA, ventilation-perfusion lung scanning was the most reliable noninvasive imaging modality to diagnose PE. Many factors have contributed to its declining use including lack of availability at some institutions, time needed to perform an examination, and frequently encountered nonspecific test results. However, lung scanning remains clinically useful in older patients with renal insufficiency or contrast allergy, or when attempting to minimize external beam radiation to the chest of young females.

In suspected PE, the performance characteristics of lung scanning improve when paired with a normal chest radiograph and pretest probability assessment. For example, a patient with high clinical probability and a high probability scan has a 96% likelihood of having PE, whereas low clinical probability paired with a low probability scan has a 4% likelihood of having PE; a normal perfusion scan essentially excludes PE. Unfortunately, the majority of patients presenting with suspected PE will have nondiagnostic imaging and require additional evaluation. The increased prevalence of abnormal chest radiographs and high pretest probability in older adults, further limits the utility of lung scanning.

Computed Tomographic Pulmonary Angiography Widespread availability and technological advances in CTPA have made it the primary imaging modality for suspected PE, except when contraindicated (severe renal insufficiency or contrast allergy). When compared to conventional pulmonary angiography, CTPA performs similarly well, essentially replacing conventional pulmonary angiography as the reference standard. The advent of multidetector CT scanners' spatial and temporal resolution has improved, increasing the sensitivity for PE diagnosis. Although the increased use of CTPA and the addition of more detectors have resulted in greater recognition of PE, a corresponding decline in mortality has not been seen, raising doubts about the clinical significance of subsegmental PE.

To minimize the number of unnecessary imaging studies and potential overtreatment of clinically insignificant PE, CTPA should be paired with clinical probability assessment. The Christopher study validated this approach by pairing a simplified version of the Wells score with D-dimer measurement and CTPA, if warranted. Patients with "unlikely" pretest probability and a negative D-dimer were not imaged. Whereas patients with a "likely" probability of PE underwent CTPA and antithrombotic therapy was withheld if CTPA findings were normal. Less than 2% of patients with a negative CTPA returned with symptomatic VTE within 3 months of follow-up.

Additional benefits of CTPA over other imaging modalities are its abilities to simultaneously diagnose PE and detect right ventricular dilation (useful in risk stratification) and to identify alternative diagnoses when PE is not present, especially useful in older adults with atypical presentations.

Laboratory testing Similar to its role in DVT evaluation, a negative D-dimer result combined with unlikely pretest probability can safely exclude the diagnosis of PE. Alternatively, a positive D-dimer result must be followed up with an imaging study. Importantly, up to 10% of patients with likely pretest probability and a negative D-dimer result suffered a VTE event within 3 months of follow-up, demonstrating D-dimer alone is not reliable enough to exclude PE in this population.

TREATMENT OF VENOUS THROMBOEMBOLISM

Management of Acute Venous Thromboembolism

Overview Historically, acute VTE management has centered on prompt administration of parenteral anticoagulation, followed by risk stratification, and initiation of long-term oral anticoagulation (OAC) to minimize recurrence and VTE-associated morbidity (postthrombotic syndrome and chronic thromboembolic pulmonary hypertension). Recent management studies have successfully used VTE risk stratification systems to identify patients that may be safely treated as outpatients. Additionally, the regulatory approval of several new TSOACs for the treatment and prevention of VTE has broadened therapeutic options and improved outcomes.

Antithrombotic therapy Initial VTE treatment requires an anticoagulant with a rapid onset of action to reduce thrombus extension, recurrence, or embolization. This is accomplished through parenteral anticoagulants such as unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). Parenteral agents rapidly achieve the desired anticoagulant effect and must overlap initiation of a vitamin K antagonist (VKA). Alternatively, select TSOACs (rivaroxaban and apixaban) can be safely administered for initial VTE treatment, forgoing parenteral anticoagulation entirely.

UFH use is declining for VTE treatment, however it remains useful in patients with renal insufficiency or high bleeding risk where rapid reversal may be needed, conditions commonly encountered in older adults. UFH may be administered as a continuous infusion or subcutaneously in doses sufficient to achieve therapeutic levels. Intravenous administration typically begins with a bolus dose of 80 U/kg followed by a continuous infusion of 18 U/kg/h. Close laboratory monitoring (every 6 hours until stable) is essential to ensure the desired therapeutic effect and to minimize bleeding. Monitoring is done with either the activated partial thromboplastin time (aPTT) or an antifactor Xa (anti-Xa) activity assay. Expert consensus recommends a therapeutic heparin range of 0.35 to 0.7 U/mL measured by anti-Xa activity, which is typically 1.5 to 2.5 times the control aPTT. Alternatively, short courses of fixed-dose subcutaneous UFH (333 U/kg load, then 250 U/kg every 12 hours) may be safely used in some patients for initial treatment and without laboratory monitoring.

Subcutaneous LMWH has more predictable pharmacology than UFH infusions. This allows outpatient VTE treatment with fixed, weight-based doses without routine laboratory monitoring in select patients. A large meta-analysis conducted by the Cochrane Collaboration recently demonstrated LMWH is associated with fewer thrombotic complications, less major bleeding, and a mortality benefit when compared to UFH for VTE treatment. Additionally, in patients with active cancer, long-term LWMH is recommended as first-line therapy over VKAs based on a lower VTE recurrence rate.

Oral antithrombotic therapy with warfarin was the cornerstone of VTE treatment for nearly 60 years, until the introduction of TSOACs. Warfarin initiation must be overlapped with a parenteral anticoagulant for a minimum of 5 days, and until the international normalized ratio (INR) is greater than 2.0 for at least 24 hours, due to its delayed antithrombotic effect. Warfarin's narrow therapeutic window (INR 2.0–3.0) and numerous food and drug interactions necessitate routine INR monitoring for the duration of therapy. Close INR monitoring is especially important in older adults as they may require lower total warfarin doses, have a higher prevalence of polypharmacy, and have higher risks of major bleeding.

Target-specific oral anticoagulants TSOACs represent a new group of anticoagulants targeting specific sites within the coagulation cascade. Dabigatran is a direct thrombin inhibitor that competitively binds to soluble and fibrin-bound thrombin, inhibiting the conversion of fibrinogen to fibrin and subsequent thrombus formation. Rivaroxaban, apixaban, and edoxaban are factor Xa inhibitors that selectively block the active site of factor Xa, inhibiting the coagulation cascade without the use of a cofactor (antithrombin). Additional appealing attributes of the TSOACs include fewer drug interactions and more predictable pharmacology than warfarin, minimizing the need for routine laboratory monitoring and frequent dose adjustments.

As with all anticoagulants, safety is an important consideration. Baseline assessment of bleeding risk, measurement of renal and liver function and platelet count, and a thorough medication review are essential prior to TSOAC administration. Unlike heparin and warfarin that can be reversed with protamine and vitamin K or plasma administration, respectively, there are currently no Food and Drug Administration (FDA)-approved, specific reversal agents for TSOACs. Four-factor prothrombin complex concentrate (PCC), comprised of coagulation factors II, VII, IX,

and X, has been evaluated in small studies and may be effective in correcting coagulation assay derangements following rivaroxaban administration. Activated forms of PCC (aPCC) or recombinant factor VIIa may be effective in reversing effects of dabigatran, although data are limited. Targeted reversal agents including a recombinant factor Xa protein without enzymatic activity and a dabigatran-specific monoclonal antibody are under development.

Several VTE management studies have demonstrated the TSOACs to be noninferior to warfarin with respect to efficacy, with some having superior safety profiles. The RE-COVER and Hokusai VTE studies compared warfarin to dabigatran and edoxaban, respectively. One important design of these studies was the requirement of an initial course of heparin (UFH or LMWH), prior to TSOAC initiation. In comparison, the EINSTEIN and AMPLIFY studies compared conventional therapy to rivaroxaban and apixaban as monotherapy, without preceding heparin. These studies also established that the bleeding risk with apixaban, edoxaban, and rivaroxaban (in EINSTEIN-PE) is significantly lower compared to warfarin. Dabigatran has a similar bleeding risk profile to warfarin. Given the generally favorable bleeding profiles, the ability to forego parenteral anticoagulation with certain agents, and avoidance of routine laboratory monitoring, VTE treatment with TSOACs provides some advantages for health care providers and carefully selected patients.

Duration of antithrombotic therapy The duration of antithrombotic therapy is determined by balancing the thromboembolic risk with the bleeding risk. Pooled analysis of several studies demonstrates a 4- to 6-week course of antithrombotic therapy compared to 3 to 6 months is associated with an unacceptably high risk of VTE recurrence (relative risk [RR] = 1.83). Longer treatment courses (6–12 months) did not significantly reduce VTE recurrence, however major bleeding events more than doubled (RR = 2.49) compared to 3 months of therapy. In general VTE provoked by a transient (ie, reversible) risk factor such as surgery or trauma is associated with a low risk of recurrence and a 3-month treatment course is sufficient. Whereas VTE without identifiable risk factors (ie, unprovoked) is associated with nearly 20% risk of recurrence at 2 years, and 30% risk of recurrence at 8 years. Extended therapy (> 3 months) is reserved for unprovoked VTE with low-moderate bleeding risk and recurrent unprovoked VTE with high bleeding risk. The decision to continue long-term antithrombotic therapy must be periodically revisited (ie, annually), especially in older patients who are at increased risk for bleeding complications.

Thrombolytic therapy Age greater than 75 is considered a relative contraindication to thrombolytic therapy and thus thrombolytics currently have a limited role in older adults. Patients presenting with massive PE, defined as acute PE with arterial hypotension (systolic blood pressure < 90 mm Hg or a drop in systolic blood pressure ≥ 40 mm Hg, sustained for 15 minutes) may benefit from systemically administered thrombolytics. Catheter-directed thrombolysis is an alternative treatment for massive PE if systemic administration is contraindicated. The role of thrombolytics for intermediate-risk PE (normotensive patients with evidence of right ventricular dysfunction) was evaluated in the PEITHO study. There was a reduction of hemodynamic decompensation without a mortality benefit, but at the cost of marked increases in major bleeding and hemorrhagic strokes. Patients over 75 years suffered significantly more major bleeding events than younger patients.

Catheter-directed thrombolysis of iliofemoral DVT to reduce the risk of postthrombotic syndrome was evaluated in the CaVenT study. Although patients over 75 years were excluded, those with iliofemoral DVT and low bleeding risk who underwent catheter-directed thrombolysis demonstrated an absolute risk reduction of 14.4% in development of postthrombotic syndrome at 24 months. No difference in clinical symptoms was evident at 6 months, highlighting the importance of proper patient selection with a life expectancy sufficiently long enough to realize a benefit. Additionally, further studies are needed to determine the relative safety and efficacy of these strategies in older adults.

Primary venous thromboembolism prophylaxis Extensive clinical practice guidelines have been published by professional societies addressing a wide range of indications for VTE prophylaxis and should be referenced for detailed guidance. In general, all hospitalized patients should be evaluated for VTE prophylaxis on an individualized basis. Clinical scoring systems exist to guide these decisions for medical and surgical patients. For example, in medical patients, the Padua Prediction Score (**Table 106-3**) incorporates intrinsic factors and acute physiologic condition, with points assigned on a weighted scale. A cumulative score greater than or equal to 4 points is considered high risk and is associated with a 32-fold increased incidence of VTE compared to a low-risk score, which is less than 4 points. When the VTE risk is high and pharmacologic prophylaxis is being considered, bleeding risk must also be estimated. Although, bleeding risk scoring systems to guide VTE prophylaxis are not well developed or validated, active peptic ulcer disease, thrombocytopenia (platelets < 50 k/μL), and age greater than 85 are considered to carry excessive bleeding risk and may preclude pharmacologic prophylaxis.

TABLE 106-3 MODEL FOR DETERMINING A RISK OF VENOUS THROMBOEMBOLISM (VTE) IN HOSPITALIZED MEDICAL PATIENTS

VARIABLES	POINTS[a]
Malignancy (ongoing treatment or within previous 6 mo)	3
Previous deep vein thrombosis/pulmonary embolism	3
Immobilization (≥ 3 d)	3
Known thrombophilic disorder	3
Recent surgery and/or trauma	2
Age ≥ 70 y	1
Respiratory and/or cardiac failure	1
Acute ischemic stroke or myocardial infarction	1
Acute infection and/or rheumatologic disease	1
Obesity (BMI > 30)	1
Active hormonal treatment	1

[a]High risk of development of VTE is defined as total score ≥ 4 points.

The choice of pharmacologic and/or mechanical prophylaxis depends on the clinical situation and provider assessment. Pharmacologic agents are generally more effective than mechanical devices and currently approved regimens include low-dose UFH, LMWH, fondaparinux, dose-adjusted warfarin, apixaban, rivaroxaban, and aspirin. Mechanical prophylaxis relies on intermittent pneumatic compression devices or graduated compression stockings to minimize venous stasis and is either used in conjunction with pharmacologic agents for high-risk indications (ie, post–total hip/knee arthroplasty or hip fracture surgery) or as a stand-alone method when bleeding risk is high and pharmacologic prophylaxis is contraindicated.

Secondary venous thromboembolism prophylaxis Indefinite antithrombotic therapy is highly effective in reducing recurrent VTE, a benefit that is offset by more major bleeding compared to shorter treatment courses. Two small studies suggest treatment with low-dose aspirin following a standard VTE treatment course may reduce recurrence nearly 50%, without significantly increasing bleeding. In a similar study, prophylactic doses of apixaban reduced recurrent VTE by 67% without increased bleeding, compared to placebo. The net clinical benefit of secondary VTE prophylaxis (reduced VTE vs increased bleeding) must be considered in older patients given their increased risks of VTE and bleeding.

HEMORRHAGIC DISORDERS

Definition and Background

Hemostasis typically refers to the process of thrombus formation at areas of endothelial or vascular wall injury (see **Figure 106-1**). Under normal physiologic conditions, this process is localized to the site of injury and is rapid, dynamic, and highly regulated. Phases of this response include initial formation of the platelet plug following endothelial injury, activation of the coagulation cascade for further hemostatic control, induction of antithrombotic control mechanisms to limit or halt thrombus formation, and, finally, fibrinolysis for thrombus removal.

Coagulation cascade While the clotting cascade is a complex series of pathways, several key events are briefly reviewed here. Classically, the coagulation cascade has been divided into the intrinsic and extrinsic pathways, as illustrated in **Figure 106-2.** In more years, investigators have proposed a cell-based model of coagulation that occurs on the cell surface in four overlapping steps: (1) initiation, (2) amplification, (3) propagation, and (4) termination (**Table 106-4**). The primary event for initiation of the clotting cascade and subsequent thrombus formation is interactions of activated factor VII (FVIIa) with exposed tissue factor, an integral membrane glycoprotein, at areas of endothelial or tissue injury. The TF-FVIIa complex then activates factors IX (FIX) and X (FX), leading to the release and activation of factor V (FV) from platelet α-granules. Activated FX (FXa) links with activated FV (FVa)

converting factor II (FII, also known as prothrombin) to thrombin (FIIa). Thrombin then converts fibrinogen to fibrin and overlapping fibrin strands are cross-linked and stabilized by activated factor XIII (FXIIIa).

TABLE 106-4 KEY PHASES OF THE CELL-BASED MODEL OF COAGULATION*

PHASE OF COAGULATION	DESCRIPTION OF KEY EVENT(S)	LOCATION OF KEY EVENT(S)
Initiation	Factor VIIa/TF complexes activate factors V, X, and IX resulting in conversion of prothrombin to thrombin	TF-expressing cells, including monocytes, endothelial cells, and platelets
Amplification	Smaller amounts of thrombin generated during the initiation phase activate platelets and factor VIII/vWF complexes	The surface of activated platelets
Propagation	Platelets generate more substantial amounts of thrombin and form stable fibrin plugs	The surface of activated platelets
Termination	Endogenous anticoagulants, such as TFPI, PC, PS, and AT limit widespread thrombotic occlusion	The site of injured endothelium or vasculature

AT, antithrombin; PC, protein C; PS, protein S; TF, tissue factor; TFPI, tissue factor pathway inhibitor; vWF, von Willebrand factor.
*This is a complex series of pathways still incompletely understood but critical events during each phase of this model are described.

Platelets Platelets are integral directors and mediators of hemostatic responses. Following activation by collagen, laminin, microfibrils, and other elements in the exposed subendothelium, platelets are activated, resulting in enhanced aggregatory, secretory, and adhesive responses. For example, following platelet activation, there is a conformational change via inside-out signaling in the platelet glycoprotein (GP) IIb/IIIa receptor (also referred as integrin $\alpha IIb\beta_3$), leading to platelet binding of von Willebrand factor (vWF) and fibrinogen. Exposure of active conformation of the GP IIb/IIIa receptor leads to enhanced platelet aggregation as well as platelet spreading and clot retraction. Genetic absence of either the α-IIb or β_3 subunit is found in patients with Glanzmann thrombasthenia, characterized by abnormal bleeding, which is mostly mucocutaneous. Agents that block the GP IIb/IIIa receptor (eg, abciximab, tirofiban, eptifibatide) are currently used clinically for the treatment of patients with acute coronary syndromes and/or undergoing percutaneous coronary intervention.

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

This risk of hemorrhage rises with age and is most commonly due to acquired bleeding disorders affecting coagulation factors and/or platelet number and function. For example, bleeding due primarily to disorders of coagulation factors may seen in older patients with sepsis and disseminated intravascular coagulation (DIC), liver disease, acquired hemophilia with inhibitors to FVIII, acquired von Willebrand syndrome, or a coagulopathy due to anticoagulant use. Disorders in older adults that may primarily affect platelet number and/or function include adult-onset immune thrombocytopenia (ITP), chronic kidney disease, myeloproliferative disorders, drug-induced thrombocytopenia, and use of antiplatelet agents (APAs). The precise incidence and prevalence of these vary depending on the patient and clinical situation studied. Some of these disorders are described in more detail below.

In addition, and while still incompletely understood, aging itself—devoid of any comorbid influences or anticoagulant/antiplatelet use—has been associated with dysregulation of coagulation factors, fibrinolytic proteins, and activation molecules. Nevertheless, while age-related changes are not uniform, the net effect seemingly results in a tendency toward thrombosis, rather than bleeding. For example, plasma fibrinogen levels, which correlate with an increased risk of cardiovascular disease, increase with age, with an approximate 10 mg/dL incremental rise per decade in healthy subjects. Similarly, levels of vWF, which are stored within platelets and bind collagen at areas of damaged endothelium, increase with aging. FVIII levels also increase with aging and are associated with an increased risk of cardiovascular disease. vWF binds to FVIII, providing a stable platform for continued propagation of thrombin generation.

Components of the fibrinolytic pathway are also altered in older adults. Plasma levels of PAI-1, the major inhibitor of fibrinolysis, increase with aging. While not the only source of PAI-1, platelets synthesize, store, and release large amounts of functional PAI-1. Interestingly, transgenic mice that overexpress a stable variant of human PAI-1

demonstrate spontaneous coronary artery thrombosis that only occurs in older mice (ie, in an age-dependent fashion). While mouse models may not always precisely recapitulate human physiology, these observations provide intriguing mechanistic insights and support clinical observations in older adults.

Aging is also associated with alterations in some the vitamin K–dependent coagulation factors and older adults typically have increased sensitivity to the anticoagulant effects of the vitamin K antagonists (VKAs) (eg, warfarin, Coumadin). Practically, this translates into older adults usually requiring a lower mean daily dose in order to achieve their target INR. While dose requirements will obviously be very patient specific, at least one study reported that adults 75 years and older required less than one-half of the average daily warfarin dose to achieve target INR, compared to younger patients.

PRESENTATION AND DIAGNOSIS

The initial steps to evaluating bleeding in older adults, like many assessments in medical practice, begin with a careful history and physical examination. Identifying and integrating key components of the patient's history and physical examination with laboratory data often allows providers to more precisely diagnose the underlying etiology of a bleeding diathesis. Patients should be asked about the initial onset and site of bleeding, prior bleeding episodes, a history of iron deficiency anemia or transfusions, significant bleeding following minor procedures (eg, tooth extraction), and a history of heavy or long menses (in women).

The presence of other family members with similar bleeding tendencies, particularly in the presence of bleeding that began after birth or during childhood, may suggest an inherited bleeding diathesis. A thorough medication history, including the use of anticoagulants, herbal agents, and over-the-counter (OTC) products, should be obtained. Patients may need to be asked specifically about the use of aspirin, nonsteroidal anti-inflammatories, or other OTC antiplatelet agents. To assess for the possibility of dietary vitamin K deficiency, providers should inquire as the patient's typical diet and whether there have been any changes recently to the diet.

Physical Examination

The physical examination may identify petechiae (small capillary hemorrhages most common on the legs, feet, and ankles), small ecchymotic lesions, epistaxal bleeding, or gingival bleeding if the disorder is primary one of platelet number/function or blood vessels. In contrast, older patients with an inherited or acquired coagulation disorder typically present with large, palpable ecchymoses, soft tissue hematomas, hemarthrosis, and extensive postprocedural bleeding.

Laboratory Evaluation of Coagulation Pathways in Older Adult Patients

Laboratory evaluation includes routine tests available through most laboratories as well as more specialized tests that may require a reference laboratory and the expertise of a hematologist for interpretation. General screening tests include a platelet count, hemoglobin and/or hematocrit, prothrombin time (PT), INR, and aPTT. The PT assay adds calcium and thromboplastin (tissue factor) as a platelet substitute to measure the function of the extrinsic and final common pathways (see **Figure 106-2**). As such, the PT detects deficiencies in the vitamin K–dependent coagulation factors: factors II, VII, IX, and X. If a deficiency in factor VII is suspected, the PT is the most sensitive test available. The aPTT measures components of the intrinsic and common pathway and can detect deficiencies of—or inhibitors to—factors II, V, VIII, IX, X, XI, and XII (see **Figure 106-2**). The aPTT can also be prolonged in patients with abnormalities in fibrinogen levels. Other routine testing (eg, liver or renal function panels, peripheral smears, disseminated intravascular coagulation panel, etc) may be indicated depending on the patient's clinical presentation, history, and physical examination.

Causes of a prolonged PT with a normal aPTT In older patients suspected of having a coagulopathy, examination of any abnormalities in the PT and/or aPTT can help guide clinicians as to the differential diagnostic and appropriate management steps (**Table 106-5**). Causes of a prolonged PT with a normal aPTT include warfarin or other VKA use, vitamin K deficiency, systemic heparin exposure, factor VII deficiency (inherited or acquired), early liver disease, and in some early cases of DIC.

TABLE 106-5 PATTERNS AND EVALUATION OF A PROLONGED PROTHROMBIN TIME (PT) AND/OR ACTIVATED PARTIAL THROMBOPLASTIN TIME (aPTT)*

PT RESULT	aPTT RESULT	POTENTIAL ETIOLOGY
Prolonged	Normal	Intended or surreptitious VKA use Dietary vitamin K deficiency (mild) Factor VII deficiency[a] Early liver disease Early DIC Heparin exposure (high doses)
Normal	Prolonged	Circulating lupus anticoagulant Antiphospholipid antibody syndrome Factor VIII, IX, XI, XII deficiency[a] von Willebrand disease[a] Heparin exposure
Prolonged	Prolonged	Inherited disorder of common pathway Advanced liver disease Systemic fibrinolytic therapy Dietary vitamin K deficiency (severe) Combined heparinoid and VKA exposure Deficiency or inhibitor of factor II, V, X[a] Deficiency or inhibitor to fibrinogen[a] Supratherapeutic anticoagulation

DIC, disseminated intravascular coagulation; VKA, vitamin K antagonist.

[a]May be inherited or acquired.

*This list represents common causes of PT/aPTT prolongations. Other less common causes may also exist and the reader is referred to more comprehensive reviews on this subject.

Causes of a normal PT with a prolonged aPTT Causes of a normal PT with a prolonged aPTT include anticoagulant use (eg, heparin), deficiencies in factor VIII (hemophilia A, von Willebrand disease), factor IX (hemophilia B), and factor XI. Patients with hemophilia A and B, which are the most common causes, usually present earlier in life with recurrent soft tissue and joint bleeding. Factor XI deficiency has a more variable bleeding history, often following surgical procedures, and has been characteristically described in Ashkenazi Jews but is also reported in other ethnic groups. An isolated prolongation in the aPTT may also be due to the presence of a circulating acquired inhibitor. These disorders include antiphospholipid antibody syndrome, although this disorder causes thrombosis instead of bleeding and usually presents earlier in life. In addition, acquired inhibitors to factor VIII may be seen in older adults with solid tumors (adenocarcinoma being most common among these), hematologic malignancies (chronic lymphocytic leukemia being most common among these), rheumatoid arthritis, systemic lupus erythematosus, and drug reactions (penicillin, phenytoin, interferon, fludarabine, and others). The incidence of an acquired factor VIII inhibitor is rare, reported to be approximately 1.5 cases per million per year in unselected patients from the United Kingdom and Wales. In up to 50% of patients, there may be no underlying, identifiable disorder. Older adults presenting with the abrupt onset of a large spontaneous hematoma or ecchymoses without a history of trauma or prior known bleeding diathesis should prompt consideration by clinicians of an acquired factor VIII inhibitor secondary to an underlying disorder, as described above. Often, this bleeding may be severe with one survey reporting a mortality rate of 22% in these patients.

Causes of a prolonged PT and a prolonged aPTT Finally, patients with prolongation of both the PT and aPTT should be suspected of having either an inherited disorder of the common pathway or an acquired disorder that affects the intrinsic, extrinsic, and/or common pathways in combination. In older adults, the most common causes of a prolonged PT and aPTT include anticoagulation with a VKA or heparinoid or simultaneous treatment with a VKA and heparin, such as may occur during the treatment of acute venous thromboembolism. Other possible causes include vitamin K deficiency, more advanced liver disease or DIC, and administration of systemic fibrinolytic agents. Additional diagnostic measures in this setting may include measurements of fibrinogen and fibrinogen degradation

products.

Abnormal Platelet Number in Older Adult Patients The normal half-life of circulating platelets in healthy humans is 8 to 10 days. Any process that disrupts this, leading to reductions in platelet number, may increase the risk of, or cause, bleeding in older adults. Quantitative disorders of platelet number in older adults are numerous and some of the more common of these are outlined in **Table 106-6**. Broadly, the etiology of thrombocytopenia in older adults can be typically thought of decreased platelet production, increased platelet destruction or consumption, increased platelet sequestration, dilutional effects, and spurious thrombocytopenia.

TABLE 106-6 COMMON CAUSES OF THROMBOCYTOPENIA IN OLDER ADULTS

ETIOLOGY OF THROMBOCYTOPENIA	POSSIBLE DISORDER(S)
Decreased Platelet Production	Nutrient deficiencies (B12 or Folate) Myelodysplastic syndrome Bone marrow failure (e.g. aplastic anemia, PNH) Bone marrow infiltration (e.g. tumor, TB, Sarcoidosis) Prescription or over-the-counter medications Chronic alcohol abuse[a] Acute or chronic infection[b]
Increased Platelet Destruction	Immune thrombocytopenic purpura Acute or chronic infection[b] Heparin-induced thrombocytopenia Drug-induced thrombocytopenia Systemic lupus erythematosus Disseminated intravascular coagulation Mechanical prosthetic valve Thrombotic thrombocytopenic purpura Antiphospholipid antibody syndrome
Platelet Sequestration/Other	Chronic alcohol abuse[a] Liver disease Pulmonary embolism or hypertension Spurious (e.g. pseudothrombocytopenia) Dilutional (e.g. in setting of trauma with massive transfusion) Hypersplenism

PNH, paroxysmal nocturnal hemoglobinuria; TB, tuberculosis.

[a]Thrombocytopenia in the setting of infection is most commonly due to bone marrow suppression. Nevertheless, immune-mediated processes during infectious syndromes may also result in thrombocytopenia.

[b]There may be more than one mechanism leading to thrombocytopenia

Decreased production of platelets is most often encountered in patients with disorders that impair bone marrow thrombopoiesis. These disorders commonly include nutrient deficiencies, myelodysplastic syndromes, and acute or chronic infectious syndromes. These are particularly common in older adults. For example, vitamin B_{12} and folate deficiency can be found in up to 24% and 10% of older adults, respectively. Similarly the median age at diagnosis for patients with myelodysplastic syndromes exceeds 65 in most studies, with an onset of disease earlier than 50 being very uncommon. Finally, older adults are at markedly increased risk of infection from bacterial, viral, and fungal causes—many of which may result in bone marrow suppression and associated thrombocytopenia. Many of these disorders are covered in more detail in other chapters within this book. Increased destruction or consumption can be a result of accelerated, antibody-mediated clearance from medications, ingested substances, or an autoimmune process.

Primary Immune Thrombocytopenia Primary ITP (previously also referred to as idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura) is characterized by persistent thrombocytopenia (platelet count < 150 k/μL) as

a result of antibodies (mostly IgG and less commonly IgM and IgA) produced against platelet membrane glycoprotein GPIIb-IIIa. Antibody-coated platelets are then rapidly cleared and destroyed by the reticuloendothelial system via recognition by Fc-receptors on macrophages and dendritic cells. These antibodies may also result in defective platelet production. ITP is a commonly encountered cause of thrombocytopenia in adults. The prevalence of ITP, which rises with age, varies with different populations, ranging between 9 and 23 cases per 100,000. In patients over the age of 65, there is an equal incidence between men and women.

Many patients (20%–30%) will be asymptomatic and the thrombocytopenia will be noted incidentally. Recent guidelines recommend that a platelet count of less than 100 k/μL should be the threshold for a diagnosis of ITP. Further classifications can include newly diagnosed (< 3 months duration), persistent (3–12 months duration), and chronic (> 12 months duration). For patients with symptoms, the most common presentation is bleeding in the skin or mucous membranes, ranging from the rare severe hemorrhage to the more commonly encountered mild petechial or purpuric lesions on the extremities and epistaxis. Symptom onset is usually insidious but occasionally can be abrupt.

ITP is a diagnosis largely made by exclusion. In ITP, the peripheral blood smear is usually normal except for the identification of low numbers of platelets with the occasional large-appearing platelets. However, platelet morphology is normal without identifiable defects in intracellular platelet granules or uniformly small or large platelets. While the evaluation for ITP in older adults may include a thorough history and physical, complete blood cell counts, reticulocyte counts, peripheral blood smear, and a direct antiglobulin test, a low platelet count may be the only identifiable abnormality. Often, diagnostic tests are usually helpful only in excluding other potential etiologies of the thrombocytopenia. Bone marrow biopsies may be undertaken in select patients but are typically not routinely required.

Secondary Immune Thrombocytopenia Thrombocytopenia due to other underlying immune-mediated disease processes are common in older adults. For example, medications can also induce thrombocytopenia, particularly in patients with recurrent acute thrombocytopenia not otherwise explained by other processes. While the timing, severity, and duration of drug-induced thrombocytopenia can vary substantially, in many patients thrombocytopenia will be first evident within 1 week of initiation of the causative drug (**Figure 106-3**). Common drugs associated with thrombocytopenia are shown in **Table 106-7** and an exhaustive list of drugs linked to low platelet counts can be accessed online (http://www.ouhsc.edu/platelets). Providers may also consider reporting cases of drug-induced thrombocytopenia to the US FDA (or similar organizational bodies in other countries) Adverse Event Reporting System at www.fda.gov/medwatch.

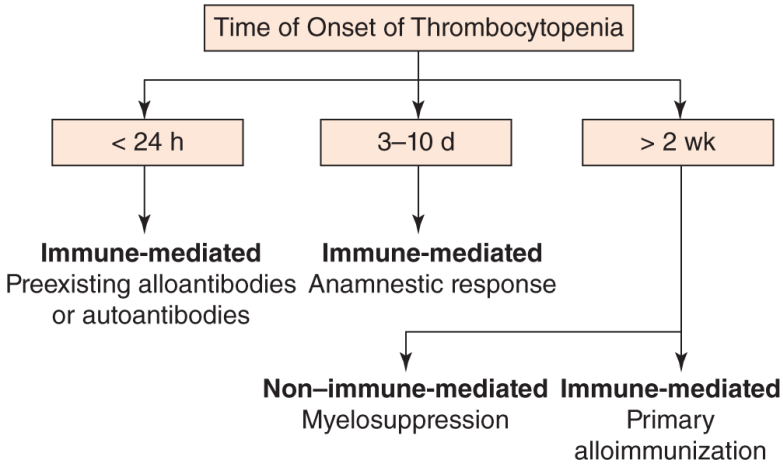


FIGURE 106-3. Categorization of drug-induced thrombocytopenia by time of onset of the thrombocytopenia. (Adapted from Kenney B, Stack G. Drug-induced thrombocytopenia. *Arch Pathol Lab Med*. 2009;133(2):309–314. With permission from Archives of Pathology & Laboratory Medicine. Copyright 2009 College of American Pathologists.)

TABLE 106-7 COMMON MEDICATIONS IMPLICATED AS CAUSES OF DRUG-INDUCED THROMBOCYTOPENIA

Abciximab	Hydrochlorothiazide
Acetaminophen	Ibuprofen
Cilastatin/imipenem	Inamrinone
Clopidogrel	Interferon-γ

Cyclosporine	Linezolid
Diazepam	Oxaliplatin
Dactinomycin/actinomycin	Phenytoin
Diclofenac	Piperacillin
Digoxin	Quinine
Dipyridamole	Ranitidine
Eptifibatide	Rifampin
Famotidine	Tirofiban
Fludarabine	TNF-α
Furosemide	Trimethoprim/sulfamethoxazole
Heparinoids	Valproic acid
Hepatitis B vaccine	Vancomycin

Data from http://ouhsc.edu/platelets/InternetPostingLitGroup2_18_11.htm. Accessed October 14, 2014.

In hospitalized patients, heparin is one of the most common causes of thrombocytopenia and in some cases may result in marked increases in the risk of both arterial and venous thrombosis (eg, HIT). The diagnosis of HIT can be challenging and providers are encouraged to use validated clinical prediction rules in combination with the results of serologic testing and/or functional platelet assays.

Acute and chronic infections, including hepatitis C, HIV, influenza, and *Helicobacter pylori* may also cause a secondary immune thrombocytopenia, although precise mechanisms and pathways remain incompletely understood. In some of these infectious syndromes, thrombocytopenia can also result from ineffective thrombopoiesis as a result of bone marrow infiltration and/or megakaryocyte infection. Finally, secondary ITP can also be a complication of rheumatologic and autoimmune disorders, including systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome, IgA deficiency, and common variable immunodeficiency (CVID).

Nonautoimmune Thrombocytopenia In addition to immune-mediated thrombocytopenias, low platelet counts in older adults can be the result of other, nonimmune causes. One of the most commonly encountered causes is spurious thrombocytopenia, also referred to as pseudothrombocytopenia, being identified in about 0.1% of all blood samples in adults. Spurious thrombocytopenia is due to exogenous platelet clumping in the presence of ethylenediaminetetraacetic acid (EDTA), which is found within some vacutainer tubes. This can be identified by examining the blood film for platelet clumping and repeating a platelet count using blood drawn into an alternative anticoagulant such as citrate buffer. In addition, enhanced platelet consumption can occur in processes such as DIC and thrombotic thrombocytopenia purpura and hemolytic uremic syndromes (TTP-HUS). Dilutional thrombocytopenia may be seen in trauma patients who have undergone massive fluid resuscitation protocols that include large number of packed RBC transfusions.

Abnormal Platelet Function in Older Adult Patients Bleeding in older adults may stem not from absolute reductions in platelet count but rather from inhibition of normal platelet functions (eg, activation, adhesion, and aggregation) that impair hemostasis. Traditional antiplatelet agents, including aspirin, nonsteroidal anti-inflammatories, clopidogrel, ticagrelor, dipyridamole, and cilostazol may all increase the risk of bleeding in older adults. The relative risk increase for bleeding varies among different agents and between different patients. A number of other medications commonly prescribed to older adults may also inhibit platelet activation or aggregation. These include nitrates, calcium channel blockers, and selective serotonin reuptake inhibitors (SSRIs). Many of the mechanisms underlying these drugs' effects on platelet function remain incompletely understood.

Acquired abnormalities of platelet function in older adults may be due to acute or chronic disease processes. For example, liver disease may cause abnormalities in platelet aggregation even in the absence of absolute thrombocytopenia. Similarly, acute and chronic kidney disease has been associated with various pathophysiologic effects on platelet function. For example, patients with renal dysfunction have abnormal platelet aggregation responses to adenosine diphosphate (ADP) and epinephrine as well as impaired platelet adhesion. While the underlying etiologies of this platelet dysfunction is likely multifactorial, kidney disease does appear to cause defects in platelet glycoprotein IIb/IIIa, an integral membrane protein mediating both platelet aggregation and adhesion. Interestingly, recent evidence

also suggests that uremia is associated with differential changes in the platelet proteome that may contribute the bleeding seen in older adults with kidney disease.

Anticoagulant Use in Older Adults Anticoagulants, including VKAs, TSOACs, heparinoids, and others, increase the risk of bleeding. Additional information on these various anticoagulants and their use in specific disease settings (eg, atrial fibrillation, stroke) is beyond the scope of this chapter but can be found in other chapters in this book.

While bleeding rates may vary substantially based on the population, disease, and anticoagulants studied, in general 2% to 3% of patients on anticoagulants will have a major bleeding complication each year and another 14% experience minor bleeding. Compared to younger subjects, older adults have an increased risk of anticoagulant-associated bleeding. This relative risk increase depends to some degree among the patient group being studied, the anticoagulant class and intensity prescribed, and the presence or absence of comorbidities such as kidney disease, uncontrolled hypertension, a history of bleeding, liver disease, concomitant antiplatelet agent or nonsteroidal anti-inflammatory drug (NSAID) use, and others. While the magnitude of the risk varies, in general the risk of bleeding increases approximately 40% for every 10-year incremental age increase.

This increased risk may present a challenging clinical dilemma for practitioners as older patients, while having an increased bleeding risk, also have a significantly higher risk of thromboembolic disease, including venous thromboembolism, cardiovascular disease, and stroke, compared to younger subjects. As a result, providers may be more hesitant to anticoagulate older patients, even in the absence of contraindications, due to the perception that the risks of treatment outweigh the benefits. This hesitation may be reflected in utilization studies where 50% or fewer older adults with atrial fibrillation are prescribed OACs for stroke prevention. In addition to age being cited as a deterrent to OAC prescription, other reasons include concerns with compliance, monitoring, falls, cognitive impairment, decreased drug clearance, and polypharmacy. A recent systematic review of 30 studies reinforced that these and other patient factors remain significant obstacles to OAC use. Each advancing decade of life is associated with a 14% reduction in OAC use (especially VKAs) and, additionally, patients may frequently refuse anticoagulation due to their fears of bleeding. As one example, approximately one-third of atrial fibrillation patients enrolled in the AVERROES and ACTIVE A studies declined to take a VKA partly as a result of their perceptions of bleeding risk.

Compared with VKAs, TSOACs such as dabigatran, rivaroxaban, apixaban, and edoxaban, offer some safety and efficacy advantages. A growing body of literature also demonstrates that TSOACs generally have a favorable profile in older adults as well, although there are some differences between the various TSOACs. The reader is referred to several recent reviews for more information on this topic.

While bleeding risk increases with age, TE risk rises as well. In many older adults, there is an overall net clinical benefit with appropriate OAC prescription. This has been most rigorously examined in older adults with atrial fibrillation. Typically, the “net clinical benefit” is defined as the annual rate of ischemic strokes prevented by warfarin minus the annual rate of intracranial hemorrhage (ICH) caused by warfarin, the latter multiplied by a factor of 1.5 to reflect the greater clinical severity of ICH than ischemic stroke (and the greater impact of OAC on TE risk compared to ICH risk). The net clinical benefit of OAC increases progressively with age and patients 85 years and older may have the greatest benefit. Reflective of these and other emerging data, many guidelines, recommendations, and clinical practice patterns in OAC prescription and management are shifting away from a focus on identifying high-risk patients who should be treated with OAC and toward identification of truly low-risk patients in whom OAC may safely be deferred.

Management of Bleeding Risk in Older Patients Prescribed OACs As noted above, recent changes in antithrombotic management emphasize a careful bleeding risk assessment in patients considered for OAC. To assist providers in this assessment, various bleeding risk assessment tools have been published. These tools have been validated with VKAs but not yet with the TSOACs. A recent review concluded that the HAS-BLED score (**Tables 106-8** and **106-9**) provides the best risk estimation for major bleeding risk, at least in atrial fibrillation (AF) patients treated with OAC. Nevertheless, the performance of the HAS-BLED was only modest (c-statistic 0.58–0.80) and remains to be validated with the TSOACs. These bleeding risk assessment tools are also limited in that the majority of predicted bleeds are extracranial with low mortality rates and disability. As a result, tools such as the HAS-BLED should not be used to exclude patients from OAC, but rather to identify and eliminate modifiable bleeding risk factors (**Table 106-10**).

TABLE 106-8 THE HAS-BLED BLEEDING RISK SCORE

	RISK FACTORS	SCORE
	[a]	

H	Hypertension	1
A	Abnormal liver[b] or kidney function[c]	1 or 2
S	Stroke	1
B	Bleeding[d]	1
L	Labile INR[e]	1
E	Elderly[f]	1
D	Drugs[g] or alcohol[h]	1 or 2

[a]> 160 mm Hg systolic.
[b]Cirrhosis, bilirubin > 2 × ULN (upper limit of normal), Aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3 × ULN.
[c]Renal dialysis, history of renal transplant or serum creatinine ≥ 2.26 mg/dL.
[d]Requiring hospitalization, decrease in hemoglobin > 2 g/L or requiring blood transfusion.
[e]Time in therapeutic range < 60%.
[f]Age > 65.
[g]Use of antiplatelet agents or nonsteroidal anti-inflammatory drugs.
[h]> 8 drinks per week.

TABLE 106-9 THE NUMBER OF ESTIMATED BLEEDING EVENTS PER 100 PATIENT-YEARS BASED ON THE HAS-BLED RISK CATEGORY

SCORE	RISK CATEGORY	BLEEDS/100 PATIENT-YEARS
0–1	Low	1.2–2.8
2	Moderate	3.6–5.4
≥ 3	High	6.0–9.5

TABLE 106-10 MODIFIABLE BLEEDING RISK FACTORS IN OLDER ADULTS PRESCRIBED ANTICOAGULANTS AND POTENTIAL STRATEGIES TO REDUCE THE RISK

RISK FACTOR	POSSIBLE INTERVENTION(S)
Concomitant NSAID use	Replace NSAID with acetaminophen or selective COX-2 inhibitor
Concomitant use of an antiplatelet agent	Eliminate antiplatelet agent if not indicated
Highly variable time in therapeutic range (TTR)[a]	Consider referral to anticoagulation clinic, if available, or switch to TSOAC
Frequent falls or high risk of falls	Consider evaluation by Faint & Fall Clinic or geriatric specialist
Uncontrolled hypertension	Control blood pressure to appropriate goal
History of gastrointestinal bleeding	Consider proton pump inhibitor (PPI) or H_2 antagonist
Poor adherence or compliance	Education; referral to anticoagulation clinic if available

COX-2, cyclooxygenase 2; NSAID, nonsteroidal anti-inflammatory drug; TSOAC, target-specific oral anticoagulant.
[a]In patients treated with a VKA.

In addition, the real and/or perceived risk of traumatic ICH from falls in older adults may be viewed as a contraindication to OAC use. While fall risk assessment in older adults is an important aspect of geriatric care, studies of AF patients on OAC who have a high fall risk have not consistently demonstrate an increased risk of traumatic ICH. An older modeling study suggested that AF patients would have to fall more than 295 times annually before the risk of traumatic ICH would exceed the risk of ischemic stroke. However, in older patients who do fall, the average number of falls they sustain each year is fewer than two and many recommend that high fall risk by itself should not prevent OAC use if the benefits otherwise outweigh the risks. For clinicians with significant concerns about individual patients, a referral to a faint and fall clinic or a comprehensive fall risk assessment should be considered.

Other strategies to reduce the risk of bleeding in older adults prescribed OACs include a thorough medication reconciliation to identify concomitantly prescribed medications that might interact with an OAC or increase the risk of

bleeding. In addition, patients, family members, and caregivers should receive comprehensive education on OACs as insufficient education may increase the risk of bleeding. Referral to a Thrombosis or Coumadin Clinic for education and monitoring may improve compliance and the therapeutic time in range (if on a VKA) while also preventing avoidable medication interactions. These specialty anticoagulation clinics may also have a valuable role in following patients on TSOACs by providing regular patient follow-up, counseling, education, and laboratory monitoring (eg, for early identification of renal dysfunction where TSOAC dose adjustments may be needed).

CONCLUSION

Age-related physiologic changes and accumulation of comorbidities increase the risk of VTE in older adults. With frequently atypical presentations, a high level of clinical suspicion, combined with formal pretest probability assessment and noninvasive imaging, is needed to accurately diagnose this disease. Antithrombotic therapy remains the cornerstone of VTE treatment, despite the increase in bleeding risk with aging. TSOACs are emerging as safe and effective treatment options in properly selected older patients.

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Chapter 107

Plasma Cell Disorders

Tanya M. Wildes

Learning Objectives

- Differentiate the plasma cell disorders (PCDs)—monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, multiple myeloma (MM), solitary plasmacytoma, and primary amyloidosis.
- Identify the common clinical clues that should trigger concern for the PCDs.
- Apply preventive measures to reduce the risk of fractures and infection in those being treated for PCDs.

Key Clinical Points

1. **PCDs are among the few neoplasms where routine laboratory testing other than by tissue biopsy can detect a clonal population by detection of monoclonal protein in the serum or urine.**
2. **Male gender and African-American race are risk factors for all PCDs.**
3. **All patients with PCDs require evaluation for associated abnormalities, that is, "CRAB" criteria: hypercalcemia, renal insufficiency, anemia, or bone lesions.**
4. **Prevention of complications in those with MM includes intravenous bisphosphonates to reduce the risk of pathologic fractures or painful lytic lesions requiring radiation and infection prophylaxis with pneumococcal vaccine, annual influenza vaccine, and, for patients receiving proteasome inhibitors (bortezomib and carfilzomib), herpes zoster prophylaxis with acyclovir or valacyclovir.**

INTRODUCTION

Plasma cell disorders (PCDs) encompass a range of clonal conditions, ranging from monoclonal gammopathy of undetermined significance (MGUS), which is by definition asymptomatic and requires no treatment, through multiple myeloma, wherein the clonal plasma cells cause end-organ damage, require therapy, and will ultimately cause the patient's death if left untreated. The incidence of PCDs increases with age, and the presence of multimorbidity may make it a challenge to distinguish between end-organ damage (ie, anemia, renal insufficiency, or vertebral compression fractures) related to a plasma cell disorder versus another underlying comorbid condition.

Laboratory Evaluation

Plasma cell disorders are among the few neoplasms where routine laboratory testing other than tissue biopsy can detect the "fingerprint" of a clonal population, in this case detection of a monoclonal protein in the serum or urine. This protein may be referred to as a paraprotein, M-component/M-spike or restricted peak. The monoclonal protein may be an intact immunoglobulin (comprised of both heavy and light chains), light chain only or, rarely, heavy chain only. Advances in laboratory technology have allowed more sensitive and specific detection and identification of a paraprotein and have improved our ability to monitor response to treatment in those PCDs that require treatment.

Serum protein electrophoresis In serum protein electrophoresis (SPEP), the serum proteins are separated by an electric field on an agarose gel and stained with Amido black, and quantitated by densitometer tracing of the gel. An

alternate, more sensitive SPEP method, involves separation of serum proteins in a capillary tube in a liquid phase buffer by a high-voltage current and quantitation by light absorbance. The latter mechanism is more accurate as it does not rely on uptake of dye. Monoclonal proteins are named for the protein region in which they migrated, such as α_1, α_2, β, or γ (eg, "γ-restricted peak").

Serum immunofixation Immunofixation is more sensitive than is SPEP, allowing for confirmation of monoclonality and determination of the type of immunoglobulin heavy and light chain class of the involved protein. However, it is purely qualitative and does not allow quantitation. In this test, the separated serum proteins are tested with specific antibodies (eg, anti-γ, anti-μ, anti-α, anti-κ, anti-λ) and stained.

Urine protein electrophoresis Urine protein electrophoresis (UPEP) is performed in a similar manner as described for SPEP. It allows quantitation of the types of protein found in the urine. Generally the percentage of each type of protein is reported, allowing distinction between proteinuria caused primarily by albumin versus light chain production. Coupled with the total amount of protein in a 24-hour urine collection, this allows quantitation of the total quantity of monoclonal protein eliminated in the urine.

Urine immunofixation Urine immunofixation, like serum immunofixation, is more sensitive for the presence of a paraprotein. Given that only the light chains are freely filtered at the glomerulus, generally only kappa or lambda light chains are detected on immunofixation of the urine, though occasionally heavy chain fragments are detectable. Urine immunofixation is a qualitative test only.

Serum-free light chain assay The serum-free light chain is a quantitative measure of excess kappa or lambda light chains produced by a plasma cell clone. Under normal circumstances, a slight excess of light chains is produced relative to heavy chains in the production of intact immunoglobulins, resulting in small quantities of kappa and lambda light chains free in the serum. The ratio of kappa to lambda light chains is roughly 1:1, with the normal range of ratios of kappa to lambda ranging from 0.26 to 1.65. In a clonal plasma cell disorder, the ratio will either be greater than the upper limit of normal with a kappa paraprotein, or less than the lower limit of normal with a lambda paraprotein. Notably, as the light chains are renally cleared, the absolute level of kappa and lambda light chains may be elevated in patients with renal impairment, but the ratio will remain close to normal.

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Definition

MGUS is an asymptomatic premalignant condition characterized by the presence of a monoclonal protein in the serum or urine. The 2014 International Myeloma Working Group (IMWG) criteria defined that a diagnosis of MGUS requires a total serum M-component less than 30 g/L, with bone marrow plasma cells (or lymphoplasmacytic cells in the case of an IgM paraprotein) less than 10% and no end-organ damage related to the monoclonal protein (eg, "CRAB" criteria: hyper*c*alcemia, *r*enal insufficiency, *a*nemia, or *b*one lesions) or amyloidosis (**Table 107-1**).

TABLE 107-1 PLASMA CELL DISORDERS: DIAGNOSTIC CRITERIA

DISORDER	SERUM MONOCLONAL PROTEIN		END-ORGAN DAMAGE				PROGRESSION RATE AND DIAGNOSIS
		BONE MARROW PLASMA CELLS	HYPERCALCEMIA	RENAL INSUFFICIENCY	ANEMIA	BONE LESIONS	
Non-IgM MGUS	< 30 g/L	< 10%	Absent	Absent	Absent	Absent	1% per year to multiple myeloma, solitary plasmacytoma, or amyloidosis
IgM MGUS[a]	< 30 g/L	< 10%	NA[a]	NA[a]	Absent	NA[a]	1.5% per year to Waldenström macroglobulinemia or amyloidosis
Light chain MGUS	No serum heavy chain by immunofixation Abnormal free light chain ratio Urinary monoclonal protein 500 mg/24 h	< 10%	Absent	Absent	Absent	Absent	0.3% per year to light chain multiple myeloma or amyloidosis
Solitary plasmacytoma	Negative or small monoclonal protein	No clonal plasma cells	Absent	Absent	Absent	Single, biopsy-proven lesion of bone or soft tissue; otherwise normal imaging	10% in 3 y progress to multiple myeloma
Solitary plasmacytoma with minimal marrow involvement	Negative or small monoclonal protein	< 10%	Absent	Absent	Absent	Single, biopsy-proven lesion of bone or soft tissue; otherwise normal imaging	60% (bone) or 20% (soft tissue) in 3 y progress to multiple myeloma
Smoldering myeloma	Serum monoclonal protein (IgA or IgG) ≥ 30 g/L or urinary monoclonal protein ≥ 500 mg/24 h	10%–60%	Absent	Absent	Absent	Absent	10%/y for first 5 y; 70% at 10 y progress to multiple myeloma
Multiple myeloma	Generally detectable in serum or urine with modern techniques; nonsecretory myeloma is rare	Any or > 60% if CRAB criteria absent	May be present	May be present	May be present	May be present	NA

[a]As IgM paraprotein is essentially never associated with multiple myeloma, signs or symptoms of Waldenström macroglobulinemia rather than the "CRAB" criteria for myeloma should be ruled out prior to diagnosis of IgM MGUS: constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other findings attributable to underlying lymphoproliferative disorder.

Adapted from Rajkumar SV, Dimoupolos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538–e548.

Epidemiology

The prevalence of MGUS in the United States is approximately 3% and ranges from 1% to 5% in other countries throughout the world. It increases in prevalence with age, and is more common in men and African Americans. Additional risk factors include having a primary relative with a history of MGUS or myeloma, exposure to pesticides, rural residence, and possibly obesity.

Pathophysiology (Classification)

MGUS may be classified as IgG, IgA, or light chain MGUS, or IgM MGUS. IgG, IgA, or light chain MGUS may progress to multiple myeloma, solitary plasmacytoma, or primary amyloidosis. IgM MGUS does not progress to multiple myeloma, but to Waldenström macroglobulinemia or amyloidosis. The rate of progression to symptomatic myeloma is about 1% per year.

Presentation

MGUS may be discovered when the patient is undergoing evaluation for another disorder and is found to have a monoclonal protein. This may include evaluation for anemia, renal insufficiency, proteinuria, osteoporosis or fractures, hypergammaglobulinemia, or peripheral neuropathy.

Evaluation

The identification of a monoclonal protein requires evaluation for the presence of end-organ damage. The history and physical examination should focus on symptoms suggestive of CRAB criteria. A complete blood count should be obtained to rule out anemia; a basic metabolic panel estimates renal function and rules out hypercalcemia. In the presence of concomitant explanations for anemia (eg, iron deficiency) or renal insufficiency (eg, established diagnosis of diabetic nephropathy with stable renal function), the criterion for end-organ damage is not satisfied. Finally, a

skeletal survey is completed to evaluate for lytic lesions.

Management

MGUS does not require treatment. Patients identified as having MGUS are followed at 6- to 12-month intervals for progression to a malignant disorder, with monitoring for anemia, renal insufficiency, hypercalcemia, or bone lesions.

SMOLDERING MYELOMA

Definition

Smoldering myeloma is intermediate between MGUS and symptomatic multiple myeloma, defined as the presence of an IgG or IgA monoclonal protein greater than or equal to 30 g/L or urinary monoclonal protein greater than or equal to 500 mg per 24 hours and/or clonal bone marrow plasma cells 10% to 60%. End-organ damage related to the paraprotein (hypercalcemia, renal insufficiency, anemia, bone lesions, or amyloidosis) must be absent.

Pathophysiology (Classification)

Only 50% of patients with smoldering myeloma progress to require therapy in 5 years (10% risk per year), and 30% are free of progression to myeloma at 10 years. Because of this heterogeneity, subgroups of patients at highest risk for progression from smoldering to overt myeloma were identified, in order to not subject the patient to end-organ damage before initiation of treatment. About 90% of patients with more than 60% plasma cells in their bone marrow progress to multiple myeloma requiring treatment within 2 years, leading to the recent change in myeloma diagnostic criteria: patients previously diagnosed with smoldering myeloma are now categorized as having multiple myeloma requiring treatment.

Evaluation

Evaluation should be as for MGUS earlier, but also requires a bone marrow biopsy to determine the percentage of plasma cells in the bone marrow. The updated IMWG criteria recommend the use of 15-fluorodeoxyglucose positron emission tomography (PET), magnetic resonance imaging (MRI) (either whole body or spine), or low-dose whole-body computed tomography (CT) when the bone survey is negative.

Management

Nonpharmacologic Patients with smoldering myeloma should be followed at 3- to 6-month intervals for history and physical examination and laboratory evaluation including complete blood counts, a basic metabolic profile, and quantitation of the monoclonal protein. A bone survey should be completed annually.

Drugs Presently, only observation is recommended for patients with smoldering myeloma. One European study randomized patients with high-risk smoldering myeloma to observation versus the immunomodulatory agent lenalidomide and dexamethasone. Patients who received lenalidomide and dexamethasone had superior progression-free and overall survival. However, critics argue that this population was extremely high risk for progression, and that most would have met criteria for treatment by the new diagnostic criteria for myeloma. Other studies examining this question are ongoing.

MYELOMA

Definition

Multiple myeloma is the malignant clonal proliferation of plasma cells with related end-organ damage, including hypercalcemia caused by lytic bone lesions, anemia, and renal insufficiency, which may be caused by hypercalcemia or light chain nephropathy.

Epidemiology

Multiple myeloma is the second most common hematologic malignancy, with an estimated 24,000 new diagnoses in 2014. The estimated incidence is 4.6 per 100,000. Current evidence supports the fact that all cases of multiple myeloma are preceded by MGUS. As with MGUS, male gender, African-American race, and advancing age are all associated with increased incidence of multiple myeloma. With the aging of the population, there will be a 57% increase in the incidence of myeloma, and more strikingly, a 77% increase in the incidence of myeloma in people over the age of 65.

Presentation

The most common presenting symptom is bone pain, present in three out of five patients. Back pain is generally of less than 1 year in duration. Fatigue is present in one-third of patients. Other symptoms may include altered mental status or constipation due to hypercalcemia, recurrent infections, or weight loss. Patients who have developed cord compression may present with paresis. Some patients may present with abnormal laboratory findings alone, including anemia, renal insufficiency, hypercalcemia, or an elevated total serum protein level with hypoalbuminemia (an elevated "protein gap").

Evaluation

Evaluation includes a thorough history and physical examination, seeking evidence of end-organ damage. Examination may reveal pallor, indicative of anemia, kyphosis related to vertebral compression fractures, or mental status changes due to hypercalcemia. Laboratory evaluation includes complete blood counts, comprehensive metabolic profile, serum protein electrophoresis and immunofixation, urine protein electrophoresis and immunofixation, quantitative immunoglobulins, serum-free light chains, lactate dehydrogenase, and β_2-microglobulin. Radiographic evaluation begins with a bone survey, though newer methods are more sensitive for bone lesions that have not yet caused significant cortical destruction. Notably, nuclear medicine bone scans are generally negative in multiple myeloma, given that myeloma bone lesions are purely lytic. The updated IMWG criteria recommend the use of 15-fluorodeoxyglucose PET, MRI (either whole body or spine), or low-dose whole-body CT when the bone survey is negative. Finally, pathologic confirmation of the diagnosis is obtained with bone marrow core biopsy and aspirate. The bone marrow aspirate is also sent for cytogenetics and fluorescence in situ hybridization (FISH) for chromosomal abnormalities commonly seen in multiple myeloma.

Pathophysiology (Classification)

The current staging system used for multiple myeloma is the international staging system. This system replaces the older Durie-Salmon staging system, and requires only the serum albumin and β_2-microglobulin level. In addition, the prognostic importance of certain recurring cytogenetic abnormalities detected by metaphase cytogenetics of FISH is increasingly recognized. Among these are del 1p, trisomy 1q, t4;14, t11;14, deletion 13, t14;16, and del 17p.

Management

The management of multiple myeloma in older adults can be complex.

Nonpharmacologic As a systemic disease, multiple myeloma essentially categorically requires systemic therapy. However, radiation or surgery may have a role in the management of skeletal lesions or the oncologic emergency spinal cord compression. Patients who present with cord compression may undergo surgical decompression followed by radiation with a goal of preserving or restoring function. Patients who present with pathologic fractures or lesions of the long bones at risk for pathologic fracture may undergo surgical stabilization to preserve or restore function; such lesions are generally irradiated postoperatively to facilitate healing and decrease pain. Other painful bone lesions may be irradiated for pain relief.

Drugs The therapeutic options for multiple myeloma have improved dramatically in the past 15 years, resulting in a near doubling of the median overall survival times. Overall the 5-year survival rate improved from 32.8% in 1998 to 2002 to 40.3% in 2003 to 2007. In adults aged 65 to 75, the 5-year survival rate was 37.4% in 2003 to 2007 and 22.7% for adults over age 75 in the same time period. Continued advances promise continuing improvement in the duration of survival.

Melphalan For over three decades, oral melphalan was the standard of care for patients with multiple myeloma. When melphalan is combined with prednisone, about 50% of patients will have at least a partial response to therapy. Numerous alternate combinations were tested, and in some cases were associated with higher response rates, but were

not superior to melphalan and prednisone with respect to overall survival. The main toxicity of melphalan is myelosuppression.

Corticosteroids Corticosteroids are incorporated into essentially every antimyeloma regimen. Corticosteroids have rapid direct antimyeloma efficacy and act synergistically with other agents. Corticosteroids are often used when patients present acutely and highly symptomatically with a new diagnosis of multiple myeloma. High-dose corticosteroids (eg, dexamethasone 40 mg orally × 4 days) can be used to rapidly ameliorate hypercalcemia or significant bone pain. However, corticosteroid dosing should be chosen cautiously for longer-term management. In a randomized trial of lenalidomide with high-dose versus low-dose dexamethasone (lenalidomide plus dexamethasone 40 mg orally days 1–4, 9–12, and 17–20 [RD] versus lenalidomide plus dexamethasone 40 mg weekly [RD]), RD was associated with a higher response rate but *poorer overall survival* due to increased toxicity (primarily venous thromboembolic events and infections). Thus, high-dose corticosteroids should be avoided in older patients due to increased risk of treatment-related mortality.

Thalidomide The antimyeloma efficacy of the immunomodulatory agent thalidomide was first reported in 1999, heralding a revolution in the treatment of multiple myeloma. Thalidomide is utilized in a number of combinations, including with dexamethasone ("Thal-dex") or melphalan and prednisone (MPT). The combination of melphalan, prednisone, and thalidomide improves overall survival over melphalan and prednisone alone. The toxicities of thalidomide include sedation, constipation, peripheral neuropathy, and venous thromboembolic events.

Lenalidomide Lenalidomide, another immunomodulatory agent, has largely supplanted thalidomide due to improved tolerability and efficacy. Lenalidomide's toxicities include venous thromboembolism and cytopenias. A randomized trial demonstrated that continuous lenalidomide with dexamethasone improves progression-free and overall survival over MPT or lenalidomide and dexamethasone of a fixed duration (18 months), establishing this regimen as a standard of care in older adults with multiple myeloma. Dose must be adjusted for renal insufficiency.

Pomalidomide Pomalidomide is approved in the United States for patients with relapsed or refractory myeloma who have previously been treated with bortezomib and lenalidomide.

Bortezomib Bortezomib is a proteasome inhibitor administered parenterally for initial therapy or at relapse. It was initially administered intravenously and twice weekly, a regimen which was found to be excessively toxic in older adults. Once-weekly subcutaneous administration of bortezomib is tolerated much better in older adults with multiple myeloma, with similar efficacy. The main toxicities of bortezomib are peripheral neuropathy, cytopenias, and herpes zoster. Bortezomib is administered in combination with dexamethasone, and may be used in combination with another agent, such as lenalidomide or cyclophosphamide. Bortezomib does not require dose adjustment for renal impairment.

Carfilzomib Carfilzomib is the second-in-class proteasome inhibitor, approved in the United States for patients with relapsed or refractory multiple myeloma who have received bortezomib and an immunomodulatory agent (either lenalidomide or thalidomide). It is administered on 2 consecutive days weekly, 3 weeks on, 1 week off. Its toxicities include cytopenias and dyspnea.

Cyclophosphamide Cyclophosphamide is an orally or intravenously administered alkylating agent that has been studied in multiple myeloma in combination with many of the novel agents outlined earlier. It is well tolerated, with side effects including nausea, mouth sores, alopecia, cytopenias, and, rarely, hemorrhagic cystitis.

Combination Regimens Numerous combinations of the above agents have been examined in clinical trials. Generally, combination regimens result in higher response rates, but also in greater toxicity; whether the combination improves outcomes like overall survival depends on the balance of efficacy and toxicity. The IMWG recommends that older adults with multiple myeloma deemed more frail receive either well-tolerated three-drug combinations (eg, melphalan, prednisone, and bortezomib or thalidomide) or only two-drug combinations (lenalidomide and dexamethasone).

High-Dose Therapy and Autologous Stem Cell Transplantation Select, fit older adults, generally under age 75, may be candidates for high-dose therapy and autologous stem cell transplantation. Patients who will undergo high-dose therapy and autologous stem cell transplantation should not receive melphalan prior to harvest of their hematopoietic stem cells as this myelotoxic agent will impair mobilization of their stem cells into the peripheral blood.

Prevention of Complications

Skeletal-related events Intravenous bisphosphonates are effective for primary or secondary prevention of skeletal-related events (including pathologic fractures or painful lytic lesions requiring radiation). Zoledronic acid and pamidronate are utilized in the United States. Denosumab, the RANK ligand inhibitor is not indicated in patients with multiple myeloma due to concerns raised about increased mortality in patients with myeloma.

Infection prophylaxis Patients with multiple myeloma should receive the pneumococcal vaccine and annual influenza vaccinations. Patients receiving proteasome inhibitors should receive herpes zoster prophylaxis with acyclovir or valacyclovir.

Special Issues

Patient preference A discrete choice experiment found that patients with myeloma prioritized the availability of subsequent treatment options over prolongation of life. Other priorities included not always thinking about the disease, the ability for self-treatment (which many of the oral regimens allow), and the opportunity for treatment-free intervals.

Comorbidity
The presence of comorbidities is prognostic in older adults with multiple myeloma. Comorbidities may also limit treatment options or influence the rates of toxicity. For example, underlying peripheral neuropathy may limit the use of bortezomib. Diabetes may limit the dose of corticosteroids due to hyperglycemia. Patients and clinicians may have concerns about using carfilzomib in the presence of underlying cardiac disease given risk for dyspnea.

SOLITARY PLASMACYTOMAS

Definition

Solitary plasmacytomas are malignant proliferations of plasma cells located either in bone or soft tissue, in the absence of other evidence of end-organ damage, and with no or minimal (< 10%) plasma cells in the bone marrow (see **Table 107-1**).

Epidemiology

Plasmacytomas are a relatively rare plasma cell disorder, with an incidence rate of 0.34 cases per 100,000 person-years. Similar to multiple myeloma, plasmacytomas are more common among males and those of black race.

Pathophysiology (Classification)

Presentation Solitary plasmacytomas of bone occur most commonly in the axial skeleton, including the vertebrae or pelvis. Solitary extramedullary plasmacytomas occur most commonly in the upper aerodigestive tract, including the nasal cavity, nasopharynx, oral cavity, or sinuses. Presentation is generally related to local symptoms of the mass.

Evaluation

Evaluation of plasmacytomas proceeds as the evaluation for multiple myeloma, with the goal of ruling out multiple myeloma.

Management

Nonpharmacologic The treatment for solitary plasmacytoma is radiation therapy, with curative intent. Radiation is highly effective at establishing local control of the plasmacytoma and relapses within the radiation field are unusual. If patients recur, it is generally progression to multiple myeloma rather than a local recurrence or persistence of the plasmacytoma.

Drugs Systemic therapy as for multiple myeloma is utilized in the setting of a radiation-refractory solitary plasmacytoma or progression to multiple myeloma.

PRIMARY AMYLOIDOSIS

Definition

Amyloidosis is a heterogenous group of rare disorders characterized by the deposition of amyloid fibrils in soft tissues. Nearly 30 different amyloidogenic proteins have been implicated; herein we focus exclusively on AL amyloidosis, where a plasma cell disorder results in the formation of amyloidogenic kappa or lambda light chains.

Epidemiology

AL amyloidosis is extremely rare, with only 10 patients diagnosed per 1,000,000 person-years. It coexists with multiple myeloma in 10% of cases.

Presentation

Presenting symptoms may be diverse given the range of organs potentially involved in AL amyloidosis. Symptoms may include fatigue, dyspnea, edema, or neuropathy.

Evaluation

History may reveal fatigue, dyspnea on exertion or orthopnea suggestive of heart failure, lower extremity edema, or paresthesias or abnormal bruising. Examination may reveal periorbital purpura, macroglossia, signs of heart failure, hepatosplenomegaly, ecchymosis, or sensory neuropathy. Laboratory evaluation includes complete blood counts and a comprehensive metabolic profile, serum and urine electrophoresis, and immunofixation and serum-free light chain assay. A 24-hour urine collection for electrophoresis will demonstrate that proteinuria is largely albuminuria rather than light chain excretion. A bone marrow biopsy may demonstrate a small clonal plasma cell population and amyloid deposition. Echocardiography or cardiac MRI may demonstrate evidence of cardiac involvement. Serum N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin-T levels are prognostic and should be obtained. A periumbilical fat pad aspiration may provide the patient with pathologic confirmation of amyloid deposition without subjecting the patient to a more invasive endomyocardial, renal, or hepatic biopsy.

Pathophysiology (Classification)

Distinguishing AL amyloidosis from other forms of amyloidosis can be challenging; a monoclonal protein may coexist with another form of amyloid. Amyloid typing can be accomplished through direct immunofluorescence microscopy or immunohistochemistry. Staging is based on NT-proBNP levels, troponin-T levels, and serum-free light chain levels. Cardiac involvement portends a particularly poor prognosis, with a median survival of fewer than 6 months in patients with elevated cardiac markers and involved serum light chains. In patients with no high-risk factors, the median survival is nearly 8 years.

Management

Management of AL amyloidosis is essentially entirely pharmacologic. There is no role for surgery or radiation aside from skeletal issues if there is overlap with multiple myeloma. Treatment is directed at the malignant plasma cell clone. A small minority of patients is eligible for high-dose therapy and autologous stem cell transplantation and may experience complete responses and long-term survival (> 10 years). The systemic therapeutic options utilized in multiple myeloma have activity in amyloidosis, though some require lower doses for tolerability.

CONCLUSION

The plasma cell disorders share in common a clonal proliferation of plasma cells, which are detectable as a monoclonal protein in the serum or urine. MGUS is a premalignant, asymptomatic laboratory finding, which progresses to a malignant disorder at a rate of 1% per year. Solitary plasmacytomas are potentially curable with radiation therapy. Multiple myeloma remains an incurable plasma cell malignancy, but therapeutic options have substantially improved in the past decade. Amyloidosis remains a therapeutic challenge, though improved risk stratification and the use of novel agents developed in myeloma are improving the landscape.

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Chapter 108

Aging of the Endocrine System and Selected Endocrine Disorders

David A. Gruenewald, Alvin M. Matsumoto

Learning Objectives

- Identify and manage common endocrine disorders that occur in older adults.
- Describe altered presentations of endocrine disease that reflect impaired homeostatic regulation of endocrine systems.
- Describe the pathophysiology of common endocrine disorders in older adults.

Key Clinical Points

1. **Endocrine disorders often present nonspecifically or atypically in older adults. As a result, it is often necessary to perform laboratory screening to identify these disorders, but there is no firm consensus on appropriate screening practices for endocrine disorders in asymptomatic older adults.**
2. **Although there is some evidence that melatonin may be safe and effective for short-term treatment of insomnia in older adults, the long-term risks and benefits of melatonin supplementation for any indication remain to be determined.**
3. **Evaluation of pituitary tumors should include hormone measurement to exclude hypersecretion and hypopituitarism, along with visual field examination for tumors adjacent to the optic chiasm or optic nerves. Incidentally discovered pituitary microadenomas (< 10 mm in size) are less likely to grow than larger adenomas, so observation may be appropriate.**
4. **The functional significance of an empty sella discovered incidentally on imaging in apparently healthy older people is unclear. Conservative management is indicated, with visual field testing and serum hormone testing to rule out suprasellar involvement and subclinical pituitary dysfunction.**
5. **Chronic adrenal insufficiency presents with nonspecific symptoms in older adults. The diagnosis should be suspected in older people presenting with declining functional status and vague symptoms, even when hyperkalemia and orthostatic hypotension are absent.**
6. **Older people treated with 10 mg/day of prednisone for more than 3 months have a markedly increased risk of hip and vertebral fractures. Pharmacotherapy to prevent fractures should begin as soon as corticosteroids are started.**
7. **There is little evidence of long-term clinical benefit from supplementation with dehydroepiandrosterone (DHEA), testosterone, and growth hormone (GH) in older adults.**

8. **When adrenal incidentalomas are identified, consider restricting screening for corticosteroid excess and consideration of adrenalectomy to younger patients and those with a symptom complex suggesting Cushing syndrome.**

PRINCIPLES OF GERIATRIC ENDOCRINOLOGY

Impaired Homeostatic Regulation

As in other organ systems, the normal aging of the endocrine system is characterized by a progressive loss of reserve capacity, resulting in a decreased ability to adapt to changing environmental demands. This loss of homeostatic regulation reflects important alterations in hormonal synthesis, metabolism, and action, but these changes may not be clinically apparent under baseline conditions. In fact, basal plasma concentrations of many hormones and metabolic fuels are essentially unchanged with normal aging. This is illustrated by fasting plasma glucose levels that exhibit little change with normal aging, but after a glucose challenge, glucose levels increase much more in healthy older persons as compared to young adults. In some instances, the function of aging endocrine systems is maintained by compensatory changes in secretion of one hormone to offset the loss of function of another hormone in a feedback system, or to compensate for alterations in metabolic clearance. For example, in many older men with testosterone levels in the normal range, pituitary luteinizing hormone (LH) secretion and serum LH levels are increased (although levels usually remain within the normal range), partially offsetting a reduction in testicular testosterone secretion. However, in other cases, these compensatory mechanisms are inadequate to maintain normal function with aging even under basal conditions. For example, unlike cortisol, adrenal production of aldosterone and DHEA declines disproportionately to clearance rates with aging, leading to age-related decreases in plasma levels of these hormones even under baseline conditions.

Altered Presentation of Endocrine Diseases

The presenting manifestations of endocrine disorders in older adults are often nonspecific, muted, or atypical. For example, hypothyroidism and hyperthyroidism may present similarly with nonspecific symptoms in older people, such as weight loss, fatigue, weakness, constipation, and depression. Endocrine diseases may also present with signs and symptoms that are classic for older patients yet atypical compared to those commonly observed in younger patients. As illustrations, thyrotoxic older patients may exhibit apathy and depression with psychomotor retardation (“apathetic hyperthyroidism”), and diabetes mellitus may present with hyperosmolar nonketotic state, a classic presentation rarely seen in individuals younger than age 50 (see Chapters 109 and 110). In addition, with aging, it is increasingly common for illnesses to present without any appreciable symptoms, such as subclinical hypothyroidism or hypercalcemia secondary to hyperparathyroidism. Finally, the manifestations of endocrine disease may be altered or masked by coexisting illnesses and medications used to treat comorbidities that commonly occur in older people. For example, exacerbations of congestive heart failure or angina may be precipitated by hyperthyroidism in older patients with preexisting cardiac disease, but practitioners may mistakenly attribute the symptoms to worsening primary cardiac disease rather than to thyrotoxicosis in such patients.

Changes in Diagnostic and Therapeutic Approach

Based on the above discussion, it is clear that a high index of suspicion for endocrine (and other) diseases is required in older patients with nonspecific signs and symptoms or functional decline. Indeed, the presence of these diseases may be appreciated only upon routine laboratory screening. However, there is no firm consensus on appropriate screening practices for endocrine disorders in asymptomatic older adults. Furthermore, even with normal aging, alterations in endocrine system function may have an important impact on the diagnostic evaluation of the older patient. For example, several factors contribute to an age-related decrease in intestinal calcium absorption, including decreased renal production of 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) and reduced intestinal responsiveness to 1,25$(OH)_2$D. In turn, these alterations in vitamin D metabolism and action cause a secondary increase in parathyroid hormone (PTH) levels to maintain calcium homeostasis, and ultimately a reduction in bone mass. As a result of these changes, together with the effects of sex hormone deficiency (a common problem in both older women and men), many asymptomatic older people require evaluation for osteoporosis (see Chapter 118). In addition, the presence of concomitant medical problems, medications, and changes in nutritional status and body composition may lead to a mistaken impression of

endocrine disease in older as well as in younger people. For example, decreased serum triiodothyronine and thyroxine levels may occur in patients who are systemically ill but euthyroid (nonthyroidal illness syndrome), or thyroxine levels may be increased in others receiving certain medications such as estrogen supplements, falsely giving the impression of an endocrine abnormality (see Chapter 109).

Another factor complicating the evaluation of the older patient is the lack of age-adjusted normal ranges for many endocrine laboratory tests (although data on age-adjusted reference ranges are increasingly available from both cross-sectional and longitudinal studies for some tests, eg, thyroid function tests). Normal values for these tests are usually determined in healthy young subjects, or young to middle-aged blood donors, which may or may not reflect normal values in healthy older adults. Furthermore, most studies of aging and endocrine function are cross-sectional rather than longitudinal. Because interindividual variability and heterogeneity are important concomitants of aging, the usefulness of cross-sectional studies in predicting age-related changes within an individual is limited. Finally, normative studies in older populations are often confounded by the inclusion of subjects with age-associated diseases.

Alterations in the therapeutic approach for geriatric patients with endocrine disease are similar to those required in older people with illnesses involving other body systems. First, treatment plans must take into account coexisting medical illnesses, medications, alterations in clearance rate of hormones and medications, and changes in target organ sensitivity and effects. As a result of these factors, interventions such as hormone replacement may have different outcomes in older than in young persons. For example, data from the Women's Health Initiative suggest that postmenopausal estrogen replacement therapy has a favorable benefit/risk ratio in many newly postmenopausal women, whereas in older women the risk of adverse effects such as coronary heart disease events tends to outweigh the benefits. Second, to minimize the risk of drug toxicity and polypharmacy, dosage levels for hormone replacement and medications must be adjusted for changes in clearance rate with aging, and patients should receive the lowest dose of medication needed to achieve the therapeutic effect. Third, new medications should be initiated at low doses and increased very gradually if needed. Fourth, the medication regimen should be reviewed periodically and medications should be discontinued if no longer needed. Finally, approaches that improve physical or cognitive function are of paramount importance for older people.

NEUROENDOCRINE REGULATION

Neurotransmitters and Neuropeptides

Studies directly assessing parameters of hypothalamic neuroendocrine function have not been performed in vivo in humans. However, age-related effects on hypothalamic function may be studied indirectly by examining alterations in pulsatile secretion of pituitary hormones, which reflect changes in pulsatile secretion of hypothalamic releasing and/or inhibiting hormones. Other indices of the effects of aging on hypothalamic function in humans include pituitary hormonal responses to administration of (1) hypothalamic releasing hormones, (2) agents that block end-organ feedback (eg, clomiphene and metyrapone), and (3) agents that stimulate hypothalamic/pituitary hormonal secretion (eg, the use of hypertonic saline to stimulate antidiuretic hormone [ADH] secretion, or arginine to stimulate growth hormone [GH] secretion).

A number of neurotransmitters and neuropeptides within the central nervous system (CNS) have been found to affect the secretion of hypothalamic and pituitary hormones. Changes in activity of these neurotransmitters and neuropeptides are responsible for many age-related alterations in the function of the endocrine system.

Dopamine Dopamine released by hypothalamic neurons inhibits pituitary prolactin secretion. In turn, prolactin stimulates hypothalamic dopaminergic neurons, forming a short feedback loop. In humans, to a greater extent than some of the other hypothalamic neurotransmitters, changes in dopamine secretion are indirectly observable with commonly available methods. This is because dopamine is the major regulator of prolactin secretion, and changes in hypothalamic dopamine activity can be inferred through observation of changes in pulsatile prolactin secretion. The frequency of pulsatile prolactin secretion is unchanged with aging, suggesting an intact pulse generator. However, humans become relatively hypoprolactinemic with normal aging. Furthermore, the circadian rhythm of prolactin secretion is altered in older men, with a blunted or absent nocturnal rise in prolactin and reduced amplitude of prolactin pulses, as compared to young controls. Metoclopramide, a dopamine antagonist, increases nocturnal prolactin secretion to a greater degree in older people than in young subjects, suggesting that this blunted nocturnal elevation in prolactin in older men may be caused by an increase in dopaminergic tone with aging. In turn, these age-related alterations in dopaminergic activity may contribute to alterations in secretion of other anterior pituitary hormones. For example, after

administration of the dopamine precursor L-dopa, plasma gonadotropins increase and thyroid-stimulating hormone (TSH) levels decrease in old but not in young male subjects, implying altered dopaminergic regulation of these hormones with aging.

Norepinephrine Studies of postmortem brain tissue in normal older persons demonstrate a modest decrease in the number of noradrenergic neurons in the locus coeruleus, the primary source of noradrenergic innervation within the CNS. However, levels of norepinephrine (NE) in the cerebrospinal fluid (CSF) of normal older subjects are increased as compared to young adults, both in the basal state and in response to yohimbine, a stimulator of central noradrenergic activity. CSF NE is thought to be produced by noradrenergic neurons within the CNS rather than the peripheral sympathetic nervous system. Taken together with the observation that NE clearance from the CNS is unchanged in older adults, these findings suggest that central noradrenergic neuronal activity is increased with aging.

The noradrenergic neuronal system is thought to exert an important influence on pituitary secretion of a number of hormones, including GH, TSH, and LH; therefore, an age-associated increase in central noradrenergic tone may be an important factor underlying age-related changes in the secretion of these hormones.

Opioid peptides Endogenous opioid peptides are believed to be important regulators of neuroendocrine systems. The products of proopiomelanocortin (POMC) metabolism are the most extensively studied of these peptides, including adrenocorticotropic hormone (ACTH), β-endorphin, β-lipotropin, and α-melanocyte–stimulating hormone. β-Endorphin, for example, is thought to exert a tonic inhibitory influence on gonadotropin-releasing hormone (GnRH) secretion and to be an important regulator of reproductive function. In older men, administration of the opioid receptor antagonist naltrexone causes a smaller increase in LH levels than it causes in young men, and unlike in young men, there is no increase in LH pulse frequency. Taken together, these observations suggest a decrease in central opioid tone with aging. However, in the periphery, basal plasma levels of β-endorphin are unaffected, and basal ACTH levels are unchanged or increased with normal aging. Furthermore, plasma ACTH, cortisol, and β-endorphin responses to physostigmine, a drug that increases CNS cholinergic activity, and ACTH and cortisol responses to administration of corticotropin-releasing hormone (CRH), are increased in older compared to younger adults. Increased responsiveness of β-endorphin and the hypothalamic-pituitary-adrenal (HPA) axis with aging may alter the function of other endocrine systems.

POMC neurons in the hypothalamus are thought to be a primary target for mediating the actions of leptin to maintain energy homeostasis. Leptin is a hormone secreted in the periphery by adipocytes, which induces satiety in part by activating hypothalamic leptin receptors and stimulating POMC synthesis. The resulting increase in melanocortin peptides (such as α-melanocyte–stimulating hormone) acts on melanocortin 4 receptors (MC4R) to inhibit food intake. At the same time, leptin inhibits the activity of orexigenic neuropeptide Y (NPY)/agouti-related protein (AgRP)-producing neurons in the hypothalamus. The peptide hormone ghrelin counterbalances the effects of leptin; ghrelin is secreted by the empty stomach, releasing growth hormone and stimulating food intake by activating hypothalamic NPY/AgRP neurons and inhibiting POMC neurons. In older people, ghrelin agonists appear to increase nonfat mass, strength, and function. There has been interest in ghrelin receptor blocking agents as a potential treatment for obesity. However, neither the safety nor the effectiveness of ghrelin agonists and receptor blockers has been established for any clinical indication. Initial hopes that the discovery of leptin would lead to an effective treatment for obesity have been tempered by evidence that leptin resistance develops with obesity as well as aging. The mechanism(s) underlying leptin resistance have not yet been clearly defined.

Melatonin Melatonin is a hormone produced in the pineal gland that is involved in the organization of circadian and seasonal biorhythms. Its synthesis and release are stimulated by darkness and inhibited by light. Therefore, the diurnal rhythm of melatonin secretion mirrors the day-night cycle. This circadian rhythm of melatonin production is controlled by a “pacemaker” in the suprachiasmatic nucleus of the brain, but changes in environmental lighting can alter the timing of this rhythm. For example, light exposure inhibits melatonin release in a dose-dependent fashion and it is possible to reverse the diurnal melatonin rhythm within a few days by reversing the diurnal pattern of light exposure. Melatonin affects reproductive function in a variety of species, with antigonadotropic effects that are more pronounced in species with marked seasonal variation in reproductive function and breeding patterns. However, even in humans dwelling in the Arctic, conception rates and pituitary-gonadal function are reduced during the winter as compared to the summer. Melatonin levels are increased in women with hypothalamic amenorrhea, and there has been some interest in very-high-dose melatonin (75–300 mg) as a potential contraceptive agent, used in combination with a progestin.

Melatonin production is negligible in young infants, but rises markedly between 3 months and 1 to 3 years, when

nighttime levels are at their highest. After early childhood, melatonin secretion gradually decreases, with a progressive decline in melatonin secretion by the age of 30. Nocturnal and 24-hour melatonin secretion appears to be similar in healthy older men and women free of confounding conditions and medications, as compared to healthy young men. Alterations in the circadian rhythm of melatonin secretion occur with aging, with a phase advance of peak melatonin secretion in older compared to young women. The altered diurnal rhythm of melatonin production with aging may reflect generalized dysfunction of the suprachiasmatic nucleus, the site of the circadian "clock"; altered synchronization of the clock due to changes in light input or nonphotic time cues; pineal gland dysfunction; or other endogenous or exogenous factors. Increasing fragmentation of the sleep-wake pattern occurs with advancing age and is even more marked in people with Alzheimer disease (AD). Irregularities in sleep-wake pattern in AD are associated with a more irregular rhythm of melatonin secretion and lower total melatonin secretion than in nondemented older people, suggesting an important role of melatonin in sleep disturbances in AD.

Melatonin has long been known to have sedative effects, suggesting a role in sleep production. In older people with insomnia, serum melatonin levels are lower than in age-matched controls without insomnia, suggesting that insomnia in older adults is caused, at least in part, by melatonin deficiency. Older adults are often exposed to significantly less environmental light than younger adults, a factor that is associated with diminished nocturnal melatonin secretion. Supplementary exposure to bright light during midday increases melatonin secretion in older adults, and tends to improve sleep disturbances in older insomniacs. In short term (3 weeks) double-blind, randomized, placebo-controlled trials of melatonin prolonged release (PR) in people greater than 55 years with insomnia, melatonin PR improved several parameters of sleep quality and was well tolerated. In one study, daytime psychomotor performance improved with 3 weeks of melatonin PR compared to placebo. Another study found that beneficial effects on sleep parameters in the initial 3 weeks of treatment were maintained or improved during a 6-month single-blind extension phase. Melatonin PR was well tolerated in older patients with an adverse effects profile similar to placebo; the most commonly reported adverse effects were headache, nasopharyngitis, back pain, and arthralgias. Melatonin PR treatment was not associated with dependence, tolerance, rebound insomnia, or withdrawal symptoms in these trials. Ramelteon, an MT1/MT2 melatonin receptor agonist, improved some measures of sleep quality in older people with chronic primary insomnia, and is approved by the US Food and Drug Administration for improving sleep in individuals with difficulty falling asleep and has not been associated with dependence.

Based on observations that patients with dementia and delirium often exhibit sleep disturbances and alterations in circadian rhythm, there has been interest in the potential of melatonin to treat these disturbances. A systematic review reported that melatonin treatment improved sundowning and agitated behavior in two of three randomized, controlled trials performed in patients with dementia. Additionally, low melatonin levels have been reported in some conditions commonly associated with delirium, for example, intensive care unit (ICU) patients and postsurgical patients. Urinary levels of melatonin metabolites were found to be altered in patients with delirium, suggesting altered tryptophan metabolism. Taken together, these findings suggest that melatonin may play a role in the pathogenesis of delirium. Two blinded, randomized, placebo-controlled trials reported a reduction in incidence of delirium in newly hospitalized patients greater than 65 years treated prophylactically with nightly ramelteon or melatonin. Reduced delirium incidence was not associated with improvements in sleep quality in these subjects, nor was there a reduction in delirium severity, restraint use, length of hospitalization, or mortality in subjects who did develop delirium in the one study that reported these outcomes. The incidence of delirium after hip fracture repair was reduced in a single-blind, randomized, controlled trial of preoperative melatonin administration, but this was not confirmed in a subsequent multicenter double-blind, randomized, placebo-controlled trial. Melatonin is a potent-free radical scavenger and it has been proposed that if the age-related decline in melatonin were prevented, then potentially the degenerative changes of aging could also be delayed. However, others have noted that the reported antioxidant effects of melatonin probably occur only at pharmacologic concentrations. In humans, melatonin is synthesized in several types of leukocytes, and MT1 melatonin receptors are present on many of these cells. Moreover, inhibition of serotonin-*N*-acetyltransferase, the enzyme catalyzing melatonin synthesis, was reported to cause a significant decrease in interleukin-2 (IL-2) secretion that was restored by melatonin administration. It has been proposed that melatonin may be an intracrine, paracrine, and autocrine regulator of immune function.

There has been considerable enthusiasm in the lay community for melatonin supplementation, based on the assumption that a decline in endogenous melatonin levels constitutes a deficiency needing replacement, and on descriptions of potential clinical applications of its antioxidant, immune system, and other effects. Melatonin is readily available without a prescription in the United States, and many older people take melatonin without physician consultation. It is noteworthy that melatonin dosages of 1 to 5 mg contained in preparations commonly available over-the-counter boost nighttime levels 10 to 100 times higher than the usual maximum within an hour after administration,

and only very low doses (0.1–0.3 mg) achieve peak serum levels within the normal nighttime range. Thus far, no serious side effects have been reported in humans after melatonin ingestion (aside from sleepiness after the dose), even with pharmacologic melatonin doses. There is increasing evidence that melatonin is safe and effective for short-term treatment of insomnia in older adults, and that melatonin may reduce the incidence of delirium in some clinical situations such as acute medical illness. However, few longer-term studies of melatonin treatment have been performed for the treatment of chronic insomnia or other conditions, and the long-term risks and benefits of melatonin supplementation for any indication remain to be determined.

Hormonal Changes in Alzheimer Disease

Alzheimer disease is characterized by a profound impairment of cholinergic neuronal function within the CNS, but changes in the function of many other neurotransmitter and neuropeptide systems have also been described. In turn, these CNS alterations are associated with changes in pituitary and peripheral hormone levels. One important endocrine system abnormality observed in patients with Alzheimer disease is an increase in HPA axis activity with elevated plasma ACTH and cortisol levels, and lack of suppression of cortisol levels by dexamethasone, suggesting decreased glucocorticoid feedback inhibition. In addition, ACTH responses to exogenous administration of CRH are blunted, which may be a result of downregulation of pituitary responsiveness to CRH secondary to chronically increased hypothalamic CRH stimulation. Elevated cortisol levels are associated with memory impairment in older nondemented people, and appear to predict subsequent decline in memory function. Finally, cortisol and ACTH responsiveness to physostigmine, which increases central cholinergic activity, is markedly increased in patients with Alzheimer disease and normal older persons, as compared to young subjects.

This elevated glucocorticoid milieu may play a role in the pathogenesis of Alzheimer disease. It has been hypothesized that chronically increased glucocorticoid stimulation damages the hippocampal neurons that mediate glucocorticoid feedback inhibition of the HPA axis, leading, in turn, to a "glucocorticoid cascade" of neurodegeneration in Alzheimer disease (and to a lesser extent in the aging brain). While still controversial, this hypothesis remains under study to determine whether glucocorticoid levels are a potentially modifiable risk factor for Alzheimer disease.

Numerous epidemiologic studies indicate a link between type 2 diabetes mellitus and increased risk of Alzheimer disease. In normal physiology, and when exogenous insulin is administered at optimal doses, insulin appears to enhance some aspects of memory. Insulin has multiple effects within the CNS that suggest a beneficial effect on cognitive function, including modulation of *N*-methyl-D-aspartate (NMDA) receptors thought to be involved in memory formation; regulation of the neurotransmitters acetylcholine and norepinephrine; and increased cortical glucose metabolism within brain regions involved in learning and memory.

Increasing evidence suggests that insulin resistance and the metabolic syndrome are associated with an elevated risk of AD. Insulin might play a role in the pathophysiology of AD through a number of mechanisms. Whereas acute insulin administration improves memory, chronic hyperinsulinemia has a negative impact on cognition and memory. Insulin can cross the blood-brain barrier from the periphery to the CNS, where it competes with β-amyloid (Aβ) for insulin-degrading enzyme, notably in the hippocampus. In chronic hyperinsulinemia, the result is decreased degradation and accumulation of Aβ in the brain. Moreover, hyperinsulinemia in the periphery may inhibit insulin production in the brain, which is thought to impair Aβ clearance and thereby increase the risk of AD. People with AD exhibit reduced cerebral glucose metabolism on fluorodeoxyglucose positron emission tomography (FDG-PET), and even apparently cognitively normal adults with insulin resistance may exhibit abnormalities on FDG-PET in association with subtle impairments in memory. Additionally, insulin resistance is associated with negative effects on vascular function in the CNS, including decreased nitric oxide and increased endothelin-1, which promotes vasoconstriction and reduces microvascular blood flow. Finally, although low doses of insulin exert anti-inflammatory effects, chronic hyperinsulinemia increases inflammatory markers both within the CNS and the periphery, which may increase AD risk.

It has been hypothesized that strategies to improve insulin signaling within the CNS may offer the potential to prevent or treat AD and mild cognitive impairment (MCI). One approach under study is to administer insulin intranasally. Unlike intravenous insulin administration, intranasal administration results in rapid delivery exclusively to the brain, thereby increasing CNS insulin levels while avoiding the risks associated with systemic hypoglycemia and prolonged peripheral hyperinsulinemia. Initial studies suggest that compared to placebo, short-term administration of intranasal insulin may improve some aspects of memory and cognition in subjects with AD or amnestic MCI, and may delay the progression of glucose hypometabolism seen on FDG-PET imaging in these subjects. However, it is

unknown whether chronic intranasal administration will result in desensitization of insulin signaling pathways in the CNS, as is seen with peripheral administration, which might render this approach ineffective or even harmful. Larger and longer-term studies are needed to determine the therapeutic potential of intranasal insulin for people with AD and MCI.

In addition to insulin resistance, other vascular risk factors are being investigated as possible therapeutic targets for AD prevention and treatment. A number of large observational studies have found that antihypertensive agents that modulate the renin-angiotensin system (RAS) are associated with a lower incidence of AD and lower rates of cognitive deterioration in people with MCI. Clinical trials have generally not confirmed a clear effect of angiotensin receptor blocking agents or angiotensin-converting enzyme inhibitors (ACEIs) on the incidence or progression of AD, although these trials have been criticized for having short follow-up periods, problems in screening and diagnosing AD cases, and potential confounding due to comorbidity.

Many other alterations in hormone, hormone receptor, neuropeptide, and neurotransmitter levels have been reported in plasma, CSF, and postmortem brain tissue specimens in AD. In some cases, potential therapeutic candidates have emerged from such studies. For example, a small, short-term randomized, placebo-controlled trial of growth hormone–releasing hormone (GHRH) reported potentially beneficial effects on some aspects of cognition in healthy older adults and in adults with MCI. Although intriguing, larger and longer duration trials are needed to evaluate the therapeutic potential of agents such as GHRH in the prevention and treatment of AD.

Anterior Pituitary

Prolactin Healthy aging is associated with a decrease in prolactin secretion in both men and postmenopausal women, reflecting a decrease in both basal prolactin secretion and the amplitude of pulsatile prolactin release. However, serum prolactin levels may vary considerably as they can increase in many situations including stress, exercise, and sleep. Mild hyperprolactinemia observed in some older adults may result from any of several underlying causes (**Table 108-1**), including hypothalamic diseases that interfere with the production of dopamine (prolactin-inhibitory factor). A number of medications commonly used by older adults inhibit dopaminergic activity and increase prolactin levels. Hyperprolactinemia secondary to dopamine D_2 receptor blockade is more common with first-generation than with second-generation (“atypical”) antipsychotic agents, except for risperidone and paliperidone. Primary hypothyroidism increases thyrotropin-releasing hormone (TRH), which stimulates prolactin secretion.

TABLE 108-1 CAUSES OF HYPERPROLACTINEMIA IN OLDER ADULTS

Hypothalamic diseases
- Tumors
  - Metastatic disease
  - Meningioma
  - Glioma
- Granulomatous diseases
  - Sarcoidosis
  - Tuberculosis
- Irradiation

Primary hypothyroidism

Pituitary stalk section
- Suprasellar extension of pituitary adenoma
- Trauma

Pituitary prolactinoma

Chronic renal failure

Chronic liver disease

Chest wall lesions
- Herpes zoster
- Surgery

Drugs

- Antipsychotics
- Cimetidine
- Opiates
- Metoclopramide
- Estrogens

The clinical manifestations of hyperprolactinemia are typically subtle and often unrecognized. Hyperprolactinemia causes secondary hypogonadism and may exacerbate sexual dysfunction and cause gynecomastia. Rarely, galactorrhea may occur. In addition, hyperprolactinemia can accelerate age-related bone loss primarily because of the antigonadotropic effects of prolactin and resulting hypogonadism. Thus, measurement of prolactin is important in the evaluation of secondary causes of osteoporosis, especially when hypogonadism is present. A single serum prolactin measurement with prolactin level exceeding the upper limit of normal is generally sufficient to establish the diagnosis of hyperprolactinemia, as long as excessive venipuncture stress is avoided. The diagnostic approach for older adults with hyperprolactinemia is summarized in **Figure 108-1**. Levels of other pituitary hormones should be measured as part of the evaluation of hyperprolactinemia, as large pituitary tumors and/or interruption of the pituitary stalk may result in hypopituitarism. Additionally, in asymptomatic patients with hyperprolactinemia, macroprolactinemia should be ruled out because dimeric and polymeric forms of prolactin are commonly present in these patients, are less bioactive, and are not detected by many commercially available assays (macroprolactin assays are available in reference laboratories).

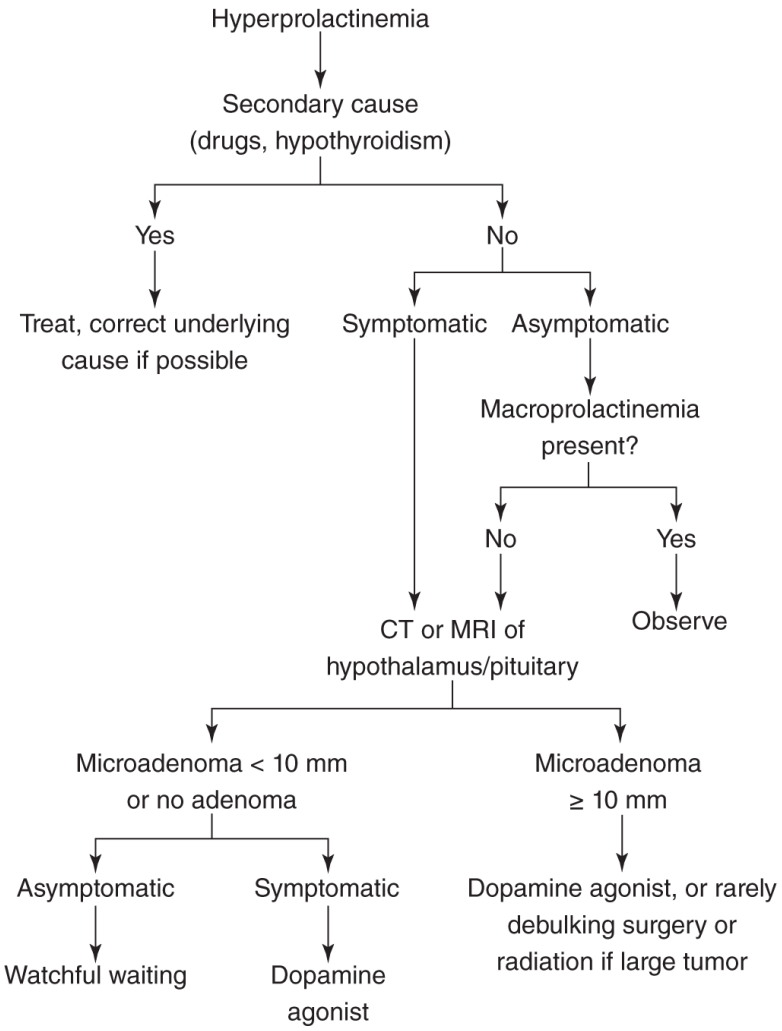


FIGURE 108-1. Diagnostic approach for older adults with hyperpro-lactinemia.

If drugs, renal failure, and hypothyroidism have been ruled out as causes of hyperprolactinemia, it is appropriate to

obtain magnetic resonance imaging (MRI) to rule out the presence of a pituitary tumor or hypothalamic lesion (computed tomography is much less sensitive). Dynamic pituitary testing, such as a TRH test, is of no value in the diagnosis of this disorder.

If the hyperprolactinemia is secondary to another disorder such as hypothyroidism or a medication, the underlying cause should be corrected or the offending medication should be discontinued if possible, which often results in normalization of prolactin levels. However, treatment of asymptomatic patients with medication-induced hyperprolactinemia may not be necessary. When patients have symptoms of hypogonadism or decreased bone mass and the medication causing hyperprolactinemia cannot be discontinued, estrogen or testosterone supplementation should be considered.

If the cause of hyperprolactinemia is a microadenoma (defined as a pituitary tumor < 10 mm in size) or idiopathic hyperprolactinemia, options include watchful waiting or dopamine agonist medications. The natural history of microadenomas is incompletely understood, especially in older adults, but most prolactin-producing microadenomas are stable or involute with time. Accordingly, observation is generally the most appropriate strategy in asymptomatic patients. Treatment with a dopamine agonist may be indicated if sexual dysfunction or additional risk factors for osteoporosis are present.

Dopamine agonists such as cabergoline or bromocriptine are effective in reducing prolactin levels and normalizing reproductive axis function in most patients, but gastrointestinal, behavioral, and other side effects such as hallucinations are common in older patients. These side effects can be minimized by following a "start low, go slow" approach when beginning these medications. Cabergoline is the preferred agent as it is more effective in normalizing prolactin levels, is more likely to reduce the size of pituitary macroadenomas (defined as a pituitary tumor ≥ 10 mm in size), and is less likely to cause side effects than other dopamine agonists. Of note, high doses of cabergoline may be associated with an increased risk of valvular heart disease. Patients starting dopamine agonists should be monitored with prolactin measurement at 1 month and at intervals thereafter with dose titration as needed to normalize prolactin levels. MRI should be repeated in 1 year or sooner if symptoms or prolactin levels increase while on treatment. Serial visual field examinations should be performed when macroadenomas are present that may compress the optic chiasm.

Surgery is rarely indicated, but may be necessary in those with macroadenomas (> 10 mm) and persistent visual field defects or inability to tolerate dopamine agonists. Alternatively, radiation therapy may be an option for patients with large tumors who are unable to tolerate medical therapy and are not surgical candidates. However, the clinical response to radiation is often delayed for months to years, and anterior pituitary insufficiency eventually occurs in many, if not most, of these patients. Age-associated alterations in secretion of other anterior pituitary hormones are discussed below, under the individual hormonal systems, and in Chapter 109 (Thyroid Diseases) and Chapter 40 (Menopause and Midlife Health Changes).

Pituitary Adenomas Although the incidence of pituitary tumors increases with aging, symptomatic pituitary tumors are uncommon even in people of advanced age. However, the prevalence of pituitary tumors at autopsy ranges from 8.5% to 27%, indicating that the vast majority of these tumors are clinically "silent." In case series of pituitary tumors in older adults, the majority of lesions are apparently nonfunctioning adenomas, whereas 9% to 17% are GH-secreting tumors and 4.5% to 10% are prolactinomas. However, many, if not most, apparently nonfunctioning adenomas actually produce quantities of gonadotropins or the α-subunit of these glycoprotein hormones. When a prolactinoma is present, the degree of prolactin elevation generally parallels the size of the adenoma, and macroprolactinomas are usually associated with prolactin levels greater than 250 μg/L. Occasionally, a discrepancy may be observed in which very large pituitary adenomas are associated with mildly elevated prolactin levels. This is due to an artifact (known as the "hook effect") that can occur with some immunoradiometric assays when high serum concentrations of prolactin are present. When such a discrepancy is present, the possibility of an artifactually low prolactin level should be ruled out by performing serial dilution of serum samples. This will distinguish between a large prolactinoma and a large nonfunctioning adenoma. Nonsecreting tumors and tumors that secrete LH, follicle-stimulating hormone (FSH), or α-subunit are usually large at the time of diagnosis, because there are few or no symptoms of hormone overproduction. Gonadotropin hypersecretion from such tumors usually does not result in excessive gonadal hormone secretion although LH hypersecretion occasionally results in elevated testosterone levels. Clinical manifestations of these tumors are usually a result of a mass effect, including visual field abnormalities caused by compression of the optic chiasm, headaches, and panhypopituitarism. Gonadotropin-secreting pituitary tumors are particularly difficult to diagnose in postmenopausal women in whom gonadotropin levels are already elevated as a result of ovarian failure. For these women, exaggerated α, LH β, and FSH β-subunit responses, and/or intact gonadotropin responses to TRH may be useful in diagnosing these tumors. However, pituitary "incidentalomas" are being increasingly identified during

neuroimaging evaluations for comorbid conditions in older adults. Most of these are asymptomatic though endocrine and visual disturbances should be sought in these patients.

Diagnosis of pituitary tumors depends on neuroimaging (especially MRI). Evaluation of pituitary tumors should include hormone measurement to exclude hypersecretion and hypopituitarism, as well as a visual field examination when the tumor abuts the optic chiasm or optic nerves. Incidentally discovered microadenomas (< 10 mm in size) are less likely to grow than macroadenomas, so it may be appropriate to manage these cases with observation. Patients with nonprolactin-secreting macroadenomas should be referred for surgery if visual or neurologic deficits due to the tumor are present, if there is hypersecretion of other anterior pituitary hormones (GH, ACTH, or TSH), or if there is concern for compression of the optic chiasm or optic nerves. Hypopituitarism alone is not an indication for surgery, as it may persist even after removal of the tumor. Management of large pituitary tumors usually involves transsphenoidal decompression and debulking, along with assessment of anterior pituitary hormone function and replacement of hormone deficiencies.

Transsphenoidal surgery has a low associated morbidity and mortality rate, with a reported mortality rate of 0.6% in adults less than 65 years. However, adults greater than 65 years have a higher reported mortality rate of 3.8% and a progressively increasing mortality risk with advancing age. These findings suggest that a careful assessment of surgical risks and benefits is indicated in frail older people, with greater weight being given to the option of conservative management than in younger, healthier people. However, the risks of postoperative hypopituitarism and other complications are substantially lower when the surgery is performed at a specialized center by a neurosurgeon with extensive experience in this procedure, and reported outcomes in older adults are similar to those achieved in the general population. Macroprolactinomas may be managed with dopamine agonists in most cases even when large or associated with visual field changes, although these agents may be less effective in older than in young adults (see **Figure 108-1**). Pituitary function should be reassessed in patients started on dopamine agonists for a prolactinoma because recovery of pituitary function occurs in some individuals treated with these medications.

Hypopituitarism and the empty sella syndrome Hypopituitarism has been reported to occur in 36% to 50% of older people with pituitary tumors. As a pituitary macroadenoma grows, destruction of normal surrounding pituitary tissue occurs. This may lead to pituitary hormone deficiency, which is classically thought to begin with loss of gonadotropins and GH followed by TSH and eventually ACTH secretion. However, pituitary hormone loss may not always occur in this order, particularly when other causes of hypopituitarism such as lymphocytic hypophysitis are present. The resulting panhypopituitarism may present clinically as a constellation of symptoms including supine and/or postural hypotension, fatigue, loss of libido, weight loss, hypogonadism, hyponatremia, and hypoglycemia. Many of these symptoms are nonspecific and common in older patients without panhypopituitarism, so a high index of suspicion is required to make the diagnosis. Causes of hypopituitarism are similar in older and young adults, and are summarized in **Table 108-2**.

TABLE 108-2 CAUSES OF HYPOPITUITARISM IN OLDER PERSONS

Pituitary adenomas
Sequelae of irradiation or surgery for pituitary tumors
Peripituitary tumors (eg, meningioma, glioma, metastatic cancer)
Vascular conditions (eg, pituitary infarction, hemorrhage into a pituitary tumor, carotid artery aneurysm, subarachnoid hemorrhage)
Traumatic brain injury (eg, stalk section)
Infiltrative or granulomatous diseases (eg, lymphocytic hypophysitis, hemochromatosis, histiocytosis X, sarcoidosis)
Infections (eg, tuberculosis, mycoses, abscesses)

Initially, measurements of basal serum levels of morning cortisol and ACTH, total or free testosterone (in men) and gonadotropins, free thyroxine and TSH, insulin-like growth factor 1 (IGF1), and prolactin may be sufficient to confirm panhypopituitarism. Measurement of both the pituitary hormone and the target hormone concentration allows assessment of the appropriateness of both levels together. Dynamic ACTH (Cortrosyn) stimulation testing is indicated to confirm the diagnosis of secondary hypoadrenalism. ACTH and other dynamic tests of adrenal function are discussed later under “Laboratory Testing of HPA Axis Function.”

As computed tomography (CT) and MRI have come into widespread use, it is increasingly common to discover incidentally the presence of both pituitary masses and empty sella syndrome. MRI studies of healthy young and older

subjects found that pituitary height and volume tend to decrease with aging, with empty sella occurring in 19% of subjects. No relationship was found between pituitary volume and anterior pituitary hormone levels. Most cases of primary empty sella syndrome (ie, not associated with prior pituitary tumor, surgery, or irradiation) occur in obese, hypertensive middle-aged women. Clinically apparent pituitary dysfunction is relatively uncommon in women with primary empty sella, although a majority of men with the syndrome have some degree of hypopituitarism. The functional significance of an empty sella as an incidental finding on imaging studies in apparently healthy older patients is unclear. In such patients, conservative management is appropriate, including visual field testing and serum hormone testing to rule out subclinical pituitary dysfunction and suprasellar involvement.

Studies of the endocrine manifestations of traumatic brain injury (TBI) have been performed primarily in younger adults. However, in light of the frequent occurrence of falls and head injury in older people, it is appropriate to consider these data in the management of older adults with TBI. Acute hypopituitarism is common after TBI, with a reported prevalence between 15% and 68%. Patients with more severe TBI may be at greater risk of hypopituitarism, but even those with mild TBI are at risk. Both anterior and posterior pituitary function may be affected. In the acute phase after TBI, it is not useful to evaluate thyroid, gonadal, and growth hormone axis function, but glucocorticoid insufficiency may be life threatening. Acute hypopituitarism may develop during the first 7 to 10 days after TBI and may be transient, so serial measurement of early morning cortisol is indicated especially in individuals with hypotension, hyponatremia, or hypoglycemia. Treatment with intravenous hydrocortisone should be considered in individuals with early morning cortisol levels below 10 μg/dL. Acute diabetes insipidus (DI) secondary to TBI is diagnosed by the presence of hypernatremia together with hypotonic polyuria in the absence of another cause such as glycosuria or acute renal failure. Treatment should include desmopressin and fluid repletion, administered only as needed because acute DI often resolves spontaneously.

In the postacute phase of TBI, hormone deficiencies that were present acutely may resolve, and new hormone deficiencies may manifest. Follow-up evaluation for signs and symptoms of hypopituitarism together with laboratory assessment for hormone deficiencies should be performed 3 to 6 months after TBI, and again at 12 months. The natural history of the endocrine consequences of TBI is incompletely understood, so it is reasonable to continue annual assessment for signs and symptoms of hypopituitarism and to perform hormone testing when suggestive clinical manifestations are present.

Posterior Pituitary

Antidiuretic hormone (ADH), or arginine vasopressin (AVP), is synthesized in “magnocellular” neurons of the hypothalamus and released into the systemic circulation from nerve terminals in the posterior pituitary gland in response to increased plasma osmolality, decreased arterial pressure, and reductions in circulating blood volume. In addition, ADH synthesized in “parvocellular” hypothalamic neurons is released into the hypothalamic-pituitary portal circulation, in turn stimulating release of ACTH from the anterior pituitary into the systemic circulation. ADH appears to be colocalized with corticotropin-releasing hormone (CRH) in parvocellular neurons of the hypothalamus. Administration of ADH together with CRH amplifies the effect of CRH on ACTH release, suggesting a role for ADH in responses to stress.

Older people are at higher risk than young adults for the development of both volume depletion and excess free water states. This is a result of age-related changes occurring in the systems that maintain volume status and osmolality, including ADH secretion, osmoreceptor and baroreceptor systems, renal concentration of urine and hormone responsiveness, and thirst mechanisms. There is evidence for a state of relative ADH excess with aging, with normal to increased basal ADH levels, increased ADH release after an osmotic stimulus such as hypertonic saline infusion, and impaired ethanol inhibition of ADH secretion in older persons, as compared with young adult subjects. Furthermore, renal free water clearance decreases with aging in proportion to declining glomerular filtration rate (GFR). With a reduction in GFR, proximal renal tubular fluid absorption is increased, leading to a decrease in fluid delivery to the distal diluting portions of the nephron. The net result is a decrease in the diluting capacity of the kidney and a decreased ability to excrete a free water load. This age-related reduction in free water clearance, together with relative ADH excess and the increased prevalence of conditions such as congestive heart failure, hypothyroidism, and the use of sulfonylurea and diuretic medication all contribute to the common occurrence of free water excess and hyponatremia in older people. When present, hyponatremia in frail older adults is usually mild and asymptomatic, but these individuals may develop more marked symptomatic hyponatremia in the setting of acute illness. Additionally, hyponatremia is a strong, independent predictor of mortality risk, and is associated with other clinically important outcomes such as falls, fractures, hospitalization, cognitive impairment, and nursing home placement.

In contrast to the increased osmoreceptor sensitivity to ADH, baroreceptor regulation of ADH is decreased with aging, resulting in decreased ADH release in response to hypotension or hypovolemia and increased risk of volume depletion. Furthermore, renal responsiveness to ADH is diminished with aging, possibly because of chronic exposure to elevated ADH levels, leading to a decrease in maximal urine concentrating ability. Decreased aldosterone and increased atrial natriuretic hormone activity with aging contribute to the potential for volume depletion by decreasing the capacity of the kidneys to conserve sodium under conditions of fluid deprivation (see "Renin-Angiotensin-Aldosterone System" later in this chapter). Finally, healthy older adults exhibit decreased thirst and reduced fluid intake in response to fluid deprivation, hyperosmotic stimuli, and hypovolemia, further contributing to the risk of dehydration with aging. Older patients with immobility or dementia, such as nursing home residents, are at particularly high risk for severe dehydration and hypernatremia.

A number of factors predispose older people to nocturnal polyuria. These include age-related blunting of the circadian rhythm of circulating ADH, with loss of the nocturnal increase in ADH levels, and an increase in nighttime plasma atrial natriuretic hormone levels. Patients with AD have lower circulating ADH levels than cognitively intact people of the same age, and appear to be particularly prone to nocturnal polyuria. Superimposed on age-related changes in bladder function and mobility, altered ADH regulation can contribute to urinary incontinence. Older patients with nocturnal polyuria may benefit from administration of the ADH analog desmopressin (DDAVP), in addition to other interventions such as detrusor muscle relaxants and behavioral interventions.

See Chapter 89 for additional information on effects of aging on salt and water regulation.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Physiology

Compared to the other hypothalamic-pituitary end-organ axes, hypothalamic-pituitary-glucocorticoid function is relatively intact with aging in humans (**Table 108-3**). The cortisol secretion rate is decreased with aging, but this is matched by a decrease in the cortisol metabolic clearance rate. As a result, basal plasma concentrations of cortisol are overall unchanged with aging even in very old subjects, although considerable interindividual variation in cortisol levels with aging has been reported. Consistent with intact cortisol secretion, basal ACTH levels are also unaffected by aging. Furthermore, glucocorticoid responsiveness of the HPA axis to stimulation is well maintained in older adults, with intact cortisol responses to exogenous ACTH stimulation (except at very low doses of ACTH [0.06 μg]) and normal or slightly prolonged cortisol and ACTH responses to metyrapone, ovine CRH, and insulin-induced hypoglycemia. ACTH pulse frequency appears to be maintained in older men, suggesting intact hypothalamic regulation of glucocorticoid function. Moreover, the circadian rhythm of ACTH and cortisol secretion is intact in healthy older subjects although the amplitude of the cortisol rhythm is reduced and the nighttime cortisol nadir is increased in older compared to young adults. In addition, a phase advance of the cortisol rhythm occurs in older people, with earlier nadir and peak secretion, as compared to young adults. This phase advance has been attributed to behavioral changes, possibly reflecting an earlier bedtime in older adults.

TABLE 108-3 ALTERATIONS IN HYPOTHALAMIC-PITUITARY-GLUCOCORTICOID AXIS FUNCTION WITH AGING

ACTH levels	↔
ACTH response to CRH stimulation	↔
Cortisol production	↓
Cortisol clearance from plasma	↓
Plasma cortisol levels	↓/↔/↑
Cortisol response to stimulation	
ACTH	↔
Metyrapone, hypoglycemia	↔/↑
Surgical stress	↓
HPA axis sensitivity to glucocorticoid feedback	↓

↓, decreased; ↔, unchanged; ↑, increased; ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; HPA, hypothalamic-pituitary-

adrenal.

The cortisol response to stress appears to be altered with aging. After a stressful stimulus such as surgery, peak cortisol levels are higher and remain elevated longer in older compared to young adult subjects. Furthermore, dexamethasone is less effective in suppressing cortisol levels in older subjects. In healthy young adults, increasing doses of dexamethasone cause a dose-dependent suppression of CRH-induced release of ACTH, but this suppression is blunted in healthy older subjects. The degree of cortisol-induced inhibition of ACTH secretion is comparable in healthy older men and women, indicating equivalent cortisol feedback sensitivity in older subjects by gender. However, ACTH escape after cortisol suppression, and recovery of cortisol levels, were attenuated in healthy older women compared to men. When metyrapone is used to remove endogenous cortisol feedback inhibition, the decline in ACTH levels after exogenous cortisol infusion is blunted and delayed in older compared to young adult subjects. These findings indicate that the sensitivity of the HPA axis to glucocorticoid negative feedback is decreased with aging. The clinical implications of this decreased responsiveness to glucocorticoid feedback inhibition, and of the attenuation in ACTH and cortisol rebound after cortisol suppression in older women compared to men, are unclear. However, it has been proposed that the resulting chronic increase in glucocorticoid exposure may damage hippocampal neurons regulating glucocorticoid secretion and important to cognitive function, leading to a vicious cycle of further glucocorticoid hypersecretion and damage to mechanisms regulating HPA feedback inhibition.

Laboratory Testing of HPA Axis Function

Although glucocorticoid function is well preserved with aging, certain factors may interfere with testing of HPA axis function in older patients (**Table 108-4**). For example, excretion of steroids commonly measured in urine is decreased with renal impairment, and measurements are unreliable in people with a creatinine clearance of less than 50 mL/min. Moreover, because the acute cortisol stress response may be higher and prolonged in older patients, testing for Cushing syndrome should be delayed for at least 48 hours after major stresses such as high fever, trauma, or surgery.

TABLE 108-4 POTENTIAL PITFALLS IN LABORATORY DIAGNOSIS OF CUSHING SYNDROME IN OLDER ADULTS

TEST	POTENTIALLY CONFOUNDING FACTORS	TEST ALTERATION	COMMENTS
24-h urine cortisol	Renal impairment, undercollection	False-negative urine cortisol	Normal level excludes Cushing syndrome
	Overcollection, severe malnutrition, stress, chronic anxiety, alcoholism, depression	False-positive urine cortisol	
DST	Obesity, estrogens, anticonvulsant medications, depression, alcoholism, acute illness	False-positive DST (pseudo-Cushing)	Cortisol nonsuppression common in older adults (high sensitivity but low specificity)
Late-night salivary cortisol	Hypertension, advanced age, psychiatric diagnoses	False-positive (increased) salivary cortisol	Repeat testing often normal in false-positive situations
Urine 17-hydroxycorticosteroid levels	Medications (eg, phenytoin, phenobarbital)	Falsely decreased urine 17-hydroxycorticosteroid levels (false-negative test for hypercortisolism)	

DST, dexamethasone suppression test.

The ACTH stimulation test is used to screen for both primary and chronic secondary (central) adrenal insufficiency. Expected cortisol responses to the standard dose of 250 μg of ACTH (absolute serum cortisol level of > 18–20 μg/dL at 30 or 60 minutes after an IV bolus of ACTH or Cortrosyn) do not change with aging. The rationale for use of this same test in assessing pituitary function is that in patients with chronic pituitary disease, the absence of sufficient stimulation of the adrenal glands by endogenous ACTH leads to adrenal atrophy and hyporesponsiveness to exogenous ACTH. Thus, a serum cortisol greater than 18 to 20 μg/dL either at baseline or after ACTH rules out

adrenal insufficiency. However, the standard ACTH stimulation test lacks sensitivity for mild secondary adrenal insufficiency. The low-dose ACTH stimulation test, performed with 1 μg of ACTH and measurement of cortisol 30 minutes after injection, may be superior to the standard dose test in the diagnosis of mild or recent-onset secondary adrenal insufficiency and mild primary adrenal insufficiency, but a meta-analysis demonstrated similar diagnostic utility for the low-dose and standard-dose ACTH tests. In patients with a positive ACTH stimulation test, a plasma ACTH level obtained at 8:00 AM may help to distinguish primary from secondary adrenal insufficiency, with a high plasma ACTH indicating primary adrenal insufficiency and normal or low ACTH indicating secondary adrenal insufficiency. However, additional dynamic testing of adrenal axis function may be indicated for borderline abnormal ACTH stimulation test results. Furthermore, the standard dose ACTH stimulation test should never be used in cases of suspected acute or recent onset of hypopituitarism, because the adrenal glands may still be able to respond normally to ACTH challenge. In patients with septic shock, a reduced increment between basal and post-ACTH cortisol level (< 9 μg/dL) may be a more useful indicator of "relative adrenal insufficiency" that is associated with improved pressor responsiveness and mortality in response to glucocorticoid treatment.

Patients with primary adrenal insufficiency demonstrated by an inappropriately low cortisol response to ACTH along with normal or elevated ACTH levels should receive additional evaluation to rule out mineralocorticoid deficiency (eg, plasma renin activity and serum aldosterone levels).

ACTH stimulation testing with salivary cortisol measurement has been proposed as an alternative to traditional ACTH stimulation with plasma cortisol measurements in the diagnosis of adrenal insufficiency. Plasma total cortisol levels may be misleadingly low in conditions associated with reduced circulating levels of cortisol-binding globulin (CBG) such as liver failure, hypothyroidism, and nephrotic syndrome. Measurements of salivary cortisol correlate well with serum-free cortisol levels and are therefore less prone to confounding in patients with these medical conditions. The cortisol response to insulin-induced hypoglycemia is a reliable test for primary or secondary adrenal insufficiency, but may be inappropriate in frail older patients because of the potential risks associated with severe hypoglycemia. In patients with a normal response to ACTH stimulation, the single-dose overnight metyrapone test can be used to confirm suspected secondary adrenal insufficiency. Metyrapone inhibits 11β-hydroxylase, the final step in cortisol synthesis, and in normal individuals ACTH secretion increases, stimulating adrenal secretion of 11-deoxycortisol. However, oral metyrapone may cause dizziness, nausea, and vomiting in some older patients, and it has been suggested that intravenous metyrapone infusion is safer and better tolerated in older people.

Hyperadrenocorticism

Cushing syndrome is an eponym for the constellation of signs and symptoms of chronic corticosteroid excess, including central obesity; catabolic effects on muscle, skin, and bone; glucose intolerance; hypertension; hypogonadism; and hirsutism and acne (in women).

Glucocorticoid therapy The most common cause of Cushing syndrome in older adults, as in other age groups, is the pharmacologic administration of glucocorticoids. The undesirable effects of glucocorticoid treatment are similar in older and younger patients, but in older people glucocorticoids may cause major adverse effects upon function (**Table 108-5**). Consider just the adverse effects on bone: continuous treatment with 10 mg/day of prednisone for more than 90 days is associated with a 7-fold increase in hip fractures and a 17-fold increase in vertebral fractures.

TABLE 108-5 ADVERSE EFFECTS OF GLUCOCORTICOIDS IN OLDER PATIENTS

Central nervous system
- Impaired cognition
- Emotional lability
- Depression
- Psychosis

Bone
- Osteoporosis
- Fractures

Muscle
- Proximal muscle wasting

• Weakness
Fluid and electrolytes
• Sodium retention, edema
• Hypokalemia
Metabolic
• Central obesity
• Hyperglycemia
• Hypertriglyceridemia
Cardiac
• Congestive heart failure
• Hypertension
Gastrointestinal
• Peptic ulcer disease
Skin
• Fragility
• Impaired wound healing
Vision
• Cataracts
• Glaucoma
Immune system
• Decreased cell-mediated immunity
• Increased risk of infections
Functional
• Impaired ambulation and transfers
• Falls
• Loss of independence

When it is necessary to use pharmacologic doses of glucocorticoids, older patients should receive the minimum necessary dosage for the shortest possible period of time, and the dosage requirement should be reviewed at frequent intervals. Because bone loss may be rapid with chronic glucocorticoid therapy, bone densitometry measurements using dual-energy x-ray absorptiometry (DXA) should be performed prior to initiating long-term corticosteroid therapy and after 6 to 12 months of therapy (**Figure 108-2**). As for the evaluation of osteoporosis not associated with corticosteroid use, all patients should be assessed for modifiable osteoporosis risk factors, secondary causes of osteoporosis, primary hyperparathyroidism, and vitamin D deficiency.

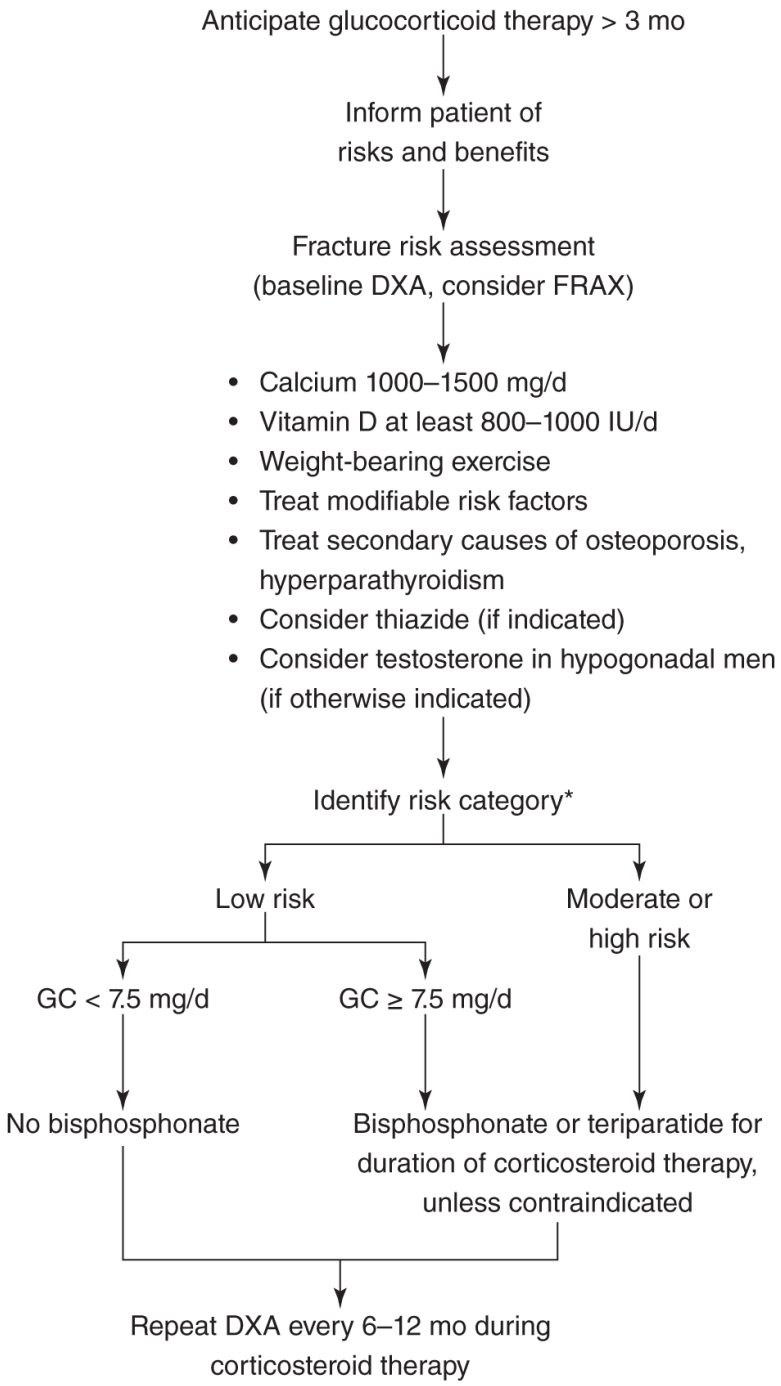


FIGURE 108-2. Prevention and management of glucocorticoid-induced osteoporosis in postmenopausal women and men greater than 50 years beginning glucocorticoid therapy. BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; GC, glucocorticoid. Glucocorticoid doses are shown in prednisone equivalents. FRAX, WHO Fracture Risk Assessment Tool.

Some of the adverse effects of corticosteroid use in older people can be minimized with other interventions (see **Figure 108-2**). For example, because corticosteroids decrease intestinal calcium absorption and increase urinary calcium losses, ensuring an intake of at least 1000 to 1500 mg elemental calcium per day together with at least 800 to 1000 IU/day of vitamin D helps to minimize bone loss. In individuals with low 25-hydroxy (25-OH) vitamin D levels (< 20–32 ng/mL), high-dose vitamin D (eg, ergocalciferol 50,000 IU) should be given weekly for 12 weeks after which a repeat 25-OH vitamin D level should be performed; the goal is to normalize the 25-OH vitamin D level.

Occasionally, high-dose vitamin D (ergocalciferol 50,000 IU weekly or twice weekly) or calcitriol (0.25 or 0.50 μg/day) may be needed to maintain vitamin D sufficiency, but follow-up of both serum and urine calcium levels is required. Furthermore, dietary sodium restriction (2–3 g/day) and thiazide diuretics (eg, hydrochlorothiazide, 25 mg/day) are useful to reduce hypercalciuria associated with corticosteroid use, although their effects on bone density have not been adequately determined in patients receiving corticosteroids.

Hormone replacement therapy can be considered to counteract corticosteroid-induced suppression of sex hormones. Estrogen supplementation (eg, conjugated estrogens 0.625 mg/day with medroxyprogesterone acetate 2.5–5.0 mg daily for women with an intact uterus) may help premenopausal or symptomatic early postmenopausal women taking corticosteroids, but its use is controversial. Men with corticosteroid-induced and/or other causes of hypogonadism should receive androgen replacement therapy (eg, testosterone enanthate or cypionate, 100–200 mg IM every 2 weeks, or daily transdermal application of a testosterone patch or gel). Although testosterone therapy in hypogonadal men has not been demonstrated to reduce fracture risk, it has been shown to improve bone mineral density and to ameliorate other manifestations of androgen deficiency. Bisphosphonates should be considered as first-line therapy for patients who will be taking the equivalent of prednisone 7.5 mg/day or more for at least 3 months, because clinically significant bone loss may occur with this dose and duration of therapy. Patients at high risk for osteoporosis require pharmacotherapy at even lower glucocorticoid doses and for shorter durations of use (see **Figure 108-2**). Bisphosphonates used for prevention and treatment of corticosteroid-induced osteoporosis increase bone mineral density at the lumbar spine and hip, and reduce the risk of fractures of the vertebral spine. However, the cost-effectiveness of bisphosphonates in the treatment of glucocorticoid-induced osteoporosis is best established in individuals of more advanced age and with lower (more abnormal) T-scores for bone mineral density. Options include alendronate 70 mg weekly (or 10 mg daily), risedronate 35 mg weekly (or 5 mg daily), or ibandronate 150 mg monthly. For patients who cannot tolerate oral bisphosphonates, intravenous bisphosphonate (eg, zoledronic acid 5 mg IV once yearly) may be considered. As an alternative to bisphosphonates in persons with severe glucocorticoid-induced osteoporosis, teriparatide (recombinant human PTH 1–34) 20 μg SC daily may be used. However, expense and daily subcutaneous injections from cartridges requiring refrigeration may make teriparatide therapy less desirable for older persons. Although denosumab is used to treat osteoporosis in men and postmenopausal women at high risk of fracture, current data are insufficient to recommend denosumab for routine use in the prevention and treatment of glucocorticoid-induced osteoporosis. However, denosumab may be an appropriate alternative for patients with renal insufficiency who are not candidates for bisphosphonates or teriparatide. Both bisphosphonates and denosumab may cause or exacerbate hypocalcemia, so preexisting hypocalcemia and vitamin D deficiency should be corrected prior to treatment and calcium levels monitored during treatment.

Corticosteroid-induced myopathy is characterized by weakness and atrophy of the muscles of the hip, thigh, and proximal upper extremities, which may result in an increased risk of falls in older people with age-related loss of muscle mass. The best approach for this difficult problem is to minimize the dose of corticosteroid or to eliminate it altogether if possible. For those who require ongoing corticosteroid therapy and cannot be tapered off these drugs, resistance and endurance exercise, and androgen replacement therapy in hypogonadal men, may help to prevent glucocorticoid-induced muscle atrophy. However, the effectiveness of these approaches in preventing functional decline in older patients has not been determined.

Hypercortisolism *Cushing disease*, or hypercortisolism caused by excessive pituitary ACTH secretion, is most common in persons between 20 and 40 years. Accounting for approximately two-thirds of cases of endogenous hypercortisolism in younger adults, Cushing disease is a much-less-common cause of cortisol excess in older people, although its exact prevalence in older adults is unclear. In contrast, the *ectopic ACTH syndrome* is more common in older people, most of whom have obvious neoplasms such as small-cell lung cancer, although occasionally such tumors may be clinically undetectable as in the case of some bronchial carcinoid tumors. Patients with the ectopic ACTH syndrome caused by small-cell lung cancer or other rapidly growing tumors typically present with cachexia rather than central obesity, hypertension, and metabolic disturbances including hypokalemia, metabolic alkalosis, and hyperglycemia. Cortisol-producing *adrenal carcinomas* are more common in older people than in young adults, with a bimodal peak incidence in children and in people older than age 50. These tumors may produce severe Cushing syndrome with virilization in women and mineralocorticoid excess, although many of these tumors are nonfunctioning and do not cause symptoms of Cushing syndrome. Adrenocortical carcinomas are typically large (> 100 g) and palpable unlike benign adrenal adenomas which are usually 10 to 20 g (size 1–6 cm) at presentation.

Diagnostic testing If there is a clinical suspicion of Cushing syndrome, first-line diagnostic options include a 24-hour urinary free cortisol, a low-dose dexamethasone suppression test (DST), or a midnight salivary cortisol level

(**Figure 108-3**). Consultation with an endocrinologist is appropriate to guide the diagnostic evaluation. Current guidelines suggest that unequivocal abnormalities in at least two first-line diagnostic tests (eg, 24-hour urinary free cortisol ≥ three times the upper limit of normal) should be identified to diagnose Cushing syndrome. False-positive results are common with the low-dose DST in older people, even in apparently normal individuals, and the urinary free cortisol test may be confounded by inadequate urine collections or the presence of renal insufficiency. Additionally, one or both tests may be confounded by other conditions commonly encountered in older adults including obesity, medications such as phenytoin, depression, active alcoholism, or other coexisting stressful illnesses (see **Table 108-4**). In these instances of "pseudo-Cushing syndrome," patients retain normal circadian variation in serum cortisol levels despite increased cortisol secretion, whereas circadian rhythmicity is lost in patients with bona fide Cushing syndrome. A midnight salivary cortisol level distinguishes patients with Cushing syndrome from those with pseudo-Cushing syndrome with a high degree of specificity and sensitivity in young and middle-aged adults. However, elevated late-night salivary cortisol levels are common in older adults and individuals with type 2 diabetes mellitus without Cushing syndrome, suggesting a need to increase the diagnostic threshold of the test in these populations. Cortisol secretion usually normalizes in patients with pseudo-Cushing syndrome with remission of the underlying condition.

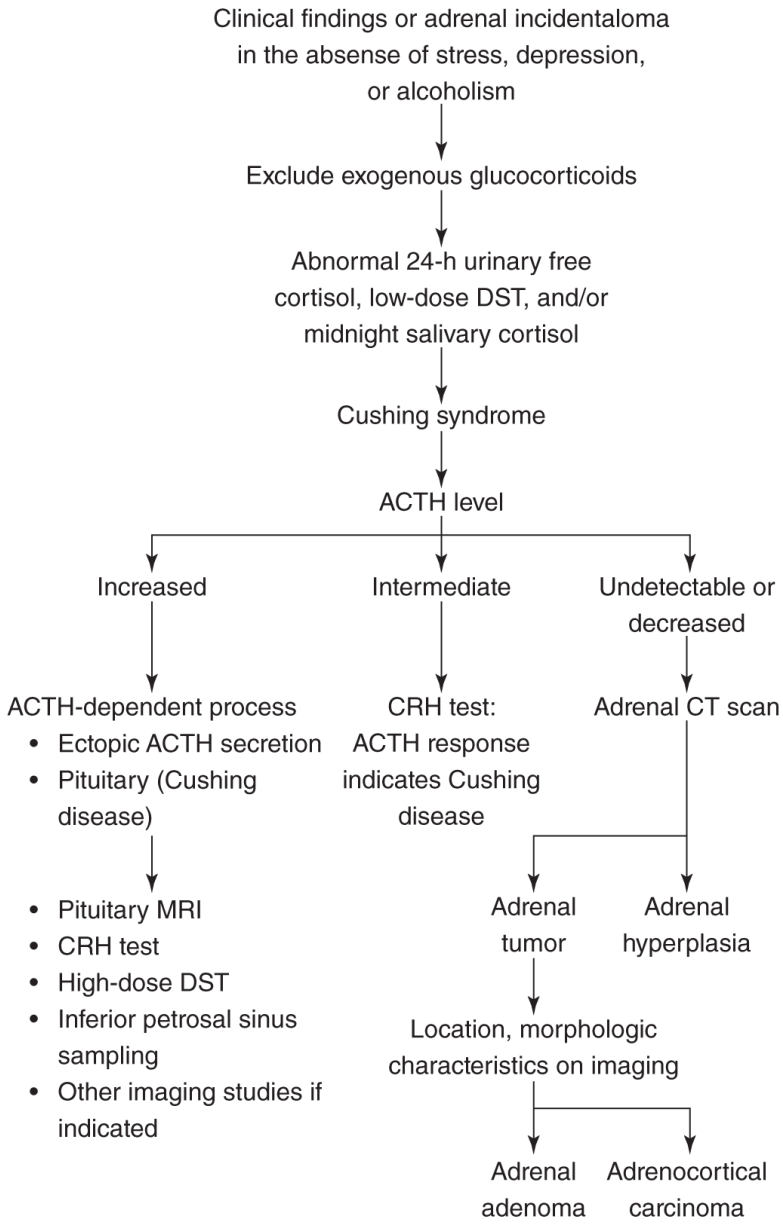


FIGURE 108-3. Diagnostic evaluation for suspected Cushing syndrome. ACTH, adrenocorticotropic hormone; CD, Cushing disease; CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test.

After the diagnosis of Cushing syndrome is established, simultaneous plasma ACTH and cortisol levels are obtained to determine whether the cortisol excess is ACTH-dependent or ACTH-independent. If ACTH levels are

undetectable or low and cortisol levels are high, then an ACTH-independent process is present, suggesting an adrenal tumor. In this case, CT scanning of the adrenals is indicated to confirm the diagnosis. ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) may be helpful to distinguish potentially malignant lesions from benign tumors when CT results are indeterminate. If ACTH and cortisol levels are increased, then hypercortisolism is ACTH-dependent, usually reflecting a pituitary adenoma (Cushing disease) or ectopic ACTH secretion. Most patients with ectopic ACTH syndrome have extremely high ACTH levels. Identification of a definite pituitary mass at least 6 mm in size on pituitary MRI in patients with elevated ACTH and cortisol levels may be sufficient for a diagnosis of Cushing disease when clinical features of an ectopic ACTH-secreting tumor are absent. However, most experts recommend additional testing to confirm a pituitary source of ACTH. Infusion of CRH can distinguish ectopic ACTH secretion from Cushing disease; most patients with a pituitary tumor will show an increase in cortisol and ACTH levels after CRH, whereas patients with ectopic ACTH-secreting tumors will not. However, many patients with Cushing disease do not meet the stringent response criteria for the CRH stimulation test. Venous sampling from the inferior petrosal sinus is required in these cases, and referral to an endocrinologist is usually indicated. Imaging to search for an occult ACTH-secreting tumor is indicated only after Cushing disease has been ruled out with inferior petrosal sinus sampling.

Treatment In patients with Cushing disease, transsphenoidal surgery performed by a neurosurgeon with extensive experience is the treatment of choice, although radiotherapy and medical therapies including mitotane, metyrapone, and ketoconazole are alternatives in those who are unable to undergo surgery. However a therapeutic response to radiotherapy may not occur for 2 to 5 years, and a high incidence of hypopituitarism has been reported after radiotherapy. When possible, surgical tumor removal is indicated for most patients with functional adrenal adenomas or the ectopic ACTH syndrome, although for those who are not surgical candidates, aminoglutethimide, mitotane, or metyrapone and spironolactone or eplerenone may be useful in reducing the symptoms of glucocorticoid and mineralocorticoid excess, respectively. Additionally, adjuvant mitotane may prolong survival after surgical resection of adrenocortical carcinoma. Mitotane is also used in the medical management of advanced adrenocortical carcinoma (although poorly tolerated in older patients), either by itself or in combination with chemotherapy regimens such as etoposide, doxorubicin, and cisplatin. However, there is little experience with mitotane either for adjuvant therapy postresection or for advanced adrenocortical carcinoma in older patients.

Adrenal Insufficiency

Primary adrenal insufficiency is less common in older persons than in young adults; less than 10% of patients with adrenocortical failure are older than age 60 at initial presentation. As in younger patients, most cases of adrenal insufficiency in older people are a result of acute stress or rapid withdrawal of glucocorticoids in patients with suppressed adrenal function caused by chronic glucocorticoid administration. Autoimmune adrenocortical insufficiency is rare in older patients, but other causes of adrenal insufficiency, including tuberculosis, adrenal hemorrhage, and metastatic disease, are much more common in older persons than in young adults. Tuberculous involvement of the adrenals is nearly always associated with evidence of past or current tuberculosis infection elsewhere in the body, and may manifest with large calcified adrenal glands on plain x-rays or CT scans. Adrenal hemorrhage typically presents acutely in anticoagulated patients with symptoms such as nausea, vomiting, hypotension, and tachycardia, and is likely to be the cause if bilateral adrenal enlargement is demonstrated on CT scan. Metastatic disease involving the adrenals occurs most commonly with lymphomas and carcinomas of the lung, colon, and prostate, although even when metastases are present, it is unusual for cortisol secretion to be impaired.

The presentation of chronic adrenal insufficiency is usually vague and nonspecific in older patients, with symptoms of “failure to thrive” including weight loss, anorexia, confusion, weakness, and decreased functional status. Examination findings may include orthostatic hypotension, supine hypotension, cachexia, and hyperpigmentation. Laboratory testing may reveal hyponatremia, hyperkalemia, azotemia, and hypoglycemia. However, one-third of older patients with primary adrenal insufficiency are not hyperkalemic at initial presentation, and hyperpigmentation, hyperkalemia, and orthostatic hypotension are not present in patients with secondary adrenal insufficiency. The signs and symptoms of adrenal insufficiency are nonspecific and common in older people and are, therefore, easily attributable to another condition. Consequently, it is important to suspect this diagnosis in older patients with worsening functional status and vague symptoms. Unfortunately, adrenal insufficiency has historically been more commonly fatal in older people and more likely to be diagnosed only at autopsy, as compared to younger patients.

Treatment for possible adrenal crisis must not be delayed while diagnostic tests are pending. Once the diagnosis is suspected, the evaluation is the same as for younger patients, as illustrated in **Figure 108-4**: the ACTH stimulation test establishes the diagnosis. Treatment is also the same as in young adults. In patients with primary adrenal insufficiency

and less severe mineralocorticoid deficiency, replacement doses of hydrocortisone may provide sufficient mineralocorticoid activity. The goal of chronic glucocorticoid therapy is to use the lowest glucocorticoid dosage to relieve symptoms of glucocorticoid deficiency (eg, hydrocortisone 10 mg twice daily to 20 mg every morning plus 10 mg every evening; or prednisone 5–7.5 mg daily; or lower). However, those with absent mineralocorticoid function (manifested by orthostatic hypotension and electrolyte abnormalities such as hyperkalemia and hyponatremia) also require fludrocortisone, titrated to normalize electrolyte abnormalities (eg, fludrocortisone 0.05–0.1 mg daily). These patients should be monitored closely to avoid volume overload and hypertension. During minor illnesses or other stresses, maintenance glucocorticoid doses should be doubled for 2 to 3 days, whereas for major surgery or trauma, much higher doses of hydrocortisone (eg, 50–100 mg intravenously every 8 hours) are usually administered initially. Patients with adrenal insufficiency should be given a parenteral glucocorticoid to be used if nausea and vomiting prevent ingestion of oral glucocorticoid replacement, and they should also have a bracelet or necklace identifying them as having adrenal insufficiency.

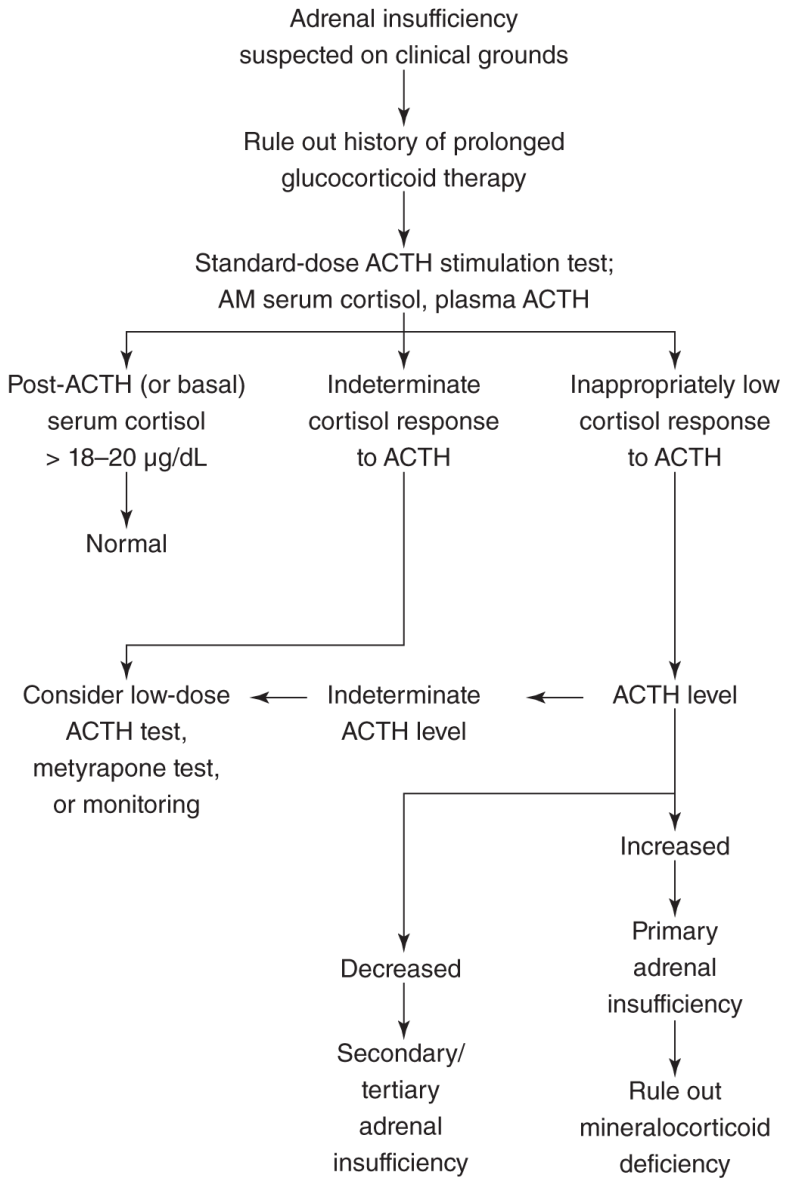


FIGURE 108-4. Diagnostic evaluation for suspected adrenal insufficiency. ACTH, adrenocorticotropic hormone.

Women with adrenal insufficiency and impaired mood and health-related quality of life may benefit from replacement of the adrenal androgen DHEA (25–50 mg/day), which has been shown to improve mood, fatigability, sexuality, and sense of well-being in these patients. Of note, high-density lipoprotein (HDL) cholesterol levels decreased in one study of DHEA replacement in women with adrenal insufficiency. The long-term safety of DHEA replacement in people with adrenal insufficiency has not yet been established, including the possible risk of sex steroid–dependent tumor growth (see Adrenal Androgens and Aging).

Chronic glucocorticoid therapy suppresses HPA axis function and results in adrenal atrophy because of the loss of ACTH stimulation. As a result, cessation of corticosteroids may be associated with a prolonged period of decreased pituitary ACTH secretion and adrenal responsiveness to ACTH. Recovery of HPA axis responsiveness is variable and may not occur for several months or as long as a year in some individuals. Older people may be particularly at risk to develop adrenal insufficiency as a consequence of withdrawal of steroid therapy for several reasons. For example, older adults may forget medicines or become confused about their medicines because of a complicated regimen or associated cognitive impairment. Other patients may discontinue medicines abruptly without consulting their physician because of expense or unacceptable side effects. The clinical features of adrenocortical insufficiency secondary to withdrawal of glucocorticoids (or hypopituitarism) are nonspecific and similar to those of primary adrenal insufficiency, although findings suggesting mineralocorticoid insufficiency (orthostatic hypotension and hyperkalemia) and hyperpigmentation (associated with high ACTH production) are usually absent. Based on the foregoing, a high index of suspicion is necessary to detect adrenocortical insufficiency in older people caused by cessation of chronic glucocorticoid therapy. It is appropriate to perform the ACTH stimulation test in such patients, and those with persistent adrenocortical insufficiency should receive glucocorticoid coverage for major surgery or other stresses until HPA axis function has normalized.

Adrenal Androgens and Aging

The adrenal steroids DHEA and its sulfated form (DHEAS) are the most abundant steroids in the human circulation. DHEA and DHEAS are precursors of both male and female sex steroids including testosterone, estradiol, and progesterone, as well as the glucocorticoid corticosterone. Neither DHEA nor androstenedione bind to or activate the androgen receptor to a significant degree, so they are considered to be very weak androgens that act mostly as prohormones. However, these prohormones may exert physiologic actions indirectly via tissue-specific conversion to more active androgens or estrogens.

In men, 5% to 30% of DHEA is of testicular origin, with the remainder synthesized in the zona reticularis of the adrenal cortex. In women, DHEA is produced almost exclusively by the adrenal cortex, whereas androstenedione and testosterone are secreted by both the adrenal glands and the ovaries. Total circulating androgens decline with aging as a result of both ovarian failure and a decrease in adrenal production of androgens and androgen precursors. However, in contrast to estrogen deficiency, ovarian androgen secretion may persist after menopause, and the decline in androgens is more gradual, typically beginning at least a decade before menopause.

Testosterone Therapy in Older Women

In 2002, the Princeton Consensus Statement proposed a definition of “female androgen insufficiency” consisting of symptoms of impaired libido and well-being in the setting of low testosterone levels and adequate estrogenization either through normal ovarian function or estrogen replacement therapy (see also Chapter 41). This definition was criticized on several grounds, including the lack of a clearly defined clinical syndrome of androgen deficiency in women, the multifactorial origin of impaired libido in most cases, the lack of correlation between serum androgen concentrations and sexual function in women, the unavailability of normative data on testosterone levels across the lifespan that can be used to define androgen deficiency, inaccuracies of many existing free and total testosterone assays in measuring the very low testosterone concentrations present in women, and the lack of consensus on the most appropriate measures to assess sexual function. Furthermore, the risks and feasibility of offering androgen replacement to all women with self-rated impaired well-being and low circulating androgen levels have been questioned.

Despite these criticisms, androgen therapies have become widely used by menopausal and postmenopausal women with diminished libido. Several randomized controlled trials of testosterone therapy for hypoactive sexual desire disorder (HSDD) in postmenopausal women and women with ovarian or pituitary failure have shown that supplementation of testosterone into the normal range for young women improves libido, arousal, pleasure, frequency of orgasm, and overall satisfaction, while decreasing distress associated with HSDD. A 3- to 6-month trial of testosterone supplementation sufficient to boost circulating levels into the normal range for premenopausal women may be appropriate for postmenopausal women with HSDD. There is no role for measuring testosterone levels in women for diagnostic purposes, as levels do not correlate with sexual function or symptoms. However, it is appropriate to measure testosterone at baseline, at 1 month, and every 6 months thereafter to monitor for overuse and androgen excess. Testosterone supplementation should be discontinued after 6 months if there is no beneficial effect of treatment. No efficacy and safety data are currently available for treatment durations beyond 24 months; a major concern is the lack of long-term safety data with regard to the risk of breast cancer.

Unfortunately, testosterone preparations appropriate for use in women are not available in all locales. Additionally, no formulations of testosterone are FDA approved for use in U.S. women. Preparations intended for use in men may result in grossly supraphysiologic testosterone levels and androgenization when used in women, and should not be used. Testosterone compounded by pharmacies into creams and other preparations cannot be recommended as their efficacy and safety are unknown. Women who have undergone bilateral oophorectomy or who develop adrenal insufficiency develop severe androgen deficiency and may present with symptoms of decreased libido, energy, and well-being. Androgen replacement therapy may be justifiable in these women to treat severe, symptomatic androgen deficiency. However, a recent Endocrine Society guideline recommended against routine androgen supplementation for women with low androgen levels due to bilateral oophorectomy, hypopituitarism, or adrenal insufficiency, based on a lack of data indicating the efficacy and long-term safety of this practice. This guideline also recommended against the use of testosterone in women for sexual dysfunction other than HSDD, or to improve cardiovascular, metabolic, cognitive, or bone health.

Dehydroepiandrosterone Supplementation for Older Adults

Studies in rodents have reported a variety of beneficial effects of DHEA administration, including enhancement of immune function and prevention of a variety of disorders including cancer, obesity, and diabetes mellitus. However, these data have limited applicability to humans, because rodents have negligible production of adrenal androgens such as DHEA, and many of these studies used grossly supraphysiologic doses of DHEA. In humans, some epidemiologic studies have reported associations between DHEA levels and overall health. For example, DHEA levels are decreased in people with active rheumatoid arthritis, acquired immunodeficiency syndrome (AIDS), cancer, and cardiovascular disease, and DHEA levels are positively correlated with vigor and longevity. Additionally, high-functioning older adults have higher DHEAS levels than low-functioning individuals. Based on these findings and the marked decline in DHEA level with aging, there has been considerable interest in the potential therapeutic effects of DHEA supplementation in older people.

However, randomized controlled trials of DHEA in older adults have not revealed clear evidence of meaningful benefits. Oral DHEA administration has not been shown to be effective for menopausal symptoms or female sexual dysfunction, although preliminary data suggest that transvaginal administration of DHEA may relieve dyspareunia due to vaginal atrophy in postmenopausal women. However, no transvaginal formulation of DHEA is commercially available at present, and additional studies are needed to determine whether this approach is safe and effective. No consistently favorable effects have been reported from randomized, controlled trials of DHEA supplementation on insulin sensitivity, lipid profiles, strength, subjective well-being, or cognition in older adults. DHEA supplementation improved bone mineral density in older subjects with low circulating levels of DHEA in some but not all studies. However, the magnitude of the improvement in bone density is small compared to the beneficial effects on bone that are seen with agents approved for the treatment of osteoporosis, and no data are available showing a reduction in fracture risk with DHEA.

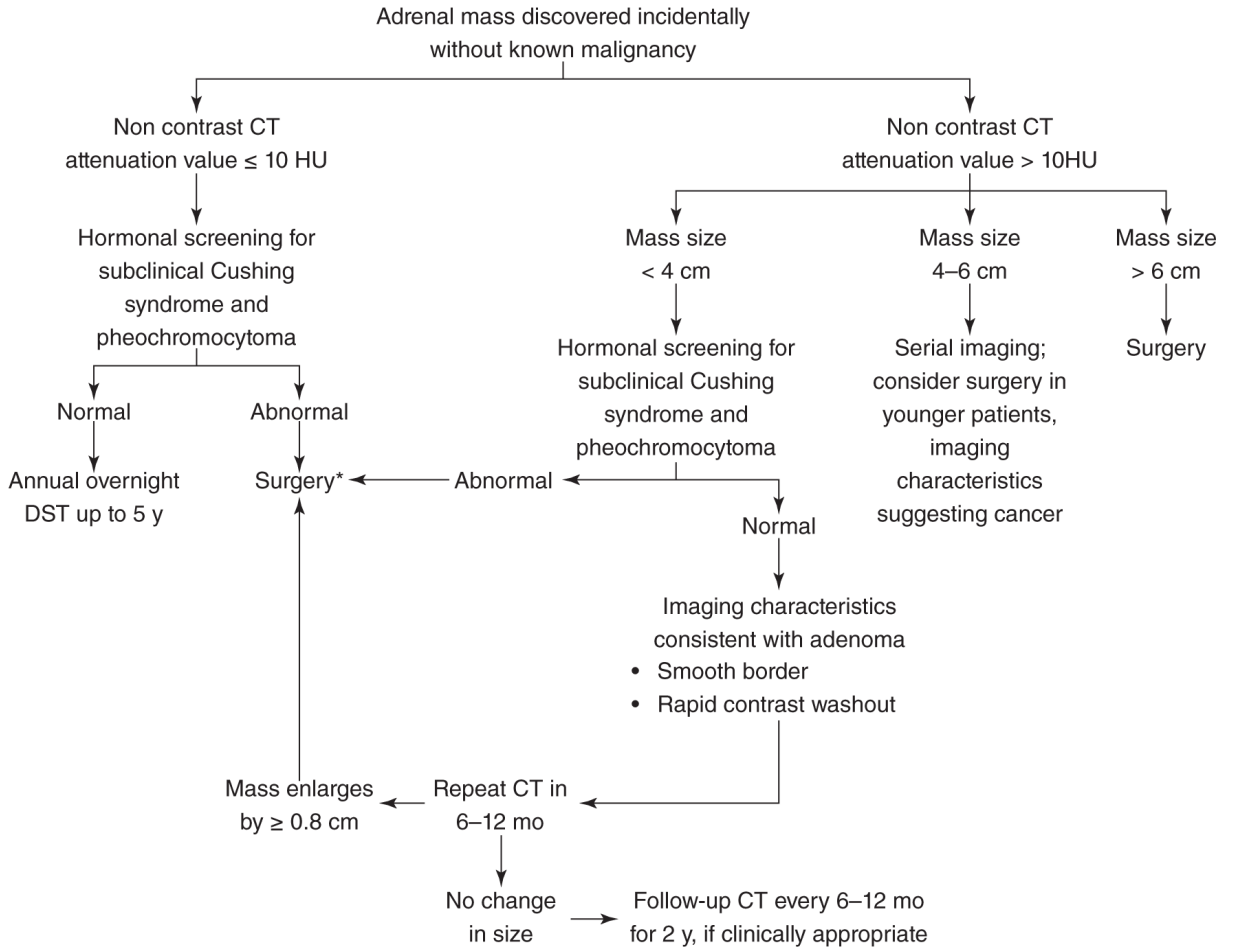
A recent Endocrine Society guideline recommended against routine DHEA supplementation in women with adrenal insufficiency based on inadequate evidence of its safety and effectiveness. However, a meta-analysis of 10 randomized, placebo-controlled trials of DHEA therapy found a small improvement in health-related quality of life and depressed mood in women with adrenal insufficiency. Accordingly, it may be reasonable to consider a trial of oral DHEA supplementation (25–50 mg/day initially) in women with marked impairments in mood or subjective well-being that persist after appropriate glucocorticoid and mineralocorticoid replacement, while monitoring for androgenic side effects such as acne and hirsutism. Insufficient data are available to recommend DHEA supplementation in men with adrenal insufficiency.

In the United States, DHEA is not FDA approved for any indication and is only available over the counter as a dietary supplement; the potency and purity of these supplements is unreliable. Furthermore, the safety of long-term supplementation of DHEA has not been established. Based on the forgoing, DHEA cannot be recommended for the treatment of any condition in older adults with normal adrenal function.

Adrenal Neoplasms

Benign adrenal neoplasms are common, with autopsy studies identifying these masses in approximately 6% of cases. Adrenocortical nodularity increases with aging, and the probability of identifying an adrenal “incidentaloma” on computerized tomography of the abdomen increases from 0.2% in people between 20 and 29 years to 6.9% in people older than 70 years. Most of these are adrenocortical adenomas, but adrenal carcinomas and pheochromocytomas also

occur. One large survey reported that 4.2% of adrenal incidentalomas are pheochromocytomas. The goals of assessment are to determine whether the incidentaloma is functional (hormone secreting) and to characterize it as benign or malignant (**Figure 108-5**).



*Consider restricting hormonal screening for Cushing syndrome to younger, healthier patients and those with symptoms suggesting Cushing syndrome. The patient's clinical condition and treatment preferences must be factored in before recommending surgery (see text).

FIGURE 108-5. Evaluation and management of adrenal incidentaloma in older adults. DST, dexamethasone suppression test; HU, Hounsfield units.

Patients with adrenal incidentalomas should be queried for a history or episodes of hypertension, palpitations, headaches, and diaphoresis, suggestive of pheochromocytoma. Examination findings of proximal muscle wasting and weakness, purple striae, osteoporosis (height loss), hirsutism, and central obesity, suggestive of Cushing syndrome, should be noted. Appropriate screening tests to determine whether the tumor is functional include a 24-hour urine collection for fractionated metanephrines, or plasma free metanephrines to rule out pheochromocytoma, and in hypertensive patients, a morning plasma aldosterone concentration to plasma renin activity ratio. Androgen-secreting tumors are rare, and endocrine screening for androgen overproduction is not indicated in the absence of clinical signs and symptoms of hormone excess.

Many adrenal cortical adenomas have a degree of functional autonomy. "Subclinical" Cushing syndrome has been reported to be present in 5% to 24% of patients with adrenal incidentalomas, depending on the diagnostic criteria used. In one study of patients with adrenal incidentalomas screened with a 2-day low-dose DST, cortisol was undetectable in only 21%, whereas all control subjects suppressed cortisol to undetectable levels. Furthermore, higher cortisol levels after the DST were associated with larger adrenal incidentaloma size, higher midnight cortisol levels, and lower basal ACTH levels. Moreover, hypertension, obesity, dyslipidemia, insulin resistance, and osteoporosis are significantly more prevalent in people with adrenal incidentalomas than in the general population. Indeed, most middle-aged patients with incidentalomas and cortisol nonsuppression after low-dose DST experienced improvement in hypertension, obesity, and diabetes control after adrenalectomy.

These data suggest that subtle autonomous glucocorticoid secretion is common in adrenal cortical adenomas and

that this secretory activity may be clinically significant. Some experts advocate screening individuals with adrenal incidentalomas for subclinical Cushing syndrome using the overnight low-dose (1 mg) DST, with confirmatory tests in people with a positive result (eg, 24-hour urinary free cortisol, dehydroepiandrosterone sulfate (DHEA-S), overnight high-dose [8 mg] DST, and plasma ACTH) to rule out false positives. A serum cortisol cutoff of greater than 5 μg/dL at 8 AM after the overnight DST has been proposed to maximize specificity without unduly sacrificing sensitivity. Adding a morning serum ACTH level improves the specificity of the low-dose DST and in the absence of a gold standard for diagnosis this combination has been proposed as the best diagnostic tool to evaluate for possible subclinical Cushing syndrome. However, screening all older people with adrenal incidentalomas for subclinical Cushing syndrome will nevertheless result in a large proportion of false-positive results and additional evaluation in these cases. Of note, patients followed longitudinally for up to 7 years showed spontaneous normalization of hormonal hypersecretion in many cases, whereas a few others with apparently nonfunctioning adenomas developed subclinical hormonal hypersecretion. Furthermore, the long-term outcomes of adrenalectomy versus medical management of hypertension, diabetes, and obesity in older patients with adrenal cortical adenomas are unknown. Therefore, it may be prudent to restrict screening for corticosteroid hyperfunction and consideration of adrenalectomy to younger patients and those with a symptom complex including weight gain, muscle weakness, osteoporosis, hypertension, diabetes mellitus, and skin atrophy suggesting Cushing syndrome. However, screening is indicated in patients with adrenal incidentalomas who are scheduled for major surgery, because postoperative adrenal crisis may occur in patients with unrecognized subclinical Cushing syndrome. For older patients undergoing surgery, laparoscopic adrenalectomy offers a less-invasive approach for masses up to 10 cm in size, but it is unknown whether adrenalectomy will prove superior to careful observation and management of the metabolic syndrome in these patients.

The other major issue in the evaluation of adrenal incidentalomas is assessment of malignancy risk. In patients known to have cancer, most adrenal incidentalomas are metastases, with lung, breast, kidney, and melanoma being the most common primary sites. However, adrenal metastases are less common than primary adrenocortical carcinomas in patients without a known malignancy. The attenuation coefficient (expressed as Hounsfield units) in noncontrast CT imaging is the most useful initial tool to distinguish benign from malignant adrenal tumors. Other useful imaging criteria include the pattern of enhancement, “washout” of contrast media, and the size of the mass. Most masses smaller than 3 cm are benign adenomas, whereas adrenal carcinomas are usually greater than 6 cm in diameter. In a survey of 1004 patients with adrenal incidentalomas, a size cutoff of 4 cm yielded optimal sensitivity but low specificity for malignant adrenal lesions (see **Figure 108-5**). However, patients with carcinoma were significantly younger than were patients with adenoma. An increase in mass size has been considered suggestive of malignancy, with one study reporting that a change in mass size of 0.8 cm offered the best compromise between sensitivity and specificity for distinguishing benign from malignant adrenal masses. However, excision of enlarging masses has generally identified as benign underlying pathology.

Some experts advise the removal of all adrenal masses greater than 4 cm that lack other imaging characteristics suggesting a benign origin. However, the natural history of adrenal incidentalomas is that most of these lesions remain clinically insignificant and morphologically unchanged. Subclinical hormone hypersecretion develops in some individuals, but the risk of progression to overt hypersecretion is minimal. Furthermore, aggressive evaluation and management of adrenal incidentalomas in all older adults would be cost-prohibitive.Based on the foregoing discussion, a conservative approach is warranted in the management of most older people with apparently nonfunctioning adrenal incidentalomas. In surgical candidates, tumors associated with overt hormonal hypersecretion and lesions larger than 6 cm should generally be removed, along with masses between 4 and 6 cm with imaging characteristics strongly suggesting malignancy. Masses less than 3 cm in size probably do not need further evaluation or follow-up. Lesions between 3 and 6 cm without other imaging characteristics suggesting malignancy may be followed with serial imaging studies, although the benefits of serial imaging have been questioned.

SYMPATHOADRENAL SYSTEM

Physiology

The sympathetic nervous system (SNS) plays a key role in the regulation of physiologic homeostasis, including cardiovascular and metabolic functions. For example, postganglionic sympathetic neurons projecting to the heart and blood vessels regulate cardiac output and arterial blood pressure. The SNS stimulates release of epinephrine from the adrenal medulla, which in turn plays an important role in the regulation of both cardiovascular function and energy

metabolism. SNS dysfunction has been implicated in the pathogenesis of a variety of age-associated disorders, including hypertension, obesity, congestive heart failure, type 2 diabetes mellitus, and sudden cardiac death.

NE is the primary neurotransmitter released by sympathetic postganglionic neurons. After release, most of the NE is taken up again into the presynaptic and postsynaptic axon terminals, whereas only a small fraction diffuses into the circulation. The adrenal medulla contains specialized postganglionic sympathetic neurons that enzymatically convert NE into epinephrine, the major secretory product of these cells.

There is a general consensus that SNS activity is increased with aging in humans. Basal plasma NE levels are increased in older people because of an increase in NE secretion and, to a lesser extent, a decrease in clearance. Furthermore, plasma NE responses to various stimuli such as upright posture, cold pressor tests, exercise, and hand grip are also increased with aging. By comparison, adrenal medullary function is relatively unchanged until 75 to 80 years of age. Clearance of epinephrine is increased with aging. However, in subjects younger than age 75, increased clearance appears to be balanced by a proportionate increase in epinephrine secretion, with no change in circulating epinephrine levels. However, in people older than age 80, levels of epinephrine are increased both at baseline and after cold pressor testing, suggesting important effects of advanced age on both the sympathoneural and the sympathoadrenomedullary components of the SNS.

Although SNS tone is increased with aging, physiologic responses to adrenergic receptor–mediated stimulation generally decrease with aging. For example, the increased NE levels in older subjects do not increase basal heart rate, and stimulation of β-receptors by isoproterenol produces less of an increase in heart rate and contractility in aging, as compared to young individuals. Furthermore, aging subjects exhibit decreased β-receptor–mediated chronotropic responses to stimuli such as hypoxia, and decreased arterial vasoconstrictor responses to α-adrenergic stimulation. This decreased responsiveness to catecholamines appears to be a result of changes at both the receptor and the postreceptor level, including reduction in receptor number, decreased receptor affinity, and receptor-effector uncoupling. In healthyolder adults, administration of angiotensin II causes greater vasoconstriction compared to young adults, and increases circulating NE levels in older but not in young subjects. With coadministration of α-adrenergic blockade, angiotensin II–mediated vasoconstriction is similar in older and young subjects, suggesting that angiotensin II may cause vasoconstriction in part by action through the α-adrenergic system.

Clinical

Hypertension Clinical consequences of this age-related hyperadrenergic state may include the development of hypertension. Several studies report unchanged α-mediated arterial vasoconstriction with normal aging. Based on these studies, together with observations that β-adrenergic–mediated vascular smooth muscle relaxation is decreased with aging, it has been hypothesized that older people are predisposed to develop hypertension as a result of relatively unopposed α-adrenergic tone. However, this hypothesis was cast into doubt by studies that found a decrease in arterial α-adrenergic responsiveness to NE in normal older people, implying an appropriate compensatory response to elevated SNS tone with aging. When compared with older normotensive people, older hypertensive subjects exhibit an increase in vascular α-adrenergic receptor responsiveness despite equal or greater SNS activity. Therefore, a combination of an increase in systemic SNS tone and enhanced α-adrenergic receptor responsiveness may contribute to essential hypertension in older adults.

Differences between men and women in the relationship between sympathetic nerve activity and blood pressure have been observed. In young healthy normotensive adults of both sexes, muscle sympathetic nerve activity (MSNA) varies widely and is not linked to resting blood pressure. The explanation for this finding varies by sex. In young men, MSNA was found to correlate with total peripheral resistance (TPR), such that men with high MSNA also had high TPR. Healthy young men with high MSNA and high TPR were also found to have lower stroke volume and cardiac output, which appeared to buffer the effect of high TPR and resulted in normal blood pressures. Furthermore, individuals with a high MSNA exhibited less responsiveness to α-adrenergic agonists, suggesting a loss of α-receptor sensitivity.

Compared to men, young women have lower α-adrenergic receptor sensitivity to α-agonists and are less able to support resting blood pressure by increasing α-adrenergic tone. Furthermore, in contrast to young men, there is no relationship between MSNA and TPR or cardiac output in young women. This difference between the sexes appears to be due to the effects of β-adrenergic vasodilatation, which offsets α-adrenergic vasoconstriction in young women and may in part explain the observation that blood pressures are generally lower in young women than in young men. It is thought that female sex hormones may increase β-adrenergic–mediated vasodilation, though the specific mechanism remains uncertain.

In both sexes, with aging MSNA becomes more tightly correlated with blood pressure, which may contribute to the increasing risk of hypertension during aging. The effect of β-adrenergic–mediated vasodilation in counteracting α-mediated vasoconstriction is lost in older women, which may play a role in the increased hypertension risk seen in postmenopausal women.

In clinical practice, antihypertensive drugs that block CNS sympathetic outflow or SNS-mediated peripheral vasoconstriction may cause orthostatic hypotension in older adults, especially postprandially when gastrointestinal vasodilation occurs.

Metabolic syndrome Several lines of evidence suggest an important role of the SNS in the pathogenesis of the metabolic syndrome. First, various components of the metabolic syndrome such as obesity and hypertension are associated with an increase in SNS activity. For example, individuals with insulin resistance, hypertension, and obesity exhibit resting tachycardia, elevated plasma NE levels, increased secretion of NE from sympathetic nerves, and adrenoreceptor downregulation. Second, increased sympathetic tone is associated with a decrease in insulin sensitivity. For example, experimental maneuvers in healthy subjects that decrease venous return cause an increase in NE release and peripheral vasoconstriction, together with an acute reduction in insulin sensitivity. Finally, adrenergic overactivity is associated with end-organ damage associated with the metabolic syndrome. Distensibility of medium and large arteries is decreased by sympathetic tone, which over time may promote atherogenesis.

Based on the foregoing discussion, inhibition of sympathetic overactivity is a potential therapeutic goal in people with the metabolic syndrome. This can be achieved either by adhering to an energy-restricted diet or by physical training. Of note, although moderate dietary sodium restriction is commonly recommended for people with hypertension, even a moderate restriction of sodium intake in people with the metabolic syndrome may precipitate SNS activation and potentially worsen insulin resistance. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists have sympathoinhibitory effects and are useful antihypertensive agents in people with the metabolic syndrome.

Autonomic insufficiency Autonomic insufficiency may result from primary peripheral nervous system failure, coexisting diseases such as diabetes mellitus or multiple system atrophy, or drugs that interfere with SNS function. The most common clinical manifestation of these conditions is orthostatic hypotension, defined as a decrease in systolic blood pressure of at least 20 mm Hg, or a fall in diastolic blood pressure of at least 10 mm Hg within 3 minutes after arising from a supine to a sitting or standing position. In addition, the pulse rate may fail to increase despite a significant fall in blood pressure in more advanced cases. Other manifestations of autonomic insufficiency may include erectile dysfunction, urinary incontinence, urinary retention, constipation, gastroparesis, and anhidrosis. Older people with symptomatic or asymptomatic carotid sinus hypersensitivity (CSH) have elevated resting SNS activity and baroreflex sensitivity compared to healthy older people without CSH. These observations suggest that autonomic dysfunction is present in those with CSH, whether or not symptoms are present. In a study of community-dwelling older adults, CSH was present in 35% of asymptomatic subjects without a history of dizziness, falls, or syncope. Taken together, autonomic dysfunction appears to be highly prevalent in older people living in the community.

Aside from identifying clinical manifestations of autonomic insufficiency, and determining the presence of underlying disorders such as diabetes mellitus, routine laboratory testing of SNS function is not indicated. Management options for orthostatic hypotension associated with autonomic insufficiency are summarized in **Table 108-6**; multiple interventions are usually employed simultaneously. Midodrine, an α_1-adrenergic receptor agonist with few cardiac or CNS side effects, is often better tolerated by older adults than fludrocortisone. For management of other clinical manifestations of autonomic insufficiency, see Chapter 43 (Sexuality, Sexual Function, and Androgen Replacement Therapy in the Aging Male), Chapter 53 (Incontinence), and Chapter 95 (Constipation).

TABLE 108-6 MANAGEMENT APPROACHES FOR ORTHOSTATIC HYPOTENSION CAUSED BY AUTONOMIC INSUFFICIENCY

Nonpharmacologic

- Eliminate or reduce medications associated with postural hypotension
- Dangle legs for several minutes prior to arising from bed
- Dorsiflex ankles several times before arising from bed or chair
- Avoid rapid changes in position when arising from bed or chair
- Avoid dehydration

- Wear elastic support stockings to maximize venous return
- Liberalize dietary sodium intake
- Eat frequent, small meals to minimize postprandial hypotension
- Elevate head of bed up to 20 degrees
- For patients with a history of prolonged bed rest, increase amount of time spent sitting up each day

Pharmacologic

- Fludrocortisone (mineralocorticoid, volume expander)
- Midodrine (α_1-adrenergic receptor agonist)
- When antihypertensive therapy is required, ACEIs, ARBs, and β-blockers with intrinsic sympathomimetic activity are less likely to worsen OH

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; OH, orthostatic hypotension.

Pheochromocytoma Pheochromocytoma is a rare tumor, occurring in fewer than 0.2% of patients with hypertension. Most cases are thought to occur in young and middle-aged adults, but epidemiologic and autopsy data indicate a progressive age-specific increase in the incidence rate. It is unclear whether some pheochromocytomas diagnosed at autopsy are nonfunctioning and of no clinical significance, or whether the disease is underdiagnosed in older patients. However, based on the foregoing discussion, the age-related decrease in responsiveness to catecholamines may result in a muting or an absence of symptoms of excessive adrenergic stimulation such as diaphoresis and palpitations. Furthermore, pheochromocytomas present with protean symptoms and signs that may mislead the clinician, earning it the title of the "Great Masquerader." The diagnosis may be especially challenging in older adults with signs and symptoms of comorbid illnesses that further confound the diagnosis, and in whom vague, muted, nonspecific, or asymptomatic presentations are more common. Therefore, a high index of suspicion is necessary to make this diagnosis in older patients. A symptom complex of headaches, palpitations, and diaphoresis; refractory or severe hypertension of unknown cause; or a paradoxical blood pressure response to β-blocking medications may suggest the diagnosis.

According to a 2014 Endocrine Society guideline, initial diagnostic testing should include measurements of both urinary fractionated metanephrines and plasma free metanephrines. However, there is no consensus on the best diagnostic test for pheochromocytoma. Plasma free metanephrines are highly sensitive, and a normal result excludes the diagnosis in most situations. However, specificity of the test is relatively poor, and is even lower (77%) in adults over the age of 60. Plasma free normetanephrine levels are affected by age, so an age-adjusted upper limit of 1.05 nmol/L has been proposed to minimize false-positive results in adults older than 60 years without unduly compromising sensitivity. Other factors that may lead to false-positive (eg, tricyclic antidepressants, sympathomimetic medications, and acetaminophen) or false-negative (eg, dopamine-producing tumors) results should also be considered. Diagnostic accuracy may be improved by using a combination of tests. Imaging studies are useful for preoperative localization of tumor but generally not for diagnosis.

Surgical intervention is indicated in older patients with resectable pheochromocytomas, in view of the potential for surgical cure and the poor prognosis with medical management. Preoperative localization of tumor should be undertaken using CT of the chest, abdomen, and pelvis, with MRI scanning for detection of metastatic foci. Functional imaging studies are indicated when conventional imaging modalities fail to locate the tumor despite compelling biochemical and clinical evidence of pheochromocytoma. ^{18}F FDG-PET/CT imaging is preferred over ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy for the detection of metastatic disease due to its superior sensitivity. However, ^{123}I-MIBG scintigraphy may be useful in patients with metastatic pheochromocytomas who are not candidates for surgery, because a positive result may indicate the possibility of radiotherapy with ^{131}I-MIBG.

A careful cardiologic evaluation is warranted preoperatively in all patients with pheochromocytoma; the presence of coronary artery disease or cardiomyopathy may influence preoperative medical management. α-Receptor blockade is usually initiated preoperatively for blood pressure control even in normotensive patients, often in combination with β-blockers. However, β-receptor blocking agents should not be given until after α-blockade is achieved, to avoid an increase in blood pressure induced by unopposed α-activity. In addition, patients with pheochromocytoma have a contracted plasma volume and saline infusion is indicated for moderate volume expansion, though caution is warranted in patients with congestive heart failure or renal failure. Minimally invasive procedures such as laparoscopy are appropriate for most adrenal pheochromocytomas. However, open resection may be necessary for large or invasive tumors.

Occasionally, a pheochromocytoma will present as an adrenal incidentaloma with normal urinary metanephrines and plasma free metanephrines, and negative imaging studies, but during surgery its intraoperative behavior and subsequent histologic findings indicate pheochromocytoma. It is important to take prophylactic measures during surgery for this possibility, including placement of an arterial line and arrangement for immediate access to intravenous nitroprusside.

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Aldosterone secretion decreases with aging. Despite a concomitant decline in clearance rate, basal plasma aldosterone levels are 30% lower in healthy octogenarians compared to younger adults (**Table 108-7**). Aldosterone secretion is also reduced after stimuli such as sodium depletion or upright posture. However, these changes do not appear to be secondary to adrenal dysfunction because aldosterone responsiveness to ACTH is intact with aging. The primary defect responsible for these changes in aldosterone secretion is thought to be a reduction in plasma renin activity, which is decreased by 50% in older persons, as compared to younger adults. This decline in active renin concentration is thought to be a result of diminished conversion of inactive to active renin. In addition, age-related increases in atrial natriuretic hormone secretion contribute to the suppression of aldosterone secretion with aging, both directly and by inhibiting renal renin secretion, plasma renin activity, and angiotensin II levels. See Chapter 89 for additional information on effects of aging on salt and water regulation.

TABLE 108-7 EFFECTS OF AGING ON HORMONAL REGULATION OF FLUID AND SODIUM BALANCE

Antidiuretic hormone (ADH)	
Basal ADH levels	↑/↔
ADH release after osmoreceptor stimulation	↑
ADH release after baroreceptor stimulation	↓
Renal responsiveness to ADH	↓
Aldosterone	
Basal aldosterone levels	↓
Aldosterone release after sodium depletion	↓
Aldosterone release after postural challenge	↓
Aldosterone release after ACTH stimulation	↔
Renin	
Plasma renin activity	↓
Atrial natriuretic hormone (ANH)	
Basal ANH levels	↑
ANH responses to stimuli	↑

↓, decreased; ↔, unchanged; ↑, increased.

The clinical consequences of decreasing aldosterone levels with aging include a predisposition to renal sodium wasting, which, in combination with reduced thirst and decreased renal ADH responsiveness, further increases the potential for volume depletion and dehydration in geriatric patients. Furthermore, this state of relative hyporeninemic hypoaldosteronism places older adults at increased risk of hyperkalemia, especially patients with diabetes mellitus and renal insufficiency (**Table 108-8**). The addition of aldosterone antagonists, β-blocking agents, nonsteroidal anti-inflammatory drugs, or heparin may lead to potentially life-threatening hyperkalemia in such patients.

TABLE 108-8 RISK FACTORS FOR HYPERKALEMIA IN OLDER PEOPLE

Diabetes mellitus[a]
Renal insufficiency or failure
Intravascular volume depletion

Adrenocortical insufficiency
Acidosis
Medications • Aldosterone antagonists (spironolactone, eplerenone) • Sodium channel antagonists (“potassium-sparing” diuretics: triamterene, amiloride) • Trimethoprim-sulfamethoxazole • Angiotensin-converting enzyme inhibitors • Angiotensin antagonists • β-Adrenergic blocking agents • Nonsteroidal anti-inflammatory agents
Potassium-containing salt substitutes
Tissue injury with rapid release of potassium from cells • Crush injury • Tumor lysis syndrome • Hemolysis

[a]Multiple contributors, including insulin deficiency, renal insufficiency, hyporeninemic hypoaldosteronism, type IV renal tubular acidosis, and use of angiotensin-converting enzyme inhibitors.

GROWTH HORMONE AXIS

Physiology

Secretion of GH from the pituitary is regulated by the hypothalamic peptides GHRH and somatostatin. These two peptides exert an opposing effect on GH secretion, with GHRH stimulating and somatostatin inhibiting GH secretion by the pituitary somatotropes. In humans, GH secretion appears to be controlled primarily by pulsatile GHRH secretion and via reduction in tonic inhibition by somatostatin. Secretion of GH is pulsatile, mostly in response to pulsatile GHRH secretion, although about a third of GH pulses are dissociated from GHRH pulses. Ghrelin may be an important factor regulating pulsatile GH release. IGF-1, which is secreted by the liver and other peripheral tissues in response to GH, mediates most of the actions of GH. In turn, IGF-1 exerts a negative feedback effect on GH secretion through a direct effect at the pituitary level and indirectly by increasing somatostatin production. Most IGF-1 circulates in ternary protein complexes with IGF-binding protein 3 (IGFBP-3) and an acid-labile subunit. IGFBPs act in concert to regulate circulating levels of free IGF-1. In addition, IGFBPs appear to inhibit as well as stimulate IGF-1–mediated bioactivity, and in some cases, they may exert effects independent of IGF-1. However, the specific roles of each of the six IGFBPs are not well understood.

Circulating levels of GH are generally very low except for several pulses occurring during the first few hours of sleep, after meals or exercise, or without apparent cause. Both basal and 24-hour total GH secretion are higher in women than in men. The pulsatility of GH secretion is more marked in men than in women over 24 hours. In young adult men, most of the GH is secreted within the first 4 hours after sleep onset, with large amplitude pulses occurring during slow-wave sleep, with IGF-1 levels remaining fairly constant over a 24-hour period. In contrast, young women have multiple episodes of GH secretion and a high basal output of GH during the daytime, with relatively low GH release during the night.

GH release is affected by numerous other factors, including other neurotransmitters and neuropeptides, medications, hormonal influences, blood glucose levels, degree of obesity, and physiologic states such as sleep and exercise. The neurotransmitter dopamine and CNS-active dopaminergic agonists such as bromocriptine exert a stimulatory effect on GH release by promoting hypothalamic GHRH release. NE, α-adrenergic agonists, and β-adrenergic antagonists also increase GHRH and GH release, whereas β-adrenergic agonists and dopamine or α-receptor blocking agents inhibit GH secretion. Estrogens stimulate GH release, whereas GH secretion is inhibited in those treated chronically with glucocorticoids. Hyperglycemia is associated with decreased GH levels and GH responses to GHRH. Similarly, obese subjects exhibit decreased spontaneous GH secretion and reduced GH responsiveness to pharmacologic stimulation compared to nonobese subjects, although IGF-1 levels are typically within normal limits. GH levels are acutely elevated during exercise, and there is evidence that regular exercise may enhance GH secretion over the long term. GH secretion is increased by fasting, high-protein meals, or insulin-induced

hypoglycemia. Taken together, these findings indicate that a complex array of nutritional, hormonal, and peptidergic factors regulate GH secretion.

Age effects

GH secretion reaches maximum levels at puberty, followed by a gradual but progressive decline with age. In adult men, GH secretion declines by approximately 14% per decade, such that by age 70 to 80, about half of all individuals have no significant GH secretion during a 24-hour period. Plasma IGF-1 levels exhibit a corresponding decline of 7% to 13% per decade, and by age 70 to 80, approximately 40% have plasma IGF-1 levels in the range found in GH-deficient children. In addition, serum levels of IGFBP-3 decline with aging in healthy adults, but it is unclear whether this affects the metabolic activity of IGF-1 with aging.

Collectively, these decreases in pituitary secretion of GH and circulating IGF-1 levels are often referred to as the somatopause. The age-related decrease in GH production appears to be primarily caused by a decrease in hypothalamic GHRH secretion and an increase in hypothalamic somatostatin release, as well as attenuation in pituitary responsiveness to GHRH (decreased GH pulse amplitude). Cross-sectional studies in healthy subjects controlled for confounding factors such as body mass index showed a decrease in circulating ghrelin levels with aging, suggesting that reduced stimulation of pituitary GH release by ghrelin may contribute to reduced GH secretion with aging. Other factors contributing to lower GH levels in older people include increased adiposity and reduced exercise. The age-related decrease in GH secretion is partially reversed by fasting in older people without an associated alteration in sleep quality, suggesting that lifestyle modification may augment endogenous GH secretion in older adults.

Growth Hormone Deficiency in Adults With Hypothalamic-Pituitary Disease

GH deficiency in adults with established hypothalamic-pituitary disease is associated with reduced lean body mass, muscle strength, and exercise capacity; diminished psychological well-being; insulin resistance; increased total body adiposity; higher waist-to-hip ratio of fat distribution; reduced bone density with increased risk of fractures; adverse effects on lipid metabolism; and increased risk of death from cardiovascular disease, despite adequate replacement of other hormones including thyroxine, cortisol, and sex steroids. Many of these effects can be improved or corrected with daily subcutaneous administration of one of a number of recombinant human GH formulations, and GH supplementation is approved in the United States for adults with hypopituitarism and GH deficiency.

GH therapy of adults with GH deficiency causes improvements in body composition, exercise capacity, some aspects of cardiovascular function, bone mass, and some metabolic indices including total and low-density lipoprotein (LDL) cholesterol that have been sustained in small trials lasting up to 15 years. Bone resorption tends to increase within 6 to 12 months after initiation of GH therapy, but with continued treatment bone mineral density (BMD) increases by 4% to 10%. Improvement in lumbar spine BMD is sustained after 15 years, whereas femoral neck BMD appears to peak at 5 to 7 years of GH therapy and then returns toward baseline by 15 years. For unclear reasons, men with GH deficiency appear to obtain greater improvements in BMD with GH treatment than women. The effect of GH therapy on fracture risk has not yet been reported in randomized, controlled trials. Measures of health-related quality of life and psychological well-being improved in many though not all double-blind, placebo-controlled trials of GH therapy in adults with GH deficiency. Subjects with the most severe impairments in quality of life at baseline were the most likely to benefit from therapy, and quality of life benefits were sustained in those who initially benefited for up to 10 years of treatment.

Long-term GH treatment is generally well tolerated. The most commonly reported adverse effects of GH treatment in adults with hypopituitarism are fluid retention/edema, arthralgias, myalgias, and carpal/tarsal tunnel syndrome. These symptoms are most likely to occur in people who are older or obese, and are more common in those with the greatest increase in IGF-1 levels during treatment. However, these symptoms often resolve spontaneously during treatment and disappear with treatment cessation. GH treatment tends to increase insulin resistance, although this effect may be countered by improvements in visceral fat mass and increased IGF-1 levels that improve insulin sensitivity. Prospective, long-term data suggest that the risk of type 2 diabetes mellitus is not increased in GH-treated patients, although an increased prevalence of metabolic syndrome has been reported after 10 years of GH treatment. Based on the foregoing, the overall effects of GH therapy on cardiovascular risk remain uncertain. Retrospective studies have reported an increased rate of neoplasia as well as cancer-related mortality in patients with pituitary adenomas although it is unclear whether these findings reflect inherent risk, increased surveillance, or the effects of treatments received. To date, no studies have reported the effect of GH replacement on mortality in adults with GH deficiency due to hypothalamic-pituitary disease.

The clinical signs and symptoms of adult GH deficiency are nonspecific, and currently available tests are prone to a high rate of false-positive results. Accordingly, testing is indicated only for patients with documented deficiencies of multiple pituitary hormones, along with a history of structural hypothalamic-pituitary disease, surgery or irradiation to these areas, traumatic brain injury, or subarachnoid hemorrhage.

Laboratory criteria for distinguishing older adults with organic GH deficiency from those with normal age-related reductions in GH secretion have not yet been clearly defined. Furthermore, assessment of GH function is complicated by the need for GH stimulation tests, the lack of adequate normative data for many laboratories, assay variability, and the unavailability of appropriate age-adjusted normal values for diagnostic tests. Static GH levels are unsuitable for diagnosis, because GH is secreted episodically. IGF-1 levels decline during normal aging and are not a reliable indicator of GH deficiency secondary to pituitary disease in people older than 40 years, although IGF-1 levels below the age-adjusted normal range may suggest the diagnosis. However, a decreased IGF-1 level together with deficiencies in at least three other pituitary hormones is sufficient to diagnose GH deficiency. Normal IGF-1 levels do not exclude the diagnosis of GH deficiency at any age. The insulin tolerance test is considered the most definitive test for GH deficiency in adults and it has been performed safely in older patients, but this test may be dangerous in older patients with ischemic heart disease or arrhythmias. Arginine-induced GH secretion remains intact with normal aging, and the arginine/GHRH stimulation test has been proposed as a safer yet reliable alternative to distinguish GH deficiency secondary to hypopituitarism from normal age-related reductions in GH secretion. GHRH is not currently available in the United States, so the combined arginine-levodopa stimulation test or glucagon stimulation test are acceptable alternatives. In adults with milder hypopituitarism, for example, two or fewer pituitary hormone deficiencies, it is advisable to use two independent stimulation tests to confirm GH deficiency.As with younger adults, older people with GH deficiency related to hypopituitarism may also benefit from GH replacement, although the relatively limited effects of GH therapy in older adults combined with the high cost and inconvenience of daily SC injections suggest the need for careful, individualized cost-benefit analysis prior to initiating therapy. People with more severe biochemical and clinical manifestations of GH deficiency are more likely to derive benefit from GH replacement. A systematic review of 11 studies of the efficacy of GH therapy in GH-deficient adults over 60 years (n = 534) reported that GH treatment reduced total and LDL cholesterol but did not affect HDL cholesterol or triglyceride levels. Waist circumference decreased by about 3 cm and waist/hip ratio decreased in treated subjects, but there was no significant change in BMD. Lean body mass increased and total fat mass decreased in most but not all studies, while measures of quality of life consistently improved. No data are available on the efficacy and safety of GH therapy in individuals older than 80 years, nor are data available on clinically meaningful end points such as cardiovascular morbidity, fracture risk, or mortality.

The GH replacement dose in older GH-deficient adults is lower than that required by younger adults. In one study, a dose of 0.5 mg of GH per day resulted in elevated serum IGF-1 levels in half of older subjects, and 25% developed side effects on this dose. By contrast, younger adults may require doses up to 1 mg/day. Treatment should begin at a low dose (eg, 0.1–0.2 mg/day) with slow upward titration at bimonthly intervals based on clinical and biochemical responses. Serum IGF-1 levels should be maintained within the age-adjusted normal adult range to optimize the beneficial effects of GH replacement while minimizing the potential for side effects such as carpal tunnel syndrome, arthralgias, fluid retention, and gynecomastia. Patients with an active malignancy should not receive GH supplementation. Longer-acting GHRH analogs, pegylated long-acting GH, and GH secretagogues are being developed for the treatment of adult GH deficiency, which may eventually increase the range of therapeutic options for older people with this disorder.

Growth Hormone Supplementation for Older People Without Hypothalamic-Pituitary Disease

Normal aging is associated with alterations in body composition similar to those in GH-deficient younger patients, including decreased muscle mass and strength, reduced bone mass, and increased adiposity. In turn, declining strength and bone mass are associated with increasing risk for falls and fractures in older people. These observations suggest that the reduction in GH secretion associated with aging (the somatopause) may contribute to alterations in body composition and increased frailty in older adults, and that GH supplementation, GHRH, or GH secretagogue treatment might be clinically useful in preventing or reversing these age-related changes.

After an early report of potentially beneficial changes in body composition with short-term GH supplementation in older men, interest in GH as an “antiaging” hormone increased dramatically. It was estimated that 20,000 to 30,000 individuals in United States used GH for this purpose in 2004, and that up to one-third of the prescriptions for GH worldwide are for “off-label” use. However, its use to prevent aging-related changes has remained controversial and it

is illegal in the United States to distribute GH for use as an antiaging remedy.

A systematic review in 2007 of randomized, controlled trials of GH supplementation for up to 1 year in healthy older people (mean age 69) found modest decreases in fat mass and increases in lean body mass in subjects receiving GH compared to placebo-treated subjects. These potentially beneficial effects on body composition were largely confined to men, possibly reflecting the observation that women require larger doses of GH over a longer period of time than men to achieve physiologic replacement of GH. Although body composition improved (increase in lean mass and decrease in fat mass) in men treated with physiologic amounts of GH for 6 months, muscle strength, endurance, and functional status did not improve. Total serum cholesterol levels tended to decrease, but no significant changes occurred in bone mineral density or other serum lipid levels with GH supplementation. Older subjects receiving GH were more likely to develop peripheral edema, carpal tunnel syndrome, arthralgias, and gynecomastia. GH-treated subjects tended to have a higher incidence of impaired fasting glucose and type 2 diabetes mellitus. Because of the limited study duration and small size of the study groups, no effect of GH treatment was reported on cancer risk or death. Overall, there is little evidence that GH supplementation improves other relevant outcomes in healthy older people, including strength, function, or quality of life. Based on the observations of minimal clinical benefit and a high rate of adverse effects, GH supplementation is not recommended as an antiaging treatment in healthy older adults.

HYPOTHALAMIC-PITUITARY-TESTICULAR AXIS

Age Effects

Significant age-related changes occur in male reproductive function with aging, including a decrease in sexual activity, libido, and fertility rates (see chapter 43). However, in contrast to the relatively rapid and complete loss of gonadal function in women at the time of menopause, changes in testicular function in aging men occur gradually, vary considerably between individuals, and often do not result in severe hypogonadism. Many healthy older men exhibit a degree of primary testicular failure, with decreases in total and free or bioavailable testosterone levels, testosterone responses to exogenous gonadotropin administration, and daily sperm production, together with increased serum gonadotropin levels (**Figure 108-6**, **Table 108-9**). Occasionally, community-dwelling older men present with overt testicular failure with total testosterone levels well below normal and symptoms of androgen deprivation including hot flashes, decreased libido, and gynecomastia. However, it is more common to see older patients with mildly decreased testosterone levels and relatively nonspecific symptoms such as impotence, loss of libido, osteopenia, and muscle weakness. In contrast, more marked testosterone deficiency is common in frail older men. For example, in male nursing home residents, it has been reported that 45% exhibit testosterone levels within the hypogonadal range. Hypogonadism does not occur in all aging men; many healthy men older than age 80 maintain serum testosterone levels within the normal young adult range.

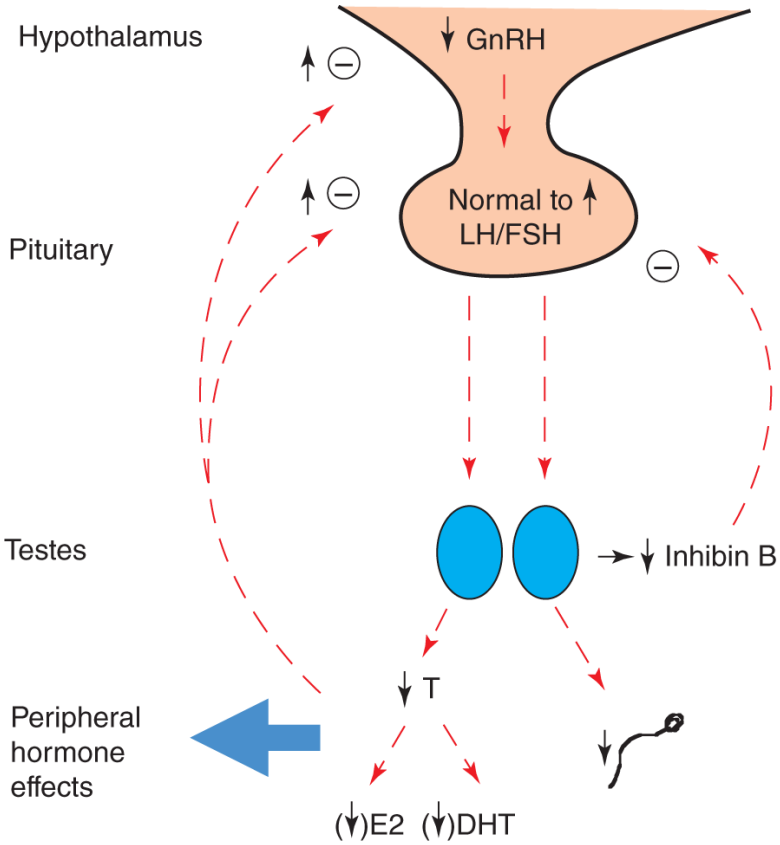


FIGURE 108-6. Age-related changes in male hypothalamic-pituitary-gonadal axis function. DHT, dihydrotestosterone; E2, estradiol; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone. LH, luteinizing hormone. T, testosterone. Small solid arrows denote direction of change with aging.

TABLE 108-9 AGE-RELATED CHANGES IN HYPOTHALAMIC-PITUITARY-TESTICULAR AXIS FUNCTION

Circulating levels of hormones and binding globulins	
• Total T	↓
• Free/bioavailable T	↓↓
• SHBG	↑ (usually within normal range until advanced age)
• Total E_2	→
• Free E_2	→/↓
• Total DHT	→/↑
• Free DHT	→/↓
• Inhibin B	↓
• LH	→/↑ (usually within normal range until advanced age)
• FSH	→/↑ (may remain within normal range until advanced age)
Other parameters of male reproductive function	
• Testicular T production in response to LH	↓
• Daily sperm production	↓
• Sperm fertilizing capacity	→
• Bioactive/immunoreactive LH	↓
• Bioactive/immunoreactive FSH	↓
• Gonadotropin responsiveness to GnRH	→
• LH pulse frequency	↓

DHT, dihydrotestosterone; E_2, estradiol; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; SHBG, sex hormone–binding globulin; T, testosterone.

Several factors contribute to this decrease in testosterone levels with aging. First, testicular testosterone production is markedly reduced with aging (see **Table 108-9**), which is reflected in the decreased number and volume of Leydig cells in the aging testis. This reduction in testosterone production capacity may manifest as a more severe and prolonged depression of testosterone levels during intercurrent illness or other stresses in older men. Second, both production rates and metabolic clearance of testosterone are reduced in aging men, but in contrast to adrenal cortisol secretion and metabolism, the decrease in testosterone production is not completely offset by a decrease in clearance. Third, the normal circadian variation in testosterone levels observed in young men, with highest levels in the morning, is blunted with aging, resulting in reduced serum testosterone concentrations. Fourth, the concentration of the major testosterone-binding protein, sex hormone–binding globulin (SHBG), increases with aging. Therefore, serum free or non-SHBG–bound (bioavailable) testosterone concentrations decline to a greater extent with aging than total testosterone.

In addition to these deficits in testicular function, hypothalamic/pituitary control of testicular function is also impaired with aging (see **Table 108-9**). Although gonadotropin levels increase with aging, they usually remain within normal limits, and the hormonal profile of a low testosterone and normal gonadotropin levels is consistent with aging-related secondary hypogonadism. Even in men with elevated levels of LH and FSH, the increases in gonadotropins are sometimes inappropriately low in comparison to younger men with similar reductions in testosterone levels, and FSH levels are more commonly elevated than LH levels. Furthermore, the ratio of bioactive to immunoreactive LH and FSH is decreased in older men, indicating that gonadotropin levels measured by radioimmunoassay may underestimate the extent of gonadotropin deficiency. Finally, healthy older men exhibit intact LH and FSH responsiveness to prolonged exogenous pulsatile GnRH administration but an inappropriately normal or decreased LH pulse frequency (an indicator of hypothalamic GnRH pulse-generator activity), as compared to young men. Based on the above evidence, it appears that age-related hypogonadism is a consequence of combined testicular and hypothalamic dysfunction. In many cases, older men may have potentially remediable functional causes of secondary hypogonadism or combined secondary and primary hypogonadism, including medications, lifestyle factors, and comorbid illnesses (**Table 108-10**). As testosterone levels decline with aging, various functional changes occur in androgen-dependent body tissues. In the testes, there are significant age-related decreases in the number of Sertoli cells, volume of seminiferous tubules, daily sperm production, and to some extent testicular volume. Serum levels of inhibin B, which is secreted by Sertoli cells and mediates feedback inhibition of pituitary FSH secretion, also decrease with aging. In studies controlled for the increased length of time between ejaculations in older men, sperm concentrations were unchanged with age, but older men exhibited lower ejaculated volume, decreased sperm motility, and a higher percentage of abnormal spermatozoa. However, these parameters remained within normal limits in most of the older subjects. Sperm fertilizing capacity by in vitro testing remains intact in healthy older men. Male fertility is thought to decrease with aging, mostly as a result of reduced sexual activity and sexual dysfunction. The causes of declining libido and sexual activity with aging are multifactorial, including the presence of chronic illnesses such as diabetes mellitus, vascular or neuropathic disease of the penis, medications, and depression (see Chapter 43).

TABLE 108-10 FUNCTIONAL CAUSES OF HYPOGONADISM IN OLDER ADULTS

Combined primary and secondary hypogonadism (usually hormonal pattern consistent with secondary hypogonadism)
• Glucocorticoid treatment
• Chronic systemic illnesses, eg, chronic renal failure, lung disease, cirrhosis
• Alcohol dependence
• Malnutrition
Secondary hypogonadism
• Chronic opioid treatment
• Administration of androgens, estrogens, and progestins
• Hyperprolactinemia
• Critical illness
• Sleep apnea

- Excessive exercise
- Morbid obesity

Testosterone and other androgens are also important in the maintenance of normal body composition in men, including bone mass, muscle mass and strength, and reduction in fat mass. Bone mass declines progressively with age in men, and hypogonadism in men is associated with premature osteoporosis and an increased risk of fractures. Additionally, younger hypogonadal men exhibit excessive visceral adiposity and reduced lean body mass that are reversible with testosterone replacement, and supraphysiologic doses of testosterone increase muscle strength and lean body mass in healthy young men. However, increasing evidence indicates that central adiposity contributes to the decline in testosterone with aging, consistent with a bidirectional relationship between visceral obesity and testosterone in older men. Weight loss results in a significant and proportionate increase in total testosterone, especially in men with morbid obesity. Free testosterone increases with weight loss as well, though not as consistently because SHBG levels increase in proportion to the degree of weight loss. Nevertheless, these findings suggest that lifestyle interventions may help to prevent or reverse the age-related decline in testosterone.

The physiologic significance of the decrease in testicular androgen production associated with aging (often referred to as “late-onset hypogonadism,” “partial androgen deficiency of the aging male,” or “andropause”) is uncertain. It remains unclear whether declining testosterone levels in older men are merely a marker for poor health or whether they constitute a deficiency state that itself contributes to morbidity. The European Male Aging Study performed in men between 40 and 79 years found that serum testosterone levels below 320 ng/dL predict three sexual symptoms (poor morning erection, decreased libido, and erectile dysfunction). Men with these findings had a lower hemoglobin, bone mineral density, and muscle mass, and poorer physical performance than men with higher testosterone levels and without sexual symptoms, but only 5.1% of subjects aged 70 to 79 met these criteria. These data suggest that it may be possible to identify older men with a recognizable low testosterone syndrome, although relatively few older men may be affected. Testosterone supplementation has been proposed not only to treat older men with frank hypogonadism caused by pathologic disease in the hypothalamic-pituitary-testicular axis, but also to ameliorate age-associated changes in body composition, sexual functioning, and overall well-being in older men with low testosterone levels related to aging per se. The role of androgens in the evaluation and management of erectile dysfunction in older men and the potential benefits and risks of testosterone supplementation in older men are discussed in Chapter 43.

Laboratory Diagnosis of Hypogonadism

The signs and symptoms of hypogonadism in older men may include diminished energy, vitality, and libido; depressed mood; erectile dysfunction; increased total and abdominal obesity, and decreased lean body and muscle mass, strength, and bone mineral density; objective impairment of cognitive function (eg, spatial ability, visual and verbal memory); mild anemia; and impaired subjective well-being. However, these manifestations are nonspecific and common in eugonadal older men, and may be attributable to other common age-associated comorbidities. Therefore, laboratory evidence as well as signs and symptoms are required to make the diagnosis of hypogonadism. Questionnaires have been developed as potential screening tools to diagnose androgen deficiency in older men, but they lack sufficient specificity to identify men requiring laboratory evaluation.

Currently, there are no clinically useful biomarkers of androgen action available, and the laboratory diagnosis of testosterone deficiency depends on measurement of low circulating testosterone concentrations. This task may be challenging for several reasons, including marked variability in the accuracy and measured levels among available testosterone immunoassays; circadian and day-to-day variability in testosterone levels; alterations in SHBG levels that affect total testosterone levels; and the effects of concurrent medical illnesses and medications (see **Table 108-10**). Although many experts recommend beginning a biochemical evaluation of hypogonadism with a total testosterone assay, older men are more likely than young men to have conditions or to be taking medications that affect circulating SHBG levels (eg, liver or thyroid disease, obesity, diabetes mellitus, glucocorticoids, anticonvulsants). Furthermore, as discussed previously, because SHBG levels increase with aging, total testosterone measurements may not fully reflect age-related reductions in biologically active testosterone. Therefore, if a condition or medication affecting SHBG is present or if the total testosterone value is near the lower limit of the normal range, a free or bioavailable (non-SHBG–bound) testosterone level should be measured using an accurate and reliable assay, for example, free testosterone by equilibrium dialysis or calculated from measurements of total testosterone and SHBG. Free testosterone assays using the direct analog radioimmunoassay method do not accurately or reliably measure free testosterone and therefore are not recommended. Although circadian variation in testosterone levels is blunted in older men, many older men with

low afternoon testosterone levels will have normal levels in the morning. Additionally, a single low testosterone level will often be normal on repeat testing due to the day-to-day biological variability in testosterone levels, so it is advisable to measure testosterone levels in the morning and to measure levels on at least two occasions. Serum testosterone should be measured only after reversible causes of low testosterone such as acute illness and malnutrition are treated, or medications such as glucocorticoids or opiates are discontinued, if possible.

The laboratory evaluation of men with suspected hypogonadism should include serum LH and FSH levels to differentiate between primary (testicular) and secondary (hypothalamic/pituitary) hypogonadism, as well as a prolactin level if gonadotropins are inappropriately low-normal or low in the presence of reduced testosterone levels. Hyperprolactinemia inhibits hypothalamic GnRH secretion, resulting in a decrease in LH and FSH secretion, and could indicate the presence of a pituitary adenoma or a hypothalamic disorder. In patients with secondary hypogonadism suspected on the basis of low serum testosterone associated with low or inappropriately normal gonadotropins, additional studies may be warranted, including magnetic resonance imaging of the pituitary fossa, measurements of other pituitary hormones such as GH and thyroid hormone levels, and an ACTH stimulation test. Furthermore, bone densitometry measurement is indicated in hypogonadal men to evaluate for asymptomatic osteoporosis.

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Chapter 109

Thyroid Diseases

Anne R. Cappola

Learning Objectives

- Understand age-related changes in thyroid function and structure.
- Recognize the symptoms of thyroid dysfunction in older people.
- Interpret thyroid function tests in the context of concurrent medication use and illness.
- Describe the evaluation and treatment of thyroid disease in older people.
- Identify thyroid nodules that require evaluation via fine-needle aspiration (FNA).
- Summarize therapy for papillary thyroid carcinoma in older people.

Key Clinical Points

1. **Aside from a slight increase in thyroid-stimulating hormone (TSH) with age, changes in thyroid function and structure are not considered normal aging and require assessment of medications or conditions that affect thyroid function and investigation for thyroid disease.**
2. **Overt hyperthyroidism and overt hypothyroidism may be difficult to recognize in older people and always require treatment.**
3. **Treatment should be considered for subclinical hyperthyroidism in older people and for patients with subclinical hypothyroidism who have higher concentrations of TSH.**
4. **The evaluation of thyroid nodules does not differ with age. Any nodule meeting criteria should undergo FNA, preferably with ultrasound guidance.**
5. **Papillary thyroid carcinoma is the most common thyroid cancer and may be more aggressive in older people. Thyroidectomy should be performed, and additional management should be tailored to the health status of the individual.**
6. **Anaplastic thyroid carcinoma presents almost exclusively in older people and has a poor prognosis.**

Thyroid hormone has widespread systemic effects and plays a critical role in metabolism at all ages. Both excess and deficiency can have severe physiologic consequences, even leading to death. The hypothalamic-pituitary-thyroid axis ensures tight regulation of thyroid hormone concentrations, even in advanced age. In addition, the thyroid gland has evolved to have sufficient redundancy so that only a minority of the gland is required for normal thyroid function. Nevertheless, the prevalence of all forms of thyroid disease, both functional and structural, increases in older people. An astute clinician is required, as recognition and management are more challenging in this age group.

CHANGES IN THYROID FUNCTION WITH AGE

Thyroid Physiology

The thyroid gland produces two thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), which differ only in the number of iodines (**Figure 109-1**). T_4 is the major hormone secreted by the thyroid gland, at an amount that is 11 times the secretion of T_3. Additional T_3 is produced peripherally by deiodination of T_4 in the liver, kidney, and brain. Within the cell, T_3 is the more potent hormone, binding to thyroid hormone receptors with higher affinity. However, because T_4 levels act as a reservoir of thyroid hormone, with a longer half-life and circulating concentrations 100 times higher than T_3, T_4 concentrations are more commonly measured in the clinical setting.

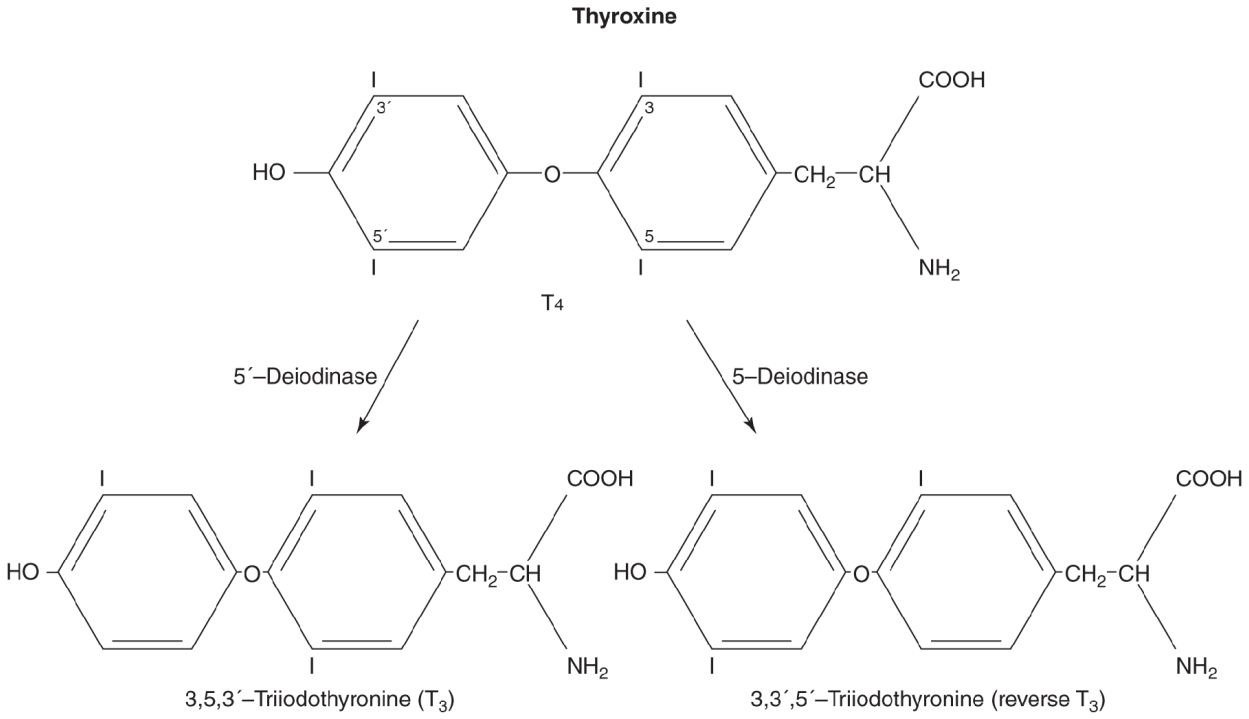


FIGURE 109-1. Structures of T_4 and the enzymatic pathways for deiodination of T_4 to its major active metabolite, T_3, and to reverse T_3 in peripheral tissues.

In addition, both T_4 and T_3 are highly protein bound. Only 0.04% of T_4 and 0.4% of T_3 circulate in the biologically active free state, with the remainder bound to thyroxine-binding globulin (TBG), thyroxine-binding prealbumin, and albumin. A variety of conditions can affect levels of these binding proteins. Therefore, measurement of free T_4 is preferable to total T_4 when T_4 assessment is required.

Thyroid hormone levels are tightly regulated by TSH through a classic endocrine feedback loop (**Figure 109-2**). Thyrotropin-releasing hormone (TRH) released from the hypothalamus stimulates pituitary production of TSH, which in turn stimulates thyroidal production of T_4 and T_3. T_4 and T_3 exert feedback control on the hypothalamus and pituitary to regulate TRH and TSH release. In essence, the pituitary and hypothalamus act as a thermostat to maintain thyroid hormone levels within a narrow range. Because of variation between individuals in thyroid hormone set point and the sensitivity of the pituitary to perturbations in the set point, TSH levels are used clinically to screen for thyroid problems, rather than levels of T_4 or T_3.

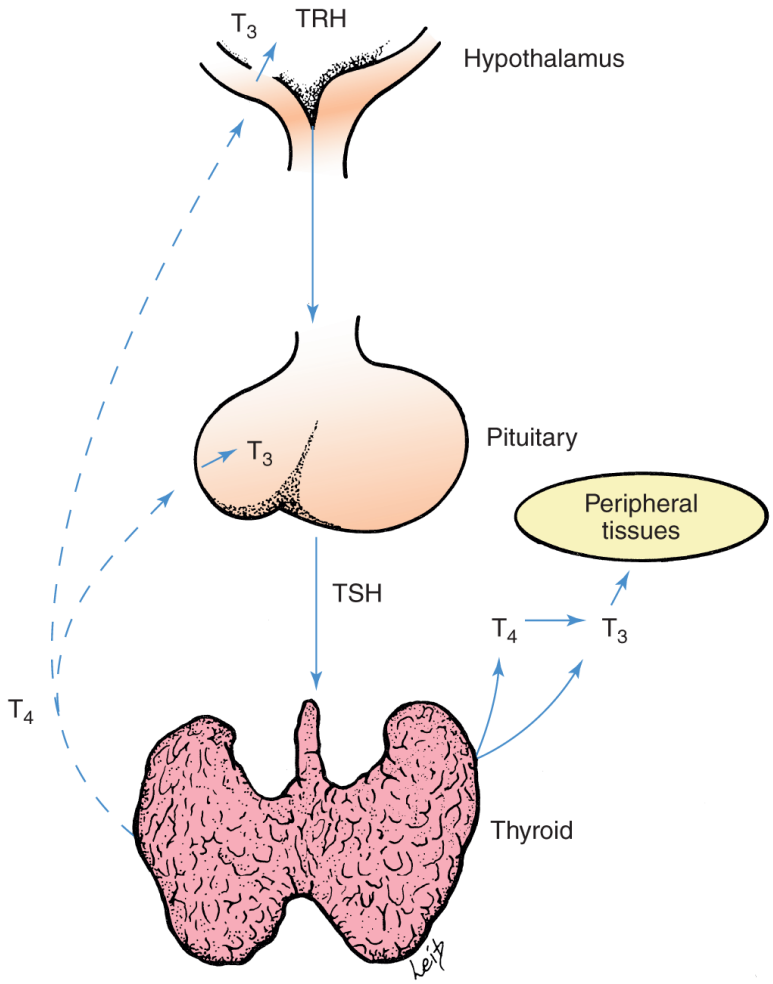


FIGURE 109-2. Feedback regulation for control of thyroid function that involves the hypothalamus-pituitary-thyroid axis. Arrows represent positive feedback; dashed lines denote the inhibitory feedback of T_4 and T_3 on pituitary thyroid-stimulating hormone (TSH) and hypothalamic thyrotropin-releasing hormone (TRH) secretion.

Physiologic Changes With Age

TSH concentrations gradually increase with increasing age, without change in free T_4 levels, in euthyroid individuals without underlying thyroid autoimmunity or thyroid disease. The increase in TSH with normal aging does not indicate occult thyroid failure, since free T_4 levels do not decline. Instead, there may be changes in the bioactivity of TSH or thyroidal sensitivity to TSH. Lower T_3 levels have been documented in healthy centenarians compared to younger people and may reflect a decrease in deiodinase activity with aging.

Clearance of T_4 and T_3 decreases with age, leading to an increase in the half-life of T_4. There is a compensatory decline in T_4 and T_3 secretion, resulting in stability in thyroid hormone concentrations with age. Production of T_4 declines from 80 to 60 μg/day, and T_3 production declines from 30 to 20 μg/day. The half-life of T_4 increases from 7 days up to 9 days in those aged 80 and older. TBG concentrations do not change with age.

The prevalence of thyroid autoantibodies increases in older people, particularly in women, consistent with an increase in autoimmune thyroid disease with age. Therefore, aside from a slight increase in TSH concentrations with age, deviations in thyroid function tests are not due to normal aging. Thus, when the TSH is abnormal in an older person, investigation of thyroid disease and exogenous processes that affect thyroid function should be pursued.

Impact of Drugs and Medical Conditions

Iodine status, medications, and comorbid conditions can each affect thyroid function, either transiently or chronically (**Table 109-1**). All thyroid hormones contain iodine (see **Figure 109-1**). The optimal iodide intake is 150 μg/day, with no changes in this recommendation for older people. Thyroidal uptake of iodine is tightly regulated by the sodium-iodide symporter (NIS) to allow adaptations to variations in dietary supply and ensure that thyroid hormone synthesis does not fluctuate with changes in iodine status. Low iodide increases NIS, and high iodide decreases NIS. The effect

of an iodine load on the thyroid gland depends on the underlying state of the gland, that is, whether it is normal or abnormal. When a normal thyroid is exposed to an iodine load, such as iodinated radiographic contrast, thyroid hormone synthesis is temporarily inhibited, followed by escape from this inhibitory effect and recovery, a phenomenon known as the Wolff-Chaikoff effect. These changes are usually clinically insignificant. In patients with underlying thyroid pathology, an iodine load can precipitate hypo- or hyperthyroidism, as detailed below. Iodine decreases thyroid hormone synthesis and release, which can be useful in treatment of severe thyrotoxicosis due to Graves disease.

TABLE 109-1 DRUGS THAT AFFECT THYROID FUNCTION

Decrease TSH secretion
Dopamine
Glucocorticoids
Octreotide
Bexarotene
Increase thyroid hormone secretion
Iodine and iodine-containing compounds
Amiodarone
Lithium
Interferon-α and IL-2
Decrease thyroid hormone secretion
Thionamides (proplythiouracil, methimazole)
Lithium
Iodine and iodine-containing compounds
Amiodarone
Aminoglutethimide
Interferon-α and IL-2
Decrease T_4 absorption
Calcium
Proton pump inhibitors
Cholestyramine, colestipol
Aluminum hydroxide, sevelamer
Ferrous sulfate
Sucralfate
Raloxifene
Increase serum TBG
Estrogen
Tamoxifen and raloxifene
Clofibrate
Fluorouracil and capecitabine
Mitotane
Heroin
Methadone
Decrease serum TBG
Androgen
Anabolic steroids (danazol)
Glucocorticoid

Inhibit thyroid hormone binding to transport proteins
Phenytoin and carbamazepine
Furosemide
Salicylates and salsalate
Fenclofenac and meclofenamate
Heparin
Sulfonylureas
Decrease T_4 5′-deiodinase activity
Propylthiouracil
Amiodarone
Glucocorticoids
Increase hepatic T_4 and T_3 metabolism
Phenobarbital
Rifampin
Phenytoin
Carbamazepine
Sertraline
Increase T_3 metabolism
Tyrosine kinase inhibitors

Amiodarone is a highly effective antiarrhythmic that can alter thyroid function in numerous ways. Some of these effects are mediated by the iodine content of amiodarone, which is 37% organic iodide by weight. In patients with a normal underlying thyroid, compared to prior to amiodarone administration, there may be transient TSH elevation and chronically higher free T_4 and lower T_3 concentrations that do not require intervention. Occasionally, a destructive thyroiditis may occur and present as new-onset thyrotoxicosis, with increase in release of preformed thyroid hormone, as a result of a direct toxic effect of amiodarone. This can be treated acutely with corticosteroids, with a gradual tapering to off. In patients with underlying thyroid nodular disease or Graves disease who receive amiodarone, increased thyroid hormone production may occur, which can be treated with methimazole. It can be difficult to distinguish among these etiologies of thyrotoxicosis at the time of presentation. Radioactive iodine scanning is not possible due to competition from the nonlabeled iodide in amiodarone, and so patients may initially be treated with both corticosteroids and methimazole. Patients with underlying Hashimoto thyroiditis may develop hypothyroidism, which is often reversible with cessation of amiodarone. In most cases, amiodarone should not be stopped when thyroid function abnormalities occur. The half-life of amiodarone is long, fat solubility is high, and the iodine load is large. It takes months for the effects of amiodarone to wear off, and the thyroid dysfunction can generally be managed while continuing amiodarone treatment.

High doses of corticosteroids and dopamine may each lower TSH levels without affecting thyroid function. This effect is important to remember when interpreting TSH testing in hospitalized patients who are administered either of these medications.

In addition, numerous medications and conditions affect production of thyroid-binding proteins. Estrogens, tamoxifen, and acute hepatitis increase TBG concentrations. This effect is compensated by increased thyroid hormone production in a normally functioning thyroid, to keep free thyroid hormones stable, but may result in changes in total T_4 concentrations. Conversely, androgens, chronic liver disease (through decreased synthesis of TBG), nephrotic syndrome, and severe systemic illness may decrease TBG concentrations. High-dose furosemide, heparin, and high doses of aspirin or salsalate decrease TBG binding to thyroid hormones without affecting TBG. When TBG concentration or binding are reduced, the thyroid produces less thyroid hormone to avoid elevation in free T_4 concentrations.

Nonthyroidal Illness Syndrome

In the setting of severe, nonthyroidal illness, alterations in thyroid function may occur, called the “nonthyroidal illness syndrome.” Alternative names are “low T syndrome” and “euthyroid sick syndrome.” This altered pattern of thyroid

function occurs in reaction to acute illness and may represent an adaptive slowing of metabolism as a physiologic response to systemic illness. It is likely that reduced caloric intake and cytokines play an important role in the pathogenesis of these changes in thyroid function. The changes alter clinical measures of thyroid function. The first testing abnormality to manifest is low T_3 levels. These are a consequence of decrease in deiodination of T_4 to T_3. In addition, there is a decrease in deiodination of reverse T_3 (see **Figure 109-1**), which has no activity at thyroid hormone receptors, to its metabolite, leading to increased concentrations of reverse T_3. Subsequent changes include a decrease in free T_4 levels, followed by a mild decrease in TSH levels in those with the most critical illnesses. Patients taking high-dose corticosteroids or dopamine may have completely suppressed TSH levels. The pattern of low TSH and low thyroid hormones is identical to that of central hypothyroidism. Central hypothyroidism is a rare cause of hypothyroidism, and does not present without other manifestations of pituitary or hypothalamic disease. Additional diagnostic testing does not need to be pursued if the clinical picture supports nonthyroidal illness as the cause of thyroid testing abnormalities. Measurement of reverse T_3 concentrations is not indicated. Patients with the full constellation of thyroid testing abnormalities have a high mortality rate, at 80%. Thyroid hormone replacement with T_4 or T_3 results in no benefit in the nonthyroidal illness syndrome. During recovery from nonthyroidal illness, TSH levels appropriately rise in order to stimulate thyroid hormone production, which may be interpreted as overt or subclinical hypothyroidism. In this setting, when the patient is also improving clinically, repeat thyroid function testing as an outpatient is preferred over initiation of levothyroxine.

THYROID DYSFUNCTION

Classification

When thyroid dysfunction is suspected clinically, the first step is to measure a TSH level. A low TSH is consistent with pituitary efforts to slow thyroid hormone production, as in hyperthyroidism, and a high TSH is consistent with pituitary efforts to stimulate thyroid hormone production, as in hypothyroidism (**Figure 109-3**). Further discrimination, based on measurement of free T_4 levels, can be made to distinguish between what have been termed "subclinical" (normal free T_4) and "overt" (abnormal free T_4) dysfunction. These unfortunate historical terms frequently cause confusion, since they suggest a role for symptoms in the assignment of thyroid status when, in fact, the distinction is made solely on the basis of thyroid function testing.

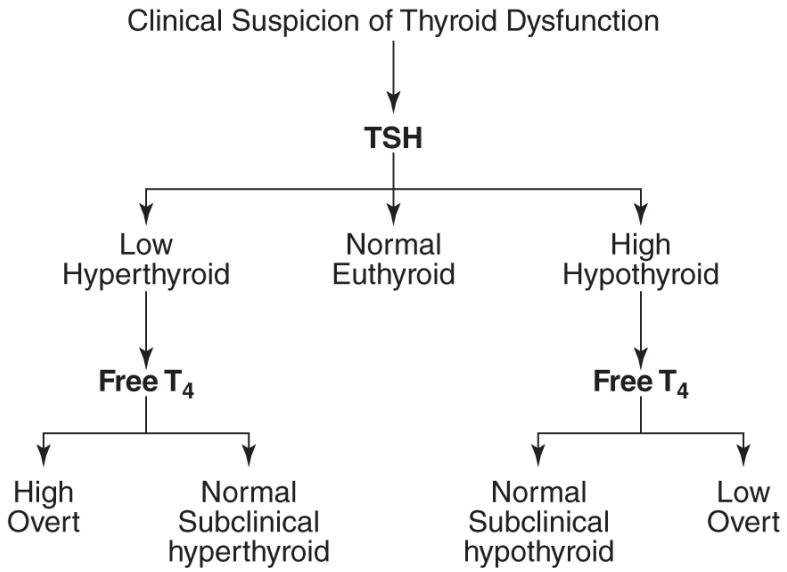


FIGURE 109-3. Classification of thyroid dysfunction based on thyroid-stimulating hormone (TSH) and free thyroxine (free T_4) testing.

Hyperthyroidism

Overt hyperthyroidism is defined as a low TSH with elevated free T_4 or T_3. The prevalence is 1% to 2% in older people. The prevalence in women is higher than in men, though this difference is only twofold in older people, compared to 10-fold at younger ages.

Symptoms Consistent with the myriad and widespread molecular effects of thyroid hormone, there are multiple symptoms associated with hyperthyroidism (**Table 109-2**). As with younger individuals, cardiovascular, psychiatric, gastrointestinal, and musculoskeletal symptoms predominate. Unfortunately, there is no single "defining" symptom that is specific to hyperthyroidism. Overt hyperthyroidism usually causes at least one symptom, albeit nonspecific. One or more of the symptoms should prompt evaluation by TSH testing. **Table 109-3** displays myriad symptoms and their frequency in a study of 84 overtly hyperthyroid patients aged 70 or older and 55 or younger. Of the 19 signs examined, the three signs found in more than 50% of older patients were tachycardia, fatigue, and weight loss. These data also show the paucity of classical symptoms of hyperthyroidism in older people, particularly hyperadrenergic symptoms, due to diminished physiologic response or concomitant β-blocker use, and increased prevalence of nonclassical symptoms such as apathy and anorexia. This presentation has been referred to as "apathetic hyperthyroidism" and can be mistaken for a chronic wasting illness. In addition, the classic symptoms associated with Graves disease, a goiter and ophthalmopathy, are often absent in older people.

TABLE 109-2 CLINICAL FEATURES OF HYPERTHYROIDISM IN OLDER PATIENTS

Cardiovascular
Palpitations
Chronic or intermittent atrial fibrillation
Congestive heart failure
Psychiatric and behavioral
Depression
Apathy
Lethargy
Irritability
Gastrointestinal
Decreased appetite
Weight loss
Nausea
Constipation
Musculoskeletal
Proximal muscle weakness
Muscle atrophy

TABLE 109-3 COMPARISON OF CLINICAL FEATURES OF HYPERTHYROIDISM IN OLDER VERSUS YOUNG PATIENTS

SYMPTOMS AND SIGNS	OLDER, > 70 Y (%)	YOUNG, < 50 Y (%)
Tachycardia	71	96
Fatigue	56	84
Weight loss	50	51
Tremor	44	84
Dyspnea	41	56
Apathy	41	25
Anorexia	32	4
Nervousness	31	84
Hyperactive reflexes	28	96
Weakness	27	61

Depression	24	22
Increased sweating	24	95
Diarrhea	18	43
Muscular atrophy	16	10
Confusion	16	0
Heat intolerance	15	92
Constipation	15	0

Etiology and diagnosis The term "hyperthyroidism" refers to overproduction of thyroid hormone by the thyroid gland, whereas "thyrotoxicosis" is a broader term that encompasses any clinical situation with thyroid hormone excess, including thyroiditis or excess exogenous thyroid hormone. The majority of endogenous thyrotoxicosis is due to overproduction of thyroid hormone, either from autoimmune stimulation of the thyroid in Graves disease or an autonomous thyroid nodule within a nodular thyroid gland. These are usually permanent conditions. In younger people, Graves disease is the most common cause of hyperthyroidism, whereas with increasing age, multinodular toxic goiter increases in prevalence. Nodules within multinodular glands may become autonomous over time. Acute worsening of thyrotoxicosis can be precipitated by an iodine load in a patient with autonomous thyroid nodules, which are lacking a normal regulatory response to iodine. Less commonly, leakage of thyroid hormone due to autoimmune or viral thyroiditis can cause transient thyrotoxicosis that resolves within several weeks. The diagnosis of thyrotoxicosis does not require elevations in both free T_4 and T_3 concentrations. "T_3 toxicosis" may occur with normal free T_4 levels, particularly with autonomous nodules; conversely, only free T_4 levels may be elevated with concomitant nonthyroidal illness syndrome.

The process of assessment of the etiology of thyrotoxicosis does not require invasive testing and does not differ between young and old adults. Although there are some clues from thyroid testing (T_4 and T_3 levels tend to be higher in Graves disease than in other etiologies) and physical examination (the presence of proptosis, skin findings of pretibial myxedema, or thyroid bruit are specific for Graves disease), radioiodine scanning is the definitive way to discriminate among thyrotoxicosis etiologies. NIS is highly expressed in the thyroid, with low levels in salivary glands, lactating breast, and placenta. It allows radioactive iodine scanning in a selective manner. It does not provide valid results in the setting of recent high unlabeled iodide intake, such as from iodinated contrast. Otherwise, it is a useful test to discriminate between high uptake (Graves disease and autonomous nodule) and low uptake (autoimmune or viral thyroiditis) states. Concomitant imaging may discriminate between diffuse uptake in Graves disease and focal uptake by an autonomous nodule. Thyroid ultrasonography may be useful when correlated with a radioiodine scan, as may be assessment of thyroid autoantibodies in cases where the etiology of hyperthyroidism remains unclear.

Management β-Blocking drugs are useful in the management of tachycardia and other hyperadrenergic symptoms from thyrotoxicosis of any etiology. However, in acutely ill patients, such as those with thyroid storm (see below), or patients with heart failure or reactive airways disease β-blocking drugs must be initiated carefully (see below). In outpatients, the longer-acting β-blocking drugs atenolol or metoprolol may be used for convenience of dosing; shorter-acting propranolol, with its additional inhibition of T_4 to T_3 conversion, is only needed in severe thyrotoxicosis in hospitalized patients.

Nonsteroidal anti-inflammatory drugs can be useful for treating patients with subacute or silent thyroiditis. Patients who do not respond may require prednisone. Since the thyrotoxicosis is due to release of preformed thyroid hormone in these conditions, antithyroid drugs are not indicated.

Antithyroid drugs are useful in the management of thyrotoxicosis due to overproduction of thyroid hormone from autonomous thyroid nodules and in Graves disease. The antithyroid drugs decrease thyroid hormone production by acting directly on the thyroid to interfere with two steps of thyroid hormone synthesis. Methimazole is the preferred drug due to a longer half-life and fewer adverse effects. Propylthiouracil (PTU) has the advantage of decreasing T_4 to T_3 conversion, but its use has been limited by reports of fulminant hepatic failure. The usual starting daily dose of methimazole is 10 to 30 mg daily, depending on the degree of thyrotoxicosis. Thyroid function testing should be performed every 4 weeks, with tapering of the dose when possible, until euthyroidism is achieved. Euthyroidism is usually achieved in 6 to 12 weeks. Subsequently, thyroid function testing frequency may diminish to every few months, with ongoing attempts to titrate to the lowest dose of antithyroid drug required to sustain testing within the euthyroid range. PTU may be considered in patients with thyroid storm or who have an adverse reaction to

methimazole, depending on the type and severity of the reaction. The most common side effects of either methimazole or PTU are skin reactions, which occur in 4% to 6% of patients. The most serious side effect is agranulocytosis, which occurs in 0.1% to 0.5% of patients. This tends to be dose dependent and occur within the first 3 months for methimazole, but it can occur at any time, at any dose. All patients should be counseled about the risk and detection of agranulocytosis prior to initiation of antithyroid drugs. Recommended measures include stopping the antithyroid drug and checking a white blood count with differential if a fever or sore throat occurs. If the granulocyte count is fewer than 500 cells, then the patient should be hospitalized and administered broad-spectrum antibiotics. If the granulocyte count is normal, the antithyroid drug can be resumed. Routine testing of white blood cell counts is not indicated. Rarely, methimazole can cause cholestasis, and both methimazole and PTU can cause antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis or severe polyarthritis.

The risk of adverse effects from antithyroid drugs limits their utility in the long-term management of hyperthyroidism. Patients with Graves disease whose hyperthyroidism is not severe and who have small thyroid glands are good candidates for achieving remission after 1 to 2 years of antithyroid medication. However, recurrence exceeds 60%, and concerns about how well the older patient may tolerate a recurrence of hyperthyroidism should be considered prior to taking this approach. Antithyroid drugs do not induce remission of hyperthyroidism caused by autonomous thyroid nodules.

Radioactive iodine is the preferred therapeutic option in patients who have thyrotoxicosis due to overproduction of thyroid hormone. Radioiodine emits γ-rays and β-particles. It is used in low doses for diagnostic purposes and at higher doses for therapy. The effects are dose dependent, and the degree of uptake and size of the thyroid gland are considerations in determining the correct dose. Any antithyroid drugs should be stopped 3 to 5 days prior to treatment, though β-blocking drugs should be continued. Radioactive iodine induces necrosis of thyroid follicular cells followed by disappearance of colloid and fibrosis of the gland over months. Contact precautions must be observed for 5 days after treatment, and, if necessary, antithyroid drugs may be resumed 5 days after treatment. A plan for managing contact precautions must be devised before treatment for patients who are caregivers of young children or who have caretakers who are in close contact. Radioactive iodine that is not taken up by the thyroid is cleared in the urine, and patients with urinary incontinence must have a plan for disposal of contaminated absorptive pads. Older patients may benefit from pretreatment with methimazole to achieve euthyroidism more quickly and “cool” down before radioactive iodine or surgery.

Autonomous nodules can be treated definitively with radioactive iodine. If the autonomous nodule is the source of thyrotoxicosis, the remaining normal gland will be unaffected by radioactive iodine therapy, resulting in normal thyroid function after ablation of the affected thyroid nodule. Radioactive iodine therapy is commonly used in the long-term management of thyrotoxicosis due to Graves disease. The goal of radioactive iodine therapy in Graves disease is ablation of all functioning thyroid tissue, with resultant hypothyroidism. Incomplete ablation increases the risk of recurrence, due to regrowth of thyroid tissue secondary to persistent stimulation by antibody binding to the TSH receptor. The advantage of radioactive iodine ablation is the permanency of treatment without the risks associated with thyroidectomy, though contact precautions must be observed for 5 days after treatment, ophthalmopathy may be exacerbated, and thyroid function monitoring is required every 4 to 6 weeks after treatment until the patient is taking a stable dose of thyroid hormone replacement.

Thyroidectomy is the fastest way to achieve euthyroidism, but because of increased operative risk in older patients, it is reserved for select cases, such as concomitant thyroid cancer or severe ophthalmopathy. Only an experienced thyroid surgeon should perform the thyroidectomy. Potential complications include transient or permanent recurrent laryngeal nerve paralysis and hypoparathyroidism. Preoperative addition of oral iodine to antithyroid drugs may lead to faster restoration of euthyroidism and reduction of vascularity of the gland.

Hyperthyroidism in Hospitalized Patients

Inpatients with mild hyperthyroidism can be treated with antithyroid medication and β-blocking drugs. However, the metabolic derangements of thyrotoxicosis can complicate the care of any condition, and there should be a low threshold to involve expertise in endocrinology in managing the complex patient with hyperthyroidism. In thyroid storm, central nervous and cardiovascular systems may be particularly compromised, and patients may present with delirium, psychosis, coma, extreme tachycardia, or heart failure. Although diagnostic criteria have been proposed for the diagnosis of thyroid storm, in reality any inpatient whose clinical status is compromised from the effects of hyperthyroidism should be managed aggressively to remove the impact of thyroid dysfunction from the clinical picture. Higher than expected doses may be required of all medications, including the antithyroid medications, due to

increased metabolism in the setting of thyroid hormone excess. One important exception is warfarin, where lower doses may be required due to increased vitamin K metabolism. As thyrotoxicosis improves, all medications should be tapered accordingly. Many patients can be effectively managed with high doses of methimazole and potassium iodide drops (SSKI). This will block new production of thyroid hormone. For those who are the most severely ill, maximum therapy should be initiated immediately. A regimen that maximizes inhibition of conversion of T_4 to T_3 is required, to reduce concentrations of the active hormone and to allow metabolism of the T_4 and T_3 already released into the bloodstream. In this case, PTU, hydrocortisone, and propranolol may each provide benefit and can be administered in combination. It is advised to give a dose of antithyroid drug at least 1 hour before the first dose of SSKI.

Severe hyperthyroidism can exacerbate underlying cardiac disease or precipitate new dysfunction. Atrial tachyarrhythmias are common. In some cases, the tachycardia is sustaining a marginal cardiac output, and β-blockade leads to acute cardiac decompensation. In patients whose cardiac status may be compromised, it is recommended to initiate low-dose esmolol, which has a short half-life and can be easily titrated, to ensure that β-blockade is tolerated, before changing to propranolol. The volume associated with esmolol detracts from its use beyond this initial test.

Subclinical Hyperthyroidism

Subclinical hyperthyroidism is defined as low TSH with normal levels of free T_4 and T_3. The prevalence of subclinical hyperthyroidism on a single test is 1% to 6% in an older population. Repeat testing is recommended 3 to 6 months later, as persistence is high, at more than 50%. The etiologies of subclinical hyperthyroidism are the same as those causing overt hyperthyroidism.

Untreated subclinical hyperthyroidism is associated with increased cardiovascular, musculoskeletal, and neurocognitive risk compared to euthyroidism. Two studies performed exclusively in older people found a two- to threefold increased risk of atrial fibrillation in subclinical hyperthyroidism. Heart failure and overall and cardiovascular mortality are also increased. Subclinical hyperthyroidism is also associated with increased risk of fracture and dementia. There are not large, randomized trials of treatment of subclinical hyperthyroidism to guide therapy. Current recommendations support treatment of older people with subclinical hyperthyroidism to achieve euthyroidism by laboratory testing. The therapeutic options are the same as those for overt hyperthyroidism.

Hypothyroidism

Overt hyperthyroidism is defined as a high TSH with low free T_4 concentrations. The prevalence is 1% to 2% in older people. It is not useful to measure T_3 concentrations when assessing hypothyroidism.

Symptoms Thyroid hormone insufficiency affects multiple organs, often with insidious onset. Symptoms of hypothyroidism are often, but not always, opposite to those of hyperthyroidism, and manifest as a generalized slowing of metabolic processes (**Table 109-4**). Cognitive changes and functional decline are late manifestations of unrecognized hypothyroidism. As with younger individuals, cardiovascular, psychiatric, gastrointestinal, and musculoskeletal symptoms predominate. Unfortunately, there is no single defining symptom that is specific to hypothyroidism. One or more of the myriad symptoms should prompt evaluation by TSH testing. **Table 109-5** displays symptoms of hypothyroidism and their frequency in a study of 121 overtly hypothyroid young and old patients. Of the 24 signs examined, fatigue and weakness were the two signs found in more than 50% of older patients. The usual clinical signs were not well represented in older people. Since the effects of hypothyroidism are reversible with treatment, clinicians caring for older patients should measure TSH at the earliest indication of hypothyroid symptoms.

TABLE 109-4 CLINICAL FEATURES OF HYPOTHYROIDISM IN OLDER PATIENTS

Dry skin
Hair loss
Edema of face and eyelids
Cold intolerance
Neurologic
Paresthesia (carpal tunnel syndrome)
Ataxia
Dementia

Psychiatric and behavioral	
Depression	
Apathy or withdrawal	
Psychosis	
Cognitive dysfunction	
Metabolism	
Weight gain	
Hypercholesterolemia	
Hypertriglyceridemia	
Peripheral edema	
Musculoskeletal	
Myopathy	
Arthritis/arthralgia	
Cardiovascular	
Bradycardia	
Pericardial effusion	
Congestive heart failure	

TABLE 109-5 COMPARISON OF CLINICAL FEATURES OF OVERT HYPOTHYROIDISM IN OLDER VERSUS YOUNG PATIENTS

SYMPTOMS AND SIGNS	OLDER, ≥ 70 Y (%)	YOUNG, ≤ 55 Y (%)
Bradycardia	12	19
Fatigue	68	83
Weight gain	24	59
Cold intolerance	35	65
Depression	28	52
Disorientation	9	0
Hypoactive reflexes	24	31
Weakness	53	67
Paresthesia	18	61
Dry skin	35	45
Hair loss	12	28
Reduced hearing	32	25
Muscle cramps	20	55
Snoring	18	22
Constipation	33	41

Etiology and diagnosis The etiologies of hypothyroidism are similar in older and younger adults. Primary hypothyroidism from thyroid failure is the most common source of thyroid dysfunction; central hypothyroidism from pituitary or hypothalamic failure is rare. Primary hypothyroidism is largely due to autoimmune destruction of the thyroid (chronic autoimmune thyroiditis; Hashimoto thyroiditis), though exogenous destruction of the thyroid from surgery or radiation (including radioactive iodine therapy) and drugs are also common (**Table 109-6**). All compounds containing iodine, including amiodarone and lithium, as well as interferon-α, interleukin 2 (IL-2), and tyrosine kinase inhibitors such as sunitinib, may accelerate hypothyroidism in a gland with underlying Hashimoto thyroiditis (see

Table 109-1). Transient hypothyroidism can also occur during recovery from thyroiditis or acute, nonthyroidal illness. Bexarotene and octreotide can cause secondary hypothyroidism. A serum TSH is the initial diagnostic test for detection of hypothyroidism; both TSH and free T4 should be measured if central hypothyroidism is a clinical consideration. Antithyroid antibody measurement is not indicated for diagnostic assessment of hypothyroidism.

TABLE 109-6 CAUSES OF HYPOTHYROIDISM IN OLDER PEOPLE

- Primary hypothyroidism
  - Chronic autoimmune thyroiditis (Hashimoto thyroiditis)
  - Radiation
    - ^{131}I therapy for hyperthyroidism
    - Radiation therapy for head and neck cancer
  - Surgical thyroidectomy
  - Drugs
    - Iodine-containing drugs: amiodarone, radiocontrast agents containing iodine
    - Antithyroid drugs (propythiouracil, methimazole)
    - Other drugs that decrease TSH or thyroid hormone secretion (see Table 109-1)
  - Central hypothyroidism
    - Hypothalamic tumors or infiltrative lesions
    - Pituitary tumors or infiltrative lesions
    - Pituitary surgery
    - Radiation

Management The aim of therapy for hypothyroidism is hormone replacement, not cure. Levothyroxine therapy should be used, and therapy is usually lifelong. Tissue deiodination in vivo of ingested levothyroxine to T_3 allows physiologic thyroid hormone replacement without the need for additional T_3 replacement. T_3 or dessicated thyroid hormones should not be used for thyroid hormone replacement in older people due to risk of adverse cardiac effects from supraphysiologic T_3 concentrations. Levothyroxine is available in 12 to 25 μg increments to allow precise titration. Side effects are largely from inappropriate dosing. Allergies to the pill excipients can occur, including coloring dye sensitivities; the 50 μg tablet is white.

Considerations for initial dosing include the age of the patient and degree of thyroid failure. In patients aged 65 or older who have cardiac disease, it is usually recommended to "start low, go slow." It should be noted that the benefit of this approach, compared with starting with a full estimated starting dose, has not been tested in a clinical trial. The smallest available doses, 25- and 50-μg tablets, are reasonable starting doses in older people. TSH testing usually occurs 6 weeks (six half-lives of levothyroxine) after initiation of treatment, but older people may benefit from 7 to 8 weeks to achieve steady state, given lower clearance of thyroid hormone. Dose increments initially may be as high as 25 μg, but finer titrations in 12 μg increments are preferred once the dose is above 75 to100 μg. The target TSH is toward the upper limit of the normal range, and could be as high as 4 to 6 mU/L in those over age 80. While there is individual variation, full replacement of thyroid hormone is often required, regardless of the severity of hypothyroidism initially. The reason for full replacement is the feedback control of TSH. As exogenous thyroid hormone is given, TSH is suppressed and endogenous thyroid hormone production falls, leading TSH to increase again, requiring more exogenous thyroid hormone, and so on until full replacement has occurred. The usual full replacement dose in older adults is lower than the 1.6 μg/kg/day recommended in younger patients. Care should be taken to avoid over-replacement, which may have adverse effects. If given intravenously, 75% of the oral dose should be administered.

The pace of progression of thyroid failure is variable, though once TSH levels stabilize, TSH testing need only be performed on an annual basis. When variability in TSH testing occurs, difficulty with adherence should be considered first. For example, a patient taking 112 μg of levothyroxine daily who misses one dose per week will have an average daily dose of 96 μg daily, which could be sufficient to cause TSH elevation.

Aside from variation in adherence, if an increase in TSH occurs after concentrations have stabilized, drugs or conditions that decrease levothyroxine absorption should be considered. Major culprits include iron (as supplements

and in multivitamins), calcium carbonate, aluminum hydroxide, sucralfate, and cholestyramine, which bind to levothyroxine. Separation from levothyroxine dosing of at least 4 hours is recommended. An increase in levothyroxine dose is required for other drugs or conditions that decrease levothyroxine absorption, increase levothyroxine metabolism, or increase TBG. Proton pump inhibitors diminish absorption by decreasing gastric acidity. Conditions that decrease levothyroxine absorption include small intestinal disease (celiac disease, *Helicobactor pylori*–associated gastritis, atrophic gastritis, Crohn disease, and short bowel). Drugs that increase levothyroxine metabolism include phenobarbital, carbamazepine, phenytoin, and rifampin. Drugs and conditions that increase TBG include estrogens and hepatitis. After exclusion of these drugs and conditions, it is reasonable to consider progression of endogenous thyroid disease.

If a decrease in TSH occurs after concentrations have stabilized, factors that decrease TBG levels should be considered. These include androgen initiation, progressive liver failure, nephrotic syndrome, and severe systemic illness. Self-administration of excess levothyroxine should also be contemplated.

Thyroid hormone replacement has a narrow therapeutic window, and iatrogenic hyperthyroidism should be avoided. As many as 40% of older individuals taking thyroid hormone replacement may have a low TSH. Potential risks from iatrogenic hyperthyroidism parallel those of endogenous hyperthyroidism, most notably atrial fibrillation and bone loss. Careful initial titration and subsequent monitoring should reduce the risk of over-replacement.

Myxedema coma Myxedema coma is a serious medical condition that occurs almost exclusively in older people. Despite the name, the patient does not have to be in coma, though an altered mental status is common. The usual presentation is long-standing untreated hypothyroidism, with decompensation often precipitated by infection, cold exposure, alcoholism, or use of narcotics, sedatives, or antipsychotic medication. It is characterized by profound slowing across systems, including hypothermia, bradycardia, and hypoventilation. Thermometers capable of reading low temperatures may be required. Close monitoring is required, and headaches, erratic behavior, and neurologic symptoms such as ataxia, nystagmus, and muscle spasms may be harbingers of impending coma. Hyponatremia and hypoglycemia may also be present, as well as elevated creatinine phosphokinase of muscle origin.

Thyroid hormone replacement may need to be initiated based on historical and clinical data, before thyroid function test results are available. There is a risk that a critically ill euthyroid patient will be treated with thyroid hormone, and the decision to treat without confirmatory thyroid function data should be considered carefully. Treatment of precipitating factors and supportive therapy for any associated metabolic disturbances is as important as initiation of thyroid hormone replacement. Serum should be obtained for cortisol measurement, and then intravenous hydrocortisone should be initiated to treat impaired adrenal reserve that may be present in profound hypothyroidism. Hydrocortisone may be stopped if the cortisol level is found to be adequate. Treatment with thyroid hormone without hydrocortisone can precipitate adrenal crisis. An initial dose of 200 to 400 μg of levothyroxine should be initiated, followed by 75 to 100 μg daily. The addition of a T_3 preparation, which has more immediate effects than levothyroxine, has the risk of acute cardiac effects, and is generally discouraged in an older patient. Metabolism of all medications is diminished in profound hypothyroidism, and sedatives should be especially avoided.

Subclinical hypothyroidism Subclinical hypothyroidism is defined as a high TSH with a normal level of free T_4. The prevalence of subclinical hypothyroidism is 4% in the general population. The prevalence increases with age, to approximately 10% of those aged 65 or higher, and it is more common in women. The majority of older people with subclinical hypothyroidism has TSH levels in the 4 to 7 mIU/L range. More than 50% of such individuals revert to euthyroidism. The etiologies of subclinical hypothyroidism are the same as overt hypothyroidism, though many older patients without any risk factors for hypothyroidism or antithyroid antibodies are found to have subclinical hypothyroidism. Studies in overt hypothyroidism underscore the difficulty with using symptoms to define the severity of thyroid dysfunction in an older person. The milder physiologic abnormalities of subclinical hypothyroidism result in an even greater diagnostic challenge, particularly given the frequency of hypothyroidism-like symptoms in older people without thyroid disease.

Potential effects of mild thyroid deficiency include hypercholesterolemia, decreased systemic vascular resistance, and diminished cardiac contractility. There is a dose-response relationship between the degree of TSH elevation and incident risk of cardiovascular disease and heart failure in people with untreated subclinical hypothyroidism. Independently of age, a TSH concentration of 10 mIU/L or higher predicts increased cardiovascular mortality, coronary heart disease, and heart failure. A TSH concentration of 7 mIU/L or higher predicts cardiovascular mortality. However, subclinical hypothyroidism is not associated with fractures, dementia, or depression. Although skeletal muscle function is impaired in hypothyroidism, one study found older individuals with subclinical hypothyroidism to have better physical function than their euthyroid counterparts, and another showed decreased mortality in older

individuals with subclinical hypothyroidism.

TSH elevations may be transient, due to recovery from silent thyroiditis or from the nonthyroidal illness syndrome. A repeat TSH should be performed 1 to 3 months after initial testing demonstrates subclinical hypothyroidism. If the repeat TSH is 7 mIU/L or higher, initiation of levothyroxine therapy at 25 μg daily should be considered. There are no adverse consequences in following patients who have TSH levels less than 7 mIU/L with annual testing. The rate of progression to overt hypothyroidism is low in this range. The average replacement dose of subclinical hypothyroidism is 1 μg/kg/day, which is lower than that of overt hypothyroidism, though the treatment goals are the same. The risk-benefit ratio of treatment of subclinical hypothyroidism has not been tested in a randomized trial with clinical end points, and the risks of iatrogenic subclinical or overt hyperthyroidism should be avoided when initiating levothyroxine therapy in this age group.

Screening

Because the adverse effects of overt hyperthyroidism and hypothyroidism are reversible with treatment, the symptoms are often less pronounced or atypical in older people, and TSH is a readily available screening test, screening older people for thyroid dysfunction has been proposed. However, the management of subclinical thyroid dysfunction, which is more common than overt disease, is not sufficiently supported by clinical trial data. Furthermore, the definition of the reference range may differ between older and younger people. If the 95% confidence interval is applied to a population free of thyroid disease, the upper limit of the reference range is 3.6 mIU/L for 20 to 29 year olds, but 7.5 mIU/L for those aged 80 and older. The US Preventive Task Force has concluded that there is insufficient evidence to assess routine screening for thyroid dysfunction. This recommendation is unlikely to change until there is clear evidence to support management of any TSH concentration found on screening.

NODULAR THYROID DISEASE AND THYROID CANCER

Thyroid Anatomy

Thyroidal size is similar in older and younger individuals, and the volume of the thyroid correlates more with body weight than with age. Pathologic evaluation shows increased frequency of lymphocyte infiltration, fibrosis, and diminished colloid and follicle size in older people. Palpation of the thyroid gland may be more difficult in older individuals in the setting of pulmonary disease or kyphosis. With increasing age, there is an increase in the frequency of both thyroid nodules and thyroid cancer. The higher incidence with age is not entirely due to detection bias from increased frequency of radiologic testing, such as computed tomography (CT) scans or carotid ultrasounds, though the initial presentation of a thyroid nodule in an older person is often as an incidental finding.

Evaluation of Thyroid Nodules

In autopsy series, 50% of thyroid glands have one or more thyroid nodules. Multinodular glands are more common in people from areas of iodine insufficiency. Patients with a history of childhood radiation to the neck or childhood exposure to ionizing radiation have an increased risk of developing thyroid nodules. The majority of these nodules are benign, though these nodules have an increased risk of thyroid cancer, which declines starting four decades after initial exposure.

The evaluation of a thyroid nodule does not differ by age. The main consideration is detecting the malignancy present in 7% to 9% of thyroid nodules. Men have a higher risk of malignancy than women do. Nonpalpable nodules discovered incidentally have the same risk of malignancy as palpable nodules of the same size. Patients with multiple nodules have the same risk of malignancy as patients with a solitary nodule. Any palpable thyroid abnormality or one found through an imaging modality should be examined via a dedicated thyroid ultrasound. In addition to size in three dimensions, high-risk nodule characteristics such as hypoechogenicity, irregular margins, taller-than-wide shape, intranodular vascularity, and microcalcifications, as well as low-risk characteristics, such as spongiform appearance or noncalcified, mixed cystic and solid composition, should be documented. The presence and characteristics of lymph nodes should be assessed. A TSH should also be measured. Patients who have a low TSH should undergo a radionuclide thyroid scan to assess for thyroid nodule functioning; functioning “hot” nodules rarely harbor malignancy and do not require cytologic evaluation.

All other patients meeting the following criteria should undergo fine-needle aspiration (FNA): nodules with abnormal cervical lymph nodes, nodules greater than 1 cm with microcalcifications or that are solid and hypoechoic,

solid nodules greater than or equal to 1 to 1.5 cm that are not hypoechoic, mixed cystic-solid nodules greater than or equal to 1.5 to 2 cm with suspicious characteristics, and all other mixed cystic-solid nodules or spongiform nodules that are greater than or equal to 2 cm. Purely cystic nodules do not require FNA, and routine FNA of nodules less than 1 cm is not advised. Ultrasound guidance improves the accuracy of FNA and should be performed if available. For multinodular goiters, any nodule that meets criteria for aspiration should undergo FNA. Categories of FNA results include benign, nondiagnostic, papillary thyroid cancer, suspicious for malignancy, atypical cells of undetermined significance, follicular lesion of undetermined significance, and follicular neoplasm or suspicious for follicular neoplasm (**Figure 109-4**). Nodules with either atypical cells of undetermined significance or follicular lesions of undetermined significance should have additional analysis of aspirates using molecular analysis, using either an mRNA classifier system or mutational analysis. Nodules determined to be benign should have ultrasound follow-up, and those at high risk of malignancy should be removed surgically, usually a total thyroidectomy.

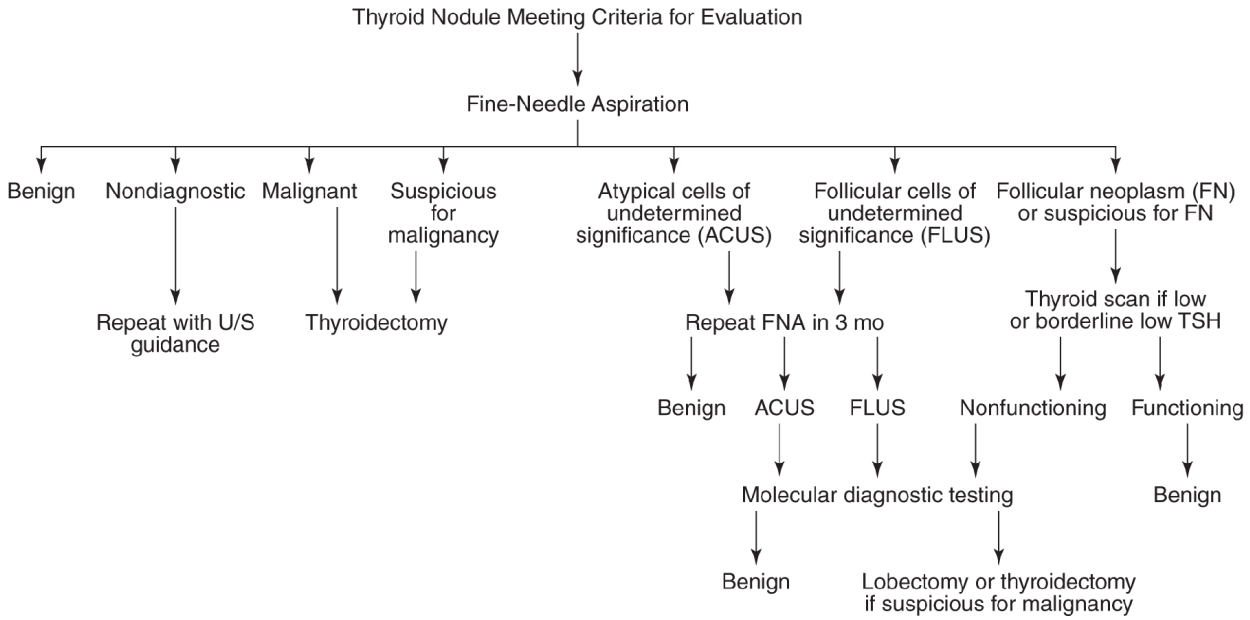


FIGURE 109-4. Algorithm for evaluation and management of patients presenting with nodular thyroid disease.

Benign Nodular Disease

Nodules that did not meet initial criteria for FNA or underwent FNA with benign pathology have a low likelihood of a later diagnosis of thyroid cancer. Current understanding of thyroid cancer biology suggests that a cancerous nodule develops as a cancerous nodule, and that benign nodules do not become cancerous over time. Therefore, ultrasound surveillance is performed to detect the nodules initially designated as benign that were false negatives. These include nodules that did not meet initial criteria for FNA, either due to size or sonographic characteristics, or whose FNA results indicated a benign diagnosis. On follow-up ultrasounds, each nodule should be evaluated for the development of size or ultrasound characteristics that meet criteria for FNA. The validity of FNA for benign nodules is excellent, with a false-negative rate with ultrasound-guided FNA of only 1%. Benign nodules should be followed up with a repeat thyroid ultrasound in 12 to 18 months, and continued ultrasound surveillance every 2 to 5 years, with FNA for development of sonographically suspicious features or significant growth. Any nodule that has undergone FNA twice does not need additional aspirations, due to the vanishingly small likelihood of two false-negative FNAs.

Nodular goiters may grow to the point of causing compressive symptoms, including dyspnea or wheezing from tracheal narrowing or disturbances of swallowing from esophageal impingement. These goiters often have a substernal component. CT scan of the neck can be helpful in evaluating the relationship of the thyroid to other structures in the neck. Flow-volume loop evaluation through pulmonary function testing can be used to evaluate extrinsic compression in the neck, and barium swallow evaluation can demonstrate the degree of thyroidal extension abutting the esophagus. Even if FNA confirms benign nodular disease, thyroid surgery may be indicated to relieve mass effect from an enlarged nodular goiter.

Thyroid Cancer

The incidence of thyroid cancer increases with age, peaking at age 65 to 69 at 26.7 per 100,000 (twice the overall incidence of 13.5 per 100,000), declining slightly at 70 to 74 years (25.6 per 100,000) and 75 to 79 years (22 per 100,000), and more rapidly thereafter (80–84 years, 16.9 per 100,000; 85 years and older, 11.3 per 100,000). Thyroid cancer can be of follicular cell origin (papillary, follicular, or anaplastic) or C-cell origin (medullary thyroid cancer). Thyroid lymphoma and metastases to the thyroid can also occur. The majority of thyroid cancers are papillary thyroid carcinomas. Older patients are more likely to present with more aggressive disease, higher recurrence rates, and multicentricity. However, the prognosis of thyroid cancer is excellent and improving, with 5-year survival rates of 98% in those aged 50 to 64, 91% in those aged 65 to 74, and 87% in those aged 75 or older.

The diagnosis of thyroid cancer is made via cytologic interpretation of FNA specimens. Total thyroidectomy is the primary modality for management of thyroid cancer, irrespective of age. This surgery should be performed by an experienced thyroid surgeon, with lymph node sampling as indicated. For thyroid cancer confined to the thyroid gland, no additional initial therapy is required. Thyroid hormone replacement is required after total thyroidectomy. Since TSH has a trophic effect on the thyroid, TSH levels were historically suppressed via high levothyroxine doses. In recognition of the potentially adverse effects of iatrogenic thyrotoxicosis, primarily on the heart and bone, along with the excellent overall prognosis of papillary and follicular thyroid cancers, TSH suppression is only recommended in high-risk patients. In low-risk patients, maintaining a TSH in the lower half of the normal range is acceptable. Cardiac effects of high levothyroxine doses can be mitigated by β-blocking drug usage, and bisphosphonates attenuate effects on bone.

A subset of patients requires additional therapy, such as radioactive iodine ablation of residual disease in the neck or metastatic outside the neck, capitalizing on the retention of sodium iodide symporter (NIS) in the majority of differentiated cancers of follicular origin. Calculation of radioactive iodine dosage through dosimetry is recommended in older people, regardless of renal function, to decrease the likelihood of exceeding maximum tolerable activity safety limits to the blood and bone marrow. Radioactive iodine scanning for residual disease can be performed with recombinant TSH treatment, avoiding the physiologic consequences associated with withdrawal-induced hypothyroidism. Newer multitargeted kinase inhibitors are available for patients with metastatic disease that does not respond to radioactive iodine therapy or in whom external beam radiotherapy is not effective.

Medullary thyroid carcinoma should be treated with total thyroidectomy, and residual disease can be monitored through assessment of calcitonin and carcinoembryonic antigen levels. Since the C-cells do not contain NIS, radioactive iodine therapy has no effect on medullary thyroid carcinoma. For extensive nodal disease or local disease in the neck, external beam therapy can be considered. Tyrosine kinase inhibitors have been used in progressive systemic disease. All patients with medullary thyroid carcinoma should undergo genetic testing for a *RET* germline mutation.

Anaplastic thyroid carcinoma is an undifferentiated thyroid cancer that is typically found in older people, with a mean age at diagnosis of 65. It has the worst prognosis of any thyroid cancer, due to rapid growth and local invasiveness. It often occurs in patients who have a multinodular goiter or history of papillary thyroid carcinoma. The presentation of anaplastic thyroid carcinoma is as a rapidly enlarging neck mass. Thyroidectomy, radiotherapy, and chemotherapy have limited benefit, and median survival from diagnosis is 3 to 7 months.

Thyroid lymphoma is also rapid growing, and usually arises in a background of Hashimoto thyroiditis. Like anaplastic thyroid carcinoma, it presents as a rapidly growing mass that may cause compressive symptoms, but the response to treatment is better. A characteristic asymmetrical pseudocystic pattern is present on ultrasound. Large needle or surgical biopsy is required to establish the diagnosis. Treatment with radiation and chemotherapy and prognosis parallel other non-Hodgkin lymphomas, and thyroidectomy is not indicated.

ACKNOWLEDGMENTS

Drs. Jerome Hershman, Sima Hassani, and Mary Samuels wrote this chapter in the sixth edition. **Tables 109-1** through **109-6** and **Figures 109-1** and **109-2** from that chapter have been retained in this edition.

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Chapter 110

Diabetes Mellitus

Pearl G. Lee, Jeffrey B. Halter

Learning Objectives

- Understand the epidemiology of diabetes and the heterogeneity of its complications and comorbidities in older adults, including geriatric conditions.
- Describe preventive strategies and initial management strategies for diabetes in the older adult.
- Determine appropriate diabetes management goals and regimens for older adults, based on their individual functional status, cognition, and available social support.

Key Clinical Points

1. **Older adults, as a result of interactions among genetics, lifestyle, and aging, are at high risk of developing prediabetes and diabetes.**
2. **Intensive lifestyle interventions, including diet and physical activity to achieve weight loss, are effective strategies for prevention of progression from prediabetes to diabetes and for management of diabetes in older adults.**
3. **Treatment of diabetes in the older adult, particularly drug therapy, should involve consideration of patient and caregiver preferences, and other coexisting medical and geriatric conditions.**

Diabetes mellitus is a common metabolic disorder affecting older people. Although it is recognized by its effects on carbohydrate metabolism to cause hyperglycemia, diabetes usually also affects lipid and protein metabolism. With time, effects of diabetes on the cardiovascular system, the kidneys, the retina, and the peripheral nervous system, often referred to as long-term complications of diabetes, substantially increase mortality and morbidity in older adults. Furthermore, diabetes may accelerate the risk and contribute to worse outcomes for other common age-related conditions, including physical function decline, cognitive impairment, and other geriatric syndromes. Older adults with diabetes are highly heterogeneous in their health and functional status. Many older adults who are relatively healthy and have good functional status may benefit from the same type of diabetes care that is recommended for younger adult diabetes patients. However, the risks of implementing such a diabetes care regimen may lead to more harm than benefit for some older adults who have many comorbidities. Therefore diabetes management and goals of care for older adults should be individualized to address the heterogeneity of this population. More research is needed to identify optimal care for older patients with diabetes that can improve their functional outcomes, so that they can preserve long-term independence.

DEFINITION

Diabetes mellitus is a heterogeneous set of disorders affecting multiple body systems; however, diabetes diagnostic criteria are based on documentation of elevated circulating blood glucose levels. While glucose levels vary during the course of the day, the diagnostic criteria for diabetes mellitus are based on standardized values that predict poor outcomes in population studies. The challenge of establishing appropriate diagnostic criteria for older adults is made

more difficult by well-described effects of aging on glucose metabolism (summarized later in this chapter in the section on "Effects of Aging"). **Table 110-1** summarizes the currently accepted diagnostic criteria published by the American Diabetes Association (ADA) in 2014.

TABLE 110-1 THREE METHODS TO DETERMINE DYSGLYCEMIA AND DIAGNOSTIC CRITERIA[a] FOR DIABETES IN ALL ADULTS, REGARDLESS OF AGE

GLYCEMIC STATUS	A_{1C}	FPG	OGTT (2-H GLUCOSE)
Diabetes	≥ 6.5%	≥ 126 mg/dL (7 mmol/L)	≥ 200 mg/dL (11.1 mmol/L)
Prediabetes	5.7%–6.4%	≥ 100–125 mg/dL (5.6–6.9 mmol/L)	149–199 mg/dL (7.8–11.0 mmol/L)
Normal	≤ 5.6%	< 99 mg/dL (5.5 mmol/L)	< 148 mg/dL (7.7 mmol/L)

FPG, fasting plasma glucose, glucose measurement after no caloric intake for at least 8 hours; A_{1c}, glycosylated hemoglobin A_{1c}; OGTT, oral glucose tolerance test, 2 hours.

[a]Any of these criteria should be confirmed on a separate day to establish a diagnosis of diabetes.

Type 1 Diabetes

Type 1 diabetes is a condition characterized by destruction of the insulin-producing β-cells of the endocrine pancreas, resulting in absolute deficiency of insulin. While evidence of cell-mediated autoimmunity is a hallmark of type 1 diabetes, some patients develop a type 1 diabetes phenotype with evidence of severe insulin deficiency and episodes of diabetic ketoacidosis (DKA) with no detectable autoimmunity. Such individuals have idiopathic type 1 diabetes. Although the incidence of new-onset type 1 diabetes in older adults is very low, effective treatment of type 1 diabetes may prevent or delay the development of long-term complications and increased mortality. Thus, people who develop type 1 diabetes earlier in life now often live to old age and therefore become a part of the spectrum of diabetes mellitus in an older adult population.

Type 2 Diabetes

Approximately 90% of older adults with diabetes have type 2 diabetes mellitus. Hyperglycemia, often asymptomatic, is the hallmark and DKA is not part of the clinical syndrome. Type 2 diabetes is associated with a progressive insulin secretory defect, but severe absolute insulin deficiency is usually not present. Coexisting obesity is common, and resistance to insulin's metabolic effects is usually a characteristic feature. While there is a strong genetic predisposition to development of type 2 diabetes, its etiology remains unknown and is likely to be both highly heterogeneous and multifactorial. The interaction between genetics, lifestyle factors, and aging in the development of type 2 diabetes is discussed later in this chapter in the section on "Pathophysiology."

Other Specific Types of Diabetes

The ADA classification for diabetes mellitus identifies a number of specific conditions that lead to development of diabetes, each of which is relatively uncommon. One group of disorders includes genetic defects of the pancreatic β-cell. The clinical phenotype for these genetic disorders is maturity-onset diabetes of youth (MODY). These genetic disorders have autosomal dominant inheritance with first presentation of asymptomatic hyperglycemia early in life. Patients with MODY can live to old age, however, and therefore become part of the spectrum of diabetes in an older adult population. The metabolic disorder in some affected individuals may be mild, whereas others may develop symptomatic hyperglycemia and long-term complications of diabetes mellitus similar to patients with typical type 2 diabetes. Another type of genetic defect has been identified in a few families in which insulin processing prior to secretion is impaired, which can predispose to development of hyperglycemia.

Other families have genetic defects affecting insulin action. Severe insulin resistance results, and when it is not adequately compensated for by increased insulin secretion, hyperglycemia occurs. Diseases of the exocrine pancreas can lead to damage to pancreatic β-cells, diminished insulin secretion, and hyperglycemia. Hyperglycemia also can occur in patients with excessive secretion of hormones that adversely affect carbohydrate metabolism, such as in

acromegaly, Cushing syndrome, glucagonoma, and pheochromocytoma. Similarly, tumors making aldosterone can cause hyperglycemia as a result of hypokalemia-induced inhibition of insulin secretion. A number of drugs or toxins can impair insulin secretion or insulin action and lead to the development of hyperglycemia. **Table 110-2** lists such drugs. Several genetic neuromuscular disorders are associated with diabetes mellitus, but they are rare in the older adult population.

TABLE 110-2 DRUGS THAT MAY INCREASE GLUCOSE LEVELS

Diuretics
α-Adrenergic agonists
β-Adrenergic blockers
Alcohol
Ca^{2+} channel blockers
Caffeine
Clozapine
Glucocorticoids
Growth hormone
Nicotine
Nicotinic acid
Nonsteroidal anti-inflammatory drugs
Female sex steroids (estrogen/progesterone)
Pentamidine
Phenytoin

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) refers to the first identification of an alteration in glucose metabolism during pregnancy. While GDM per se is not part of the spectrum of diabetes in older adults, a history of GDM may be part of the background of an older woman presenting with type 2 diabetes. GDM has been aggressively screened for and treated, thus increasing numbers of women reaching the geriatric age group will have this history, as GDM affects approximately 4% of all pregnancies in the United States. After pregnancy, 5% to 10% of women with gestational diabetes are found to have type 2 diabetes. Women who have had gestational diabetes have a 20% to 50% chance of developing diabetes in the next 5 to 10 years.

Diagnostic Criteria

The rationale for the circulating glucose level criteria shown in **Table 110-1** is based on prediction of risk for diabetes-related complications. For example, a 2-hour value during the oral glucose tolerance test (OGTT) greater than or equal to 200 mg/dL is a strong predictor of diabetes complications, even when the fasting glucose level (FPG) is less than 126 mg/dL. The term “isolated postchallenge hyperglycemia” (IPH) is sometimes used for individuals who meet the 2-hour OGTT criterion for diabetes, but who do not meet the fasting glucose criterion. There is no age adjustment in the recommended criteria for the diagnosis of diabetes mellitus because the same glucose level cut points that predict complications appear to apply regardless of age.

Since 2010, diagnostic criteria for diabetes include a hemoglobin A_{1c} level of 6.5% or higher. An A_{1c} of 6.5% or higher predicts diabetic retinopathy at approximately the same rate (ie, 10%) as in individuals who are diagnosed on the basis of the fasting and postchallenge glucose criteria.

Adding A_{1c} as a diagnostic criteria for diabetes can improve the identification of asymptomatic diabetic patients. About 25% of people who meet criteria for diabetes, or 8 million of the US population, are undiagnosed. The A_{1c} test does not require the patient to be fasting, can be done at any time that a clinical visit is scheduled, is simpler to perform than the OGTT, and is less dependent on the patient’s health status at the time a blood sample is obtained. On the other hand, the A_{1c} level will be falsely lowered by any health condition that shortens red blood cell survival such

as acute or chronic blood loss, hemoglobinopathies, hemolytic anemia, thalassemia, spherocytosis, and severe hepatic and renal disease. Among certain ethnic populations such as African Americans, the A_{1c} level has been shown to be slightly higher than nonhispanic whites when matched for actual degree of glycemia.

The three different criteria are not entirely concordant in diagnosing diabetes. For example, in a sample of adults aged 70 to 79 years without known diabetes, 36% of them met the criteria for diabetes using both A_{1c} and FPG test; another 36% met the criteria using A_{1c} only and 28% using FPG only. When comparing FPG, OGTT, and A_{1c} tests to diagnose diabetes, A_{1c} identified the fewest individuals as having diabetes. Such studies suggest that A_{1c}, FPG, and OGTT measure different aspects of glycemia, and the discordance among these tests is particularly significant among older adults. At this time, unless there are clear clinical hyperglycemic symptoms, the ADA recommends repeating the same diagnostic test for confirmation. If a patient has discordant results on two different tests, then the test with the result higher than the diagnostic threshold should be repeated to confirm the diagnosis. For example, if FPG is less than 126 mg/dL (7 mmol/L) but A_{1c} is greater than or equal to 6.5%, then A_{1c} should be repeated, and if the repeat A_{1c} is greater than or equal to 6.5%, then the person would be considered to have diabetes.

The 2014 ADA criteria shown in **Table 110-1** also define intermediate categories of altered glucose metabolism that identify an earlier stage (prediabetes) in the development of diabetes mellitus. People with prediabetes do not meet the criteria for diabetes, but have glucose levels that are higher than normal. These people are at increased risk for diabetes and cardiovascular diseases. People with prediabetes include those with impaired glucose tolerance (IGT), impaired fasting glucose (IFG), or an A_{1c} range of 5.7% to 6.4%. IGT is based on results of an OGTT, and IFG is defined from fasting glucose levels. Because OGTTs are not routinely performed in clinical practice, the IFG category allows easy identification of some, but not nearly all, of the older individuals who would meet criteria for IGT if an OGTT were performed. There is no recommended age adjustment for the criteria for either IGT or IFG, as these criteria predict risk for subsequent diabetes and cardiovascular disease (CVD) similarly in older people.

Diagnostic Testing for Older Adults

The ADA recommends screening all individuals older than age 45 at 3-year intervals to detect prediabetes or diabetes with FPG level, OGTT, or A_{1c} level, particularly those with a body mass index (BMI) greater than or equal to 25 kg/m^2. The rationale for such screening includes the high rate of undetected diabetes mellitus in population studies and the strong evidence that early intervention delays the development of diabetes in people with prediabetes, including those older than 60 years. Yearly follow-up and retesting of people at higher risk should be considered. Such high-risk individuals include those who are overweight (BMI $\geq$ 25 kg/m^2), those with a strong family history of diabetes that includes a first-degree relative, those with a history of prior GDM, people with hypertension or dyslipidemia (particularly elevated triglyceride and/or low high-density lipoprotein [HDL] cholesterol levels), and those who have had IFG, IGT, or $A_{1c} \geq 5.7\%$ on previous testing. In addition, members of ethnic groups with higher risks of diabetes should be considered for more frequent testing. Such populations include African Americans, Hispanics, Pacific Islanders, Asian Americans, and Native Americans.

What about testing to classify the type of diabetes mellitus? The ADA does not define criteria for classifying types of diabetes mellitus. In theory, it is possible to measure insulin levels and various pancreatic islet antibodies to identify most individuals with type 1 diabetes. At this time, however, the differentiation between types of diabetes is primarily based on clinical history. While clinical history is imprecise, it is sufficient under most circumstances to guide treatment interventions. Insulin therapy should be a key part of the approach to patients with type 1 diabetes and interventions targeted at enhancing endogenous insulin secretion are unlikely to be useful for such individuals, even in the early stages of their disease. Insulin can also be used in patients with other types of diabetes depending on the clinical situation (as described in more detail subsequently in the insulin section under “Hyperglycemia Management”). Accurate classification may be more important in the future. For example, if interventions are identified to prevent progression of autoimmune diabetes, it would be important to establish a specific diagnosis early so that such interventions could be used appropriately.

EPIDEMIOLOGY

Figure 110-1A describes the prevalence of diabetes (diagnosed and undiagnosed) by age groups in the United States, along with the prevalence of people with prediabetes. Nearly 14% of the US population aged 20 years or older have diabetes. Among those with diabetes, one-third of them were undiagnosed. Additionally, 38% of the population have prediabetes.

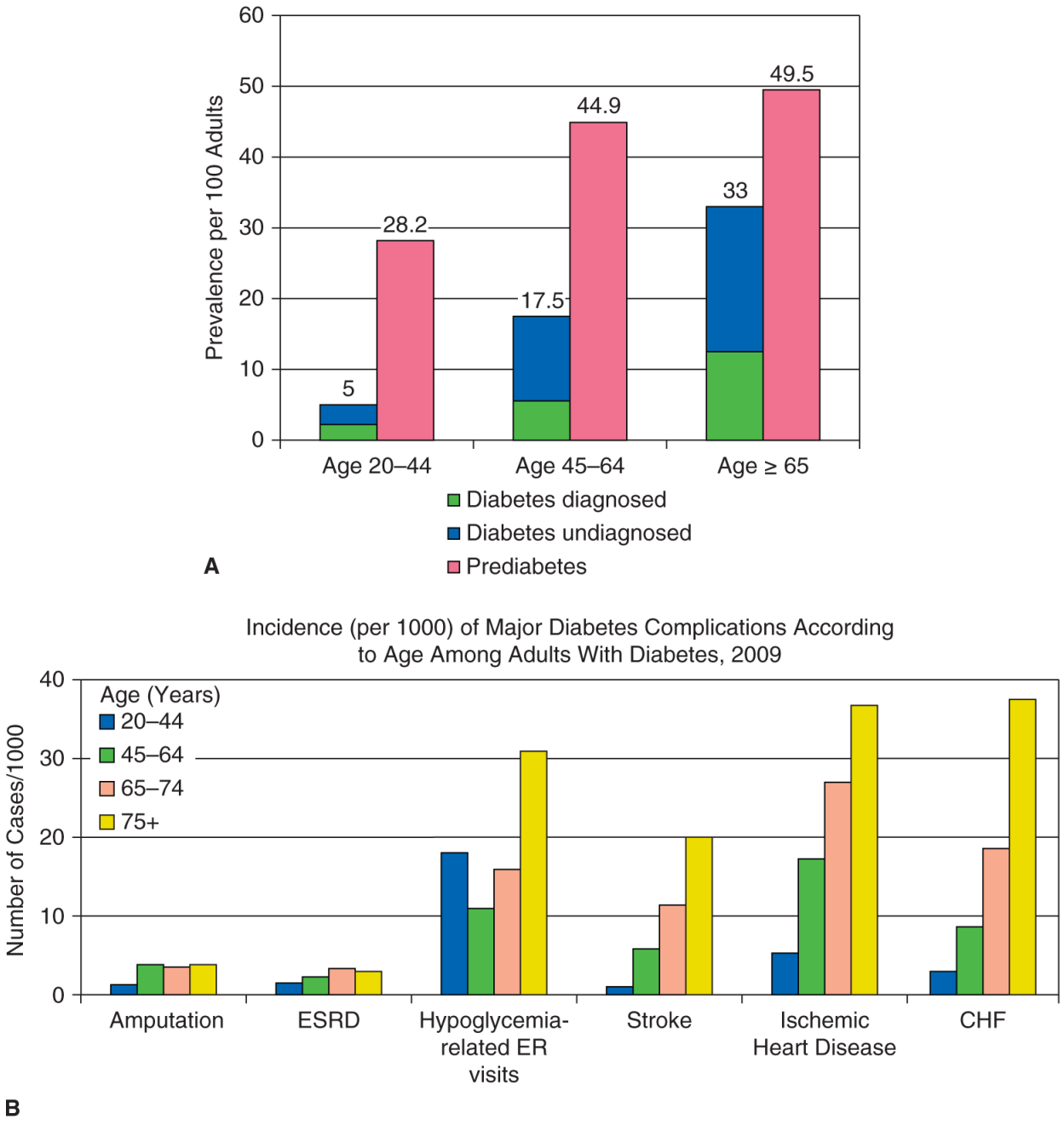


FIGURE 110-1. **A.** Diabetes (diagnosed and undiagnosed) and prediabetes prevalence in the United States by age groups (aged 20 or older, 2012). (*JAMA*. 2015; diabetes defined by A_{1c}, fasting blooglucose, or 2-h OGTT.) **B.** Incidence (per 1000) of major diabetes complications among adults with diabetes, by age, 2009. CHF, congestive heart failure; ER, emergency room; ESRD, end-stage renal disease; IHD, ischemic heart disease. (National Diabetes Surveillance System. http://www.cdc.gov/diabetes.)

Among people aged 65 or older, the prevalence of diabetes was 33%, higher than younger age groups. Among adults aged 18 or older, the incidence of newly diagnosed diabetes is the highest among those aged 45 to 64 and 65 to 79, estimated at 12 new cases/1000 people and 15 new cases/1000 people in 2011, respectively. Both the prevalence of diabetes and the rate of new cases of diabetes are projected to increase in the next three decades. These projected increases are attributable to the aging of the US population, increasing numbers of higher-risk minority groups in the population, and people with diabetes living longer due to falling rates of cardiovascular deaths.

Older adults with diabetes mellitus are susceptible to all the usual complications of diabetes. Although rates of end-stage renal disease, loss of vision, myocardial infarction, stroke, peripheral vascular disease, and peripheral neuropathy all increase with age in the absence of diabetes, and their incidence and co-occurrence are all exaggerated by the presence of diabetes in older adults, as shown in **Figure 110-1B**. Patients with diabetes are at very high risk for CVD, and this risk increases dramatically with age. In 2011, the percentage of US adults with diabetes reporting heart disease or stroke was 28% among those aged 35 to 64, 43% among those aged 65 to 74, and 55% among those aged 75

or older.

Diabetic nephropathy is defined by proteinuria greater than 500 mg in 24 hours in the setting of diabetes. Such gross proteinuria is preceded by lower degrees of proteinuria, or microalbuminuria. Microalbuminuria is defined as albumin excretion of 30 to 299 mg/24 h. Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy. Diabetic nephropathy is the leading cause of chronic kidney disease in the United States. Approximately 50% of individuals with diabetes over age 65 have diabetic nephropathy, manifested as albuminuria, impaired glomerular filtration rate (GFR), or both (**Figure 110-2**). **Figure 110-2** also shows that the prevalence of combined albuminuria and impaired GFR is much higher in older people. This is especially important as combined albuminuria and impaired GFR is a strong predictor of future risk of CVD in this population. Diabetic kidney disease accounts for nearly half of all incident cases of end-stage renal disease (ESRD) in the United States, and the rate is highest among those aged greater than or equal to 75. Five-year survival for patients with ESRD is less than 40%; therefore, prevention of diabetic kidney disease is important to improve health outcomes of older persons with diabetes.

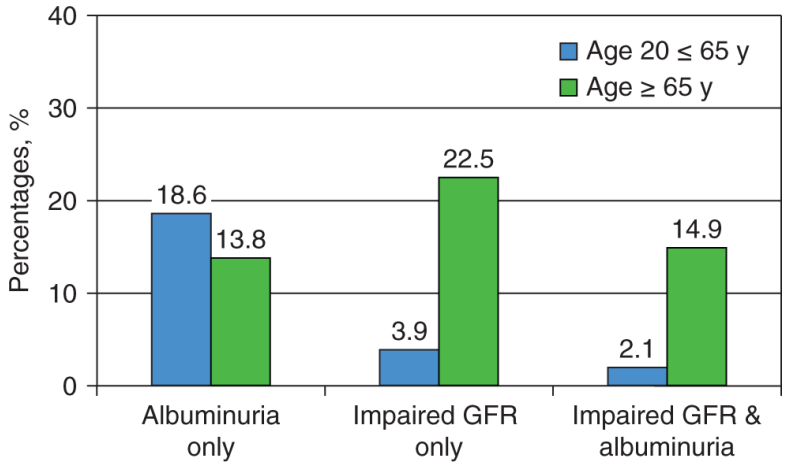


FIGURE 110-2. Prevalence of diabetic kidney disease in the United States, 2005–2008. (Derived from data in de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. *JAMA.* 2011;305[24]:2532-2539.)

Diabetic retinopathy may be the most common microvascular complication of diabetes. It is responsible for approximately 10,000 new cases of blindness every year in the United States alone. Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with type 2 diabetes.

Diabetic neuropathy is usually defined by the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes. Diabetic neuropathy is highly correlated with the duration of diabetes, and it is estimated that approximately 50% of patients with diabetes will eventually develop neuropathy. Clinical and subclinical neuropathy has been estimated to occur in 10% to 100% of diabetic patients, depending on the diagnostic criteria and patient populations examined.

Diabetes-specific pathologic findings exist for some of these complications, but pathologic information is generally not available for epidemiologic studies that depend on the more gross clinical outcomes. It is more difficult to be certain of the specific role of diabetes, and especially of hyperglycemia per se, in contributing to an outcome such as visual loss or end-stage renal disease in an older patient, as compared with a younger patient with diabetes, who would not otherwise be expected to have one of these problems.

In an older adult population, the presence of hyperglycemia and diabetes mellitus should be viewed as a risk factor for such complications, analogous to hypertension or hypercholesterolemia. The level of increased relative risk may appear modest on an individual level. However, since older people have by far the highest rates of these conditions, the increase in absolute risk is substantial. Thus a twofold relative risk increase as occurs for myocardial infarction, stroke, and ESRD, represents a very large number of added adverse outcomes in an older adult diabetes population. The risk for lower- extremity amputation is dramatically increased in older people with diabetes mellitus, approximately 10-fold greater than that for older people without diabetes.

As a result of the growing number of older people with diabetes and their high risk for diabetes complications, diabetes is costly for the US health care system. Approximately $300 billion is spent annually on patients with diabetes in the United States, and the majority of these costs is spent on older adults with long-standing diabetes and severe

complications. On average, people with diagnosed diabetes have medical expenditures approximately 2.3 times higher than those without diabetes: approximately $1 in $5 health care dollars is spent caring for someone with diagnosed diabetes and approximately $1 in $10 health care dollars is attributed to diabetes. The annual attributed health care cost per person with diabetes increases with age, primarily as a result of increased use of hospital inpatient and nursing facility resources, physician office visits, and prescription medications. For example, 63% of the inpatient hospital costs for diabetes are attributed to utilization by adults aged greater than or equal to 65 compared to 30% and 6% by adults aged 45 to 64 and less than 45, respectively.

Diabetes was the seventh leading cause of death in the United States in 2010 based on death certificate records. In fact, diabetes may be underreported as a cause of death. Only 35% to 40% of people who died with diabetes had it listed anywhere on the death certificate, and only 10% to 15% had it listed as the underlying cause of death. Overall, risk for death among those with diabetes is about twice that of people with similar age but without diabetes. The majority of diabetes attributed deaths occur among older adults, with 73% of deaths occurring among people age 70 and older.

PATHOPHYSIOLOGY

Although the rate of new onset of type 1 diabetes is relatively low in older people, the mechanism for type 1 diabetes does not appear to be different in this population. Usually, patients with type 1 diabetes have markers of immune destruction of pancreatic β-cells such as islet cell antibodies, antibodies to insulin, or other pancreatic β-cell–specific antibodies. There are also strong human leukocyte antigen associations.

Type 2 diabetes is by far the most prevalent form in older adults. Autoimmune destruction of pancreatic β-cells is rarely observed. Limited pathologic investigation suggests that total β-cell mass may be moderately reduced, but severe loss of β-cell mass is uncommon. The pathophysiology of type 2 diabetes is unknown, but it appears to occur as a result of a complex interaction among genetic, lifestyle, and aging influences, as illustrated in **Figure 110-3**. The heterogeneity of type 2 diabetes likely reflects the varying contributions of each of multiple factors to the development of hyperglycemia in a given individual or family.

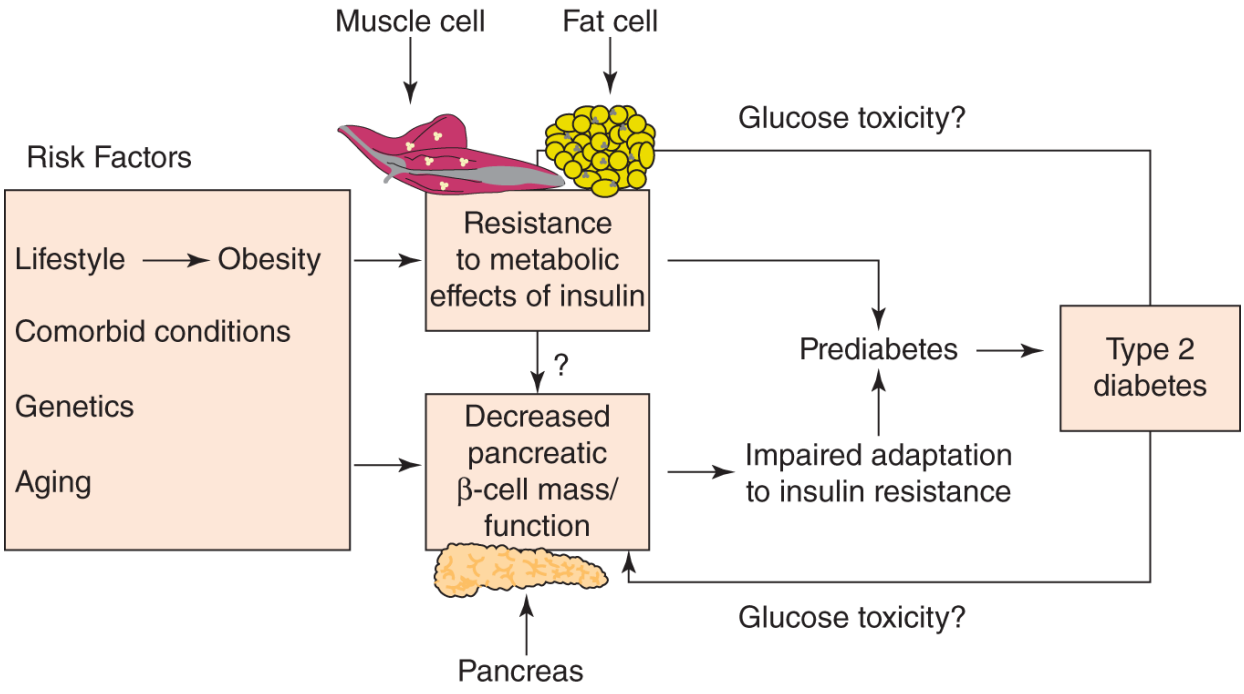


FIGURE 110-3. Model for age-related hyperglycemia. Biological changes associated with risk factors give rise to alterations in both insulin secretion and insulin sensitivity. (Source: Modified from Chang AM, Halter JB. Aging and insulin secretion. *Am J Physiol Endocrinol Metab*. 2003;284[1]:E7–E12.)

Effects of Aging

Many studies have demonstrated age-related glucose intolerance in humans. In normal people who do not meet criteria

for either diabetes mellitus or IGT, there is a slight age-related increase in fasting glucose levels and a more dramatic slowing of return to normal of glucose levels following an oral glucose challenge.

Insulin Resistance

There is a decline in sensitivity to the metabolic effects of insulin with age. An age-related impairment of intracellular insulin signaling reduces insulin-mediated mobilization of glucose transporters, which are critical to glucose uptake and metabolism in insulin-dependent tissues such as muscle and fat. There is currently little evidence for an age-related impairment of insulin effects on protein or fat metabolism.

An absolute or relative increase of body adiposity, particularly central body adiposity, has been well-documented with advancing age and appears to account in large part for the age-related increase in insulin resistance. Decreased physical activity is associated with insulin resistance, and exercise training can improve insulin sensitivity. Thus, diminished physical activity in an older individual can also contribute to decreased insulin sensitivity. Both in animal studies and in humans, it has been difficult to demonstrate a residual effect of aging on insulin action when the changes in body composition and physical activity are controlled for.

Impaired Insulin Secretion

The progression from normal glucose tolerance to IGT and type 2 diabetes in aging is characterized by progressive defects in pancreatic β-cell function. Animal studies have demonstrated an age-related decline in β-cell function. However, there has been great variability in previous studies examining insulin secretion in older people. These human studies, however, may have failed to address adequately the importance of the normal adaptive response to insulin resistance. As most older individuals demonstrate insulin resistance, a compensatory increase of insulin secretion, leading to increased circulating insulin levels, would be expected. However, both basal and stimulated insulin levels in older adults are similar to those of insulin-sensitive young people, suggesting an inadequate adaptive response to insulin resistance in older subjects. Furthermore, when older and younger people are carefully matched for degree of insulin sensitivity, absolute impairments in β-cell function are evident with normal human aging, as shown in **Figure 110-4**. Such defects are even greater in older people with IGT. Thus, impaired pancreatic β-cell adaptation to insulin resistance is an important contributing factor to age-related glucose intolerance and risk for diabetes.

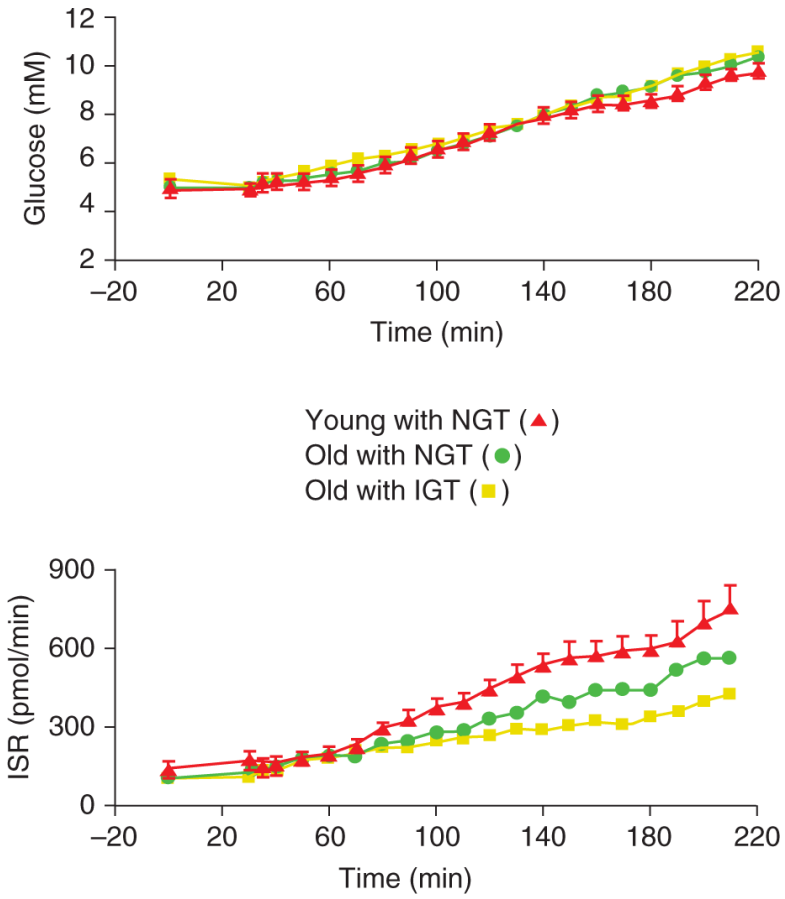


FIGURE 110-4. Effect of age on insulin secretion rate (ISR) in humans with normal glucose tolerance (NGT) or impaired glucose tolerance (IGT) by American Diabetes Association criteria. Plasma glucose concentrations and ISR are shown over time during intravenous glucose infusions, comparing young with NGT (n = 15, mean age = 26), old with NGT (n = 16, mean age = 70), and old with IGT (n = 14, mean age = 70). Glucose levels during variable rate glucose infusion begun at time 0 were well matched in the three study groups, and degree of insulin resistance was also similar in the three study groups. ISR was significantly and progressively decreased in the two older groups, with the greatest impairment in old IGT (p = 0.0002, old IGT vs young and old IGT vs old NGT; and old NGT vs young NGT). Data are means ± SE. (Adapted from Chang AM, Smith MJ, Galecki AT, Bloem CJ, Halter JB. Impaired β-cell function in human aging: response to nicotinic acid-induced insulin resistance. *J Clin Endocrinol Metab*. 2006;91:3303–3309.)

Interaction Between Impaired Insulin Secretion and Insulin Resistance

As summarized in **Figure 110-3**, in the setting of impaired β-cell function, there is a maladaptive response leading to impaired insulin secretion and progression to IGT and type 2 diabetes. Hyperglycemia, in turn, is known to contribute directly to insulin resistance and to impair pancreatic β-cell function, thereby setting up a vicious cycle of maladaptive mechanisms.

Coexisting illness is another factor affecting both insulin sensitivity and insulin secretion in an older person. Both hypertension and hyperlipidemia are common in older people and have been associated with diminished insulin sensitivity. In fact, a metabolic syndrome has been described that includes coexisting hypertension, hyperlipidemia, central obesity, and glucose intolerance. Some have proposed that insulin resistance is a unifying feature linking the components of this metabolic syndrome; however, there is uncertainty about whether the insulin resistance in these circumstances is primary or a secondary result of these other conditions. Furthermore, any acute illness can precipitate hyperglycemia because of effects of stress hormones to cause insulin resistance combined with the α-adrenergic effects of catecholamines released during stressful illness to inhibit insulin secretion. Drugs that may be used by older people may also contribute to hyperglycemia by causing insulin resistance (see **Table 110-2**).

A pathogenetic sequence common to many syndromes in old age can be readily illustrated by diabetes in an older patient: Hyperglycemia becomes frank diabetes, leading to acute complications and such syndromes as hyperosmotic nonketotic coma or, with time, to microvascular or macrovascular complications such as renal disease, stroke, or myocardial infarction. These events may in turn lead to superimposed drug treatment-induced aggravation of impaired glucose regulation and decreased physical activity, progressive disability, and functional decline: that is, a downward spiral of mutually reinforcing conditions perhaps triggered by an event such as influenza or a fall that would be readily withstood by a younger person, especially a younger person without diabetes.

Genetics

There is a strong genetic predisposition to type 2 diabetes mellitus. For example, the concordance rate for type 2 diabetes in identical twins approaches 100%. However, the genetic susceptibility to type 2 diabetes is polygenic, involving a number of variants, where each allele has a modest effect on the risk of disease in an individual person. Genome-wide association studies, linkage analysis, a candidate gene approach, and large-scale association studies have already identified approximately 70 loci conferring susceptibility to type 2 diabetes. These genetic alleles appear to affect the risk of type 2 diabetes primarily through impaired pancreatic β-cell function, reduced insulin action, or obesity risk. A goal of genetic testing would be to improve clinical prediction of an individual's risk for developing diabetes. However, no clear improvement of predictive power was seen with adding a genetic risk score, based on 11 to 20 loci associated with type 2 diabetes, to established risk prediction models composed of various clinical and biochemical factors including age, gender, family history, body mass index, fasting glucose level, systolic blood pressure, and lipid profile. Despite this result, subset analyses of the study cohorts suggest that genetic testing might be beneficial in younger patients before clinical manifestation of the phenotypic characteristics associated with type 2 diabetes.

Identification of genetic loci associated with increased risk for type 2 diabetes will likely help in understanding the pathophysiologic pathways for its development. This knowledge has the potential to be important in development of new, more effective medications, and prevention strategies.

Mechanisms for Diabetes Complications

Chronic exposure to hyperglycemia may contribute directly to the development of diabetes complications in a number of ways. One mechanism may be the interaction of glucose with proteins to cause protein glycosylation and subsequent formation of advanced glycosylation end (AGE) products. The AGE products can accumulate in proteins

of slow turnover such as collagen, potentially leading to tissue damage and injury. Tissue exposure to high concentrations of glucose can also lead to accumulation of metabolic products of the aldose reductase system including nonmetabolized molecules such as sorbitol. Such accumulation can potentially affect cellular energy metabolism and contribute to cell injury and death. Given the complexity of the genetic background contributing to type 2 diabetes, the possibility also exists that some of the genetic background of an individual may directly contribute to the risk for one or more long-term complications of diabetes (eg, end-stage renal failure) independent of the effects of hyperglycemia. However, such a possibility remains speculative. Interactions between diabetes and other comorbidities may contribute to the manifestation and severity of diabetes-related complications. Diabetic patients who also have hypertension are at greater risk for renal disease, retinopathy, and macrovascular disease than diabetic patients without hypertension. Similarly, neuropathy is more likely in a diabetic patient who is exposed to a neurotoxic agent. Growth factors, including vascular endothelial growth factor, growth hormone, and transforming growth factor β, have been postulated to play important roles in the development of diabetic retinopathy.

PREVENTION

Type 2 diabetes is a gradually progressive disorder of carbohydrate metabolism that develops over a long period of time. It has been estimated that abnormalities of glucose regulation can be detected 8 to 10 years before the clinical diagnosis of type 2 diabetes is made. Older adults have a high rate of prediabetes, and other risks for progressing to type 2 diabetes in the next few years. For example, 51% of people aged 65 or older in the United States have prediabetes based on fasting plasma glucose or A_{1C} levels.

Effective means to delay progression to type 2 diabetes in high-risk people, such as those with prediabetes, have been identified. Intensive lifestyle interventions, which include weight loss and increased physical activity, can substantially reduce the rate of progression to type 2 diabetes in such high-risk people. Lifestyle intervention appears to be especially beneficial in prevention of progression to diabetes among older adults. For example in the multicenter Diabetes Prevention Program (DPP) in the United States, a lifestyle intervention program including both caloric restriction and exercise was remarkably effective in reducing the rate of progression to type 2 diabetes, even though only 5% to 7% weight reduction was achieved. During the 3 years of active treatment in DPP, the lifestyle intervention program was more effective in people older than age 60 than in younger people, reducing progression to diabetes by more than 70% as compared to a control group, as shown in **Figure 110-5**. Metformin was also used in the DPP and was effective in slowing progression in younger adults, but had surprisingly much less effect in people older than age 60.

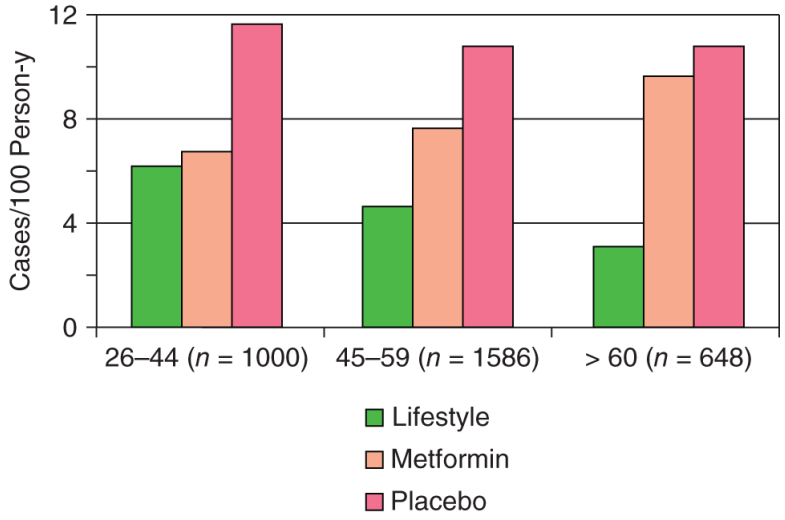


FIGURE 110-5. Diabetes incidence rates by age, Diabetes Prevention Program. (Diabetes Prevention Program Research Group, Crandall J, Schade D, et al. The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J Gerontol A Biol Sci Med Sci*. 2006;61[10]:1075–1081.)

The benefit of lifestyle intervention appears to be long term among older adults, as they had reduced frequency of developing type 2 diabetes over the 10 years of follow-up after the original lifestyle intervention. Overall, onset of diabetes was delayed by about 4 years by lifestyle intervention compared with placebo.

As more is learned about the genetics of type 2 diabetes, it may be possible to identify high-risk individuals early in life based on genotype and to effectively target interventions. The success of the lifestyle intervention trials to prevent progression has led to exciting discussion and research on how screening should be carried out to identify high-risk individuals and how to implement the lifestyle interventions effectively for more widespread impact.

PRESENTATION

The finding of an elevated glucose level on routine laboratory testing is the most common presentation for type 2 diabetes in an older person. The classical clinical hallmarks of diabetes are symptoms associated with marked hyperglycemia, including polydipsia, polyuria, polyphagia, and weight loss. Older patients with type 2 diabetes may present with such symptoms, although it is relatively uncommon for them to do so and the rate of emergency department visits by older adults for severe hyperglycemia have been declining. Some older patients may have sufficient hyperglycemia to cause mild classical symptoms, while others may have had gradual unexplained weight loss. Other older patients may present with atypical symptoms from hyperglycemia such as falls, urinary incontinence, fatigue, or confusion. Because type 2 diabetes may go undetected for years, some older adults first present with symptoms or findings related to diabetes complications, such as visual loss with classic retinopathy on examination, proteinuria, or symptomatic peripheral neuropathy.

With the profound insulin deficiency of type 1 diabetes, mobilization of fatty acids occurs leading to accelerated production of ketoacids, potentially resulting in life-threatening DKA. Although type 1 diabetes usually occurs in early life, it can occur at any age, including first presentation in an older patient. Development of DKA is the classic form of presentation for a patient with type 1 diabetes, but it is now recognized that people with type 1 diabetes may have long periods of abnormal circulating glucose levels before the development of DKA. Furthermore, with early detection of such hyperglycemia and appropriate diabetes management, an episode of DKA might never occur. An older person with type 1 diabetes may be particularly more likely to present with an indolent course.

EVALUATION

Diabetes mellitus is a complex disorder that can have effects on many body systems, and its treatment requires a complex program including lifestyle changes and medications. The choice of intervention strategies and the patient's capability to adhere to a diabetes treatment program may be limited by the presence of other health problems such as cognitive impairment, as well as by the patient's living situation, economic status, availability of caregiver support, and the like. A comprehensive geriatric assessment (Chapter 10) is highly appropriate to provide the basis for developing a treatment plan for an older person with diabetes mellitus.

Medical Evaluation

Once a diagnosis of diabetes is established, a thorough medical evaluation is needed. Because the risk for developing diabetes complications is related to the duration of hyperglycemia, effort should be made to pinpoint the time of onset. Unless patients at risk have been followed up carefully with yearly measurement of a fasting glucose level, as currently recommended by the ADA, it may be difficult to establish a time of onset for type 2 diabetes in a given patient. Given the uncertainty about time of onset, a careful search for existing diabetes complications is warranted even when a new diagnosis is made in an older adult. Such an evaluation is even more justified in a patient with a multiyear history of diabetes mellitus who is establishing a new relationship with a health care system or primary care provider. The evaluation for eye complications of diabetes should be carried out by an ophthalmologist with a detailed retinal examination, as early signs of diabetic retinopathy can easily be missed.

Evaluation of diabetic nephropathy should include a screening urine albumin and serum creatinine level, which should be followed at least annually. An elevated serum creatinine is a poor prognostic sign, suggesting that substantial kidney damage has already occurred and that an irreversible course of progressive renal insufficiency has already started. Depending on the patient's overall situation, referral to a nephrologist may be warranted to assess other potential causes of renal insufficiency. Urine screening for proteinuria should be carried out to detect earlier stages of diabetic nephropathy that are amenable to intervention. A positive qualitative urine for protein (dipstick method) indicates gross proteinuria (over 300 mg/day). If confirmed on repeat testing, this finding in itself is an indication for treatment intervention. However, a negative qualitative urine protein test does not rule out early diabetic

nephropathy. If the qualitative dipstick test is negative, a spot urine sample should be sent for quantitative measurement of urine protein and creatinine. A value greater than 30 mg/g creatinine, often referred to as microalbuminuria, suggests early diabetic nephropathy. Such a test should be repeated twice in subsequent months for confirmation. If two of three tests are positive, intervention is warranted.

A careful neurologic examination should be carried out for signs of diabetic neuropathy. This examination should include monofilament testing. This is a qualitative test with a 10-g nylon monofilament carried out at different points along the foot with simple yes or no responses by the patient about feeling the pressure of the monofilament. Vibration sense should also be tested with a tuning fork. This neuropathy evaluation should be carried out in conjunction with a careful foot examination to identify possible structural abnormalities that might contribute to risk for skin breakdown and damage.

The medical evaluation of an older patient with diabetes should also include information about other coexisting risk factors including hypertension, hyperlipidemia, and use of cigarettes. These conditions interact with diabetes to increase risk of adverse cardiovascular events and therefore need to be addressed in an overall patient management program. Blood pressure should be assessed both in the supine position and with upright posture, as an orthostatic drop in blood pressure may be another marker of diabetic neuropathy and is often associated with supine hypertension. The genitourinary system should also be assessed, as patients with diabetes may be prone to bladder dysfunction associated with autonomic neuropathy, thereby increasing the risk for urinary tract infection and kidney damage. Sexual dysfunction has been reported in a high percentage of older men with diabetes, suggesting an interaction between aging, neuropathy, and vascular disease in this population.

A thorough evaluation of the cardiovascular system also should be carried out, given the high rate of vascular disease in older people with diabetes mellitus. The history and physical examination should carefully assess evidence for cerebrovascular disease, coronary heart disease, and peripheral vascular disease. Suggestive history or physical findings should be documented with more in-depth testing including Doppler evaluation for carotid artery stenosis or extremity blood flow, or cardiovascular stress testing if there is any suggestion of coronary artery disease. Silent ischemia and myocardial infarction appear to be more common in people with diabetes mellitus. Thus, the threshold for stress testing should be rather low.

The drug history of an older patient with diabetes is important both to identify drug therapy that may be contributing to the patient's hyperglycemia (see **Table 110-2**), as well as to identify potential drug interactions that may affect diabetes management. The initial assessment should also include a diet history, a review of potential nutritional problems, and an oral health assessment, as dietary intervention is a key component of a treatment program for virtually all patients with diabetes. The assistance of a nutritionist who has a particular interest in diabetes is often very helpful for this part of the evaluation. Particular attention should be paid to dietary habits, ethnic food preferences, and meal patterns.

Other Evaluation Components

Diabetes knowledge Because of the complexity of diabetes management, usually requiring both lifestyle and medication interventions, the patient and/or caregivers must be actively involved in their own care and take responsibility for its many aspects. It is particularly important to review the patient's knowledge base regarding diabetes and its complications. Standardized diabetes knowledge tests are available, or an interview with a diabetes educator or suitably trained nurse can establish the status of the patient's knowledge base. The diabetes education program that becomes part of the treatment plan can then provide this base for new patients or fill in needed gaps for existing patients.

Cognitive function Since diabetes and aging are each independently associated with increased risk of cognitive impairment, older adults with diabetes are especially at high risk. Additionally, diabetes is a chronic disease that requires substantial patient self-care skills. Given the complexity of diabetes management programs, an assessment of a patient's cognitive status is essential to developing an appropriate treatment plan. Cognitive impairment is associated with poorer glycemic control in clinical trials, and study participants with cognitive impairment have a higher risk for severe hypoglycemia. Hypoglycemia is also associated with higher risk for dementia.

While advanced dementia may be easily identified in a routine clinical encounter, mild to moderate cognitive impairment or executive cognitive impairment may be missed. For example, despite initial screening to only enroll participants felt to be capable of adhering to a complex diabetes treatment regimen, nearly 20% of the participants enrolled in a large diabetes clinical trial (ACCORD trial, aged 40–79) were found to have undiagnosed cognitive

impairment at baseline.

Formal neuropsychological tests have shown that patients with diabetes frequently have unrecognized deficits in psychomotor efficiency, global cognition, and memory. They also frequently have abnormalities in cognitive function mediated by frontal lobes (executive function), which can affect ability to perform complex behaviors such as attention, planning, organization, insight, reasoning, and problem solving. Such complex cognitive functions are necessary for diabetic patients to manage the complex treatment regimens for their disease. Early identification of cognitive impairment will help patients, their families, and health providers to individualize their diabetes care regimens to set achievable diabetes goals without causing harm to the patients. Therefore, older patients with diabetes should have periodic screening for cognitive impairment.

Functional status A review of activities of daily living (ie, ability to perform transferring, toileting, eating, dressing, and grooming) and instrumental activities of daily living (ie, the ability to prepare meals, manage medications, manage finance, make phone calls, and arrange for transportation), should be a part of comprehensive assessment of an older patient with diabetes mellitus. Diabetes puts the patient at increased risk for functional deficits. Such functional limitations must also be considered in developing a diabetes treatment program. In addition to general assessment of functional status, the ability of the patient and caregiver to carry out diabetes-specific functional tasks needs to be evaluated. For example, the ability to carry out home glucose monitoring or self-injection of insulin requires certain functional abilities.

Overall health status The presence of other medical problems needs to be documented, as decisions about the extent of intervention for diabetes need to be put in the context of the patient's overall health situation, disease burden, and prognosis in terms of functional status and estimated longevity. The presence of psychiatric disorders such as depression or bipolar disorder could have a major impact on the decision about diabetes treatment interventions. Coexisting illness such as congestive heart failure or uncontrolled cancer may substantially limit a patient's life expectancy, thus may influence the decision about intensity of diabetes management.

MANAGEMENT

General Approach

The complexity of diabetes and its management requires a collaborative effort by a team of health providers, which may include physicians, nurse practitioners, nurses, dietitians, pharmacists, and mental health professionals. Patients and family members must also assume an active role.

The first key step in developing a diabetes management program for an older patient is to establish the treatment goals. Basic treatment goals for any patient with diabetes are to prevent metabolic decompensation and to control other risk factors that may contribute to long-term complications. Control of hyperglycemia as a means to reduce what some have termed glucose toxicity as a contributing factor to long-term diabetes complications is one part of an overall strategy of risk reduction. Such a strategy must include intensive effort at identifying and controlling hypertension, lipid disorders, and cigarette smoking. Thus, a complex, multifaceted treatment program is important for many older patients with diabetes. As other chapters cover the management of hypertension (Chapter 82) and lipid disorders (Chapter 111), these will be referred to only briefly in this chapter. This chapter will focus on management of hyperglycemia. However, control of the traditional cardiovascular risk factors is absolutely critical to successful diabetes management. Unfortunately, many studies have documented the overall lack of success of standard clinical practice in achieving these goals.

Any decision about the level of intensity for a treatment program must take into account coexisting conditions and the overall complexity of the patient's medical regimen. For example, the existence of advanced diabetes complications in an older patient may provide a rationale for less strict goals for hyperglycemia or dyslipidemia. A significant psychiatric or cognitive disorder may also preclude an intensive management program. The target for hyperglycemia control would need to be higher for a patient at risk for severe hypoglycemia (see the section on "Hypoglycemia" later in this chapter). On the other hand, some older adults are able to devote a substantial amount of time to their own health care and are able to manage complex multidrug interventions for multiple health problems. Based on the initial comprehensive patient assessment as described here, many older adults with diabetes may fit in a category for which intensive treatment goals are appropriate.

It may be neither feasible nor appropriate to attempt to implement a complex diabetes management program for

some patients. It is true that a limited remaining life expectancy shortens the time for long-term complications to develop and progress. Given the increasing life expectancy of older adults, only the very oldest segment of the population or those with coexisting illness that markedly shortens remaining life expectancy should be excluded from consideration for an aggressive treatment program. For example, it would be hard to justify abandoning risk reduction goals in an otherwise healthy 75-year-old woman with a recent diagnosis of type 2 diabetes, as such a person's remaining life expectancy may be 15 years or more. Given the potential complexity of treatment programs designed to minimize diabetes risks, the commitment on the part of an adequately informed patient is clearly critical. Availability of a supportive environment including a strong diabetes treatment team and adequate economic support for an intensive treatment program are also important. Such a treatment goal is also difficult to achieve without commitment of the health care team, which must believe that achievement of the treatment goal will really make a difference in the patient's long-term health.

Information about a diabetic patient's cognitive status, socioeconomic and living situation can also help guide the care plan for an older adult. Limitations in cognition and economic support may affect the patients' ability to adhere to the medical regimen. The health provider may need to simplify the diabetes regimen or loosen the glycemic and/or blood pressure targets to minimize risks for hypoglycemia and/or hypotension. The health provider may need to enlist the patient's caregivers to be more involved in the patient's care. The availability of caregivers in the home or nearby can compensate for some limitations in the patient's self-care abilities and influence lifestyle factors that can affect diabetes management. For patients who have moderate or advanced cognitive impairment, support for basic home care will be needed, including the task of obtaining daily meals, administering medications and monitoring home glucose levels. Some patients may need to be transitioned from the home setting to assisted living facilities or long-term care facilities to receive necessary care. This decision will be influenced by their financial resources and the support of other family members. The availability of a social worker or suitably trained nurse to assist in this aspect of the patient's care program can be extremely helpful.

Several approaches have been proposed by diabetes specialists and geriatricians to better identify older adults who would benefit from more strict diabetes control versus less stringent control of diabetes. Age alone is not a good marker to identify older adults with diabetes who might benefit from tight diabetes control, as age alone is a poor predictor of overall disease complexity and mortality risk. In **Figure 110-6**, a group of nationally representative older adults with diabetes were grouped by their comorbidities, physical function status, and cognitive status. While the oldest age group includes many people with very complex/poor health, over 50% of people older than 75 years are relatively healthy. Thus, a classification based on a patient's comorbidities, physical function status, cognitive status, social support, history of hypoglycemia, etc, provides the basis for individualized goals to optimize the risk and benefit ratios of diabetes treatments for a given patient. **Table 110-3** outlines the recommendations from a 2012 Consensus Development Conference on Diabetes and Older Adults convened by the American Diabetes Association. This consensus framework was published to guide the treatment of hyperglycemia, hypertension, and dyslipidemia for older adults with diabetes. Based on the patient's health status, cognitive status, and physical function status, s/he may be categorized into one of the three groups. For each group, the panel made specific recommendations for glycemic, blood pressure, and lipid goals. The healthy group will likely benefit from more stringent glycemic, blood pressure, and lipid managements; the recommended targets for individuals in this group are A_{1c} less than 7.5%, BP less than 140/80 mm Hg, and statin use unless contraindicated. The intermediate healthy group will likely have some difficulty in achieving stricter goals, especially for glycemia; thus the recommended goals are A_{1c} less than 8%, but the same BP and statin goals as the healthy group. The poor health or very complex patients will likely not benefit greatly from intensive treatment of hyperglycemia, hypertension, or dyslipidemia. The recommended goals for this group with a large comorbidity burden are A_{1c} less than 8.5%, BP less than 150/90 mm Hg, and consider statin if possible benefit.

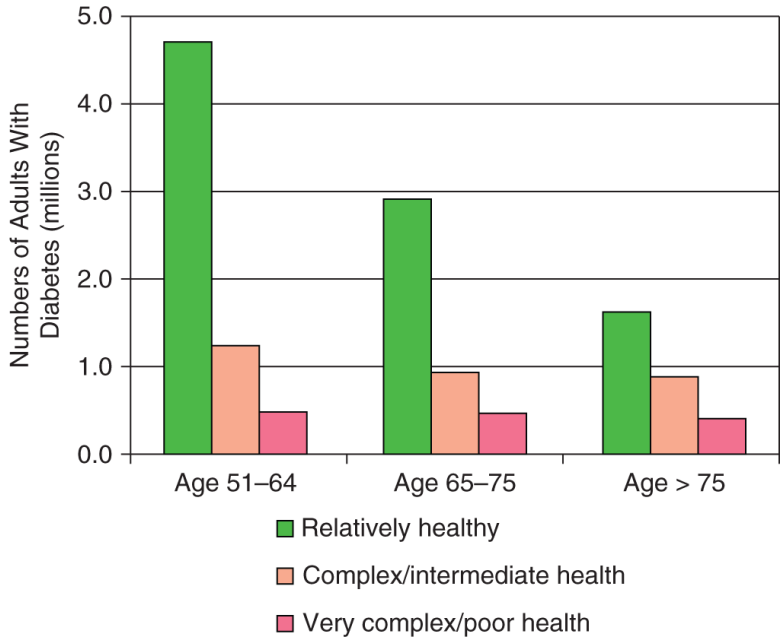


FIGURE 110-6. Health status by age group of people over age 50 in the United States who have diabetes, based on data from the Health and Retirement Study. Definitions of the three health status categories illustrated are as stated in Table 110-3. (Data from Blaum C, Cigolle CT, Boyd C, et al. Clinical complexity in middle-aged and older adults with diabetes: the Health and Retirement Study. *Med Care.* 2010;48[4]:327–334.)

TABLE 110-3 A FRAMEWORK FOR CONSIDERING TREATMENT GOALS FOR GLYCEMIA, BLOOD PRESSURE, AND DYSLIPIDEMIA IN OLDER ADULTS WITH DIABETES

HEALTH STATUS	RATIONALE	REASONABLE A_{1C} GOAL[a]	FASTING OR PREPRANDIAL GLUCOSE (MG/DL)	BEDTIME GLUCOSE (MG/DL)	BLOOD PRESSURE (MM HG)	LIPIDS
Healthy	Longer life expectancy	< 7.5%	90–130	90–150	< 140/80	Statin unless contraindicated or not tolerated
Complex/intermediate health	Intermediate life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	< 8%	90–150	100–180	< 140/80	Statin unless contraindicated or not tolerated
Very complex/poor health	Limited remaining life expectancy makes benefit uncertain	< 8.5%	100–180	110–200	< 150/90	Consider benefit with statin (secondary prevention > primary)

[a]A lower goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.

Healthy, few coexisting chronic illnesses, intact cognitive and functional status; coexisting chronic illnesses are conditions serious enough to require medications or lifestyle management and may include arthritis, cancer, congestive heart failure, depression, emphysema, falls, hypertension, incontinence, stage III or worse chronic kidney disease, myocardial infarction, and stroke.

Complex/intermediate health, multiple (3+) coexisting chronic illnesses, or 2+ instrumental activities of daily living (IADLs) impairments or mild to moderate cognitive impairment.

Very complex/poor health, long-term care or end-stage chronic illnesses, or moderate to severe cognitive impairment, or 2+ ADL dependencies. *Adapted from Kirkman MS, et al. Diabetes in Older Adults: A Consensus Report. JAGS 2012;60:2342–2356.*

Diabetes Education

Patients and caregivers need to be well educated in diabetes, its associated complications, how to modify lifestyle to improve diabetes management, how to monitor and threat complications associated with diabetes, and the risks and benefits of various medications they are prescribed. People with diabetes should receive diabetes self-management education (DMSE) when diabetes is diagnosed and as needed thereafter. DMSE is an ongoing process of facilitating

the knowledge, skills, and ability necessary for diabetes self-care. This process is evidence based, and can be individualized for each patient, incorporating the needs, goals, and life experiences of the individual. DMSE is associated with improved diabetes knowledge and self-care behavior, improved quality of life, lower A_{1c}, and lower costs.

Recognizing the effectiveness and the need for DMSE, the Centers for Medicare and Medicaid Services (CMS) provide Medicare reimbursement for Diabetes Self-Management Training (DSMT) (the formal term used by CMS for reimbursement) to beneficiaries under certain conditions. The benefits include up to 10 hours of diabetes-related training within a consecutive 12-month period, and up to 2 hours of follow-up training each year. CMS will reimburse the training if the program is accredited by either the American Diabetes Association or the American Association of Diabetes Educators. Yet, despite Medicare reimbursement, only 55% of adults aged 65 to 74 and 47% of adults aged 75+ reported ever attending a diabetes self-management class. Increasing the utilization of diabetes education classes presents a great opportunity for health care providers to improve diabetes care.

Cardiovascular Risks

Some of the risk factors for CVD among diabetic patients include hyperglycemia, dyslipidemia, hypertension, and age-related changes of the cardiovascular system including diminished vascular responsiveness (**Table 110-4**). Additional risk factors include obesity, insulin resistance, autonomic dysfunction, and inflammation. Individuals with diagnosed diabetes are at higher risk for coronary heart disease (CHD), and CHD risk also is elevated modestly among individuals with prediabetes. However, interventions targeting hyperglycemia have thus far had limited or no benefit on CVD risk reduction for older adults with diabetes. In fact, one trial—ACCORD, had to be terminated early due to a higher rate of mortality in the intensively treated glycemic group. Also of concern is that the intensive therapy group with a lower A_{1c} goal had more adverse events, predominantly hypoglycemia.

TABLE 110-4 CARDIOVASCULAR DISEASE RISK FACTORS AMONG OLDER ADULTS WITH DIABETES, IN ADDITION TO FASTING PLASMA GLUCOSE LEVEL

Systolic blood pressure
Total cholesterol
Non-HDL cholesterol
Duration of the diabetes
2-h plasma glucose concentration during an oral glucose tolerance test
Age-related changes to cardiovascular system
Heart:
Slowing kinetics of diastolic filling
Left ventricular wall thickening
Left atrial enlargement
Augmentation in the atrial contribution to diastolic ventricular filling
Decreased cardiovascular reserve function
Increased risk for arrhythmia
Altered regulation of cardiomyocyte calcium homeostasis
Arterial system
Diffuse intimal thickening
Stiffening of the aorta and carotid arteries
Endothelial dysfunction

There are no large trials of lipid-lowering interventions specifically in older adults with diabetes. Results have been extrapolated from trials of older adults at risk for cardiovascular disease that include but are not limited to those with diabetes. A statin study in older adults (participants aged 70–82) found a 15% reduction in coronary artery disease events with pravastatin. The Collaborative Atorvastatin Diabetes Study (CARDS) enrolled diabetic patients aged 40 to 75 (mean age 62), and found that atorvastatin was associated with a 36% reduction in acute coronary events; the result remained after adjustment for baseline age. Several trials have investigated statins for the secondary prevention of

cardiovascular disease in adults with diabetes. In general, these trials demonstrated a beneficial effect of statins on lipid profiles and a reduction in cardiovascular events. The only two trials that included an analysis of older adults reported either no change in the magnitude of risk reduction after adjustment for age (cholesterol and recurrent events trial), or an 18% reduction in major vascular events for adults age 65 and older (heart protection study). Cardiovascular prevention with statins, especially secondary benefit, emerges fairly quickly (within 1–2 years), suggesting that statins may be indicated in nearly all older adults with diabetes except those with an end-stage disease and very limited life expectancy. The ACCORD lipid trial found no benefit of adding fenofibrate to statin therapy.

Lowering blood pressure from very high levels (eg, systolic blood pressure [SBP] 170 mm Hg) to moderate targets (eg, SBP 150 mm Hg) reduces cardiovascular risk in older adults with diabetes. However, the ACCORD-BP trial showed no benefit on major adverse cardiovascular events of SBP targets less than 120 mm Hg compared with less than 140 mm Hg, but found a significant reduction in stroke. Other studies found no benefit when lowering SBP to less than 140 mm Hg, and low diastolic blood pressure (DBP) (eg, < 70 mm Hg) may actually be a risk factor for mortality in older adults.

As diabetes and aging both are associated with higher risk for cardiovascular events, and aspirin has well known benefits for secondary prevention of CVDs, aspirin therapy (75–162 mg) seems logical for older adults with diabetes and known CVD. However, aspirin use remains controversial for primary prevention of CVD events in older adults with diabetes as the benefits of aspirin may not outweigh the risk of adverse events such as bleeding.

Microvascular Complications

Older adults are particularly overrepresented among those with microvascular complications due to diabetes. The risk of developing microvascular complications is thought to be proportional to the duration and magnitude of exposure to hyperglycemia and hypertension.

Diabetic nephropathy Lowering blood glucose levels reduces the risk of developing albuminuria and other microvascular diabetes complications. There is no evidence that age of the patient limits this beneficial effect of glucose lowering. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers reduce the rate of progression from microalbuminuria to overt proteinuria and diabetic nephropathy. An ACE inhibitor or angiotensin receptor blocker should be added to a treatment program for any patient with diabetes to prevent progression of nephropathy. Also, rigorous blood pressure control is particularly important for such individuals. However, for older adults with diabetes, the optimal blood pressure target remains unclear as lowering blood pressure to less than 130 mm Hg may cause more harm than benefit.

Diabetic retinopathy Diabetic retinopathy (**Figure 110-7**) is generally classified as either nonproliferative or proliferative. Nonproliferative retinopathy is characterized by nerve fiber layer infarcts (cotton wool spots), hard exudates, intraretinal hemorrhages, and microvascular abnormalities (microaneurysms, dilated or tortuous vessels). Proliferative retinopathy is characterized by the formation of new blood vessels on the surface of the retina and can lead to vitreous hemorrhage. If proliferation continues, blindness can occur through vitreous hemorrhage and traction retinal detachment. With no intervention, visual loss may occur. Laser photocoagulation and intraocular injection of inhibitors of vascular growth can often prevent proliferative retinopathy from progressing to blindness; therefore, close surveillance for the existence or progression of retinopathy in patients with diabetes is crucial. Macular edema may occur at any stage of the diabetic retinopathy, especially in older adults. It is characterized by retinal thickening and edema involving the macula. Retinal edema may require intervention because it is sometimes associated with rapid visual deterioration. Despite clear evidence of efficacy of retinopathy screening by ophthalmologic examination and appropriate intervention, only 50% or fewer of diabetic patients receive recommended annual screening for retinopathy.

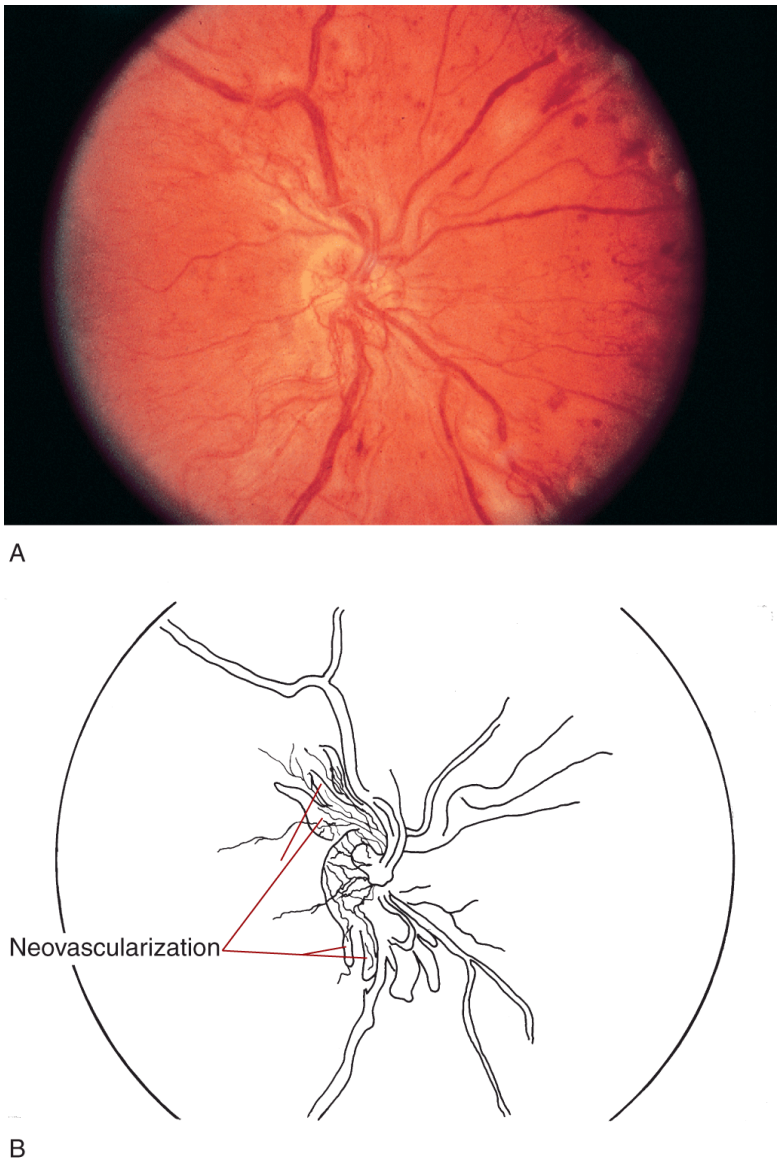


FIGURE 110-7. Proliferative diabetic retinopathy (**A**). In addition to the signs seen in background and preproliferative diabetic retinopathy, neovascularization is seen here coming off the disk (shown schematically in **B**). (From Knoop KE, et al [eds]. *The Atlas of Emergency Medicine*, 3rd ed. New York: McGraw-Hill, 2010, Fig. 3-17. Photo contributor: Richard E. Wyszynski, MD.)

Diabetic neuropathy Diabetic neuropathy can lead to substantial morbidity, including foot ulcerations, infections, and potentially amputations; hence, diabetic neuropathy screening and vigilant foot care are critically important for diabetic patients. Diabetic neuropathy is classified into distinct clinical syndromes. A characteristic set of symptoms and signs exist for each syndrome, depending on the component of the peripheral nervous system that is affected. The most frequently encountered diabetic neuropathies include distal symmetric polyneuropathy; autonomic neuropathy; thoracic and lumbar nerve root disease, causing polyradiculopathies; individual cranial and peripheral nerve involvement causing focal mononeuropathies, especially affecting the oculomotor nerve (cranial nerve III) and the median nerve; and asymmetric involvement of multiple peripheral nerves, resulting in a mononeuropathy multiplex. Diabetic autonomic neuropathy causes significant morbidity and even mortality in patients with diabetes. Neurologic dysfunction may occur in most organ systems and can be manifested by gastroparesis, constipation, diarrhea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia, silent ischemia, and even sudden cardiac death. Cardiovascular autonomic dysfunction is associated with increased risk of silent myocardial ischemia and mortality.

There is no specific treatment of diabetic neuropathy. The treatment of diabetic neuropathy primarily consists of controlling hyperglycemia, which has been shown to be effective in clinical trials, pain control, and vigilant foot care by health providers, and patient's self-monitoring. A number of medications have been used for pain control, but no single drug is universally effective. The only agent shown to be effective in treatment of diabetic neuropathy pain is

pregabalin; other agents are probably effective: gabapentin, amitriptyline, duloxetine, venlafaxine, tramadol, and local capsaicin. Lidocaine patch is possibly effective.

Hyperglycemia

The A_{1c} level is the primary tool for setting goals for hyperglycemia management and monitoring progress toward the goal for most patients. A major challenge in diabetes management is that there is no single best A_{1c} goal for all older adults with diabetes. The relationship between A_{1c} and mortality appears to be U-shaped, rather than linear. Older patients with diabetes have lower risk for death or other complications at an A_{1c} between 6% and 9%, but higher risk at both lower or higher A_{1c}. As older adults with diabetes are quite heterogeneous with respect to their health status, the A_{1c} goal should be individualized based on their risk for complications. The framework described by the expert panel convened by the ADA in 2012 (see **Table 110-3**) can be used to guide A_{1c} targets for older patients with diabetes. Providers should measure the A_{1c} at least two times a year in patients who are meeting treatment goals, and more frequently for those not meeting glycemic goals or who have changes in their therapy. Providers should recognize that certain medical conditions can affect the usefulness of the A_{1c} measurement (see discussion of the A_{1c} test in the section on diagnostic criteria).

Essential components of hyperglycemia management include patient self-monitoring of blood glucose (SMBG) and recognition and self-treatment of hypoglycemia. The ability to perform these tasks is especially important for those individuals being treated with insulin or a sulfonylurea drug. Coexisting geriatric syndromes and comorbidities may create difficulties for older adults to handle these tasks. For example, individuals with hand arthritis may have difficulty operating the SMBG instruments, individuals with vision impairment may have difficulty reading the results, or individuals with cognitive impairment may have difficulty in reacting appropriately to treat hypoglycemia. Therefore, providers should routinely assess the patient's ability to perform SMBG and to appropriately recognize and treat hypoglycemia.

Nonpharmacologic

Exercise An exercise program is an important part of diabetes management, particularly for older patients. Exercise programs can be beneficial by helping to control hyperglycemia, improve physical functioning, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being. The ADA recommends that all adults with diabetes should perform at least 150 min/week of moderate-intensity aerobic physical activity (PA), spread over at least 3 days/week with no more than 2 consecutive days without exercise. As part of the exercise routine, resistance training should be performed at least twice per week.

However, over 60% of adults with type 2 diabetes are not physically active. Older adults are especially likely to be sedentary; only 12% of adults aged 75 or older engage in 30 minutes of PA 5 or more days per week, and 65% report no leisure PA. While many barriers to PA exist, health providers can also leverage motivators to improve exercise participation among older adults (**Table 110-5**). Many different PA intervention approaches currently exist, but no single type of intervention has been shown to be superior. Furthermore, many older adults with chronic medical conditions and geriatric syndromes have been excluded from studies of PA interventions. Additional research on PA is needed to target older adults with diabetes who have functional limitations.

TABLE 110-5 COMMONLY REPORTED PHYSICAL ACTIVITY BARRIERS AND MOTIVATORS BY OLDER ADULTS

BARRIERS	MOTIVATORS
1. Poor health	1. Pleasure from exercise
2. Exercise is not motivating	2. Positive attitude toward exercise
3. Emotions	3. Health
4. Lack of knowledge about exercise	4. Enhanced self-regulatory skills
5. Lack of awareness of being inactive	5. Tools for monitoring own exercise
6. Lack of social support	6. Social support and encouragement
7. Lack of facilities for exercise	
8. Religious and cultural barriers	
9. Weather	

Although exercise training alone has not had consistent effects to improve circulating glucose levels in patients with diabetes mellitus, it is a useful adjunct to drug therapy and may well contribute to enhanced effectiveness of glucose-lowering agents. Given the high prevalence of coronary artery disease in older patients with diabetes mellitus, which may be asymptomatic or atypical in symptoms, it is important for such patients to have medically supervised stress testing before entering any challenging exercise training program. Even PA at levels lower than usually recommended for cardiorespiratory conditioning (eg, below 50% VO_2max) may have enhance glucose tolerance, improve coronary risk factor profile, and reduced cardiovascular-related mortality. Furthermore, patients with lower baseline PA status are likely to experience greater health benefit with a given increase in PA, especially with longer and/or more frequent exercise sessions. Thus, adults with diabetes may benefit from PA of lower intensity but longer duration and/or greater frequency.

Additional issues to consider in an older person participating in an exercise program include the potential for foot and joint injury with upright exercise such as jogging, unstable comorbidities, autonomic neuropathy, peripheral neuropathy or foot lesions that may predispose to injures, and the ability to promptly identify and treat hypoglycemia. Therefore, each patient's exercise prescription needs to be individualized based on their capability to safely participate in an exercise program. A more detailed discussion of the effects of exercise training in older individuals is provided in Chapter 115.

Obesity/diet As part of diabetes management, the ADA recommends that overweight adults with type 2 diabetes lose 2 to 8 kg weight through lifestyle changes. However, the benefits versus risks associated with weight loss in older patients with diabetes remains unclear. Among nondiabetic severely obese adults aged 65 or older, individuals who lost weight by caloric restriction and exercise had the least reduction in lean muscle mass, had increased bone density, and more improvement in physical function than individuals who lost weight by calorie restriction alone or by exercise alone. Therefore, a combination of calorie restriction and exercise may be the best approach for obese older adults with type 2 diabetes.

Dietary intervention has long been a cornerstone of hyperglycemia management. There are many challenges with diet programs in older people, and these are further addressed in Chapter 34 on nutrition. The ADA currently recommends that medical nutrition therapy be included in any diabetes care program, but that it should be individualized for each patient. Fundamental to any dietary recommendation is ensuring that essential dietary needs are met with adequate provision of vitamins and minerals. Over the years, dietary supplements have been proposed to assist in diabetes treatment such as vitamins C, E, or B complex, or minerals such as zinc or chromium to replace possible diabetes-related losses, thereby improving the metabolic state and possibly reducing the rate of various complications. There is, however, no convincing evidence that any of these dietary supplements improves hyperglycemia control or influences diabetes complications. Two aspects of diet need to be addressed in any dietary program: the total caloric intake, which is a key to maintenance of body weight or weight reduction; and dietary composition, or the distribution of fat, carbohydrate, and protein calories.

Caloric Intake Caloric restriction is usually part of the initial approach to management of overweight patients with diabetes mellitus. Because it is generally desirable to maintain muscle and bone mass, the target of caloric restriction is reduction in adiposity, particularly the central adiposity that seems to be critical in mediating obesity-related insulin resistance. One widely accepted criterion for obesity is a BMI over 30 kg/m^2. A serious effort at weight reduction should be considered for any patient with a BMI in excess of 30 kg/m^2. A BMI greater than 25 kg/m^2 is used as a marker of overweight and may also be an indication for caloric restriction. Because of an age-related decline in lean body mass, older individuals may have increased adiposity and central adiposity without being overweight by usual BMI criteria. Documentation of central adiposity by waist measurement or computed tomography may suggest a role for caloric restriction in such individuals. Relatively normal-weight people with central adiposity likely already have diminished lean body mass, which will be further threatened by caloric restriction. For individuals who are not overweight and who do not have central adiposity, there is no role for caloric restriction as part of the hyperglycemia treatment program.

Although many types of diets are successful in the short term in achieving weight reduction, long-term maintenance of weight reduction continues to be a major challenge. Some individuals are able to lose a significant amount of weight and maintain it. Therefore patients should be offered assistance with caloric restriction and supported for a weight loss program. In general, behavioral modification to change dietary habits is the most successful approach long term. Relatively modest weight reduction can have a significant impact on the degree of insulin resistance and on control of glucose levels. Part of the approach should be to set a realistic goal of no more than 5% to 10% reduction of

body weight, even if that will not achieve a normal BMI of less than 25 kg/m . The role for medications to assist weight loss in an older person with diabetes mellitus is uncertain. With the current explosion of knowledge about regulation of food intake in relation to obesity, it is likely that new medications will appear in the market to assist in weight reduction. These should be integrated into diet treatment if justified by results of clear studies of efficacy and risks in an older adult population.

Diet Composition The average American diet includes approximately 45% of calories as carbohydrate, 40% as fat, and 15% as protein. Limited research exists concerning the ideal amount of fat for individuals with diabetes. People with diabetes should follow the guidelines for the general population for the recommended intakes of saturated fat, dietary cholesterol, and trans fat. Increased consumption of foods containing long-chain omega-3 fatty acids, such as fatty fish, and omega-3 linolenic acid is recommended.

Consistency of dietary intake in terms of meal composition, carbohydrate intake, and timing is particularly an issue in patients treated with insulin. The ADA's diet exchange program is one means of providing guidance to such patients to maintain consistency of dietary intake. Nutritional counseling can be particularly helpful in assisting patients to adhere to a dietary program.

Dietary Issues in Older People Caloric restriction is appropriate for healthier overweight and obese older patients as part of the diabetes management. However, it is not appropriate for some older patients who are in a catabolic state due to undernutrition and comorbidities. For such persons, more pressing dietary issues are eating regularly and coordinating food intake with administration of glucose-lowering agents appropriately to avoid hypoglycemia. As summarized in **Table 110-6**, there are a number of special issues that increase an older adult's vulnerability to poor dietary habits. Older adults with a significant mobility limitation and/or lacking transportation are likely to have limited access to healthy and fresh food. Convenient preprepared food that may have high calorie, high cholesterol, and high sodium levels can become a major portion of an older patient's diet. Older persons, especially men living alone, may have limited food preparation skills. The presence of impaired cognitive function may make following a dietary prescription particularly difficult. Furthermore, dietary habits established for a lifetime and often with a cultural background may be particularly difficult to modify. Problems with taste and oral health, which are common in older people, may further limit adaptation to a prescribed diet. Oral health problems can be exacerbated by diabetes, which may increase the rate of periodontal disease. This may be a growing issue as more older adults are keeping their teeth for longer periods. Xerostomia is also more common in older people owing to decreased salivary gland flow, sometimes exacerbated by coexisting medication use. Social isolation (ie, living alone, eating alone), poverty, and functional reliance on others to purchase food are all risk factors for decreased food intake. A social worker may be able to help older adults to access resources from local community social services organizations and involve the patient's caregivers to improve the dietary support.

TABLE 110-6 DIETARY THERAPY: SPECIAL CONSIDERATIONS FOR OLDER ADULTS WITH DIABETES MELLITUS

Access to food
Functional disability
Poor meal preparation skills
Lack of formal or informal support to obtain food
Limited financial resources
Food intake
Decline in taste and smell appreciation
Poor dentition and/or xerostomia
Ingrained dietary habits
Past experience and ethnic food preference
Impaired cognitive function
Depression

Drugs A growing range of therapeutic options enables the treatment program to be tailored to the specific situation of the individual patient, as determined in part by the initial comprehensive assessment carried out. A summary of

currently available glucose-lowering drugs is provided in **Tables 110-7** and **110-8**. Note that among the 12 classes of drugs available, only insulin and sulfonylureas pose a significant risk for hypoglycemia.

TABLE 110-7 ■ NONINSULIN GLUCOSE-LOWERING AGENTS FOR TREATMENT OF TYPE 2 DIABETES

CLASS	ROUTE OF ADMINISTRATION AND USUAL DAILY DOSAGE	PRIMARY PHYSIOLOGIC ACTION	ADVANTAGES	DISADVANTAGES
Biguanide • Metformin	Oral • 500–1000 mg BID • Max 2500 mg/d	• ↓ Hepatic glucose production, possible ↑ insulin-mediated uptake of glucose in muscles	• No weight gain • Minimal hypoglycemia • Likely ↓ in both microvascular and macrovascular events • Extensive clinical experience	• Gastrointestinal side effects (diarrhea and abdominal discomfort) • Lactic acidosis (rare) • Contraindicated in presence of progressive liver, kidney, or cardiac failure
Sulfonylureas • Glipizide • Glyburide • Glimepiride • Gliclazide[a]	Oral • 2.5–10 mg qd BID • 2.5–20 mg qd • 1–4 mg qd • 40 mg qd – 160 mg BID	• ↑ Insulin secretion from pancreatic β-cells	• ↓ Microvascular events • Extensive clinical experience	• Hypoglycemia (esp. with longer half-life: glyburide) • Weight gain • Skin rash (including photosensitivity)
Meglitinides • Repaglinide • Nateglinide	Oral • 0.5–4 mg QAC • 60–120 mg QAC	• ↑ Insulin secretion from pancreatic β-cells	• ↓ Postprandial glucose excursions • Dosing flexibility (before meals)	• Hypoglycemia • Weight gain • Frequent dosing schedule
Thiazolidinediones • Pioglitazone • Rosiglitazone[b]	Oral • 15–45 mg qd • 2–8 mg qd or divided BID	• ↑ Insulin sensitivity	• Minimal hypoglycemia • ↑ HDL-C • ↓ Triglycerides (pioglitazone)	• Weight gain • Edema/heart failure • Bone fractures • ↑ LDL-C (rosiglitazone) • ?↑ MI
DPP-4 inhibitors • Sitagliptin • Saxagliptin • Vildagliptin[a] • Linagliptin • Alogliptin[c]	Oral • 100 mg qd • 2.5 5 mg qd • 50 mg qd BID • 5 mg qd • 25 mg qd	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent)	• Minimal hypoglycemia • Well tolerated • Once a day dosing	• Urticaria/angioedema • ? increased risk of pancreatitis • ? ↑ Heart failure hospitalization • High cost
GLP-1 receptor agonists • Exenatide (Byetta) • Exenatide extended release • Liraglutide • Dulaglutide • Albiglutide • Lixisenatide[a]	Injection • 5–10 μg SC bid • 2 mg SC qwk • 0.6–1.8 mg SC qd • 0.75 mg/0.5 mL SC qwk • 30–50 mg SC qwk • 10–20 μg SC qd	• ↑ Insulin secretion (glucose-dependent) • ↓ Glucagon secretion (glucose-dependent) • Slows gastric emptying • ↑ satiety	• Minimal hypoglycemia • Weight reduction • ↓ Postprandial glucose excursions	• Gastrointestinal side effects (nausea, vomiting) • ↑ Heart rate • ? Acute pancreatitis • C-cell hyperplasia/ medullary thyroid tumors in animals
α-Glucosidase inhibitors • Acarbose • Miglitol	Oral • 25–100 mg TID with meals • 25–100 mg TID	• Slows intestinal carbohydrate digestion or absorption	• Minimal hypoglycemia • ↓ Postprandial glucose excursions	• Generally modest A_{1c} reduction • Flatulence

• Miglitol	• 25–100 mg TID with meals		• ? ↓ CVD events (STOP-NIDDM)	• Abdominal discomfort • Contraindicated in cirrhosis • Frequent dosing schedule (with meals)
Bile acid sequestrant • Colesevelam[d]	Oral • 3750 mg qd (or 1875 mg BID) with meals	• Unclear • ? ↓ Hepatic glucose production • ? ↑ Incretin levels	• Minimal hypoglycemia • ↓ LDL-C	• Generally modest A_{1c} efficacy • Constipation • ↑ Triglycerides • Reduce absorption of fat soluble vitamins • High cost
Dopamine-2 agonist • Bromocriptine, immediate-release form[c]	Oral • 1.6–4.8 mg QAM	• Modulates hypothalamic regulation of metabolism • ↑ Insulin sensitivity	• Minimal hypoglycemia	• Nausea; headache; orthostatic hypotension; potential exacerbation of psychosis • High cost
Amylin-like • Pramlintide[c]	Injection • 60–120 μg SC QAC	• ↓ Glucagon secretion • Slows gastric emptying • ↑ Satiety	• ↓ Postprandial glucose excursions • Weight reduction	• GI side effects (nausea; vomiting) • ↑ Hypoglycemic risk of insulin • Frequent dosing schedule • High cost
SGLT-2 inhibitors • Canagliflozin • Empagliflozin • Dapagliflozin	Oral • 100–300 mg qd • 10–25 mg qd • 5–10 mg qd	• ↓ Glucose reabsorption by the kidney • ↑ Urinary glucose excretion	• Minimal hypoglycemia • Weight reduction • ↓ Blood pressure • Effective at all stages of T2DM • Once-a-day dosing	• Caution in patients with renal insufficiency • Genitourinary infections • Genital yeast infections • Polyuria • Hyperkalemia • Orthostatic hypotension • Pancreatitis

BID, twice a day; CVD, cardiovascular disease; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide 1; SGLT2 inhibitors, inhibitors of sodium glucose cotransporter 2; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; QAC, before meals; QAM, every morning; qd, once daily; SC, subcutaneous injection; STOP-NIDDM, Study to Prevent Noninsulin-Dependent Diabetes Mellitus; T2DM, type 2 diabetes mellitus.

[a]Not licensed in United States.

[b]Prescribing highly restricted in the United States; withdrawn in Europe.

[c]Not licensed in Europe.

[d]Limited use in the United States/Europe.

TABLE 110-8 ■ INSULIN FOR TREATMENT OF TYPE 2 DIABETES

INSULIN AGENTS	ONSET OF ACTION	PEAK EFFECT	DURATION OF ACTION
Long acting • Glargine 100 • Detemir	 • About 2 h • About 2 h	 • No peak • 3–9 h	 • 20–> 24 h • 6– 24 h (duration of action is dose dependent; at ≥ 0.8 units/kg, mean duration of action is longer

			and less variable—22–23 h)
Ultra-long acting • Degludec • Glargine 300	 • About 2 h • About 6 h	 • No peak • No peak	 • > 40 h • 28–36 h
Intermediate acting • Human NPH • Neutral protamine lispro[a]	 • About 2 h • About 2 h	 • 4–12 h • 6 h	 • 18–28 h • 15 h
Short acting • Human regular	 • About 30 min	 • 2–4 h	 • 5–8 h
Rapid acting • Lispro • Aspart • Glulisine	 • 5–15 min	 • 45–75 min	 • 2–4 h
Inhalation powder • Human insulin[b]	 • 5–15 min	 • 50 min (wide variation)	 • 2–3 h

The insulin agents lead to increased glucose disposal and decreased hepatic glucose production. They are nearly universally responsive and likely lead to decreased microvascular risk (UK Prospective Diabetes Study [UKPDS]). Disadvantages are hypoglycemia risks, which vary based on the individual agent's dose and its course of the action.

[a]Only available in the United States in a premixed combination with insulin lispro.

[b]Inhaled human insulin (Afrezza) is contraindicated in patients with chronic lung disease such as asthma or chronic obstructive pulmonary disease (COPD).

Noninsulin agents A growing number of medications other than insulin are available for hyperglycemia management of older adults with diabetes mellitus. **Table 110-7** lists the available drugs with their common dosages and mechanism of action. The table also highlights some advantages and disadvantages associated with each agent.

As the different classes of drugs have different mechanisms of action, there is increasing opportunity to individualize therapy as more is learned about the heterogeneity of type 2 diabetes. All of these agents are effective in lowering glucose levels in clinical trials of patients with type 2 diabetes mellitus. Some of them may also assist in lowering glucose levels as an adjunct to insulin therapy in patients with type 1 diabetes. The potential risks associated with these agents must be considered in relation to the patient's comorbidities and their hypoglycemia risks.

Biguanide Metformin is widely recommended as the first-line oral medication for hyperglycemia in type 2 diabetes, unless there is a specific contraindication. Metformin primarily suppresses hepatic glucose production, and may also enhance peripheral sensitivity to insulin as well. An advantage of metformin is that it rarely causes hypoglycemia when used alone. The most common side effect of metformin is some gastrointestinal (GI) discomfort, which in some patients can be associated with decreased appetite and modest weight loss. While some have viewed this as a potential benefit for a patient on a weight-reduction program, this effect needs to be balanced against the degree of symptoms and the appropriateness of decreased caloric intake and weight loss in a given individual. The biguanide class of drugs is also known to be associated with development of life-threatening lactic acidosis under some circumstances. Although this complication appears to be very rare in patients using metformin, this drug should be avoided in situations that may put people at risk for development of lactic acidosis. The drug should not be used in patients with unstable congestive heart failure, and it should be withheld during acute hospitalization for any major illness that could result in decreased tissue perfusion as a precipitating factor for lactic acidosis. Metformin is recommended to be avoided in patients with renal insufficiency, and traditionally the criteria are a creatinine level greater than or equal to 1.5 mg/dL in men and greater than or equal to 1.4 mg/dL in women. However, given the importance of the agent and rarity of lactic acidosis, metformin is now widely accepted for use in patients with stable chronic kidney disease unless the estimated GFR (eGFR) is below 30 mL/min/1.73 m^2.Monitoring of renal function and perhaps dose adjustment of metformin to account for reduced renal clearance is highly appropriate for older diabetes patients with chronic kidney disease.

Sulfonylurea Drugs Sulfonylurea drugs have been on the market for many years and are still commonly used in older adults with type 2 diabetes. As first-generation sulfonylureas are rarely used, **Table 110-7** only includes second-generation agents. Because of their long history, there is a substantial body of knowledge about the mechanism of action and side effect profile of sulfonylureas. Their primary mechanism of action is to enhance insulin secretion by the β-cells of the endocrine pancreas. There is also some evidence that sulfonylurea drug treatment can enhance sensitivity to insulin in peripheral tissues. While enhancement of insulin action may be a direct effect of sulfonylureas on peripheral tissues, it is more likely that improved sensitivity to insulin is secondary to lowering of glucose levels, as hyperglycemia per se appears to contribute to insulin resistance in patients with diabetes mellitus.

Sulfonylurea drugs have established a long record of safety, with hypoglycemia being the main side effect about which to be concerned. Conservative dosing is recommended for older people. Glyburide has been associated with a higher risk for hypoglycemia in older patients due to its long half-life, so is not recommended in this population. Glipizide may be safer to use in older patients, but all of these drugs should be avoided if there is concern about hypoglycemia. These drugs should not be used in patients with renal insufficiency or with significant liver disease, as they depend on the liver for metabolism and the kidney for excretion. Hyponatremia has also been observed as a complication in some patients. Because of similar risk with use of thiazide diuretics, the combination of thiazide and sulfonylurea drugs should be avoided if hyponatremia is a concern.

α-Glucosidase Inhibitors These agents work by inhibiting the key GI enzyme responsible for breakdown of carbohydrates prior to absorption. They are particularly helpful to reduce postprandial increases of glucose levels and may be a useful adjunct to therapy with other agents. The major side effects are local to the GI tract (flatulence, diarrhea, abdominal pain) because these drugs are not absorbed to any significant degree. These agents may be useful and relatively safe in older people with fairly well-controlled diabetes. One can expect an approximate 0.5% decrease in hemoglobin A_{1c}.

Thiazolidinediones This class of drugs appears to work primarily by enhancing peripheral and hepatic sensitivity to insulin. This mechanism of action complements that of the other drug classes available. As peripheral resistance to insulin is a key part of the metabolic syndrome that predisposes to development of diabetes, use of a drug that targets this abnormality is attractive. These drugs have been shown to have similar efficacy and adverse events in older adults. However, this class of agents can cause fluid retention, peripheral edema, weight gain, and increases the risk for congestive heart failure, so should not be used in patients with heart failure. Use of these agents in any patient at risk for cardiovascular events, such as people with diabetes, is controversial. There is also concern for increased risk of bone fractures in women.

Meglitinide and D-Phenylalanine Derivative Both repaglinide and nateglinide act directly on pancreatic β-cells to rapidly stimulate insulin secretion, but by a mechanism that differs from the sulfonylureas. Both drugs were designed to be used immediately before meals and both improve postprandial glucose levels. No dose adjustments are necessary in older people. Repaglinide should not be combined with gemfibrozil because of increased repaglinide levels. Nateglinide has no known drug interactions, and can be used in patients with renal insufficiency.

Amylin Analog: Adjunct to Mealtime Insulin Therapy Amylin is cosecreted with insulin and is absent in type 1 diabetes and deficient in type 2 diabetes. Pramlintide acetate (Symlin) is an analog of amylin available in the United States that overcomes the tendency of human amylin to aggregate and form insoluble particles. It reduces postprandial glucose in conjunction with mealtime insulin. It is used as an adjunct treatment in some patients who use mealtime insulin therapy and have failed to achieve desired glucose control despite optimal insulin therapy with or without a concurrent sulfonylurea agent and/or metformin. Pramlintide is administered as a subcutaneous injection via an insulin syringe before each major meal, but cannot be mixed with insulin. There is limited experience with pramlintide use in older patients.

Glucagon-Like Peptide-1 (GLP-1) Agents GLP-1 is an incretin, an intestinal hormone that is released with meals and causes glucose-dependent insulin secretion. Two classes of GLP-1 drugs are used clinically.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors and GLP-1 Agonists Native incretin hormones such as GLP-1 have very short half-lives as they are degraded by the enzyme, DPP-4, and thus cannot be used therapeutically. Inhibitors of DPP-4 are orally effective agents that increase and prolong the action of endogenous incretin hormones, and several are now available. These agents are used once daily and result in modest reductions of A_{1c}. Used alone, they rarely cause hypoglycemia, as GLP-1's effect on insulin secretion is reduced as glucose levels fall. They do not cause weight loss, but may have a few nonspecific side effects including nasopharyngitis and headache. Safety and efficacy studies

in older people show no overall differences compared to use in younger patients.

GLP-1 agonists are injectable analogs of GLP-1 that are much less susceptible to DPP-4 and so provide prolonged GLP-1 effects. They can be used in pharmacologic doses. As a result they are more potent at enhancing glucose-dependent insulin secretion. They also suppress glucagon secretion, slow gastric emptying, and reduce food intake, usually resulting in some loss of body weight. Overall, they usually lead to greater reductions of A_{1c} than DPP-4 inhibitors, but also, when used alone, rarely cause hypoglycemia. Exenatide, the first GLP-1 agonist approved for clinical use, became available in 2005. It is a peptide derived from frog skin that has GLP-1 agonist activity. There is now a long-acting form of exenatide that can be administered once a week. More recent GLP-1 agonists are actual modifications of GLP-1 itself. These agents are recommended as adjunctive therapy in patients who have not achieved adequate glycemic control when treated with metformin alone, or with other combinations of therapy. Side effects of GLP-1 agents include nausea, vomiting, and increased heart rate. There are reports of possible associated acute pancreatitis with GLP-1 agents, and development of C-cell hyperplasia or medullary thyroid tumors in animals.

SGLT-2 Inhibitors Two sodium glucose transporters (SGLT) cause glucose reabsorption: SGLT-1 and SGLT-2. SGLT-2 is found only in the proximal tubule of the kidney, and accounts for 90% of the reabsorption of glucose. SGLT-1 is found in the gut and other tissues, and accounts for approximately 10% of glucose reabsorption. SGLT-2 inhibitors are oral agents that lower glucose levels in patients with diabetes by increasing urinary excretion of glucose. They are approved for use in both type 1 and type 2 diabetes. They are used once daily, result in modest lowering of A_{1c}, and rarely cause hypoglycemia. They are contraindicated in chronic kidney disease if the eGFR is below 30 mL/min/1.73 m^2. Use when the eGFR is 30 to 60 mL/min/1.73 m^2 varies with the specific product, but may be best to avoid until more data are available. These agents increase urine volume and sodium excretion, so usually lower BP modestly, but may cause volume depletion. This volume effect may contribute to increased risk for DKA in susceptible patients. There is increased risk for genital yeast infection and urinary tract infection, likely due to the induced glucosuria. Because of these side effects, relatively high cost, and limited duration of experience with these drugs (especially in older adults), their use is usually reserved for situations in which other classes of drugs are not tolerated.

Other Drugs Two other types of drugs are approved for lowering glucose levels: the bile acid sequestrant colesevelam and the dopamine-2 agonist bromocriptine, immediate-release form (Cycloset). Because of limited experience with these drugs (especially in older adults) and modest glucose lowering, they are rarely used.

Combination Therapy Combinations of oral agents or a combination of one or more of these oral/injectable agents with insulin are theoretically attractive because of the different modes of action of the various classes of drugs. Thus, combination therapy addresses various aspects of the pathophysiology of hyperglycemia in diabetes, offering the possibility of synergism in therapeutic efficacy without synergism in toxicity. Many of the potential combinations have been studied, and the glucose lowering effects of such combinations are additive.

For older patients, the logic of combination therapy must be balanced against incremental costs and incremental risks of side effects with each additional drug. Furthermore, the potential for polypharmacy for multiple coexisting conditions such as hypertension, hyperlipidemia, osteoarthritis, and coronary artery disease needs to be considered. The overall treatment goal for the patient must also be kept in mind. Adding a second or third oral or injectable agent without achieving the glycemic goal can be an indication to proceed to use insulin.

Insulin therapy Use of insulin is required in patients with type 1 diabetes mellitus. Insulin is also often used in patients with type 2 diabetes either as a primary hypoglycemic agent or to maintain reasonable glucose control in the hospital setting during acute stressful illness or in the perioperative period when oral agents may be less acceptable or useful.

Advantages of Insulin There are now more than 90 years of clinical experience with use of insulin since its discovery in 1922 and the dramatic demonstration of its effectiveness to save the lives of patients with type 1 diabetes in DKA. Many formulations of insulin with varying duration of action allow individualization of treatment plans. Insulin is the natural hormone that is deficient in relative or absolute terms in diabetes, so its use fits with the overall concept of hormone replacement for endocrine deficiency syndromes. Virtually all forms of insulin currently in use are identical to human insulin or with only slight molecular modifications, so the incidence of allergic reactions is very small. There are virtually no known pharmacokinetic drug interactions and virtually no absolute contraindications to insulin use.

With appropriate dosage modification and monitoring of glucose levels, insulin can be used safely for patients with renal or hepatic insufficiency, patients unable to eat, and during major illness. Insulin itself is relatively inexpensive. However, the overall program of insulin treatment, including use of modern insulin analogs and frequent glucose monitoring, may be expensive. While appropriate insulin use can be a challenge, it encourages active self-care by the

patient and/or caregivers. Finally, and perhaps most important from the point of view of achieving treatment objectives, insulin can effectively lower glucose levels in virtually any patient and, in sufficient dosage, has at least the potential to normalize circulating glucose levels if the regimen intensity is sufficient.

Disadvantages of Insulin One disadvantage of insulin is that it requires injection to be effective, although approval of Afrezza (human insulin) Inhalation Powder provides a rapid-acting insulin option for patients unable or unwilling to perform injections. Injection may represent an insurmountable psychological barrier for a small number of patients. For others, insulin injections may not be feasible owing to functional limitations or insufficient caregiver support. Most older adults can, however, be trained to use insulin appropriately. Insulin is a potent agent, and so the dose must be carefully measured to minimize risk of hypoglycemia. Accidental overdose is also a risk. The most common issue to address with insulin management is risk for hypoglycemia, which is discussed later in the section titled "Hypoglycemia."

Insulin Regimens Before prescribing any insulin, the provider should have a good understanding of the different duration of each agent's glucose-lowering effect. As described in **Table 110-8**, insulin agents have variable onset of action, peak effect, and duration of action; these characteristics are important when selecting which agent to prescribe. Long-acting agents include insulin glargine 100 (Lantus) and detemir insulin (Levemir); ultra-long-acting agents are degludec (Tresiba) and glargine 300 (Toujeo). These four insulins are modified to slow degradation, and have a stable time course of action over 24 hours, so can be given once daily for basal insulin replacement. These long-acting insulin analogs can improve management of diabetic patients, with a low incidence of nocturnal hypoglycemia (especially the two ultra-long-acting agents), no pronounced peak, a long duration of action, and little interpatient absorption variability. Insulin glargine can be dosed as 0.2 units/kg/day subcutaneously once daily or initiated at 10 units once daily and adjusted as needed. Insulin detemir (Levemir) can be initiated at 0.2 to 0.5 unit/kg/day (0.1 to 0.2 unit/kg/day for insulin naïve patients) with one injection daily in the evening or at bedtime.

Insulin aspart (NovoLog), insulin lispro (Humalog), and insulin glulisine (Apidra) were developed as agents with a very rapid onset and short duration of action. These insulins are used for injection just prior to meals and are less likely to result in postmeal hypoglycemia than human regular insulin. They can even be given within 20 minutes after starting a meal. Thus a combination of once-daily, long-acting insulin analog plus premeal injections of a rapid-acting insulin analog may be used for intensive insulin therapy. Similar results can be achieved with such a regimen as with use of a subcutaneous insulin pump system delivering a continuous basal insulin infusion plus bolus injections with meals. Intensive insulin therapy of selected older adults with uncomplicated type 2 diabetes using either of these two regimens achieved an average hemoglobin A_{1C} of 7% over a period of 1 year with minimal adverse effects.

Initiation of Insulin Therapy In developing an insulin treatment regimen for an older adult, it is useful to keep in mind a target total dose range per 24 hours, even though the initial starting dose may be substantially lower. The total daily insulin dose required for a thin patient with type 1 diabetes is typically 0.5 to 1.0 units/kg. The total daily insulin dose for a type 2 diabetes patient with insulin resistance may vary considerably, but up to 1.0 to 2.0 units/kg may be needed to achieve the glucose control target selected. For most such patients, insulin should be initiated at a much lower dose, such as 0.1-0.2 units/kg/day. Of course, there will be substantial variation among individuals in total dose needed, depending on the target treatment goal, patient adherence to lifestyle modification recommendations, degree of insulin resistance, and individual variation of insulin dose pharmacokinetic patterns. Thus, a low starting dose of a single injection of long-acting insulin 10 to 20 units daily, depending on the degree of obesity, is reasonable. Initiation of insulin treatment is usually done as an outpatient and in conjunction with a diabetes education program for the patient and family members.

Frequent follow-up should be provided initially to ensure that the treatment program is progressing smoothly and that hypoglycemia does not occur early on. Given the metabolic stability of most older patients with type 2 diabetes, there is no need to escalate the insulin dose rapidly. Doses can be adjusted in 2- to 5-unit increments every 3 to 5 days (or every 7 days for long-acting insulin analogs) while glucose levels are being monitored. Patients should be prepared from the outset to progress to at least two injections per day, although some patients may achieve the treatment goal with a single dose.

As insulin doses continue to be gradually adjusted upward, an obese patient with type 2 diabetes may need a total well in excess of 100 units/day to achieve an aggressive treatment goal. Also, as doses are increased, it makes sense to add use of a rapid-acting insulin to help cover meal-related increases of glucose levels.

As glucose levels are reduced, insulin sensitivity will likely improve owing to amelioration of the direct effects of hyperglycemia. Thus, an overweight older patient who appears relatively unresponsive to a moderate dose of insulin

initially may begin to respond dramatically to modest further increases of insulin dose. In fact, the patient may progress to having episodes of hypoglycemia even with reduction to a total insulin dose that previously was not very effective. It is apparent that close follow-up with the diabetes care team, careful attention to glucose monitoring, and coaching about symptoms of hypoglycemia are all critical to a successful treatment program. A suitably trained diabetes nurse educator can play a particularly critical role during this phase of treatment.

Combination of Insulin and Oral Agents Insulin therapy can be combined with use of one or more oral agents, although there are little data on such regimens specifically in older adults. One option is use of an evening or bedtime injection of a long-acting insulin analog to target control of the fasting glucose level plus use of an oral agent for daytime use. A comparison of several insulin regimens added to oral therapy among people with type 2 diabetes with mean age of 62 found that less than 25% of patients achieved a stringent hemoglobin A_{1C} target of 6.5%. The average hemoglobin A_{1C} was a little lower with multiple injections of short-acting insulin than with a single injection of detemir insulin, but the rate of hypoglycemia was higher with multiple injections.

There are theoretical advantages to combining insulin with an agent that enhances insulin sensitivity in a patient with insulin resistance or with an agent that reduces meal-related glucose excursions. However, insulin regimens alone with dose adjustments can achieve remarkably similar control of hyperglycemia as combinations of lower doses of insulin with an oral agent. Given the minimal incremental cost of additional insulin to a patient already on insulin and the potential for adverse drug reaction with any addition of a different therapeutic agent, the practical gain of such combination therapy remains unclear.

Another theoretical advantage of combination therapy is that lower doses of insulin can be used to achieve similar glycemic control. It has been argued that high doses of insulin may have adverse cardiovascular effects. Such concerns are based in part on epidemiologic studies demonstrating that (in people without diabetes) higher circulating insulin levels are associated with coronary artery disease. There is also some evidence for direct effects of insulin on the cardiovascular system, some of which might be detrimental. There are, however, no convincing data linking dose of insulin in patients with diabetes to adverse cardiovascular effects.

Another concern about using a high dose of insulin is the potential for weight gain with an intensive insulin treatment program. For patients for whom the indication for insulin is a period of substantial weight loss caused by decompensated diabetes, insulin therapy should be expected to cause weight gain back toward baseline with accompanying restoration of lean body mass. For other patients, it may be necessary to balance the potential risk of weight gain versus the benefit of substantial lowering of circulating glucose levels. In general, weight gain with insulin therapy is modest (in the range of a few kilograms) except for those individuals who have lost substantial weight prior to insulin therapy. By emphasizing and reinforcing lifestyle modifications as insulin therapy is instituted, substantial weight gain can generally be avoided.

Follow-Up Care and Quality Indicators

Diabetes mellitus is a complex disease that requires long-term follow-up and involves multidisciplinary health providers. Routine diabetes care should involve a dilated retinal examination by an ophthalmologist, urine analysis to screen for early nephropathy (urine micro albumin), a foot examination and testing for neuropathy (microfilament test), measurement of fasting lipids, reassessment of blood pressure and smoking status, and review of key aspects of diabetes self-management and education. Measurement of hemoglobin A_{1c} is a very useful way of assessing overall glycemic control and should be performed every 3 to 4 months for most patients. At regular follow-up visits, which can vary from monthly to every 3 months depending on the patient's situation, body weight and blood pressure should be assessed, a review of lifestyle components of the treatment program should be carried out, home glucose monitoring data should be evaluated, interim health problems and psychosocial problems should be reviewed, and appropriate adjustments in the overall treatment plan should be made. For patients with type 1 diabetes or with type 2 diabetes who have an aggressive treatment goal or with multiple diabetes complications, participation by a specialized diabetes care team in the overall management program should be carefully considered.

Frequency and intensity of follow-up depend on the treatment goal for the patient and the type of treatment program that the patient is on. As a means to standardize and improve the quality of health care for diabetic patients, a number of health insurance providers, including the CMS, have adopted certain measurements to assess the quality of diabetes care. Monetary incentives are being used to encourage improvement of quality of care. These measures are designed to assess the care of groups of patients in a given care setting, not the care of individual patients. Furthermore, these quality measures do not include all older patients, some measures are not appropriate for patients with poor health status, and measures that may have a larger impact on older adult's safety are not included. For

example, patients older than age 75 are traditionally excluded from such quality assessment. While the quality measures routinely include the proportion of patients with poor glycemic or blood pressure control (ie, A_{1c} > 9% or blood pressure > 135/90 mm Hg), virtually none of them currently assess the proportion of patients with hypoglycemia events or hypotension events. Diabetes quality measures that are based on the health status of the patient rather than age may be more appropriate for older patients given their heterogeneous health status.

SPECIAL ISSUES

Patient Preference

The overall management of diabetes, including achieving a certain glycemic target and reducing microvascular and macrovascular risks, can be very complex. The process to achieve such goals may be burdensome for older adults who are also likely managing other comorbidities. For some patients, the risks of trying to achieve certain diabetes goals may outweigh their potential benefits. As such, the risks and benefits of each treatment approach should be clearly discussed with the patient and caregiver, and the goals of treatment should be individualized based on shared decision making between the patient, caregiver, and health provider.

Geriatric Syndromes and Functional Disability

Geriatric syndromes (described in Chapters 45–54), including visual impairment, hearing impairment, urinary incontinence, and polypharmacy, occur at higher frequency in older adults with diabetes than those without diabetes. The geriatric syndromes may affect self-care abilities and quality of life as much as, or more so, than traditional diabetes complications in older adults with diabetes.

Dementia, including both Alzheimer type and vascular, is approximately twice as likely to occur in those with diabetes compared with age-matched nondiabetic control subjects. In addition to overt dementia and associated memory loss, more subtle impairments of cognition such as impaired executive decision making are frequent in older people with diabetes. In the Health and Retirement Study of US people aged 53 or older, over 23% of those with diabetes had cognitive impairment, and nearly 20% of those with prediabetes had cognitive impairment. Cognitive dysfunction is linked to hypoglycemia in a bidirectional fashion: cognitive impairment increases the subsequent risk of hypoglycemia, and a history of severe hypoglycemia predicts the future incidence of dementia. A cognitively impaired patient would have a difficult time performing many of the complex tasks required for good diabetes care.

Physical function impairments, such as mobility limitations, are also prevalent among older patients with diabetes. These impairments may limit the patient's ability to participate in physical activity programs and live independently. The prevalence of mobility limitation, which was reported by over 80% of diabetic patients aged 75 or older, has not changed in the last 20 years. In contrast, the macrovascular and microvascular outcomes among diabetic patients have been improving.

Both aging and diabetes are risk factors for functional impairment. Even after controlling for age, people with diabetes have more functional impairment than those without diabetes. The etiology of functional impairment in diabetes may include interactions among coexisting medical conditions, peripheral neuropathy, vision and hearing difficulty, and gait and balance problems. Peripheral neuropathy, present in 50% to 70% of older patients with diabetes, increases the risk of postural instability, balance problems, and muscle atrophy, limiting physical activity and increasing the risk of falls. Other medical conditions that commonly accompany diabetes such as coronary artery disease, obesity, osteoarthritis, stroke, and depression negatively impact physical activity and functionality. Women with diabetes have a higher risk of hip and proximal humeral fractures after adjustment for age, BMI, and bone density.

The relationship between depression and diabetes appears to be bidirectional. Depression, with its associated poor health behaviors and probable physiologic abnormalities, is associated with increased risk of type 2 diabetes (up to 60% per one meta-analysis). Individuals with diabetes have twice the odds of depression as those without diabetes. Patients, especially those who are older, have higher mortality risk if they have both diabetes and depression.

Hypoglycemia

Hypoglycemia is the primary short-term risk of a hyperglycemia treatment program, particularly one that is targeted at achieving near-normal control of glucose levels. Multiple mechanisms exist to maintain adequate circulating glucose levels because glucose is a fuel particularly targeted to meet the needs of the brain and other tissues that are not

dependent on insulin for glucose uptake. Muscle and fat, the major peripheral tissues, have a glucose transport system that primarily depends on insulin for activation. Brain cells, however, have a different type of glucose transporter molecule that is continually expressed on the cell surface and does not depend on insulin for activation. After an overnight fast, when insulin levels are low, the brain does not have to compete with other major tissues for access to glucose. This is in contrast to fat-related fuel such as free fatty acids and ketones, which have ready access to muscle and fat tissue and therefore are less available to the brain. Because of the brain's dependency on glucose as a fuel, it is particularly vulnerable to injury from hypoglycemia, a fact that must be carefully considered as the overall benefits and risks of a diabetes treatment program are reviewed. Thus, an older diabetic adult on a hypoglycemic agent must be counseled to carry glucose tablets or food at all times. An older adult on insulin therapy and their family or caregiver should be given a glucagon emergency kit and teaching on its use.

Hypoglycemia counterregulation Hypoglycemia can be the result of absolute therapeutic hyperinsulinemia, but more commonly is the result of compromised physiologic and behavioral defenses against falling plasma glucose concentrations. **Table 110-9** lists factors that are important in recovery from hypoglycemia by increasing the glucose level either from endogenous sources or from ingestion of glucose. The major source of endogenous glucose is the liver. The liver contributes to recovery from hypoglycemia by increasing glucose production under the influence of counterregulatory hormones. As the insulin effect fades during insulin-induced hypoglycemia, there is a decline in peripheral glucose uptake, preserving more circulating glucose for recovery. The degree of fall of glucose levels determines the magnitude of counterregulatory responses and the speed with which normal glucose levels can be restored. Normally, there is a hierarchy of responses to hypoglycemia with release of counterregulatory hormones such as epinephrine and glucagon occurring before a patient becomes symptomatic and aware of hypoglycemia. The initial symptoms are caused by autonomic nervous system activation with tachycardia, nervousness, and a sweating response, all of which can alert the patient to the need to seek exogenous sources of glucose to facilitate recovery. Hunger is often a part of this behavioral response. However, as glucose levels fall lower and brain cell function becomes compromised, confusion, lethargy, and progression to coma can occur. Fortunately, the response to glucose administration is quick, and dramatic recovery normally occurs.

TABLE 110-9 FACTORS AFFECTING RECOVERY FROM HYPOGLYCEMIA

Hepatic glucose production
Glucose uptake by tissues
Degree of hypoglycemia
Wearing off of drug effect
Counterregulatory hormone responses
Behavioral responses

It is now recognized that the history of the glucose level that the brain is exposed to influences the counterregulatory response mechanisms, perhaps by affecting the brain glucose transport system. For example, there appears to be adaptation to chronic hyperglycemia in patients with diabetes, with resulting elevation of the glucose level at which counterregulatory responses begin to occur. Thus, a patient with diabetes may begin to develop symptoms of hypoglycemia at a glucose level in the range of 80 to 100 mg/dL, well above the symptomatic threshold in nondiabetic individuals of 50 to 60 mg/dL. Conversely, the brain appears to adapt to low glucose levels as well, with a shift downward of the glucose threshold for activation of counterregulatory responses. Prior exposure to hypoglycemia leads to diminished counterregulatory hormone responses. This can set up a vicious cycle by which patients are less able to counterregulate hypoglycemia and have more recurrent episodes. A key issue seems to be that as the glucose threshold for counterregulation drops, it becomes perilously close to glucose levels that can adversely affect brain function. Thus a patient may have a very narrow margin for error, proceeding from relatively normal function without symptoms to profound hypoglycemia and loss of consciousness. This so-called hypoglycemia unawareness syndrome is in part iatrogenic in origin and generally responds to strict avoidance of hypoglycemia.

Hypoglycemia in older patients with diabetes Hypoglycemia is dangerous for older patients as it is associated with increased risks for falls and dementia, and it can be fatal. A self-reported history of severe hypoglycemia (requiring the assistance of another person) predicts increased mortality 5 years later. ED visit rates for hypoglycemia are highest

among adults with diabetes aged 75 or older, almost three times as high as in patients aged 45 to 64. Thus, prevention of hypoglycemia among older adults should be an important priority in the management of diabetes. **Table 110-9** summarizes the risk factors for hypoglycemia in an older patient with diabetes. While some risk factors are physiologic changes associated with aging, which may be difficult to prevent, other risk factors are health behaviors that can be modified through targeted interventions.

Impairment of autonomic nervous system reflexes can contribute to risk for hypoglycemia. Aging is associated with a decrease in β-adrenergic receptor function, which is an important part of the body's counterregulation to combat hypoglycemia. As a result, the sympathoadrenal system that stimulates catecholamine secretion to induce the rapid elevation of blood glucose levels is less effective. Some older patients may have autonomic neuropathy because of long-standing diabetes or other causes, and many older patients are treated with antiadrenergic agents for cardiovascular diseases. For example, β-adrenergic blocking drugs can potentially interfere with counterregulation of hypoglycemia. Given the substantial benefit of β-adrenergic blockade to patients with cardiovascular disease, a combination with hypoglycemic drug therapy should not be viewed as an absolute contraindication, but only as a concern to keep in mind and share with the patient.

Fortunately, the counterregulatory system is redundant. Glucose counterregulation can be maintained quite well as long as there is an adequate glucagon response even when the adrenergic nervous system is blocked. However, normal aging is associated with reduced glucagon responses to hypoglycemia, and older adults with type 2 diabetes have further impairment in glucagon responses to hypoglycemia when compared to age-matched control subjects. The growth hormone response to hypoglycemia is reduced with normal aging, and it is also further impaired in older adults with type 2 diabetes. Epinephrine and cortisol responses are similar or reduced in older adults with type 2 diabetes.

Patients who have relatively poor nutrition and an irregular meal pattern are at increased risk of hypoglycemia, in part because of inadequate maintenance of muscle and liver glycogen stores. Use of alcohol or a sedating agent should be avoided in patients receiving hypoglycemic agents, particularly if an aggressive treatment program is being pursued. Clearly, a cognitive disorder will interfere with recognition of hypoglycemia and possibly affect decisions about responding to hypoglycemia. Patients with underlying renal or hepatic insufficiency may have problems eliminating hypoglycemic agents, particularly an issue for sulfonylurea drugs. Insulin is partly cleared by the kidney, and the insulin dose must often be reduced substantially in patients with renal insufficiency. A patient with severe hepatic insufficiency may have difficulty mobilizing a counterregulatory increase of glucose production. Finally, any complex drug regimen may include agents that influence the pharmacokinetics of hypoglycemic agents, or counterregulatory or behavioral responses to hypoglycemia, and therefore should be an issue when considering risk for hypoglycemia. Older adults often have impairments in vision, dexterity, and mobility, which may limit their ability to self-monitor for hypoglycemia and react quickly to avoid more disastrous consequences.

Despite all of these issues and concerns, many older patients with diabetes can be treated aggressively with low risk for hypoglycemia. The risk for severely hypoglycemia may be reduced by assessing the patient's overall health and social support status thoroughly on a regular basis, providing a strong educational program focused on hypoglycemia recognition and treatment, and considering and perhaps intervening on the risk factors outlined in **Table 110-10**.

TABLE 110-10 RISK FACTORS FOR HYPOGLYCEMIA IN OLDER DIABETIC PATIENTS

Physiologic
Impaired autonomic nervous system function
Diminished glucagon secretion
Kidney or liver failure
Cognitive disorder
Sensory impairment (vision, hearing)
Functional impairment (mobility, hand dexterity)
Behavioral
Poor or irregular nutrition
Use of alcohol or other sedating agent
Others
Polypharmacy

Hyperosmolar Coma and Diabetic Ketoacidosis

DKA and hyperosmolar coma are the extreme examples of impaired metabolism in patients with diabetes mellitus. DKA is relatively uncommon in older people, but it can occur in an older patient with type 1 diabetes mellitus. As in younger people, the hallmarks of DKA are substantial hyperglycemia, hyperosmolarity, and volume depletion, and the presence of systemic acidosis caused by marked elevation of ketoacids. Ketoacids result from metabolism of elevated free fatty acids released by lipolysis as a result of severe insulin deficiency. DKA can occur in a patient with type 1 diabetes when insulin is inappropriately discontinued, but in an older adult, this may be a result of a major underlying illness that interferes with the patient's self-care capability. In the setting of severe coexisting major illness in an older individual and decreased tissue perfusion, lactic acidosis may occur in the setting of hyperglycemia. It is important to document the presence of significant ketonemia to ensure that DKA is contributing to the systemic acidosis observed. Treatment of DKA should focus on immediate insulin replacement to inhibit lipolysis and reverse the ketoacidosis, vigorous replacement of fluids and salt to replace losses, and a thorough evaluation to identify underlying illness. Careful monitoring is required to ensure response and particularly to monitor the cardiovascular system for signs of failure.

Hyperosmolar coma, which occurs primarily in older people, is characterized by marked hyperglycemia, hyperosmolality, severe volume depletion, and associated renal insufficiency. The mortality rate is high because there is often a severe underlying illness such as pneumonia or a cerebrovascular accident. Metabolic acidosis is notably absent, or, if present, it is caused by lactic acid rather than ketoacids. The reason for failure to mobilize fatty acids despite severe insulin deficiency in these patients is unclear. While insulin should be provided as part of the initial therapy, the focus should be on volume and sodium replacement and on identification and intervention for major underlying illness. In fact, as volume status is corrected, in the presence of recovering renal function, glucose levels can fall precipitously. Therefore attention must be paid to avoidance of hypoglycemia.

Diabetes in Long-Term Care Facilities

Diabetes mellitus is very common among nursing home residents. Based on national surveys the prevalence of diabetes mellitus in nursing homes is 26% in men and 22% in females. Residents in nursing homes who have diabetes, compared to those without diabetes, tend to have a greater disease burden, are more likely to be frail and have cognitive decline, and have an increased risk for aspiration pneumonia and fecal incontinence. Because of the degree of disability and limited life expectancy of these patients, basic diabetes care should usually be the goal, rather than a stringent set of goals for A_{1c}, BP, or lipids. In fact, based on a number of observational studies, residents in long-term care facilities have better survival if their A_{1c} levels are higher, between 8% and 9%.This goal is consistent with the ADA Consensus panel recommendations listed in **Table 110-3**.

When prescribing medications, particularly hypoglycemic and hypotensive agents, various nursing facility limitations should be considered: who administers the medications (ie, registered nurses [RN] vs non-RN aides [eg, licensed practical nurse or pharmacy technician]), the staff to resident ratio, training of the staff to understand the risks associated with these agents, the ability of the staff to recognize and treat hypoglycemic symptoms rapidly, and the ability to provide residents' meals in a timely fashion after administration of rapid-acting insulin. Except for residents who have type 1 diabetes, few nursing home residents with diabetes require frequent insulin injections as tight glucose control is not recommended. However, a simple short-acting insulin regimen may be safer for those patients who require insulin but whose nutrient intake is very irregular. Also, short-acting insulin can be given immediately after nutrient ingestion, which allows adjustment for the actual intake.

As undernutrition may be a much more important health problem than obesity for nursing home patients, diet therapy should focus on matching caloric intake to meet nutritional needs rather than restriction of calories. Nursing home residents may lose weight for a variety of reasons, and weight loss in older adults is associated with increased risk of death. Some common causes of weight loss in nursing home residents are depression, swallowing problems, poor dentition, restrictive diet (eg, low-salt and low-cholesterol diet), and occult infections. Thus, assessment for preventable causes of weight loss should be performed. Furthermore, for a nursing home patient with limited remaining life expectancy, the priority should be to stimulate the patient's appetite and take advantage of opportunities for the patient to enjoy life, rather than introduction of unnecessary dietary restrictions. Consistency of caloric intake is important for a patient treated with insulin and may be a particular challenge in a disabled nursing home resident. The facility dietician can play a key role by educating facility aides and nurses in appropriate estimates of consumption.

Similarly, regular physical activities should be provided for residents in a safely monitored environment. Both aerobic and resistance exercise may improve physical function, decrease injurious falls, decrease depression, improve

cognition, and decrease agitated behavior in this setting.

In nursing home patients already at high risk for developing urinary tract infection, diabetes may increase this risk because of bladder dysfunction secondary to autonomic neuropathy. Particular attention should be paid to keeping the bladder free of infection and carrying out intermittent catheterization as needed. Careful attention to skin and foot care is important to avoid problems with healing and infection.

Palliative and End-of-Life Care

Appropriate diabetes care for patients at the end of life currently lacks quality standards and guidance on best clinical practices. There is a lack of well-designed studies to provide insight into goals for glucose regulation, diabetes self-management, or use of particular glucose-lowering therapies for patients at the end of life. Diabetes UK (formerly British Diabetes Association) commissioned a panel of professional groups and developed recommendations on diabetes care at the end of life. These recommendations are endorsed by the UK National Health Service. The panel recognized that no published evidence justifies any particular glucose or hemoglobin A_{1c} target for end-of-life diabetes care management. The optimal glucose range will vary according to the stage of illness, ability of the patient to eat and drink normally, the presence of hypoglycemia, the nutritional status, and the treatment given. The panel recommended glucose control target ranges between 6 mmol/L (108 mg/dL) to 15 mmol/L (270 mg/dL). Several principal goals for diabetes care of patients at the end of life were recommended as described in **Table 110-11**.

TABLE 110-11 RECOMMENDED PRINCIPAL GOALS FOR DIABETES CARE OF PATIENTS AT THE END OF LIFE

Be respectful and supportive

- Provision of an appropriate level of intervention according to stage of illness, symptom profile, and respect for dignity
- Supporting the individual patient (in diabetes self-management) and caregivers to the last possible stage

Avoid pain or discomfort

- Provision of a painless and symptom-free death
- Tailoring glucose-lowering therapy and monitoring to minimize burden of the treatment and adverse treatment effects
- Avoiding metabolic decompensation and diabetes-related emergencies such as frequent and unnecessary hypoglycemia, diabetic ketoacidosis, hyperosmolar hyperglycemic state, or persistent symptomatic hyperglycemia
- Glucose target between 6 mmol/L (108 mg/dL) and 15 mmol/L (270 mg/dL)
- Avoiding foot complications in frail, bed-bound patients with diabetes
- Avoiding symptomatic clinical volume depletion

Tailoring treatment plan according to 4 stages of the end of life

- Stage A—Diagnosis stable with year plus prognosis
  - Evaluate the time to benefit of some cardioprotective therapies, and consider withdrawal or dose reductions on some therapies (eg, ACE inhibitors/ARBs, aspirin, statins)
  - Evaluate oral intake and weight stability, and consider dose reduction of antiglycemic agents to avoid hypoglycemia
- Stage B—Unstable/advanced disease with months prognosis
  - Simplify antiglycemic regimens
  - Relax dietary restrictions, particularly among patients with poor oral intakes
- Stage C—Deteriorating with weeks prognosis
  - Discuss with caregivers and patients, consider relaxing glucose targets
  - Avoid long-acting sulfonylureas
- Stage D—Final days/terminal care with days prognosis
  - For patients with type 2 diabetes and diet controlled/metformin treated → stop monitoring glucose
  - For patients with type 2 diabetes on other oral antiglycemics/insulin/GLP-1 agonists → stop pills and GLP-1 injections, and consider stopping insulin depending on dose.
    - If insulin stopped, urinalysis for glucose daily → if over 2+ glucose, check capillary blood glucose
      - If blood glucose over 20 mmol/L (360 mg/dL) → 6 unit rapid-acting insulin and recheck glucose after 2 h

- If > 2 doses of rapid-acting insulin per day → consider daily long-acting insulin (eg, glargine)

If insulin to continue → once-daily morning dose of glargine based on 25% less than total previous daily insulin dose

- Check daily blood glucose after an afternoon snack → ↓ insulin by 10%–20% if < 8 mmol/L (144 mg/dL) or ↑ insulin by 10%–20% if > 20 mmol/L (360 mg/dL)

For patients with type 1 diabetes, continue insulin at reduced dose and monitor and adjust dose as above.

Diabetes UK, https://www.diabetes.org.uk/upload/Position%20statements/End-of-life-care-Clinical-recs111113.pdf.

Based on the prognosis, the panel made detailed recommendations on different approaches to control glucose. Patients with diabetes near the end of life may still require hypoglycemic drugs and monitoring in order to stay comfortable. Severe hyperglycemia such as 350 mg/dL or higher may impair comfort if it leads to thirst, dehydration, infections, urinary incontinence, and falls. A more complicated glucose-lowering regimen that requires more monitoring may be appropriate if the prognosis is several months to a year, whereas minimizing glucose-lowering treatment and monitoring needs would be appropriate if the prognosis is days to weeks.

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Chapter 111

Dyslipoproteinemia

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Learning Objectives

- Describe changes in lipoproteins with aging and their mechanisms and impact on cardiovascular disease.
- Review the therapeutic options to address dyslipidemia.
- Address special considerations germane among older individuals.

Key Clinical Points

1. **Total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) concentrations increase in both men and women from the third to seventh or eighth decades of life, with more pronounced increase in LDL-C concentration in women and important changes in lipoprotein classes of women at menopause. Typically, there is a decline in LDL-C and total cholesterol concentration in oldest age cohorts.**
2. **Dyslipidemia is a well-established risk factor for cardiovascular disease in older adults age 60 to 80 years. However, there are limited data in patients above the age of 80.**
3. **Current recommendations for screening and treatment of dyslipidemia that employ risk-based algorithms represent a fundamental change in the approach to cardiovascular disease management. Using this approach, potentially millions of adults over the age of 75 are candidates for statin therapy based solely on their age. We advocate a more measured patient-centric approach where the patient and clinician together discuss individual treatment preferences and goals of care.**

INTRODUCTION

Dyslipoproteinemia encompasses a range of disorders of lipoprotein metabolism that include both abnormally high and low lipoprotein concentrations, as well as abnormalities in the composition of the lipoprotein particles. Dyslipoproteinemias are clinically relevant in older adults primarily due to their role in the pathogenesis of atherosclerotic cardiovascular disease (ASCVD), which includes coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease (PAD), and chronic renal disease. Older patients account for greater than 75% of total cardiovascular disease (CVD) mortality and 50% of all acute myocardial infarctions (MIs) in the United States. Although CVD morbidity and mortality have declined over recent decades, the percent reduction of CVD events is nearly 50% less in older patient groups. Dyslipidemia is a risk factor for ASCVD in older adults aged 60 to 80, and strong outcome data support pharmacologic therapy in this age group; however, the data are more limited among those above 80 years.

The American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines issued new guidelines in 2013 for the management of dyslipidemia in adults. These guidelines have explicit treatment recommendations for adults across the age span based on the presence or absence of clinical ASCVD, and the use of pooled cohort equations to estimate the 10-year risk of developing ASCVD. These guidelines make stringent recommendations for patients with CHD equivalents such as diabetes and renal disease, and for other high-risk

individuals with multiple CVD risk factors. The guidelines highlight that heart-healthy lifestyle habits should be encouraged for all individuals. In addition, they emphasize the use of statins to treat dyslipidemia and reduce ASCVD risk. The recommendations for statin therapy for individuals at elevated absolute risk for CVD represents a paradigm shift from prior Adult Treatment Panel III guidelines that emphasized treatment thresholds for LDL-C. Application of the 2013 guidelines will substantially increase the number of older adults for whom statin therapy is recommended, especially using the threshold of 7.5% 10-year mortality risk for primary prevention of ASCVD, since most individuals above 75 years would qualify for statin therapy based solely on their age. Additional research is needed to determine the most meaningful guidelines by which to risk stratify and identify older adults who would benefit the most from primary and secondary ASCVD preventive therapy and minimize risk for untoward drug side effects.

Given the high prevalence of physical inactivity, hypertension and type 2 diabetes in older people, secular changes in dyslipoproteinemias, and their heightened metabolic risk for ASCVD, the geriatrician must have a firm understanding of the pathogenesis and treatment of dyslipoproteinemia. In this chapter we review the regulation of lipoprotein metabolism, the epidemiology and mechanisms underlying age-associated changes in lipoprotein levels, clinical trial data, as well as controversies regarding the screening and treatment of primary and secondary dyslipidemias in older people.

PATHOPHYSIOLOGY OF DYSLIPOPROTEINEMIA

Lipoprotein Subclasses and Apolipoprotein Metabolism

TGs and cholesterol of both exogenous (dietary) and endogenous origin are transported in the bloodstream as lipoprotein particles composed of neutral lipids (cholesterol esters [CE] and TGs), polar lipids (phosphatidylcholine, sphingomyelin, and free cholesterol), and specialized proteins called apolipoproteins (apos). Ultracentrifugation identified five major subpopulations of lipoproteins differing in composition, metabolic function, and atherogenic potential, from the least dense chylomicrons, very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), and LDLs, to the high-density lipoproteins (HDLs).

The distribution of apos among these lipoprotein classes determines their metabolic and cardioprotective effects. Most apos are soluble and contain amphipathic helices that mediate binding to lipid surfaces. ApoA-I and apoC-I are activators of cholesterol esterification via lecithin-cholesterol acyltransferase (LCAT). This enzyme is central to reverse cholesterol transport (RCT), the process by which cholesterol is transferred from peripheral tissues to the liver for disposal or recycling. LCAT converts cholesterol to its ester, which does not transfer to membranes and lipoproteins, and also converts HDL from a disk to a sphere with a core containing mostly CEs. Since peripheral, extrahepatic tissues synthesize, but cannot degrade cholesterol, RCT is essential for CE efflux to HDL and esterification to produce a mature form of HDL that is eventually cleared from the circulation by the liver. This prevents the lipotoxic, pathologic state caused by cholesterol accumulation in macrophages and other tissues. Therapies that enhance LCAT activity should reduce cellular cholesterol accumulation, and mitigate plaque formation and atherosclerosis. ApoC-II stimulates lipoprotein lipase (LPL), the rate-limiting enzyme mediating hydrolysis of chylomicrons and clearance of VLDL-TG, preventing hypertriglyceridemia in patients with hyperlipoproteinemia phenotypes. These hyperlipoproteinemia phenotypes are defined by the degree of hypercholesterolemia and hypertriglyceridemia: one is the monogenic deficiency in LPL causing lipemia and chylomicronemia with pancreatitis (type I); another is familial hypercholesterolemia, an autosomal dominant disorder of absent or grossly malfunctioning LDL receptors; and four are polygenetic familial hyperlipidemias called combined hyperlipidemia with elevated TG and cholesterol (type IIB), familial dysbetalipoproteinemia (type III hyperlipoproteinemia), primary hypertriglyceridemia (type IV—high TG), and mixed hyperlipidemia (type V—high TG with chylomicronemia). ApoC-III inhibits LPL and levels correlate directly with plasma TG levels; mutations causing the loss of apoC-III function are associated with reductions in plasma TG, elevated HDL-C, and protection from CVD. ApoA-V occurs at low levels in human plasma, and it may be antilipemic.

ApoE is the ligand for the hepatic uptake and processing of IDL and chylomicron remnants, modulating the metabolism of apoB-containing lipoproteins present in chylomicrons, VLDL, and HDL. The gene that codes for apoE is polymorphic, with single amino acid substitutions resulting in E2, E3, and E4 isoforms and thus the six common apoE genotypes: E2/2, 2/3, 2/4, 3/3, 4/3, and 4/4. The relative frequencies of the 2, 3, and 4 alleles in adult populations are approximately 8%, 78%, and 14%, respectively. LDL-C concentrations are in part determined by the *apoE* gene locus. Individuals with the apoE2/3 genotype on average have LDL-C concentrations 20% lower than the common

apoE3/3 genotype, whereas subjects with apoE4/3 have LDL-C concentrations 10% higher than apoE3/3. Gene-gene interactions between the apoE polymorphism with other loci (cholesteryl ester transfer protein [CETP], cholesterol 7-α-hydroxylase [CYP7A1], and others) as well as gene-environment (exercise and dietary factors) interactions influence HDL levels. Because only a minority of apoE2 homozygous subjects have familial dysbetalipoproteinemia, additional genetic and/or environmental factors are necessary for the clinical manifestation of these monogenetic variants.

ApoB is required for the synthesis and assembly of TG-rich VLDL in the liver, and is the ligand for low-density lipoprotein receptor (LDLR)-mediated clearance of LDL particles from the blood. The apoB-48 and apoB-100 isoforms play crucial roles in the metabolism of plasma lipoproteins. ApoB-48 is a truncated form essential for the formation of chylomicrons and the absorption of dietary fats in the intestine. ApoB-100 contains the ligands for the cellular uptake of LDL via its receptor and is the major apo in all of the atherogenic lipoproteins—LDL, IDL, lipoprotein(a) [Lp(a)], and TG-rich remnants of VLDL and chylomicrons, and because of this, elevated plasma levels of apoB-100 are a strong predictor of increased cardiovascular risk.

The molecular mechanisms regulating apoB-containing lipoproteins, and their cellular uptake and clearance from plasma, are central to developing therapeutic targets for the prevention of CHD. For example, Lp(a) is a cholesterol-rich lipoprotein particle similar to LDL in which apo(a) is covalently bonded to apoB by a disulfide bridge. Its atherogenic pathogenicity is partially attributed to the strong homology of apo(a) and plasminogen, linking atherosclerosis and thrombosis.

The downstream health-related effects of dysregulated apo- and lipoprotein metabolism are affected by genetics, lifestyle (dietary and activity habits), comorbidities, insulin resistance, and muscle and adipose tissue metabolism. These are important therapeutic targets for the prevention of ASCVD, diabetes, and renal failure, all prevalent diseases in older people.

Cellular Mechanisms Underlying Dyslipoproteinemia

Lipoprotein metabolism begins with the absorption of exogenous dietary fat from the gastrointestinal (GI) tract, and the endogenous synthesis and secretion of TG-rich lipoproteins by the liver. The distribution of apos among lipoproteins affects their metabolic regulation by enzymes and lipid transfer proteins, thus making them central to the pathogenesis of the dyslipoproteinemias and the development of atherosclerosis. Knowledge of the metabolic regulation of the lipoprotein subclasses and apos by enzymes, cofactors, transfer proteins, and various receptors provides a framework for understanding the pathogenesis of disorders of lipoprotein metabolism. The primary and secondary forms of dyslipoproteinemia arise either from accelerated synthesis, decreased degradation of the lipoproteins, or both at the key regulatory sites of lipoprotein metabolism. The primary dyslipoproteinemias can be caused by biochemical defects resulting from single-gene mutations, polygenetic effects, or multifactorial interactions that include environmental and lifestyle factors. Secondary dyslipidemias, caused by systemic disorders such as obesity, diabetes, hypothyroidism, renal and liver disease, are more common in older people. Age, environmental factors, diet, and other lifestyle factors affect the phenotypic expression of both the single-gene and polygenetic disorders. The prevailing dogma is that dyslipidemias arising from the single-gene mutations are associated with an earlier age of onset and expression of clinical atherosclerosis than the polygenetic disorders. Strategies for developing drug and dietary treatments for hyperlipidemia and the prevention of CVD in older people should consider the overall medical condition of the patient, including familial and secondary causes of dyslipidemia, medications, and the assessment of hepatic and renal function, as well as adipose and muscle metabolism, key organs underlying the regulation of dyslipoproteinemia. In summarizing these metabolic processes, we highlight key regulatory sites in lipoprotein metabolism, its CVD and metabolic consequences, and potential sites for therapy (**Figure 111-1**).

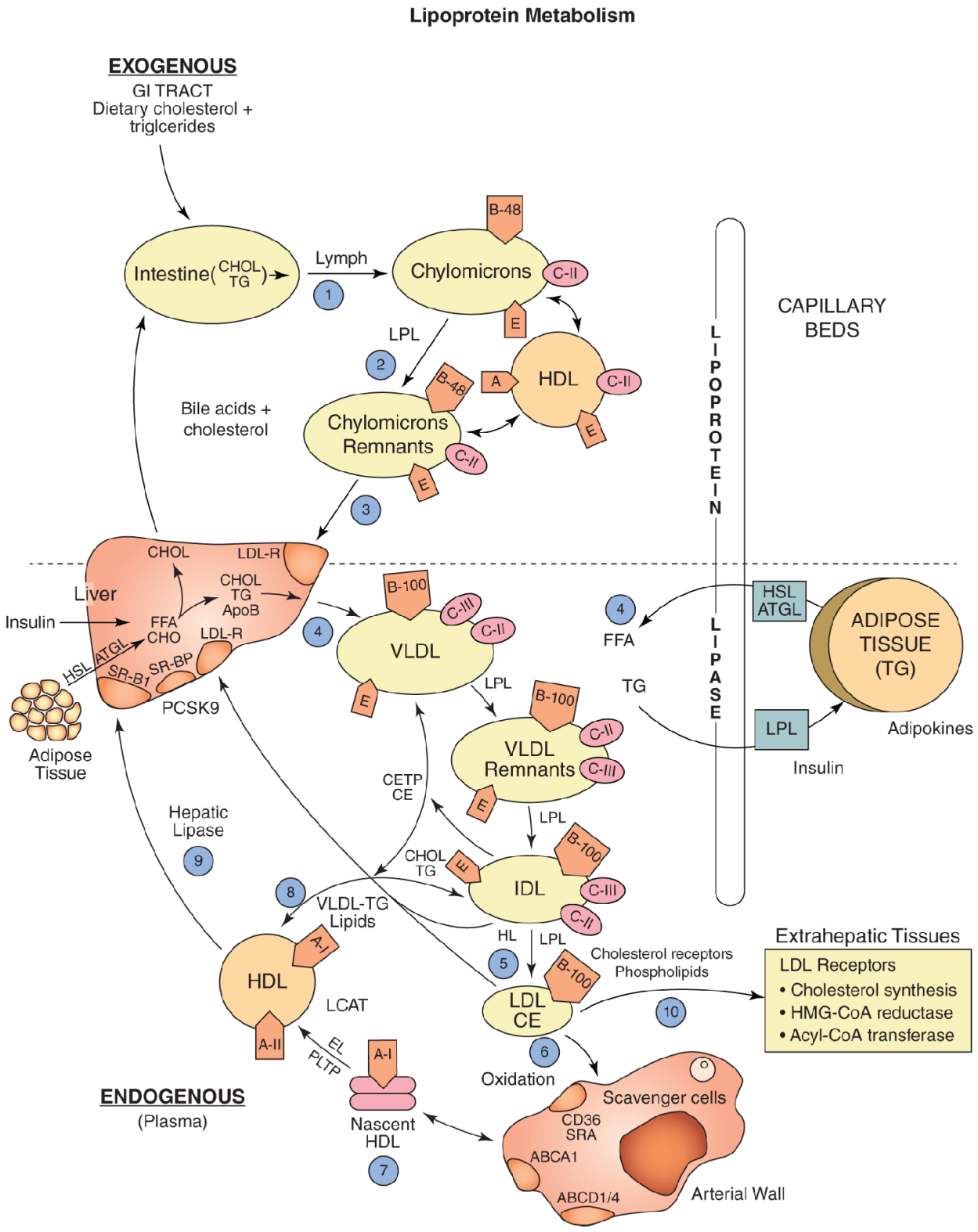


FIGURE 111-1. Lipids in the diet are hydrolyzed in the small intestine, and the resultant fatty acids and monoglycerides are repackaged with apoB-48 into TG-enriched chylomicron particles by the intestinal enterocytes and secreted into the lymphatics (1). Dietary chylomicrons bypass the liver and enter the plasma via the thoracic duct, and AHA diets low in saturated fat attenuate their atherogenic metabolic effects. Chylomicrons acquire apoE and apoC-II from HDL, and are hydrolyzed by LPL to smaller TG-depleted, cholesterol-rich chylomicron remnants (2). These apoB-48 and apoE-enriched remnants are taken up by the liver primarily by the LDL receptor-related protein receptor (LDLR) and degraded (3). Endogenous TG is synthesized in the liver from carbohydrate and free fatty acids (FFA) derived from adipocyte hydrolysis by hormone-sensitive lipase (HSL) and adipocyte TG lipase (ATGL), precursors assembled in the Golgi with apoB-100, E, C-II, C-III, and secreted as TG-rich very low-density lipoproteins (VLDL-TG) (4). Obesity-associated hyperinsulinemia stimulates VLDL production, hence, insulin sensitizers and fibric acid derivatives that block VLDL assembly lower insulin-mediated VLDL synthesis and production, and raise LPL to enhance VLDL-TG hydrolysis to apoB-100 and apoE containing VLDL remnants and IDL. These remnant lipoproteins are taken up by scavenger cells or apoE-specific hepatic receptors and degraded in the liver. ApoC-III inhibits LPL-mediated TG

hydrolysis and blocks the clearance of apoB-containing lipoproteins from the plasma. The VLDL and IDL remnants are removed irreversibly or hydrolyzed further by LPL and hepatic lipase (HL) to IDL and LDL cholesterol-rich particles (5) to produce apoE, TG-poor LDL particles containing apoB, and CE. The hydrolysis of TG-rich VLDL by LPL also generates free cholesterol and phospholipids (PL), substrates for LCAT. Cholesterol is removed from LDL by the LDLR or oxidized and taken up by CD36 scavenger receptors on macrophages to generate an intracellular free cholesterol pool in the arterial wall (6). Nascent HDL interacts with the ATP-binding cassette transporter-1 (ABCA1) on peripheral lymphocytes to remove excess cholesterol from cells and then binds with apoA-I, the principal activator of LCAT, to esterify cholesterol to form large, spherical cholesterol-ester-rich HDL_2 particles (7). Endothelial lipase (EL), a member of the *LPL* gene family derived from the vascular endothelium, hydrolyzes phosphoglycerol lipids from HDL, reducing HDL size and concentration. Phospholipid transfer protein (PLTP) also transfers phospholipids from lipoproteins to modify the composition of HDL and its conversion into large or smaller particles. Cholesterol is then transported back to the liver directly by HDL or via transfer to apoC-II containing VLDL or IDL by the cholesterol ester transfer protein (CETP). The CETP-mediated interaction of VLDL with HDL exchanges apoCs and apoE from HDL to VLDL, CE from HDL to VLDL and TG from VLDL to HDL. In hyper-TG states a larger pool of TG exchanges with a small pool of HDL- and LDL-CE, resulting in TG-enriched VLDL, LDL, and HDL (8). This lowers the apoA-I content and stability of HDL to reduce HDL levels and change the structure of LDL to a sphere, which impairs binding to the LDLR. Hepatic lipase hydrolyzes TG and PL-enriched HDL, converting HDL_2 back to smaller HDL_3 particles, reducing the efficient clearance of cholesterol from cells (9).

The association of hypertriglyceridemia with atherogenic VLDL remnant particles, low HDL-C, and high apoC-III suggests that TG is an important biomarker of CVD risk. This is supported by the finding that loss-of-function mutations in apoC-III are associated with dramatic reductions in TG, VLDL remnants, and LDL-C levels, increases in HDL-C, and a reduced incidence of CVD. Furthermore, a gain-in-function mutation of LPL is associated with lower TG and higher HDL-C, and is used as gene therapy for severe chylomicronemia. In contrast, clinical trials with CETP inhibitors that increased HDL-C by greater than 50% and reduced LDL-C and TG levels by 10% to 25%, or with niacin that increased HDL-C by 17% and decreased TG and LDL-C were terminated because of the lack of reduction in CVD outcomes. Mutation studies of LCAT, ABCA1, and SR-B1 deficient mutations also found no association with CVD risk or clinical outcomes, despite higher HDL-C levels. This has led some to question the importance of RCT in the protection against CVD.

Statins' ability to inhibit endogenous cholesterol synthesis reduces intracellular cholesterol and LDL-C beyond that achieved by other lipid-lowering drugs and reverse cholesterol transport. However, this process upregulates sterol regulatory-element-binding proteins (STRBPs) thus increasing the transcription of LDLR and serine protease proprotein convertase subtilisin/kexin type 9 (PCSK9) by approximately 40%. PCKS9 is secreted by the liver and small intestine into the plasma and binds to LDLRs, increasing their degradation to limit intracellular cholesterol removal. This would presumably blunt the LDL-C-lowering effect of statin therapy. Clinical trials with PCSK9 inhibitors alone or in combination with statins are promising, with approximately 40% to 65% reductions in LDL-C, good clinical tolerance, and no untoward effects on liver, nonhepatic tissues, cognition, or muscle.

LIPOPROTEINS AS RISK FACTORS FOR CORONARY HEART DISEASE

Many case-control and prospective studies examining lipoprotein risk factors for atherosclerosis focus on the impact of the traditional lipoprotein risk factors, that is, total cholesterol, LDL-C, and HDL-C. However, many older individuals have abnormalities in lipoprotein metabolism that are not detected by routine lipid profiles. These dyslipidemic syndromes include the apoE4 genotype, elevated levels of Lp(a), and the atherogenic LDL pattern B phenotype. These disorders are more common than familial heterozygous hypercholesterolemia and combined dyslipoproteinemia, and thus play major roles in the pathogenesis of ASCVD in older individuals. This section reviews the evidence that dyslipidemia is a risk factor for ASCVD in older people.

Elevated Total and LDL-C Concentrations

Elevated levels of total and LDL-C clearly increase the risk for ASCVD in middle-aged men. However, the evidence supporting elevated levels of LDL-C as a risk factor for CVD in older people, particularly older women, is mixed. The relative risk for CHD in older individuals with hypercholesterolemia is lower than that observed in men less than 65 years. There are several factors that account for these disparities: first is the nonlinear relationship between cholesterol levels, CHD events, and total mortality, that is, a J- or U-shaped curve, wherein individuals with either the highest or the lowest cholesterol levels are at increased risk for CHD, as compared to those with intermediate levels; second is that measured cholesterol levels may not accurately reflect the lifelong average exposure to plasma cholesterol in an older person, leading to spurious conclusions about the association between cholesterol levels and CVD outcomes. For example, at age 70, one's measured total cholesterol level may be 220 mg/dL, whereas the average cholesterol level

over the adult lifespan could be 180 or 250 mg/dL. As a result, longitudinal studies that examine both the baseline cholesterol level and its change over time are needed to provide insight into the predictive values of cholesterol levels for subsequent CHD and all-cause mortality in the older adult population. Cholesterol levels may decrease in older age due to the presence of underlying multimorbidity, malnutrition, inflammation, and anorexia-associated weight loss of chronic disease, all of which are associated with mortality. Furthermore, in a Finnish 30-year longitudinal study such a U-shaped relationship was described between the *change* in cholesterol level and coronary and all-cause mortality.

The relative risk of hypercholesterolemia for ASCVD morbidity and mortality has received much attention, but the attributable risk is a more useful parameter for making clinical decisions regarding treatment of hypercholesterolemia in older people. In this context, attributable risk is the difference between the CHD mortality rate in subjects with a high lipid concentration and the CHD mortality rate in subjects with a lower or desirable lipid concentration. It provides an estimate of the degree to which cause-specific (in this case CHD) mortality would be lowered if the putative risk factor were lowered to a normal level. Unlike relative risk, attributable risk is very sensitive to the underlying mortality rate in "normals," that is, the mortality rate in subjects with normal or desirable cholesterol levels. The MRFIT data permits an analysis of the variance in the relative and attributable risk of hypercholesterolemia for CHD mortality with age. As the relative risk for CHD mortality in a man in the upper quintile of cholesterol of the population declines (as a result of age-associated increases in the CHD death rate in older men with "normal" cholesterol) from over 7 in men aged 35 to 39 to 2 for men aged 55 to 59, the attributable risk for CHD in the upper versus lowest quintile progressively increases with age, from 0.7% for men aged 35 to 39 compared to 1.9% for men aged 55 to 59. Thus, treating hypercholesterolemia has the potential to prevent a large numbers of deaths in older people. Since the number of subjects who need to be treated to prevent one death, or the inverse of the attributable risk, is substantially lower in older than in younger adults, pharmacologic interventions to decrease morbidity and mortality from CHD may be more cost-effective in older than younger people.

Reduced Concentrations of HDL-C

Although there is an inverse association between HDL-C and risk for CHD and stroke in older adults, questions remain about whether it is the association of low HDL with impaired reverse cholesterol transport, chronic inflammation and oxidative stress, or visceral adiposity and insulin resistance, rather than HDL-C *per se*, that results in ASCVD. Measurement of apoA-I (the main apo constituent of HDL), HDL size and particle concentrations, and HDL biological activities (ie, promoting RCT and inhibiting proinflammatory, oxidative, and thrombotic ASCVD pathways or both) might provide superior discriminatory power to measurement of HDL-C and LDL-C in predicting CVD morbidity and mortality in older adults. However, the results of several clinical trials with CETP inhibitors and niacin that raise HDL levels cast doubt on these associations.

Nonetheless, the 4- and 12-year follow-up data from the Framingham Study demonstrated inverse relationships between HDL-C concentrations and CHD incidence, which appears to be maintained in people age 50 to 79 years. In this group, the relative risk for all-cause mortality in men with an HDL-C less than 35 mg/dL was 1.9 and risk of CHD mortality was 4.1 compared to those whose HDL-C was greater than 54 mg/dL, while in women, the relative risk for all-cause mortality was 1.5 and the risk for CHD mortality was 3.1 for HDL-C less than 45 mg/dL versus greater than 69 mg/dL. Subjects in the Established Population for the Epidemiologic Study of the Elderly aged 71 to 80 in the lowest HDL-C category (< 35 mg/dL) were four times more likely to die from CHD than those with HDL-C above 60 mg/dL. A 10-year prospective study of lipid risk factors for CHD in older subjects in Marshfield, Wisconsin, showed not only that survival among men was associated with higher HDL-C and a lower total cholesterol/HDL ratio, but also that there was a 1.24-fold higher risk of having PAD and a 1.36-fold higher risk of having a stroke for a 10 mg/dL decrement of HDL-C in older men and women, even after controlling for other risk factors. However, there was no relationship between any of the lipid concentrations and all-cause mortality in women older than 65 years. In the Uppsala Longitudinal Study, Swedish men aged 77 who were in the first, second, and third quartiles of apoA-I levels had a relative risk of subsequent death of 10.2, 5.0, and 3.0 compared to the quartile with the highest apoA-1 concentration. In older (> 70 years) patients with diabetes, the apoB concentration and the ratio of apoB to apoA-I predicted CHD events independent of LDL-C. These findings support the measurement of HDL-C along with total cholesterol as an index of CHD risk in older individuals.

These associations of HDL with CHD risk have accelerated the development of pharmacologic treatments to raise HDL-C, but none have been effective thus far. Inhibition of CETP is one such strategy, but clinical trials with torcetrapib, despite 60% increases in HDL-C and reductions in LDL-C beyond that seen with atorvastatin, were stopped prematurely because the torcetrapib plus atorvastatin group had substantially higher mortality and

cardiovascular events than the group on atorvastatin monotherapy. AIM-HIGH and HPS2-THRIVE, two large secondary prevention trials of niacin plus statin therapy, showed no reduction in CHD events, but excess side effects. Subgroup analyses by age, other CVD risk factors, and medications are not yet available; but, the outcomes of these studies are relevant to older people since they involve secondary prevention of CHD in high-risk patients with existing ASCVD already on statins in whom HDL may have limited ability to reduce calcified, fibrotic plaque. Current trials with two new CETP inhibitors report no adverse effects, but clinical outcome data are not yet available despite a doubling in HDL-C levels. A better understanding of the preventive effects of combined treatments on the interaction of HDL and TG with apoB-containing lipoproteins may provide insights into potential benefits of raising HDL to reduce ASCVD risk in older people.

Atherogenic LDL Pattern B Phenotype

LDL comprises a spectrum of heterogeneous particles that differ in their metabolism and propensity for promoting atherosclerosis. There are two general phenotypes of LDL particle distribution that affect ASCVD risk: large, buoyant LDL particles coined the LDL pattern A phenotype, and small, dense LDL particles termed the LDL pattern B phenotype. The former is associated with a lower prevalence of hypertension, CVD, metabolic syndrome, and increased homozygosity for the I405V variant in the *CETP* gene, while the latter have increased atherogenicity due to their increased susceptibility to oxidation and endothelial permeability. Furthermore, individuals with the LDL pattern B also typically have other lipoprotein abnormalities, including mildly elevated TG and reduced HDL-C concentration, as well as hypertension, leading some to speculate that the LDL pattern B phenotype may be a biochemical marker for familial combined hyperlipidemia and the metabolic syndrome. Assessment of LDL size and LDL subclass distribution by nuclear magnetic resonance is commercially available, but not routinely employed in clinical practice.

There appears to be an association between LDL pattern B and increased risk for prevalent CHD and subclinical manifestations of atherosclerosis detected by assessment of carotid intima media thickness (CIMT). In the Physicians' Health Survey, LDL pattern B was prospectively associated with a threefold increased risk of CHD, independent of total cholesterol, HDL, and body mass index (BMI). The prevalence of the atherogenic LDL pattern B phenotype increases from 10% to 15% in young men to 30% to 35% in middle-aged and older men, and from 5% to 10% in young women to 15% to 25% in postmenopausal women; hence, it may be the most common abnormality in lipoprotein metabolism that predisposes to CHD. Family studies suggest that LDL pattern B is inherited as a mendelian-dominant or polygenetic trait that interacts with other genes to increase apoB production. The phenotypic expression of the pattern is affected by age, visceral obesity, diet, sedentary lifestyle, and the presence of type 2 diabetes. The LDL pattern B is linked to a number of genetic loci, but there is no consensus as to which of these is responsible for the syndrome. The National Cholesterol Education Program (NCEP) III guidelines recognize small, dense LDL as a CVD risk factor. Individuals with exceptional longevity (mean age 98) and their offspring have larger HDL and LDL particle sizes than control families, suggesting that lipoprotein particle size affects longevity.

Individuals with the LDL pattern B also have a different metabolic response to drug and dietary interventions than those with the LDL pattern A phenotype. Certain classes of drugs appear more effective at lowering the concentration of the small, dense LDL particles than other drugs, and these reductions are associated with angiographic evidence of either decreased CAD progression or regression in plaque size. In the St. Thomas' Atherosclerosis Regression Study (STARS) comparing usual care intervention with lipid-lowering diet and lipid-lowering diet plus cholestyramine, small dense LDL was reduced in the groups showing regression. The dense LDL concentration during the trial was the best predictor of arteriographic outcomes, and those with the lowest treated levels of dense LDL showed the greatest regression. Similarly, in the Helsinki Heart Study (HHS), the subset of subjects having an elevated TG and low HDL-C, that is, patients who presumably had LDL pattern B, received substantial clinical benefit from gemfibrozil. These findings have implications for lowering TG and non-HDL-C, and raising HDL to reduce CVD risk.

Because statins lower the concentration of all LDL subclasses, their net effect on LDL subclass distribution or mean size of the LDL particles may be only moderate. However, different statins have differential effects on the LDL subclass distribution. Pravastatin and simvastatin have a limited ability to modify particle size and their subclasses, while fluvastatin and atorvastatin seem to be much more effective, and rosuvastatin seems to be the most potent in altering particle size toward a less atherogenic profile. The clinician must realize that lipid-lowering drugs have differential effects on the lipoprotein subclasses that are not detected by routine measurements of TG, LDL-C, and HDL-C and could affect plaque regression. However, until large-scale clinical trials comparing the effect of the different statins on morbidity and mortality in older individuals with different LDL subclass distributions and apolipoprotein profiles are performed, we will not know if the theoretical advantages of medications particularly

effective in decreasing the dense LDL subfraction concentration translate into improved clinical outcomes.

Non-HDL-C, Total, LDL, and HDL Cholesterol Ratios and CVD Risk

There may be differing cardiovascular risk associated with individual lipid fractions in older people. A high total cholesterol (TChol) HDL-C ratio appears to consistently predict CHD. The TChol/HDL-C ratio declines progressively with advancing age in men, but rises in women; thus, it is comparable in both genders by age 80, partially explaining the narrowing gender gap in the incidence of CHD with aging. The role of TGs as an independent risk factor remains controversial in many populations, including older people; however, lower levels of HDL-C, and higher non-HDL-C and LDL-C/HDL-C ratios, which are often associated with elevated TGs, may predict CVD risk better than TChol or LDL-C alone. For example in the TNT and IDEAL trials, non-HDL-C levels were superior to LDL-C levels as predictors of major CHD events. The assessment of non-HDL-C levels is particularly relevant in older obese populations that have insulin resistance and the metabolic syndrome, which are associated with elevations in the apoB–TG-enriched remnant lipoproteins—VLDL, remnants, and IDL and reduced HDL-C, and high non-HDL-C levels. The International Atherosclerosis Society recognizes the value of non-HDL-C as a useful measure of TG-, cholesterol-, and apoB-rich atherogenic lipoproteins, as well as a primary metric of ASCVD risk and intervention outcomes. Future research using this ratio to analyze outcomes of clinical trials in older people will confirm its clinical relevance. Yet, considering the prevalence of insulin resistance, hypertriglyceridemia, and low HDL-C in Western society, non-HDL-C less than 130 mg/dL is now recommended as a therapeutic target for patients with TG levels greater than 200 mg/dL.

Genetic Dyslipidemias

An older patient rarely presents with major genetic disorders of lipid metabolisms (ie, familial hypercholesterolemia, familial combined hyperlipidemia, familial hypertriglyceridemia, chylomicronemia, and dysbetalipoproteinemia) as these are usually detected and treated at an earlier age. Most adult patients with extreme lipid values have a polygenic component of susceptibility because not all individuals with secondary, contributing factors have the same severity of dyslipidemia. This is often seen in obese people with insulin resistance-associated dyslipidemia, type 2 diabetes, or medication-associated dyslipidemia, where genetic susceptibility may explain interindividual variation in the degree of dyslipidemia given the same dietary, medical, or other secondary factors.

Genetic variants, or single nucleotide polymorphisms, each may have a small effect on the plasma lipid level associated with the trait, but the accumulation of these traits within a patient's genome, especially in the presence of additional secondary causes for dyslipidemia, may produce a large net effect, and ultimately, clinically severe dyslipidemia and accelerated atherosclerosis. These genetic variants segregate on different chromosomes; hence, the resulting phenotypes do not display classic mendelian segregation patterns. There are more than 100 highly replicated, small-effect, lipid-related single nucleotide polymorphisms genetic variants that affect lipid traits; the key ones for (1) LDL-C include apoE, LDLR, apoB, sortilin 1, and PCSK9; (2) TG include apoA5, LPL, glucokinase regulator, apoB, apoE, and angiopoietin-like proteins 3 and 4; and (3) HDL-C include CETP, hepatocyte nuclear factor 4 (HNF4A), hepatic lipase (LIPC), LCAT, and ABCA1. The concomitant presence of secondary factors in these individuals worsens their dyslipidemia.

Apolipoprotein E4

ApoE is of fundamental interest to geriatricians because of its role in the pathogenesis of a number of diseases, including diabetes (apoE2/4), Alzheimer (apoE4) and Parkinson disease (apoE2), as well as dementia and CVD (apoE4). Studies also suggest the apoE genotype affects immune function, risk for cancer, and mortality. However, the impact of the apoE genotype on health, in particular the apoE4 allele, is complex because it demonstrates antagonistic pleiotropy (appearing to have beneficial effects on some traits and detrimental ones on others). In this section we will focus on the impact of the apoE genotype on ASCVD risk and mortality.

The apoE4 allele is a risk factor for CHD and is also associated with increased mortality and decreased survival into older age; thus, the frequency of the apoE4 allele is lower in older compared to younger populations. In one cross-sectional study, the apoE4 allele frequency declined progressively across the age span: 0.198 in young adults to 0.116 in nonagenarians. Similarly, in another study, the frequency of the apoE4 allele was lower in older women (0.098) compared to younger women (0.122), whereas the allele frequency of apoE2 was higher and associated with lower total and LDL-C concentrations in the older cohort. The results of these cross-sectional studies are supported by longitudinal ones. For example, in older Finnish men (mean age at entry 72), the death rate from CHD over 5 years of

follow-up for those with the apoE4 allele was double that of men with the other apoE genotypes. In multivariate analyses of middle-aged and older men followed over 20 years in the Baltimore Longitudinal Study of Aging (BLSA), apoE4 was an independent predictor of coronary events (relative risk of 2.9). These studies provide strong evidence that the apoE4 allele, on average, decreases longevity by around 4 years, with its greatest impact on mortality occurring in people 70 years and older. Selective mortality is likely the cause of the reduced prevalence of apoE4 in older populations. Conversely, the apoE2 allele appears to promote longevity, possibly through an association with lower concentrations of apoB-containing lipoproteins. The apoE genotype may also affect the metabolic response to statin therapy, with carriers of apoE2 being more responsive to therapy. It is not known whether lifestyle or pharmacologic interventions specifically targeted at older individuals with the apoE4 allele would reduce CHD deaths and all-cause mortality.

Given its prevalence, the apoE4 allele may be the most common genetic lipid abnormality associated with CHD. The mechanism underlying the increased CHD in individuals carrying the apoE4 allele is not known with certainty, but is in part related to changes in LDL- and TG-rich remnant metabolism. Patients with the apoE4 allele tend to have lower HDL-C and higher TG concentrations than individuals with the common apoE3/3 genotype. Understanding the mechanisms by which the apoE polymorphisms modulate risk for atherosclerosis, mortality, and morbidity, and the effects of apoE on the brain and lipoprotein metabolism may shed light on the role of environmental change, lifestyle, and genetics on longevity. As we move forward in this era of personalized medicine, ethical issues related to genetic screening, employment, and health insurance will need to be addressed prior to widespread measurement and treatment based on apoE, Lp(a), and other genotypes in clinical practice.

Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a cholesterol-rich lipoprotein particle similar to LDL consisting of an apolipoprotein B-100 particle attached by a disulphide bridge to apo(a). It is estimated that elevated Lp(a) levels, defined as greater than 25 mg/dL, are present in 30% of Caucasians and 60% to 70% of African Americans, but unfortunately there is no universally accepted standardization program for Lp(a) assays, limiting its reproducibility and reliability. However, direct measures of LDL-C, IDL-C (β-quantification), and Lp(a) (immunoturbidity) show LDL-C also contains contributions from Lp(a) and IDL-C. Clinical trials show variable reductions in Lp(a) by PCSK9 inhibitors, niacin and estrogen, and 10% to 50% increases by statins; however, other lipid-lowering drugs, such as resins and fibrates, have minimal effects.

The genetic locus for apo(a) is polymorphic, and there are a large number of genetically determined isoforms of Lp(a). Lp(a) concentration is highly heritable, and one study estimated that 98% of the variance in Lp(a) concentration could be explained by the apo(a) locus. As a result, Lp(a) concentration is essentially constant across the lifespan. Elevated Lp(a) levels are risk factors for CAD, MI, ischemic stroke as well as markers of restenosis after coronary angioplasty, calcific aortic stenosis, saphenous vein bypass graft atherosclerosis, and accelerated atherosclerosis after cardiac transplantation. The pathogenicity of Lp(a) is attributed in part to the strong homology of apo(a) and plasminogen, thereby providing a link between atherosclerosis and thrombosis. Lp(a) inhibits the activation of transforming growth factor and contributes to the growth of atherosclerotic lesions by promoting the proliferation of vascular smooth muscle cells as well as the migration of smooth muscle cells to endothelial cells. Moreover, Lp(a) inhibits plasminogen binding to the surfaces of endothelial cells and decreases the activity of fibrin-dependent tissue-type plasminogen activator. Lp(a) also acts as a proinflammatory mediator that accelerates the formation of plaques. Knowledge of a patient's Lp(a) concentration might provide the clinician with additional insight into their risk for CHD, thus complementing the standard lipoprotein profile in determining therapy.

Challenges and Controversies

Despite impressive advances in our understanding of the pathogenesis of atherosclerosis, there are several ongoing questions to be resolved concerning the assessment and management of lipoprotein risk factors for CHD in older people: (1) Does direct measurement of the lipoprotein subfractions (Lp[a], LDL, HDL, non-HDL-C, LDL pattern B), apos, or their ratios (TChol/HDL-C, apoB/apoA1, etc) improve the prediction of CHD morbidity, mortality, or total mortality?; (2) Should the interpretation of a given lipoprotein concentration take into account the age of the patient?; (3) Does the longitudinal measurement of lipoprotein concentrations improve prediction of CHD?; (4) Would genetic screening for high CHD risk–associated polymorphisms identify individuals for whom early therapy might reduce CHD risk and prolong survival?; and (5) What role should coronary risk equations, and noninvasive measurements of atherosclerotic plaque or calcium score on cardiac computed tomography scan have in the assessment of

cardiovascular risk and treatment?

AGE-ASSOCIATED CHANGES IN LIPIDS

Many cross-sectional studies have examined age-associated changes in lipoprotein concentrations in both men and women. Unfortunately, cross-sectional studies cannot distinguish lipoprotein changes caused by biological aging from those caused by lifestyle and disease; this requires longitudinal studies. Our knowledge is further limited by the inherent difficulties in following cohorts of individuals over extended periods of time, divergent methodologies that limited widespread measurement of HDL-C and apos prior to the mid-1970s, and the treatment of clinically apparent dyslipidemia in standard clinical practice, closing the window of opportunity to perform longitudinal studies and assess the relationship of natural history of lipoprotein changes to CVD with aging. In general, the cross-sectional studies demonstrate that total cholesterol, LDL-C, and TG concentrations increase in both men and women from the third to seventh or eighth decades of life, with more pronounced increase in LDL-C concentration in women and important changes in lipoprotein classes of women at menopause. In general, these increases in total cholesterol, LDL-C, and TG parallel age-associated changes in body composition and physical activity.

Typically, there is a decline in LDL-C and total cholesterol concentration in oldest age cohorts. For example, in the National Health and Nutrition Examination Survey (NHANES) III of 1988 to 1991, total cholesterol concentrations were on average 189 mg/dL in men aged 20 to 34 and 221 mg/dL for men aged 55 to 64, but down to 205 mg/dL for men older than the age of 75. In the Honolulu Heart Study, total cholesterol levels were 8% lower in men older than age 85, as compared to men aged 71 to 74. This decline in cholesterol levels in the population older than age 75 could reflect selective mortality, or be related to changes in body composition, coexistent comorbid diseases, and frailty. Indeed, longitudinal changes in body weight over 8 years independently predicted changes in total cholesterol, LDL-C, and HDL-C in older men and women in Rancho Bernardo, California.

The overall pattern of change in total cholesterol profiles across the age span in women is similar to that for men, but on average is 20 to 30 mg/dL above that of men from age 55 to 75. Indeed from early adulthood through middle age, men have higher LDL-C levels than women. However, in the sixth and seventh decades there is a crossover where LDL-C is, on average, higher in women. In NHANES III, 39% of women and 22% of men aged 65 to 74 had a total cholesterol concentration above 240 mg/dL. However, the implications of “elevated” cholesterol in older people are not as straightforward as in younger age groups. For example, in a subgroup of men aged 71 to 93 from the Honolulu Heart Study, the age-adjusted incidence rates of CHD exhibited a significant U-shaped relationship with both total and LDL-C. The prevalence of individuals with a predominance of small, dense apoB-enriched LDL particles also increases with age. In the Framingham Offspring Study, postmenopausal women had 16% higher values of total cholesterol, 62% higher TG, 23% higher LDL-C, and smaller LDL particles than premenopausal women. These changes in LDL composition are not routinely measured and worsen CAD risk.

There are also changes in HDL-C concentrations across the age span in both men and women. In men, the HDL-C concentration remains fairly constant from puberty until the seventh decade of life, at which point there may be an increase in the HDL-C concentration, while in postmenopausal women HDL-C concentrations may decrease. Analogous to LDL, there are also compositional changes in the HDL subfractions associated with menopause that may increase CVD risk. These changes in HDL-C concentrations at older age noted in cross-sectional studies may be the result of reduced androgen and estrogen levels or selective morbidity and mortality, as opposed to true age-related changes in HDL metabolism.

The role of fasting TG concentrations as an independent risk factor for CVD remains a matter of debate. However, plasma TG concentrations measured in the postprandial (fed state), that is, postprandial lipidemia (PPL) are strongly associated with CVD. Older individuals have exaggerated PPL compared to younger individuals, even taking into consideration differences in fasting TG levels. The increased PPL reflects an increase in the accumulation of ingested lipid in lipoprotein particles of hepatic origin together with decreased clearance of TG-rich particles.

Based on prior Adult Treatment Panel (ATP) III guidelines, the marked age-associated increase in the prevalence of hypercholesterolemia (60% of men and 77% of women older than 65 years with total cholesterol > 200 mg/dL) means that millions of older adults are candidates for lifestyle intervention. It is estimated that using the 2013 ACC/AHA guidelines, an additional 16 million older adults in the United States would become candidates for statin therapy for the prevention of ASCVD. Millions of older individuals with prevalent CVD, CHD equivalents (diabetes, stroke, peripheral vascular disease, chronic kidney disease), or with multiple risk factors for CHD events also are candidates for cholesterol-lowering drugs. An increasingly informed and proactive older population and changes in

professional opinion toward ever more aggressive therapy for hyperlipidemia are reflected in the large number of older people prescribed statins. Controversies on who to treat and the target criteria are discussed in our review of the 2013 AHA/ACC guidelines.

MECHANISMS UNDERLYING AGE-ASSOCIATED DYSLIPOPROTEINEMIAS

The age-associated changes in lipoprotein concentrations can be attributed to a number of mechanisms, including primary genetic dyslipidemias, age-associated lifestyle habits such as increased dietary calorie and fat intake and declines in physical activity and fitness leading to central obesity, insulin resistance, mitochondrial dysfunction, sarcopenia, and decreases in the number and function of the hepatic LDL receptor.

Lipoprotein Synthetic and Catabolic Rates

Age-associated increases in the plasma concentrations of lipoproteins can be caused by increased production, decreased clearance, or a combination of decreased clearance and increased production. Given the high use of statins in older adults and ethical concerns about not treating dyslipidemia, it is now difficult to examine the effect of natural aging on the metabolism and kinetics of lipoproteins. Many of the reported age-related changes in lipoprotein concentrations likely reflect interactions between primary age-related changes in LDL metabolism, the effects of obesity, physical inactivity, diet, and other lifestyle habits, as well as medications.

Role of Dietary Modification

It is extremely difficult to quantify longitudinal age-associated changes in dietary content, as extensive secular changes in dietary eating patterns have occurred. Historic data from men in the BLSA showed that the total caloric and cholesterol intake, as well as the percent of calories obtained from fat and saturated fat declined with age. Such age-associated changes in dietary content would be expected to result in lower levels of total and LDL-C, a result that is opposite the commonly observed age-associated increase in these parameters. As discussed in Chapter 34, changes in the pattern and distribution of energy consumed in older adults may be related to changes in appetite, smell, and vision, depression, social isolation/loneliness, cognitive dysfunction, reduced mobility and transportation, and ability to prepare food, as well as declining health and polypharmacy.

Obesity, Insulin Resistance, and Dyslipidemia

The prevalence of obesity increases with aging, with a preferential accumulation of fat in visceral abdominal sites. The 2010 NHANES found that the prevalence of overweight people (BMI > 25 kg/m^2) greater than 60 years in America approaches 77% for men and 74% for women, and approximately 37% of men, and approximately 42% of women are obese (BMI > 30 kg/m^2); hence, only approximately 25% of the American population has a normal body weight. Greater body fat, especially in the abdomen (termed central or visceral obesity—waist circumference > 100 cm in men, > 88 cm in women), is associated with tissue resistance to insulin, the development of hyperinsulinemia, and a cascade of metabolic abnormalities that increase risk for metabolic syndrome, type 2 diabetes, and CVD. The obesity-associated hyperinsulinemia increases VLDL-TG synthesis and production, and is associated with high TG and glucose, low HDL-C, and atherogenic LDL phenotype pattern B (**Figure 111-2**).

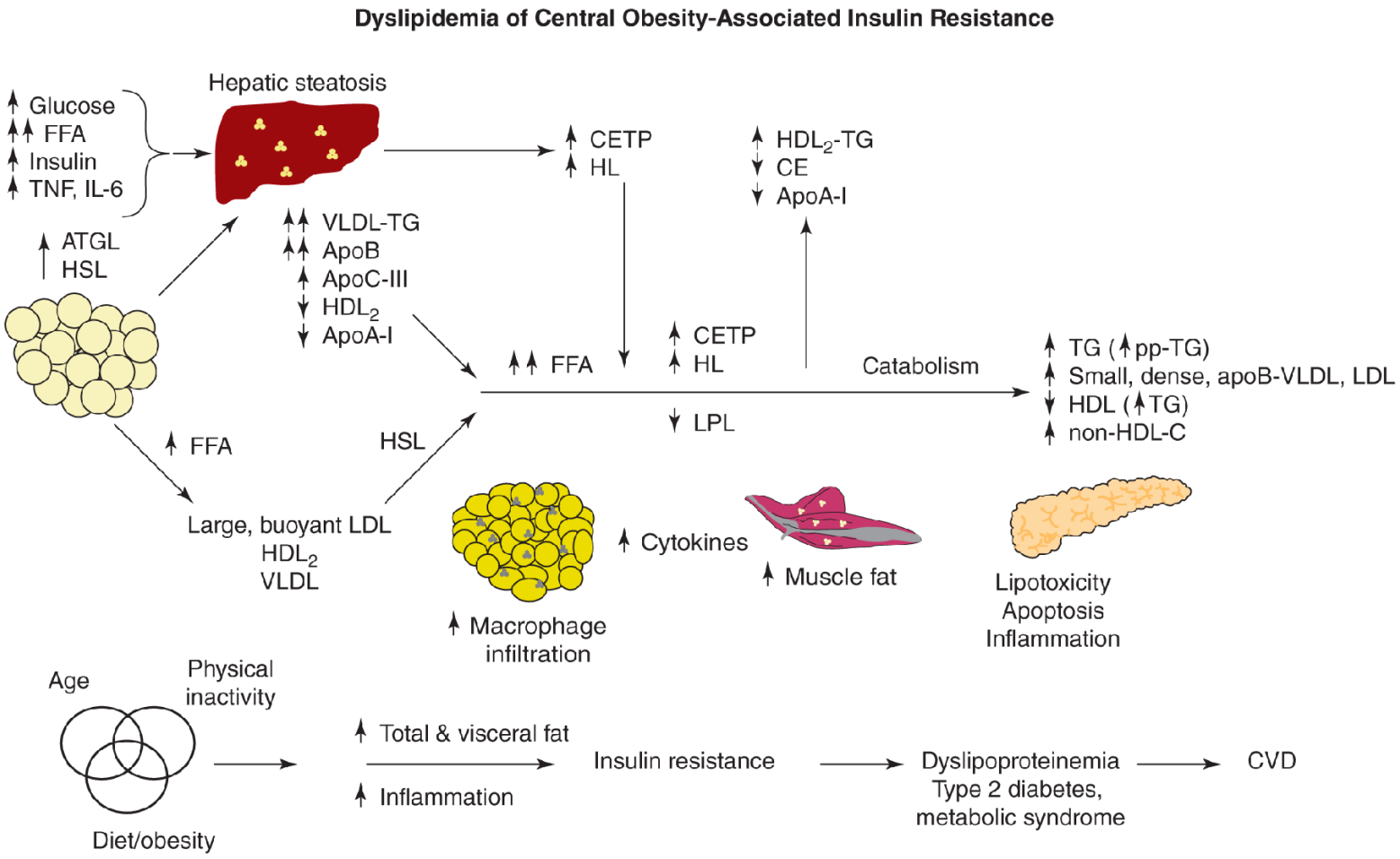


FIGURE 111-2. The dyslipidemia associated with metabolic syndrome is similar to that of obesity-associated insulin resistance. Insulin resistance is associated with macrophage infiltration of adipose tissue that triggers inflammation, cytokine secretion, and lipotoxicity, which worsen hepatic, muscle, and pancreatic function, elevating plasma glucose and FFA levels, precursors for hepatic synthesis of atherogenic lipoproteins. This increases the production of apoB-100–containing TG-rich VLDL particles, leading to fasting and postprandial elevations in TG, VLDL, and apoB-enriched VLDL and LDL. A concomitant increase in the activity of CETP and HL and reduction in LPL raise the TG content of VLDL, LDL, and HDL, increasing non-HDL-C and lowering HDL-C and CE.

Metabolic Syndrome, Type 2 Diabetes, and Dyslipidemia

There is ongoing controversy as to the utility of metabolic syndrome as a disease construct because there is no consensus as to its underlying pathophysiology and little evidence that it denotes greater CVD risk than the sum of its constituents: abdominal obesity, waist greater than 40 in in men, greater than 35 in women; HDL-C $\leq$ 40 mg/dL in men, $\leq$ 50 mg/dL in women, hypertension > 135/85 mm Hg, impaired fasting glucose $\geq$ 100 mg/dL, and TG $\geq$ 150 mg/dL. NHANES III data show the prevalence of metabolic syndrome and type 2 diabetes approaches approximately 44% and approximately 25% in older adults and represent a substantial risk for ASCVD. The prevalence of metabolic syndrome among older people with type 2 diabetes is high, with substantial overlap in their metabolic abnormalities. Older people with diabetes and metabolic syndrome have the highest prevalence of CHD compared to diabetics without metabolic syndrome; however, the prevalence of CHD appears to be no greater in individuals with diabetes without metabolic syndrome than those with neither. Metabolic syndrome enhances risk for CVD mortality in postmenopausal women to a greater extent than in men or premenopausal women; therefore, identifying risk factors other than obesity, sedentary behavior, and aging that result in metabolic dysfunction may provide insight into potentially therapeutic strategies to prevent its ASCVD complications in older women.

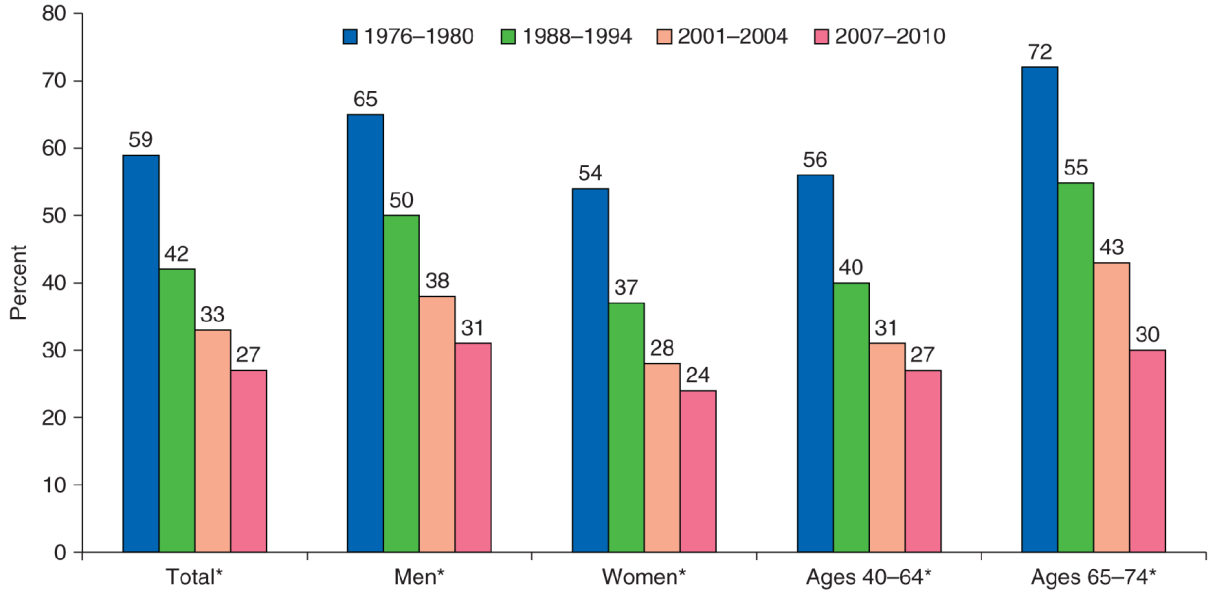
Overweight and obese adults with metabolic syndrome and/or type 2 diabetes have central obesity-induced insulin resistance, macrophage infiltration of fat, and a reduced adipogenetic capacity of subcutaneous adipocytes for TG storage than metabolically obese healthy adults. This increases lipolysis, cytokine secretion, and the "spill-over" of FFA-TG to the liver causing hepatic lipotoxicity (steatosis) and the overproduction of VLDL-TG, apoB and C-II, and reduced apoA-I and HDL-2 synthesis, muscle lipotoxicity-associated mitochondrial dysfunction and sarcopenia, and impaired pancreas function. The association of body fat phenotypes with metabolic health extends across the age and

BMI span, with a greater prevalence of metabolic abnormalities in adults with greater degrees of total and visceral obesity. Identifying older, obese individuals who have metabolic syndrome would target individuals who might benefit most from lifestyle modification with weight loss and exercise to upregulate adipogenic gene expression, lipid clearance, and reduce visceral fat and inflammation.

Among older subjects with type 2 diabetes, insulin resistance combined with insulin deficiency increase the atherogenic composition of lipoproteins by raising glucose, TG, free cholesterol, and apoB, E, and C-III levels and lowering HDL-CE, apoA-I, and particle size to increase atherogenic small, dense apoB-rich LDL. Glucose and lipid toxicity promote inflammation, the formation of reactive oxygen species, protein glycation, and foam cells to worsen atherogenesis. Diabetes is considered a CHD equivalent for setting lipoprotein treatment goals because of the heightened ASCVD risk for subsequent complications and mortality, and similarities in metabolic dysfunction with the metabolic syndrome. Thus, statin therapy is recommended to lower LDL-C, while blood pressure and other CVD risk factors are aggressively treated to target levels prescribed for patients with documented CHD (see Chapter 110). Home glucose monitoring, lifestyle diet and physical activity modification with pharmacologic treatment of hyperglycemia, dyslipidemia, hypertension, and other CVD risk factors are recommended. The ADA recommends statin therapy to reduce LDL-C less than 70 mg/dL and the addition of fibrates to lower TG less than 100 mg/dL. We advocate aggressive risk factor modification that includes therapeutic lifestyle changes and physical activity to modify obesity, and appropriate pharmacologic interventions for other CVD risk factors according to AHA/ACC guidelines in patients with type 2 diabetes and metabolic syndrome.

SECULAR CHANGES IN LIPOPROTEIN LIPIDS

There have been substantial changes in lipoprotein lipid concentrations in the US population over the past four decades. NHANES and Centers for Disease Control and Prevention (CDC) data demonstrate that from 1960 to 2010, secular changes in diet, increased use of lipid-lowering medications, and other factors resulted in lower mean total cholesterol concentrations with no change in mean HDL-C and a trend for an increase in TG across the age span in both men and women (**Figure 111-3**). The greatest declines have occurred in the older populations. The increase in the proportion of adults using lipid-lowering medication, particularly in older age groups, likely contributed to the decreases in total and LDL-C concentration, while the heightened prevalence of obesity in the US population probably contributed to the increase in plasma TG levels. The secular decline in cholesterol has contributed to the decline in CVD morbidity and mortality.



*Significant decreasing linear trend ($p < 0.05$).
NOTES: High LDL cholesterol is measured levels above the treatment goals established by the National Cholesterol Education Program's Adult Treatment Panel III guidelines. Estimates are age adjusted by the direct method to the 2000 US census population using age groups 40–64 and 65–74.

FIGURE 111-3. Secular changes in LDL-C levels. The prevalence of high LDL-C (ATP III criteria) significantly decreased for men,

women, and adults aged 40 to 64 (56%–27%) and 65 to 74 (72%–30%). (From Kuklina EV, Carroll MD, Shaw KM, Hirsch R. Trends in high LDL cholesterol, cholesterol-lowering medication use, and dietary saturated-fat intake: United States, 1976–2010. *NCHS Data Brief,* no 117. Hyattsville, MD: National Center for Health Statistics. 2013.)

In 1997, fewer than 12% of the 38 million Medicare beneficiaries (4.4 million persons) used at least one statin. Cholesterol-lowering medication use has more than tripled between 1997 and 2008 with greater than 40% of older adults using statins (**Figure 111-4**). Despite the large increase in number of prescriptions, many feel that statin therapy is underutilized. In one study, older individuals with the highest cardiovascular risk and risk for death were paradoxically the least likely to be prescribed statins. This problem of underuse of statins is further compounded by patient noncompliance. Concerns about adverse side effects may also deter health care providers from prescribing these medications to older people (see the text under Evaluation and Management). Of note, the protective effects of statin therapy may go beyond simple lipoprotein reduction to include possible anti-inflammatory, antioxidant, and antithrombotic effects, as well as effects on nitric oxide metabolism.

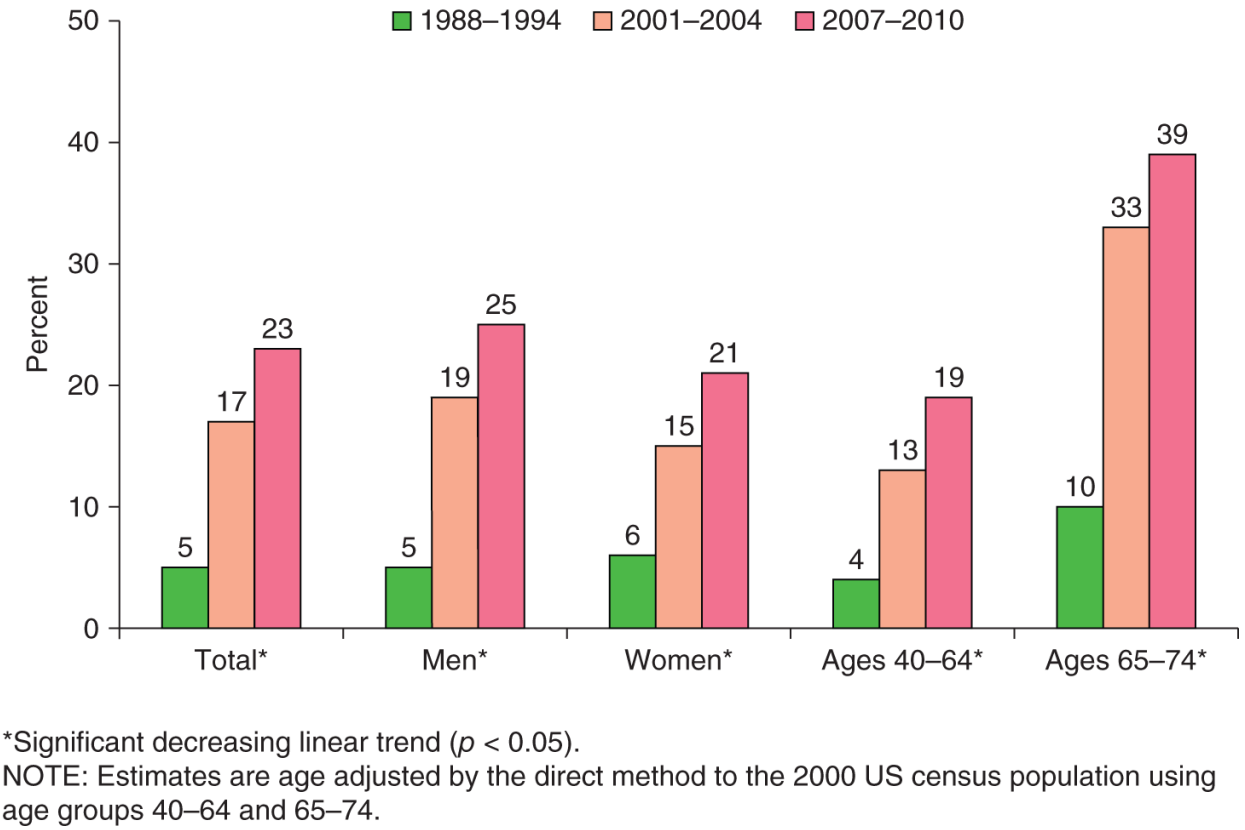


FIGURE 111-4. Secular changes in the use of cholesterol-lowering medications. In adults aged 65 to 74, medication use increased from 10% to 39%. (From Kuklina EV, Carroll MD, Shaw KM, Hirsch R. Trends in high LDL cholesterol, cholesterol-lowering medication use, and dietary saturated-fat intake: United States, 1976–2010. *NCHS Data Brief,* no 117. Hyattsville, MD: National Center for Health Statistics. 2013.)

INTERVENTION TRIALS

Treatment of hypercholesterolemia in high-risk older adults (at least up to the age of 80) with statins reduces both LDL levels and CHD event/death rates, supporting the use of statins in older individuals—particularly in those with prevalent CHD or CHD equivalents (**Table 111-1**). Early trials with statins (eg, 4S, WOSCOP, HPS) demonstrated approximately 25% reductions in LDL-C as well as coronary events and mortality irrespective of initial cholesterol, and to a greater extent than would be predicted based solely on their effects on LDL levels. These lipid improvements are clearly seen in both middle-aged and older individuals. The JUPITER, CORONA, SAGE, and IMPROVE-IT trials, using more potent statins and other concomitant LDL lowering agents, extend these to "real" clinical benefits of reduced CVD events, even among apparently healthy individuals and patients with acute coronary syndrome and CHD. The PROSPER trial focused on those over 70 years and demonstrated LDL benefits similar to those in younger individuals, as well as improvements in rates of major coronary events. Similarly, the Register of Information and

Knowledge About Swedish Heart Intensive Care Admissions (RIK-HIA) showed reductions in both CVD and overall mortality in acute myocardial infarction patients over the age of 80 after hospital discharge. Nonetheless, enthusiasm over these demonstrated benefits of statins among older individuals is tempered by their side effects (myalgia, elevated liver enzymes, and increased glucose levles), as well as consideration of time to benefit. Unfortunately, although in HPS2-THRIVE and AIM HIGH niacin raised HDL-C by 17% to 25%, and lowered TG by 12% to 31% and LDL-C by 13% to 20% below the initial mean of 70 mg/dL achieved by statins and ezetimibe in high CVD risk individuals over almost 4 years, these secondary prevention trials did not reduce the risk of major vascular events; but there were more skin-associated, muscle, GI, diabetes, and hepatic adverse side effects.

TABLE 111-1 MAJOR RANDOMIZED CLINICAL TRIALS OF LIPOPROTEIN LIPID LOWERING INVOLVING OLDER ADULTS

TRIAL	STUDY SUBJECTS	INTERVENTION	LDL REDUCTION	CHD/OTHER OUTCOMES
Scandinavian Simvastatin Survival Study (4S)	4444 ♂/♀ aged 50–75, h/o angina/MI	Dietary counseling ± simvastatin (20 mg titrated to TC response)	−35% ($p < 0.0005$)	↓Major coronary events −34% and mortality −30% ($p = 0.003$); ↓CHD death: −43% ≥ 65 y vs −42% < 65 y ($p = 0.0005$)
Pravastatin Limitations of Atherosclerosis in the Coronary Arteries (PLAC I)	408 ♂/♀ aged 50–75, h/o CAD & 130 ≤ LDL-C < 190 despite an AHA step I diet	40-mg pravastatin	−28% ($p < 0.0001$)	↓Atherosclerosis progression −40% and coronary events −55% ($p < 0.05$ for both)
Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC II)	151 ♂/♀ aged 50–75, h/o CAD & diet-resistant elevated LDL-C	Pravastatin (20 mg titrated to LDL response)	−28%	↓New coronary artery lesions and MI −55% ($p = 0.014$)
Cholesterol and Recurrent Events (CARE)	4159 ♂/♀ aged 21–75, h/o MI and baseline TC < 240, 115 < LDL < 175, TG < 350 mg/dL	40-mg pravastatin	−32% ($p < 0.001$)	↓Major coronary events −32% and stroke −40%, ↓CHD events −23% ≥ 65 y vs −19% < 65 y ($p < 0.005$ for all)
West of Scotland Coronary Prevention Study (WOSCOPS)	6595 ♂ aged 45–64, LDL 154 despite dietary therapy, no h/o MI	40-mg pravastatin	−26% ($p < 0.001$)	↓Cardiac end points −31% ($p < 0.001$), a greater decrease than predicted by ↓LDL-C
Medical Research Council/British Heart Foundation Heart Protection Study (HPS)	20,536 ♂/♀ aged 40–80, h/o DM, PVD, or CHD	40-mg simvastatin	−44% ($p < 0.001$)	↓Major vascular events −24% ($p < 0.0001$) irrespective of initial LDL-C levels and proportional across the age span
Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)	5804 ♂/♀ aged 70–82, h/o vascular disease or at high risk for CHD due to HTN, smoking, or DM	40-mg pravastatin	−34%	↓CHD death −24% and major CVD events −19% ($p \leq 0.014$), no effect on stroke
Treating to New Targets (TNT)	10 001 ♂/♀ aged 35–75, clinically evident CHD	Atorvastatin 10 mg vs 80 mg	10 mg → −35% 80 mg → additional −24%	↓Composite end point (death from CHD, nonfatal MI, resuscitation after cardiac arrest and stroke): −10.9% vs −8.7%, ($p < 0.001$)
Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)	9014 ♂/♀ aged 31–75, h/o MI or hospitalization for USA and 155 < TC < 271	Dietary counseling ± 40-mg pravastatin	−28%	↓Mortality −22%, and CVD outcomes (MI death from CHD, stroke, coronary revascularization) −24% ($p < 0.001$ for all); both ↓ −20% in those > 70 y
Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT-TIMI22)	4162 ♂/♀ mean age 58 ± 11 recently hospitalized for ACS, TC ≤ 240	400-mg gatifloxacin + 40-mg pravastatin or 80-mg atorvastatin	Pravastatin → −22%; atorvastatin → −51% ($p < 0.001$)	↓Recurrent MI or vascular death −16% ($p = 0.005$)
Study Assessing Goals in the Elderly (SAGE)		Atorvastatin 80 mg vs pravastatin 40 mg	Pravastatin→ −32%; atorvastatin → −56% ($p <$ 0.001 for all, and between)	Similar reductions in ischemic burden (ambulatory monitoring) in both groups, but ↓all-cause mortality in atorvastatin vs pravastatin ($p = 0.014$)

Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)	5011 ♂/♀ aged ≥ 60, NYHA class II, II, or IV ischemic, systolic heart failure	Rosuvastatin 10 mg	−45% ($p < 0.001$)	↓CRP −37%, ↓hospitalizations for CVD ($p < 0.001$ for both), no difference in deaths, coronary outcomes
Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)	17,802 ♂ ≥ 50/♀ ≥ 60, w/o CAD, LDL < 130, hsCRP ≥ 2.0	Rosuvastatin 20 mg	−50% ($p < 0.0001$)	↓Combined MI, stroke, arterial revascularization, CVD death, hospitalization for unstable angina: −44% ($p < 0.00001$), ↓hsCRP −37%, ↓TG 17% ($p < 0.001$)
IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)	18,144 high-risk post-ACS patients	Simvastatin +/− ezetimibe	−43% vs −25% ($p < 0.001$)	↓Composite end point (cardiovascular death, MI, hospitalization unstable angina, coronary revascularization, or nonfatal stroke (−34.7% vs −32.7%; $p = 0.016$), ↓CVD risk −47.6% ≥ 75 vs −38.95% < 75 y ($p = 0.005$)
Heart Protection Study-2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)	25,673 ♂/♀ aged 50–80, h/o MI, CVD, PAD, or DM with symptomatic CAD	2-g niacin + 40-mg laropiprant	↓LDL-C −19.9% ↑HDL-C +16.9% ↓TG −12%	No effect on major vascular events; ↑↑adverse events (skin, musculoskeletal myopathy, GI, diabetes)
Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM HIGH)	3414 ♂/♀ aged ≥ 45 with established CAD and atherogenic dyslipidemia	1.5–2 g niacin + simvastatin +/− ezetimibe (to maintain LDL-C < 80 mg/dL)	↓LDL-C −13.6% ↑HDL-C +25% ↓TG −30.8%	No effect on CAD death, nonfatal MI, ischemic stroke, ACS hospitalization or revascularization; minimal adverse events
Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM)	2341 ♂/♀ mean age 60 ± 10 with CAD/CAD equivalent or familial hypercholesterolemia with LDL not at goal on maximal statin therapy	Alicumab (PCSK9 inhibitor)	−62% ($p < 0.001$)	↓CVD events (1.7% vs 3.3%, $p < 0.01$)
Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy for Easing Lipid Levels (MENDEL-2)	614 ♂/♀ age 18–80, with 100 ≤ LDL< 190 mg/dL & Framingham risk score ≤ 10%, not on statin	Evolocumab (PCSK9 inhibitor)	−57% ($p < 0.001$)	Not available
Durable Effect of PCSK9 Antibody Evolocumab Compared with Placebo in hyperlipidemia (DESCARTES)	901 ♂/♀ age 18–75, LDL ≥ 75 & TG < 400	Evolocumab, after titrated background lipid Rx (diet, +/− atorvastatin +/− ezetimibe)	↓LDL-C vs placebo: −57% ($p < 0.001$), +10-mg atorvastatin: −61.6% +80-mg atorvastatin: −56.8% +80-mg atorvastatin + 10-mg zetia: −48.5%; ($p < 0.001$) ↑HDL-C: +5.4% (p < 0.001)	Not available

Another agent, ezetimibe, reduces cholesterol absorption. The Vytorin Efficacy International Trial (IMPROVE-IT) showed that the addition of ezetimibe to statin therapy resulted in 24% additional lowering of LDL-C and reduced the primary end point, a composite of cardiovascular death, myocardial infarction, hospital admission for unstable angina, coronary revascularization (> 30 days after randomization), and nonfatal stroke, from 34.7% in those on simvastatin alone to 32.7% in the simvastatin plus ezetimibe group (an absolute risk difference of 2%, $p = 0.016$), at 7 years of follow-up in 18,144 high-risk patients within 10 days of acute coronary syndrome. More details about ezetimibe are provided in the Pharmacologic Therapy section later. Clinical trials of several potent LDL-C-lowering injectable monoclonal antibodies against PCSK9 are in phase II to III clinical trials, with clinical outcome studies in progress. PCSK9 inhibition lowers LDL-C levels by up to 50% as monotherapy and nearly 75% when combined with statins. There is a dose effect, with administration of up to 300 to 400 mg/q2–4wk reducing LDL-C by up to 73% versus 44% for 150 mg/q2wk and reducing Lp(a) from 9% to 30% compared to placebo, over 12 to 52 weeks. There were few safety concerns regarding adverse effects related to muscle, liver, diabetes, neurocognitive/neurologic, hypersensitivity, and immunogenicity, and the drugs are now approved by the Food and Drug Administration (FDA). However, the impact of this LDL-C lowering on CVD outcomes, long-term clinical effectiveness, and high CVD risk older populations with multiple comorbidities remains to be compared to that of statins and other lipid-lowering therapies. The number of people potentially eligible for PCSK9 inhibitors will be in the millions based on ACC/AHA 2013 Cholesterol Treatment Guidelines, and at an estimated cost of $7 to $12,000/year, the annual expenditures for these drugs would be huge. Since this is chronic therapy, the total cost of the drug to the US health care system could be $100 to $200 billion/year, not including physician and hospital-related costs.

Nevertheless, there is little evidence to support aggressive treatment of elevated LDL-C in patients older than 80 years, and we recommend using good clinical judgment based on existing multimorbidity, likelihood for drug complications, and medication burden. Competing morbidities and disabilities reduce the association between high serum cholesterol and the risk for atherosclerosis among the oldest patients. However, this group has the highest

burden of atherosclerotic disease, and meta-analyses show a steeper relationship between CAD mortality and cholesterol levels among the oldest people. Furthermore, despite a trend for a positive relationship between total cholesterol and survival in the Jerusalem Longitudinal Cohort Study, subjects on statins had greater survival up to the age of 90, suggesting statins have beneficial effects, which appear independent of cholesterol levels. The outcomes of the ongoing Clinical Trail of Statin Therapy for Reducing Events in the Elderly (STAREE) (atorvastatin vs placebo) on overall and disability-free survival in individuals over age 70 may provide guidance.

EVALUATION AND MANAGEMENT

Consensus Guidelines for the Treatment of Hyperlipidemia

The consensus guidelines for the evaluation and management of dyslipidemia are periodically revised. Over the past two decades, several organizations have issued recommendations on the evaluation and management of dyslipidemia in adults. Although many commonalities exist among them, there are significant differences as well. The 2002 NCEP guidelines recommended that all patients older than 20 years undergo lipid testing at least every 5 years with no defined upper age limit for this testing. The ATP III guidelines published in 2004 and slightly updated in 2012 recommended a more comprehensive assessment with measurement of fasting total cholesterol, LDL-C, HDL-C, and TG. They also stated that if any of these concentrations are abnormal, the physician should evaluate the patient for causes of secondary dyslipidemia (see section Secondary Hyperlipidemia and Other Medical Concerns).

In late 2013 the ACC/AHA Task Force on Practice Guidelines issued new guidelines for the management of dyslipidemia in adults (**Figure 111-5**). They recommended the assessment of traditional ASCVD risk factors and estimate of 10-year ASCVD risk (using pooled cohort equations) every 4 to 6 years in adults 20 to 79 years who are free from ASCVD. There were no specific recommendations for evaluating those patients 80 and above. These guidelines have explicit recommendations for adults above and below 75 years based on the presence or absence of clinical ASCVD based on 10-year calculated ASCVD risk using pooled cohort equations. These guidelines make stringent recommendations for patients with CHD equivalents such as diabetes and renal disease, and for individuals with multiple CVD risk factors who are at increased risk for CVD events. Although the guidelines emphasize that heart-healthy lifestyle habits should be encouraged for all individuals, there is increased emphasis on the use of statins to treat dyslipidemia to reduce ASCVD risk. Although the ACC/AHA recommendations for statin therapy for individuals with overt ASCVD or ASCVD equivalents are essentially similar to the ATPIII guidelines, their extension to those at elevated absolute risk for CVD using a risk-based approach represents a paradigm shift from prior ATP III guidelines that emphasized treatment thresholds for LDL-C.

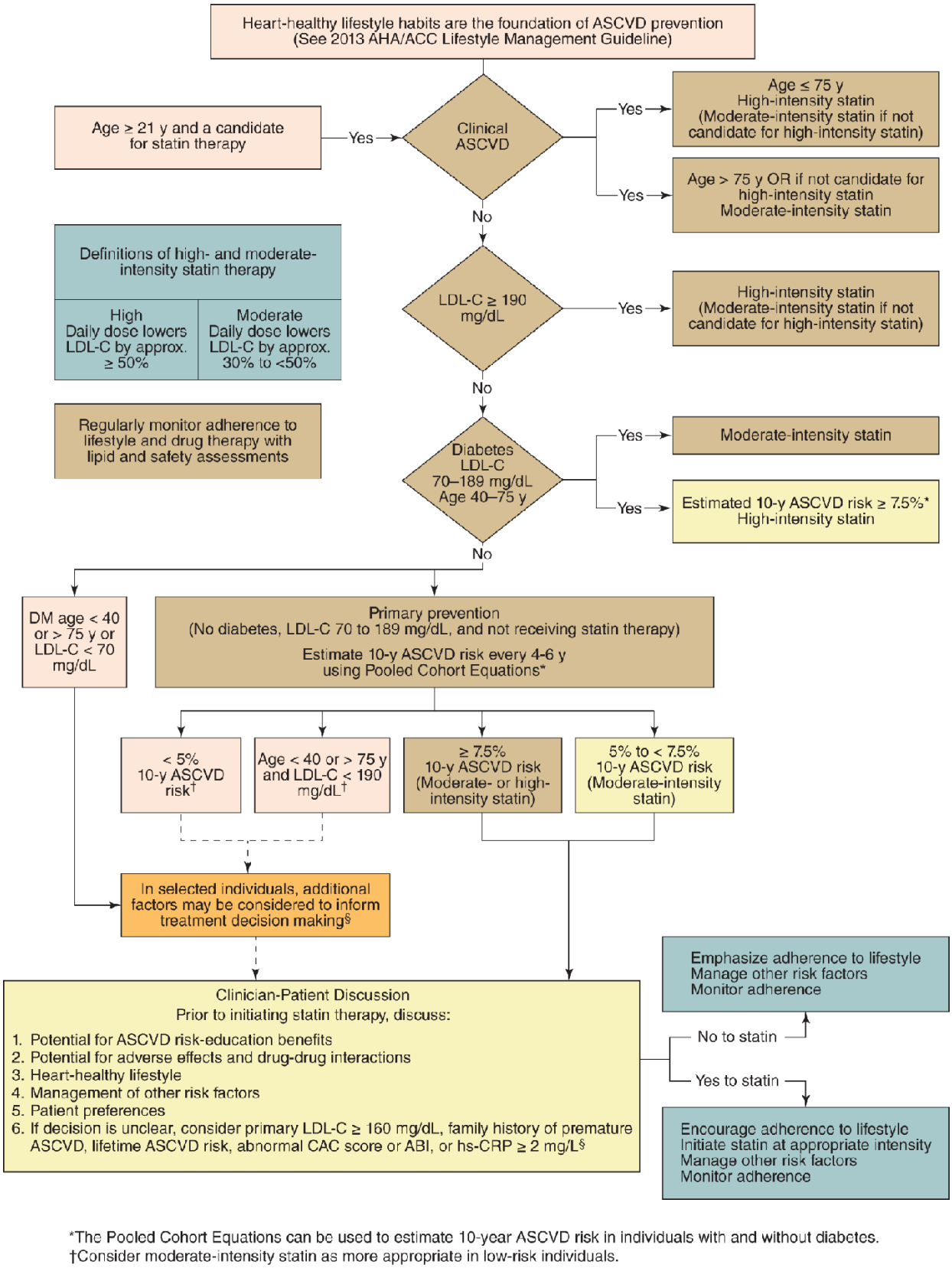


FIGURE 111-5. Summary of the ACC/AHA statin initiation recommendations for the treatment of blood cholesterol to reduce ASCVD risk in adults. Note difference decision points based on the age of the patients and presence or absence of overt ASCVD and diabetes. The reader should consult the source guidelines for a more complete explanation of the nuances in the decision pathways. (From Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63[25 pt B]:2889–2934.)

The new guidelines suggest the use of statins for the primary prevention of CVD in anyone with an LDL-C greater

than 190 mg/dL, individuals aged 40 to 75 with diabetes, and those aged 40 to 75 with LDL-C greater than 70 mg/dL but less than 190 mg/dL who have at least a 7.5% estimated 10-year risk of developing ASCVD. The use of the risk-based equations substantially increases the number of older adults eligible for statin therapy, particularly if one uses the threshold of 7.5% for 10-year mortality risk for primary prevention of ASCVD, since individuals above the age of 75 would qualify for statin therapy solely based on their age. However, the outcomes of the IMPROVE-IT trial reinforce the tenets of the LDL hypothesis and the analyses of CTT collaborators that on average, a 1 mmol/L reduction in LDL-C by any means results in a consistent 23% reduction in major CVD events over 5 years; this may lead to future modifications in the ACC/AHA guidelines. Additional clinical trials are needed to determine meaningful equations and guidelines to risk stratify those above the age of 75 and identify older adults who would benefit the most from primary and secondary ASCVD preventive therapy.

The 2015 National Lipid Association Expert Panel consensus recommendations were similar in many regards to the NECP and ATP III guidelines. They include obtaining a fasting or nonfasting lipoprotein profile in all adults greater than 20 years at least every 5 years. The lipoprotein profile should be considered in conjunction with other ASCVD risk determinants in setting treatment goals and strategies. It is important to note that there is no explicit upper age limit to this recommendation.

The relative risk of hyperlipidemia for CHD is lower in older adults than in younger people because of competing causes of mortality and cumulative effects of comorbid diseases, due to both the high absolute and attributable risk for CHD events among older individuals. Thus, a given therapeutic treatment such as statin therapy will prevent a greater number of events in older than in younger people. Based on Cholesterol and Recurrent Events (CARE) data, Lewis and colleagues estimated that 225 cardiac events (27 of them fatal) would be prevented for every 1000 older (> 65 years) CHD patients with baseline cholesterol concentration less than 240 mg/dL treated with statin therapy for 5 years compared to 121 events (11 of them fatal) prevented in younger patients. ATP III estimates that the number needed to treat (NNT) with statin therapy with the aim of preventing a single CHD event by age 80 is only 10 for a 65-year-old person with a 10-year risk for hard CHD end points of 10%. The NNT for a 65-year-old patient with a 20% 10-year risk for hard CHD end point is 5. Thus, older adults with CHD and those with multiple risk factors would be expected to particularly benefit from pharmacologic therapy because of their high absolute and attributable risk.

The risk-based algorithms of ACC/AHA and Framingham Risk Score focus on 10-year risk. Such an approach is criticized by numerous experts because the equations might not accurately estimate risk in some ethnic populations. Furthermore, the paucity of data in the oldest old people leads to errors when extrapolating the estimate to those above 80 years. The equations are also criticized because they do not take into consideration values and habits from earlier life, that is, exposure of dyslipidemia, cigarettes, diabetes, etc over time, and the progressive risk for the development of atherosclerosis.

The screening of older individuals, particularly those without overt CVD for dyslipoproteinemia, and the treatment of hyperlipidemia in older individuals with CVD remains controversial because of the paucity of data in patients greater than 80 years and in ethnic minority populations. There is no value in screening for dyslipidemia if these results will not be used to guide lifestyle and/or pharmacologic interventions. Most geriatricians emphasize a patient-centric approach (focused by the patient's values) to the consideration of all therapies (including the evaluation and treatment of dyslipidemia), with considerations of both short-term and longer-term treatment goals informed by the presence or absence of CHD as well as multimorbidity, polypharmacy, and functional status.

The foregoing arguments about evaluation (and therapy) need to be viewed in the context of several secular changes. First, the published screening guidelines generally assume that the clinician is faced with a de novo decision of whether the older patient should be screened for hyperlipidemia, when most of these individuals have had prior evaluations in middle age or earlier. Indeed, cholesterol profiles are routinely obtained as part of the automated battery of laboratory tests in patients admitted to the hospital, and widespread cholesterol screening has occurred over the past 30 years. Thus, most older individuals, particularly those at risk or with CVD, have already had multiple measurements of their lipid profiles. Therefore, whether or not to screen de novo is often a moot point.

Second, given secular increases in the use of hypolipidemic drugs for both the primary and secondary prevention of CHD in middle-aged and older individuals, an increasing number of older patients referred to geriatricians will already be on lipid-lowering medications. National data indicate that at least 40% of older adults have been prescribed statins. For these patients, the geriatrician in consultation with the patient will have to decide on the appropriateness of continuing or increasing therapy. Unless there are compelling reasons, it will be difficult to discontinue medications in older patients with overt CVD and in those with multiple risk factors for CVD.

Third, there is growing emphasis on maintaining or increasing functional independence and quality of life in older adults. The prevention of coronary or vascular events that contribute to disability in older adults must be factored into

any decision related to the screening and treatment of hypercholesterolemia. Some of the pharmacologic agents appear to have beneficial effects independent of their lipid-lowering effects (ie, pleiotropic effects). For example, statins may have antioxidant properties and are associated with improvement in endothelial function, improved nitric oxide metabolism, and reduced inflammation. Statin users appear to have a lower prevalence of Alzheimer disease than nonstatin users. Two studies have demonstrated that the decline in cognitive function in older adults is slower in patients treated with statins than in control groups. However, in more recent randomized clinical trials statins did not reduce the incidence of Alzheimer disease. Thus, some clinicians will place older patients on statins hoping for the secondary (pleiotropic) benefits, despite a lack of convincing evidence that the therapy will be efficacious.

Fourth, the results of the PROSPER, HPS, IMPROVE-IT, and other studies support the use of pharmacologic interventions for the secondary prevention of CVD in older individuals up to the age of 80. With no definitive data demonstrating a lack of effectiveness among older individuals (> 80 years), delaying evidence-based preventive therapy on the basis of age alone, while awaiting definitive studies, may be untenable.

Finally, the question of when and in which patients to pharmacologically intervene will be influenced by the development of new pharmacologic agents that target the underlying mechanisms of CVD. A multitude of new agents are currently in development and are undergoing clinical trials. New experimental agents, including PCSK9 inhibitors, which are monoclonal antibodies that target and inactivate proprotein convertase subtilisin kexin 9 in the liver and dramatically lower LDL-C by as much as 60%, have shown promising results to reduce major CHD events in early clinical trials. This class of drugs is now FDA approved for LDL-C lowering and may become the first-line drug for subjects who don't tolerate statins, as well as for the primary and secondary prevention of ASCVD in high-risk, statin-resistant patients with familial hypercholesterolemia. Lomitapide, an inhibitor of microsomal triglyceride transfer protein (MTP) decreases the secretion of apoB containing proteins by the liver, and is now approved by the FDA as an adjunct to a low-fat diet and other lipid-lowering therapies for reducing LDL-C in patients with homozygous familial hypercholesterolemia. However, gastrointestinal side effects and other toxicities may limit its use.

Therapeutic Lifestyle Intervention

ACC/AHA diet Epidemiologic and interventional studies provide strong support for the role of nutrition in preventing and treating heart disease by reducing modifiable CVD risk factors. In 2013 the ACC/AHA released evidence-based recommendations for dietary patterns that reduce total and LDL-C associated CVD risk by reducing the amount of saturated fatty acid (SFA) and trans fatty acid (TFA) and replacing them with unsaturated fat and unrefined carbohydrates. The guidelines encourage the consumption of a Dietary Approaches to Stop Hypertension (DASH), USDA, or AHA diet plan consisting of nutrient-dense foods high in dietary fiber (> 14 g/1000 calories consumed), whole grains, vegetables, and fruit sources. Meals should be prepared without solid fats and sugars, should limit sweetened beverages and should include poultry, lean meat, fish-seafood, eggs, low-fat dairy, nontropical vegetable oils and nuts, vitamin D, calcium, and potassium. To meet macronutrient targets, calories from fat should be reduced to 25% to 30% and consist mainly of mono- and polyunsaturated fat with saturated fat limited to 5% to 6%, TFA less than 1%, sodium intake less than 2400 mg/day, and alcohol to one drink/day in women and two drinks in men. Additional suggested lifestyle behaviors are to reduce and maintain weight at desirable levels as well as participate in regular aerobic exercise. National Heart, Lung, and Blood Institute (NHLBI) evidence is high that this diet plan reduces LDL-C by approximately 11 to 13 mg/dL, TG approximately 1 to 2 mg/dL, and blood pressure approximately 5 to 6/3 mm Hg, and that replacing 10% carbohydrate with 8% monounsaturated fatty acids (MUFA) and 2% polyunsaturated fatty acids (PUFA) will reduce elevated TG by an additional approximately 10 mg/dL. There is insufficient evidence to determine whether lowering dietary cholesterol below 200 mg/day reduces LDL-C levels.

Mediterranean diet The Lyon Heart Study, the PREDIMED trial, and several large prospective cohort studies have shown that the Mediterranean diet, which emphasizes the consumption of fresh fruits and vegetables, whole grains, beans, nuts, fish, olive oil, and even red wine, is associated with lower cholesterol, TChol/HDL, and systolic blood pressure levels, and reductions in CHD and total mortality. In the PREDIMED multicenter clinical trial, adults aged 55 to 80 with diabetes or three or more major CVD risk factors who abided by the diet for a median of 4.8 years were 30% less likely to develop heart disease than those on the control, low-fat diet. Adherence to the Mediterranean diet also has been linked to reduced risk of diabetes, lower blood pressure, better success at weight loss, and decreased risk of dementia. Potential downsides to the Mediterranean diet include the need for calcium supplementation, as people on this diet consume few dairy products, and the potential for weight gain due to the high caloric content of nuts and olive oil, and consumption of wine, which is not a good option for some people. We advocate mixing the best features of the

Mediterranean diet with the DASH and AHA diet.

Weight loss In obese individuals, moderate weight loss in combination with aerobic exercise will decrease total and LDL-C concentrations by 10% to 15%, TG by 15% to 20%, increase HDL-C by approximately 15%, improve glucose tolerance, and lower blood pressure. Moreover, the lipid-lowering response to lifestyle interventions is related to the initial lipoprotein profiles (ie, those with the highest baseline cholesterol concentrations show the greatest improvements) and probably selected gene polymorphisms. However, the beneficial effects of low-calorie, low-fat diets in reducing total and LDL-C concentrations may be tempered by reductions in HDL-C, and without concomitant weight loss, the LDL-C/HDL-C ratio may actually increase. This suggests that high carbohydrate diets might not be optimal for older women in whom HDL-C concentrations are a major determinant of CHD risk; however, the beneficial effects of reduced atherogenic LDL-C concentrations may outweigh any putative harmful effects of reductions in HDL-C. The exchange of mono- and polyunsaturated fat for dietary carbohydrate may lessen the decline in HDL-C.

Exercise/physical activity The AHA/ACC guidelines and the American College of Sports Medicine strongly recommend that adults participate in regular aerobic physical activity to reduce dyslipidemia, as well as lower blood pressure and glucose-/diabetes-related CVD risk factors. They advise adults to participate in moderate- to vigorous-intensity aerobic exercise lasting on average 40 minutes per session at least 3 to 4 days per week for approximately 150 minutes per week for high-risk asymptomatic (no angina on exertion) older individuals with multiple CVD risk factors. We recommend these patients be evaluated by their physician before exercising independently, and those with overt manifestations of CVD, for example, angina, congestive heart failure (CHF), and stroke should be supervised. Some of the health benefits of exercise are related to accompanying weight loss and changes in body fat distribution. Weight loss combined with aerobic exercise improves lipid concentrations, as well as glucose tolerance and blood pressure in middle-aged and older women and men more than either intervention independently, whereas aerobic training without weight loss yields substantially less beneficial metabolic effects. Additionally, for older adults we recommend the incorporation of strength training exercises to improve muscle strength, mass and endurance, prevent osteoporosis and sarcopenia, and aid balance. Machines are recommended over free weights for ease and safety, and the addition of yoga and Tai Chi will enhance balance function. Strength training exercises ideally should involve 10 to 15 repetitions of each major muscle group at an intensity of 65% to 75% of the maximum weight that can be comfortably lifted for a given muscle group (one repetition maximum) three times per week for approximately 30 minutes. Progressing the program in frequency, intensity, and duration for each muscle group maximizes the benefits. A complete lifestyle intervention of aerobic and strength training exercises that achieves and maintains optimal weight is likely to lead to the greatest reductions in CVD risk factors, maximize their long-term maintenance, enhance quality of life, and have a positive societal effect for older individuals.

Pharmacologic Therapy

In many older patients with hyperlipidemia at risk for CHD, therapeutic lifestyle interventions do not effectively lower LDL-C within the target range. Although for many adults, monotherapy with a statin can safely achieve LDL-C target goals, several classes of drugs are available to treat hyperlipidemia, as outlined later. The clinician should consult package inserts and other pharmacologic resources to obtain the most up-to-date information before prescribing these medications. A large number of nutraceuticals and dietary supplements are also employed to improve lipoprotein profiles, although their use is beyond the scope of this chapter.

HMG-CoA reductase inhibitors (statins) and ACC/AHA treatment guidelines The new ACC/AHA guidelines emphasize the role of statins to treat dyslipidemia, and de-emphasize the use of other classes of medications. Statins inhibit hepatic hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme catalyzing the rate-limiting step in hepatic cholesterol synthesis, thereby reducing cholesterol production. This upregulates LDL receptors by hepatocytes and increases removal of apoE- and B-containing lipoproteins from the circulation and reduces the synthesis and secretion of lipoproteins from the liver. Statins lower LDL-C, increase the removal, and reduce the secretion of remnant particles, VLDL and IDL (non-HDL-C). Therefore statins are effective in treating patients who have an elevation of both LDL-C and TG. Depending on the dose and statin employed, the anticipated lipoprotein effects of statins include lowering LDL-C by 18% to 55%, increasing HDL-C by 5% to 15%, and lowering TG by 7% to 30%.

There remains controversy regarding the adverse risks associated with statin therapy for muscle, liver, and diabetes events. The consensus statements from the 2014 Statin Task Force on Liver Safety and recent comprehensive reviews

on these risks are that although statins potentially may cause these events in patients already at high risk, the cardiovascular-related health risks of not taking a statin far outweigh them. They stress the benefits of prior measurement of baseline liver and muscle enzymes, glucose, and renal function both prior to and during therapy. The most common side effects are those related to muscle and liver toxicity. Meta-analyses of 35 randomized controlled trials and examination of Medicare databases demonstrate that statins are safe with a risk of transaminase elevation in about 4/1000 patients and rarer cases of fatal rhabdomyolysis and hepatotoxicity. Contrary to some clinical observations, the rate of myalgia (5%) and creatine kinase elevations (1%) in the meta-analysis for statins was similar to placebo.

Data from clinical trials also demonstrate an increase in the incidence of new-onset type 2 diabetes with the use of statins, although estimates of this risk are highly variable with the greatest risk in those on the higher statin doses and in those at higher risk for diabetes. A meta-analysis showed that treatment of 498 people for 1 year with high-dose statins would result in one excess case of diabetes. By contrast, treatment of 155 people for 1 year would prevent one CVD event. This suggests greater than three CVD events would be prevented for every excess case of diabetes. Concerns about other side effects, especially cognitive dysfunction and cancer are largely not supported by the available data. The protective effects of statin therapy may go beyond simple lipoprotein reduction to include possible anti-inflammatory, antioxidant, and antithrombotic effects, as well as effects on nitric oxide metabolism. Thus, the data from multiple meta-analyses of objective, large-scale clinical trials indicate that statins are remarkably safe, that severe side effects are rare and can be screened, treated, and monitored concomitant with statin therapy. Considering the high prevalence of well-known factors that increase the short-term risk for CHD and the high attributable risk associated with factors that affect the long-term development and progression of ASCVD in older adults, moderate statin therapy for at-risk older people is justified.

Proprotein convertase subtilisin/kexin type 9 inhibitors The PCSK9 inhibitors are a new class of drugs (FDA approval June 2015) that inhibit a protein that controls the number of LDL receptors which play a critical role in regulating blood cholesterol levels by binding to LDL particles and regulating the removal by the liver of most excess cholesterol from the body. There are several PCSK9 mutations that cause an inherited form of high or low cholesterol due to a change of amino acid sequence in the PCSK9 protein. The mutations responsible for hypercholesterolemia are referred to as “gain in function” and those for hypocholesterolemia as “loss of function” because they enhance or reduce the activity of the PCSK9 protein to reduce or increase the number of LDLRs on hepatocytes, thereby giving the protein a new, atypical function. Individuals with “gain-in-function” mutations have excess cholesterol that is deposited abnormally in walls of coronary arteries and other tissues, increasing the risk of having a heart attack and death. In contrast, people with the more common “loss-of-function” mutations have very low LDL-C (14–57 mg/dL) and a lower-than-average risk of developing CVD.

PCSK9 inhibition lowers LDL-C from 39% to 62% as monotherapy versus placebo and up to 73% in combination with statins (at a 75 mg q2wk dose) and 62.6% as monotherapy versus placebo at 150-mg q2wk. It also lowers Lp(a), which can contribute 30% to 45% of total LDL-C, by 9% to 25%. Although the FDA did not require an outcomes study, approval was provided for PCSK9 administration as monotherapy or in combination with a statin or other nonstatin, as well as in patients who cannot tolerate statins, to lower LDL-C to target. Long-term clinical CVD and other outcome studies are currently in progress.

Second-line drugs for treatment of dyslipidemia

Fibrates The fibrates decrease the production of VLDL and increase the clearance of triglyceride-rich lipoproteins. The latter is mediated by the peroxisome proliferator-activated receptor (PPAR)-α and by an increase in lipoprotein lipase, and the expression of apoA-I and A-II, ABCA1, and SR-BI, which play a role in RCT. Fibrates also increase HDL-C and apoA-I, and may lower VLDL-apoB. Fibrates are indicated in the treatment of patients with high TG, low HDL-C, and combined hyperlipidemia.

Ezetimibe Ezetimibe is an inhibitor of intestinal cholesterol absorption. It reduces the amount of biliary and dietary cholesterol delivered to the liver and reduces the cholesterol content of atherogenic remnant particles, VLDL, and LDL. The reduced delivery of intestinal cholesterol to the liver increases hepatic LDL receptor activity and increases clearance of circulating LDL. The use of ezetimibe alone or in combination with statins remains controversial as the additional lowering of LDL-C with this medication has not consistently been associated with improved CVD outcomes. Results of the IMPROVE-IT trial emphasize the CHD preventive value of adding ezetimibe to statin therapy, as the 24% additional LDL-C lowering by combined therapy was associated with a 2% absolute risk reduction in the primary composite CVD end point. The effect occurred primarily due to reductions in rates of myocardial

infarction and ischemic stroke. There also was an absolute 9% greater CVD risk reduction in patients greater than or equal to 75 years in the statin-ezetimibe–treated group (39% vs 48%), and a 5.5% greater reduction in events in patients with diabetes (40 vs 45.5%). There were no differences in prespecified safety end points of muscle, hepatobiliary, or cancer side effects between groups. The reduction in major CVD events achieved with the addition of ezetimibe to simvastatin was comparable to the 23% estimated to be achieved by a 1 mM reduction of LDL-C with statin therapy. Thus, the IMPROVE-IT outcomes reinforce the value of further reduction in LDL-C, even by a nonstatin, for the prevention of CVD end points. Conversely, the results of the ENHANCE trial questioned the CHD preventive value of adding ezetimibe to statin therapy, since combined therapy did not affect CIMT in patients with familial hypercholesterolemia, despite a 20% greater reduction in LDL-C and C-reactive protein (CRP) levels compared to statin alone. However, considering the impact of IMPROVE-IT, the vascular outcome used in ENHANCE raises questions as to the validity of surrogate end points in patients who primarily develop coronary, not carotid atherosclerosis.

Bile Acid Sequestrants Bile acid resins are generally considered second-line agents for the treatment of hypercholesterolemia and are currently used only in people who are intolerant of statins or have contraindications to the use of statins. Bile acid sequestrants bind them in the intestine, thereby reducing the enterohepatic recirculation of bile acids. This promotes the upregulation of the enzyme 7α-hydroxylase and the conversion of more cholesterol in the hepatocyte into bile acids. This decreases the cholesterol content in the hepatocyte, which enhances LDLR expression, leading to increased clearance of LDL and VLDL remnants from the circulation. However, this also results in an increased synthesis of cholesterol and VLDL by the liver, thereby partially negating the LDL-C-lowering effects of the sequestrants. Caution is indicated in the use of the resins in patients with elevated TG, as they may increase hepatic VLDL production, thereby raising TG levels. Bile sequestrants also can augment statin-associated LDL-C reductions by 10% to 25% in patients who cannot tolerate high statin doses. However, they can impair statin absorption, and so administration must be delayed by 4 to 6 hours. Bile sequestrants combined with statin and niacin in the Familial Atherosclerosis Treatment Study resulted in 30% to 40% reductions in LDL-C, increases in HDL-C, and regression/decreased progression of atherosclerosis, but drug side effects limited compliance.

Nicotinic Acid (Niacin) Nicotinic acid inhibits the peripheral mobilization of free fatty acids, thus reducing hepatic synthesis of TG and the secretion of VLDL, increases the production of apoA-I, thereby raising HDL-C and reduces the number of LDL particles. Despite the favorable lipoprotein changes in the AIM HIGH and HPS2-THRIVE studies, there was no incremental clinical benefit in reduced CVD outcomes from the addition of niacin (vs placebo) to statin therapy in patients with ASCVD and LDL-C levels less than 70 mg/dL. In the HPS2-THRIVE study there was considerably more pruritus, rashes and flushing, GI and hepatobiliary symptoms, myopathy and diabetic complications when extended-release niacin (ERN) plus laropiprant (prostaglandin D2 receptor inhibitor) was used with statins, compared to the AIM HIGH study, which used ERN alone with statin. Due to the lack of clinical benefit and side effects of niacin when added to statin, we recommend caution, gradual dosing, and careful monitoring when using niacin in older people.

Recommendations for the Primary and Secondary Prevention of ASCVD

Our position is that lifestyle interventions, particularly exercise training/increased physical activity by running/walking for 150 min/week and adherence to the 2014 ACC/AHA or DASH diet are beneficial to improve quality of life and function in older adults, and should be universally recommended. Weight loss and medical nutrition therapy is particularly beneficial in obese individuals with the metabolic syndrome and type 2 diabetes. The adoption of the DASH diet, restriction of saturated and trans-unsaturated fats, and increase in dietary fiber are recommended to improve lipids. Many also advocate the Mediterranean diet.

The use of pharmacologic therapy to prevent CVD in older adults without prevalent CHD (true primary prevention of CVD) remains controversial. About 40% of older adults are already on statins and about 75% of statins are prescribed for primary prevention. Age has a substantial effect on predicting absolute risk, and many older patients exceed thresholds for treatment solely based on their age. Estimation of lifetime risk provides a useful conceptual framework for the primary prevention of CVD. In the Framingham Heart Study, among men free of prevalent CHD at age 50, the lifetime risk of developing CHD was 52%, while the estimated lifetime risk was 39% in women. Factors associated with survival to age 85 include female gender, lower total cholesterol, lower systolic blood pressure, better glucose tolerance, not smoking, and higher education levels. At the age of 50, the lifetime risk for men with an optimal CHD risk profile for developing CHD was 5% compared to 69% for men with two or more risk factors. In women,

those with optimal CHD risk profile had an 8% risk compared to a 50% risk in women with two or more risk factors. Median survival was more than 11 years longer and 8 years longer, respectively, in 50-year-old men and women with optimal CHD risk factors. This suggests that there are substantial long-term benefits from optimal control of CVD risk factors. Thus, older patients with CHD and those with multiple risk factors would be expected to particularly benefit from pharmacologic therapy because of their high absolute and attributable risk.

In the area of primary prevention, we advocate a patient-centered approach where decisions regarding statin use in older patients are made on a case-by-case basis. Before initiation, or continuation of lipid-lowering therapy, the geriatrician should discuss with their patients the goals of treatment, the potential for adverse side effects, and the importance of adherence to lifestyle modification and pharmacologic therapy for an extended period of time. There may also be value in the noninvasive assessment of structural, functional, and circulating biomarkers of arterial vulnerability (CIMT, coronary artery calcium, brachial artery reactivity, ankle-brachial index, hs-CRP, and advanced glycation end products) to identify older adults with evidence of subclinical disease who may particularly benefit from aggressive pharmacologic intervention. However, the clinical utility of these measures may be limited due to their lack of standardization, paucity of clinical trial data supporting their use, and costs associated with subsequent evaluations for abnormal and incidental findings.

SECONDARY AND OTHER MEDICAL CAUSES OF HYPERLIPIDEMIA

Secondary Hyperlipidemias

In evaluating an older patient with dyslipidemia, the geriatrician should consider the possible contributions of secondary factors. Identifying potentially treatable or modifiable secondary factors is important because they occur more often in older patients than in younger adults, and it helps considerably with overall management. These secondary causes include obesity, diabetes hypothyroidism, obstructive liver disease (primary biliary cirrhosis, etc), nephrotic syndrome, chronic renal failure, human immunodeficiency virus (HIV), the use of certain drugs, alcohol consumption, and smoking. The measurement of thyroid function is of particular importance in older subjects, as clinically silent hypothyroidism may occur with associated secondary elevations of LDL-C and TG. In one series of patients referred to a lipid clinic for hyperlipidemia, 3% had overt hypothyroidism and 4% had subclinical hypothyroidism.

Dyslipidemia associated with lifestyle habits of sedentary behavior, high-fat diets, cigarettes, and the development of obesity represents the primary modifiable CVD risk factors in older people. Their treatment is difficult due to noncompliance in maintaining healthy habits. Our recommendations are to follow the guidelines from AHA/ACC, Obesity Society and American Diabetes Association for improving these behaviors.

Lipoprotein abnormalities are also common in a host of other diseases. Elevated LDL-C often exists in patients with nephrotic syndrome, obstructive liver disease, and anorexia nervosa, while high TG and low HDL-C are seen with insulin resistance, metabolic syndrome, type 2 diabetes, nonalcoholic fatty liver disease and hepatosteatosis, Cushing syndrome, and polycystic ovarian syndrome. All the lipoprotein subclasses can be abnormal in patients with chronic kidney disease depending on the severity of renal disease, and the presence of diabetes, autoimmune disease, and certain medications. As patients with human immunodeficiency virus infection are living longer, the geriatrician may see them for combined hyperlipidemia, falls, and dementia. Elevated TG and low HDL-C are common and may worsen with antiretroviral treatment, particularly with ritonavir. In addition, chronic inflammation, caused by systemic autoimmune conditions, lupus, rheumatoid arthritis and myeloma, may be associated with high TG and low HDL-C.

There are several basic screening investigations that will help exclude the most common non–drug-related secondary causes of dyslipidemia before initiating lipid-lowering treatment. These include (1) renal disease—urine analysis with protein, creatinine, urea nitrogen, serum protein electrophoresis; (2) diabetes—HbA_{1C}, glucose; (3) thyroid disease—thyroid-stimulating hormone (TSH), T_4; (4) liver disease—bilirubin, aspartate and alanine aminotransferase, alkaline phosphatase; (5) Cushing—cortisol stimulation or suppression test; and (6) HIV testing.

Medications

A number of medications commonly used in older adults can adversely affect lipid profiles. Although diuretics and β-blockers can raise TG and lower HDL-C, the beneficial effects of these medications on blood pressure in general outweigh their adverse effects on lipids. The effect of steroid hormones on lipoprotein lipids varies with the drug, dose, and route of administration. In general, anabolic steroids lower HDL-C and have a variable effect on LDL-C. The

effects of progestins to lower HDL-C and raise LDL-C vary greatly depending on their androgenicity, and estrogens can cause hypertriglyceridemia. Glucocorticoids raise HDL-C, TG, and LDL-C, and retinoids increase TG and LDL-C and reduce HDL-C. Interferons can cause hypertriglyceridemia, and medications used to prevent rejection following organ transplantation such as cyclosporine and CellCept (mycophenolate mofetil) can also cause dyslipidemia that may result in accelerated atherosclerosis. Antiretroviral therapy for HIV, particularly protease inhibitors, can cause combined dyslipidemia characterized by elevated TG and LDL-C and low HDL-C and other metabolic abnormalities (lipodystrophy syndrome) that increase risk for atherosclerosis.

If a secondary cause for the dyslipidemia is found, the underlying cause should be treated before consideration of a lipid-lowering agent. A dyslipidemia associated with secondary factors usually improves, but may not resolve completely with treatment of the secondary factors.

Hypocholesterolemia

The relationship between total cholesterol and both CHD and all-cause mortality is positive until around the seventh or eighth decade of life, when these relationships start to become negative. Thus, in the oldest age groups there is increased mortality in those with the lowest cholesterol levels. The prevalence of hypocholesterolemia (typically defined as total cholesterol concentrations < 160 mg/dL, the sixth percentile in the Multiple Risk Factor Intervention Trial), increases with age. Age group–specific analyses suggest increased total and specifically non-HDL-C are associated with a lower risk of nonnoncardiovascular mortality in adults greater than 65 years, and that the hypocholesterolemia-associated mortality seems cancer and chronic disease related. A J-shaped relationship between cholesterol and mortality is sometimes observed, suggesting that hypocholesterolemic individuals are at increased risk of death. Biologically plausible mechanisms linking low total cholesterol to death include inflammation-mediated cytotoxic alterations in cell membrane structure and function, abnormalities in growth factors and steroid metabolism, and fat-soluble vitamin deficiencies. Multiple cohort studies show that men and women with cholesterol concentrations less than 160 mg/dL are at a 40% higher risk for noncardiovascular deaths more than 5 years after baseline measurement than individuals with cholesterol concentrations 200 to 239 mg/dL. These associations can be confounded by weight loss, especially when associated with the presence of active or subclinical/occult disease, such as chronic infection and inflammation, cancer, diabetes, CHF, and chronic obstructive pulmonary disease, and polypharmacy. These diseases are associated with inflammation, which suppresses hepatic cholesterol synthesis and/or accelerates cholesterol catabolism. This bias potentially can be eliminated by the longitudinal analysis of cohort data after excluding individuals with early deaths (who may have had an undiagnosed disease). Such studies, in a variety of populations, have revealed correlations of low cholesterol with nutritional and functional status, as well as cognitive function.

In evaluating an older patient with hypocholesterolemia, we recommend consideration of the pattern of change of cholesterol concentrations over time and their relationship with other diseases, changes in appetite and taste, intentional and unintentional weight loss, multiple medications, and life events. In patients with a lifelong history of low cholesterol level and excellent CVD health, and a family history of low cholesterol associated with reduced incidence of CVD should alert the geriatrician to consider familial hypobetalipoproteinemia. This autosomal dominant condition is associated with LDL-C levels below 75 mg/dL and apoB below 50 mg/dL with no evidence of underlying dietary, chronic disease (hyperthyroidism, cancer) or nutritional etiology. ApoB nonsense variants that change the translation of apoB and loss-of-function mutations of the *PCSK9* gene cause marked reductions in LDL-C and the incidence of CHD. Once these possibilities are excluded, we recommend screening blood tests of renal, liver, nutrimetabolic, and hematologic function and noninvasive cancer evaluations (prostate-specific antigen [PSA], chest x-ray, mammogram, colonoscopy, etc) in otherwise healthy community-dwelling individuals with hypocholesterolemia. There are sparse data on the association of medically, statin-lowered cholesterol concentrations below 180 mg/dL (4.65 mmol/L) to cancer in older people over prolonged periods, or whether nutritional therapy should be provided for middle-aged and older people with hypocholesterolemia of undetermined etiology.

Dyslipidemia in the Nursing Home Setting

CVD is prevalent in nursing home patients, and many nursing home residents already are on statins or potentially could be prescribed them based on 2013 ACC/AHA guidelines for high CVD risk. Nonetheless, management of dyslipidemia in extended care facilities remains controversial, and there is only limited data to suggest benefit. Data collected in the late 1990s, when only a small percentage of older patients in nursing homes were on statins, demonstrated that after adjusting for age and a variety of comorbidities, nursing home residents over the age of 65 with an active clinical

diagnosis of CVD on statins were 31% less likely to have died and 12% less likely to have the composite end point of either death or hospitalization at 1 year than comparable nonusers. The difference in morality was most striking in women above the age of 75. Extrapolation of this data to the current era is problematic given the different prescribing patterns and the possibility that the nursing patients prescribed the statins in the above analysis were healthier than those who were not prescribed statins even after adjusting for numerous covariables. In addition, the benefits of statins must be balanced against their adverse effects. In one study of 381 palliative care patients with prognoses of 1 month to 1 year treated with statins for at least 3 months, total quality of life was better among those who discontinued statin therapy, despite no difference in survival.

The aforementioned concerns regarding hypocholesterolemia and mortality are also particularly relevant in this population. Although low cholesterol is linked to a greater than sixfold adjusted relative odds rate for death compared to nursing home residents with stable or increasing cholesterol, this association is likely due to unintentional weight loss related to chronic disease, loss of muscle and bone mass, generalized frailty and cancer, rather than to aggressive statin therapy. Yet, the majority of nursing home residents with hyperlipidemia are not on lipid-lowering agents, regardless of age or the presence of cardiovascular or other diseases. It should be noted that the reductions in cardiovascular events and overall mortality seen in the PROSPER study in 70 to 80 year olds favor the use of statins for cardioprotection, although not by lowering cholesterol to the lowest levels as there is no evidence to support primary prevention even in the presence of a high total or LDL-C in the oldest old population.

Although there is no evidence to support treatment with statins in nursing home residents with dementia, frailty or multimorbidity, for those with CHD and good functionality, we recommend using good clinical judgment in considering low-dose therapy for cardioprotection. As with all medication use in older patients potential musculosketal, hepatobiliary, and diabetes side effects of statins should be monitored. Similar to the International Association for Geriatrics and Gerontology, which has proposed the need to determine the relative benefits of statins and other potentially beneficial preventive drugs in nursing home residents, we do not advocate the routine treatment of hypercholesterolemia in older, chronically ill, frail nursing home patients, but rather suggest good clinical judgment in identifying patients in whom the potential benefit outweighs the risks of drug toxicity and treatment costs.

SUMMARY AND CONCLUSION

Atherosclerotic cardiovascular disease is very common in older adults, and clinical trial data provide strong evidence for the treatment of dyslipidemia for both primary and secondary prevention of ASCVD in patients up to 75 to 80 years, with a paucity of clinical data in those above 80 years. Looking ahead, it is not clear how the absence of therapeutic targets for LDL-C in the ACC/AHA guidelines and dramatic LDL-C and Lp(a) lowering effects of PCSK9 inhibitors with and without statins will impact the management of dyslipidemia in older adults. There may be increased pressure for aggressive lipid-lowering therapy in older adults, particularly in the oldest old patients as they are at the highest absolute risk for ASCVD events. The approach to the treatment of dyslipidemia in older adults should be patient centric with all management decisions reflecting patient preferences and taking into consideration the presence or absence of medical comorbidities, risk for drug-induced complications, and goals of care.

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Chapter 112

Hyperparathyroidism and Paget Disease of Bone

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Learning Objectives

Hyperparathyroidism

- Learn how to diagnose primary hyperparathyroidism.
- Evaluate when treatment may be needed in primary hyperparathyroidism.
- Understand the role of medical versus surgical therapy in primary hyperparathyroidism.

Paget Disease of Bone

- Learn how to diagnose and monitor Paget disease of bone.
- Understand when treatment is indicated in Paget disease of bone.

Key Clinical Points

Hyperparathyroidism

1. **Primary hyperparathyroidism is often asymptomatic and is detected using routine laboratory tests.**
2. **When primary hyperparathyroidism is symptomatic, the most common presentation in those over the age of 61 involves nephrolithiasis, fatigue, and bone disease.**
3. **Observation may be appropriate in some patients.**
4. **Surgical treatment should be considered if the patient is symptomatic and/or there are signs of end-organ damage.**
5. **Medical treatment with a bisphosphonate and/or cinacalcet may be an option for nonsurgical candidates who require intervention.**

Paget Disease of Bone

1. **Paget disease of bone is a focal disorder of osteoclasts resulting in increased bone turnover and lytic skeletal lesions that primarily affects older individuals.**
2. **Paget disease is often asymptomatic, but can cause bone and joint pain. A therapeutic trial of bisphosphonates may aid in distinguishing bone pain from nonbone pain.**
3. **Observation and supportive measures may be appropriate for many patients with Paget disease of bone.**
4. **When treatment is indicated, the treatment of choice for Paget disease is an intravenous (IV) infusion of zoledronate 5 mg over 15 minutes. Treatment is targeted to achieve a serum alkaline phosphatase in the lower half of the normal reference range.**
5. **Treatment can normalize bone turnover markers and decrease bone pain; however, there is no evidence that this results in improved long-term outcomes such as prevention of fractures or**

deformity.

HYPERPARATHYROIDISM

Background and Epidemiology

Hyperparathyroidism is a common disorder of calcium, phosphorus, and bone metabolism caused by increased circulating levels of parathyroid hormone (PTH). This disease is important to geriatricians because its incidence increases with age, and it is most common in older people. Hyperparathyroidism is considered primary when hypersecretion of PTH is caused by a fundamental defect of the parathyroid glands resulting from a single parathyroid adenoma, diffuse hyperplasia, multiple adenomas, or, rarely, a parathyroid carcinoma. Secondary hyperparathyroidism occurs when there is a hypocalcemic stimulus, as in cases of vitamin D deficiency or chronic renal failure that results in parathyroid stimulation. Tertiary hyperparathyroidism occurs in patients with chronic secondary hyperparathyroidism who develop autonomous hypersecretion of PTH and hypercalcemia, for example, patients with end-stage renal disease. This chapter focuses on primary hyperparathyroidism.

The incidence of primary hyperparathyroidism in the United States is approximately 1 per 1000. The Rochester Epidemiological Project reported that the peak incidence of primary hyperparathyroidism is 63.2 per 100,000 person-years at ages 65 to 74. Primary hyperparathyroidism can affect both genders at any age; however, the disease affects women more than men by almost 2:1, and in women, it most often occurs in the first decade after menopause. According to the Kaiser Permanente insurance database in Southern California, the incidence of primary hyperparathyroidism varies according to race and is highest in blacks, followed by whites, and then Asians/Hispanics.

The prevalence of asymptomatic primary hyperparathyroidism has increased since calcium was included in basic laboratory panels obtained for routine screening. The Southern California Kaiser insurance database reported the prevalence of primary hyperparathyroidism tripled from 1995 to 2010; increasing from 76 to 233 per 100,000 person-years in women and 30 to 85 per 100,000 person-years in men. Since older people have more frequent contact with medical providers than other age groups, they are likely to have asymptomatic or mildly symptomatic primary hyperparathyroidism identified on routine screening laboratories.

Etiology

In most cases of hyperparathyroidism no specific causation can be identified; these represent sporadic cases. However, a gain-of-function mutation in the *cyclin D1* gene may be involved in the development of parathyroid adenomas in 20% to 40% of cases. Previous exposure of the neck to ionizing radiation is associated with an increased incidence of hyperparathyroidism. Hypercalcemia and increased PTH levels occur in up to 10% of patients treated with lithium for bipolar disorder; hypercalcemia usually, but not always, disappears when lithium is discontinued. Thiazide diuretics can contribute to hypercalcemia, but the persistence of hypercalcemia 6 weeks after stopping a thiazide usually means the use of the drug has unmasked underlying primary hyperparathyroidism by inhibiting renal calcium excretion and allowing hypercalcemia to become manifest.

At all ages, primary hyperparathyroidism is most commonly caused by a benign, single parathyroid adenoma (80%). Less commonly, primary hyperparathyroidism can be due to two or more parathyroid adenomas (< 5%) or four-gland hyperplasia (10%–15%). Determining whether hyperparathyroidism is due to an adenoma or hyperplasia is often difficult to ascertain by histologic features alone, so the gross pathology seen at operation is necessary to determine if there is multiple gland involvement. An adenoma is diagnosed when only one abnormal gland is found (all other glands are normal). Chief cell hyperplasia is diagnosed when more than one abnormal gland is found. A rare form of parathyroid hyperplasia is called “water-clear cell” hyperplasia, in which large, membrane-lined vesicles fill the cytoplasm. The differentiation of multiple adenomas from parathyroid hyperplasia is difficult.

Identification of multiple-gland hyperplasia should prompt the astute clinician to consider the genetic syndromes typically associated with parathyroid hyperplasia (multiple endocrine neoplasia type 1 or type 2A, hyperparathyroidism–jaw tumor syndrome). Although it would be rare for primary hyperparathyroidism to be the presenting manifestation of these inheritable conditions in a geriatric population, it can occur and may alter management for the patient and their family. The presence of these syndromes should be suspected when other family members have had hyperparathyroidism, or other components of the syndromes have been present in the patient or family members (eg, pituitary adenoma, medullary carcinoma of the thyroid).

Very rarely (< 1%), primary hyperparathyroidism can be due to underlying parathyroid carcinoma. This should be suspected when there is severe hypercalcemia with a palpable neck mass that is adherent to surrounding structures or has local or distant metastases at the time of surgery. Pathologically, there are mitotic figures in the parathyroid gland or vascular or capsular invasion.

Pathophysiology

Under normal conditions, the level of calcium in the blood is tightly regulated by PTH. The parathyroid calcium-sensing receptor (CaSR) responds to extracellular calcium levels and modulates PTH production and release to maintain physiologic levels of ionized calcium via a classic feedback mechanism. The CaSR is activated by hypercalcemia resulting in the inhibition of PTH synthesis and secretion. Conversely, when hypocalcemia is present, the synthesis and secretion of PTH is increased.

PTH acts to maintain the physiologic calcium level through three primary mechanisms (**Figure 112-1**):

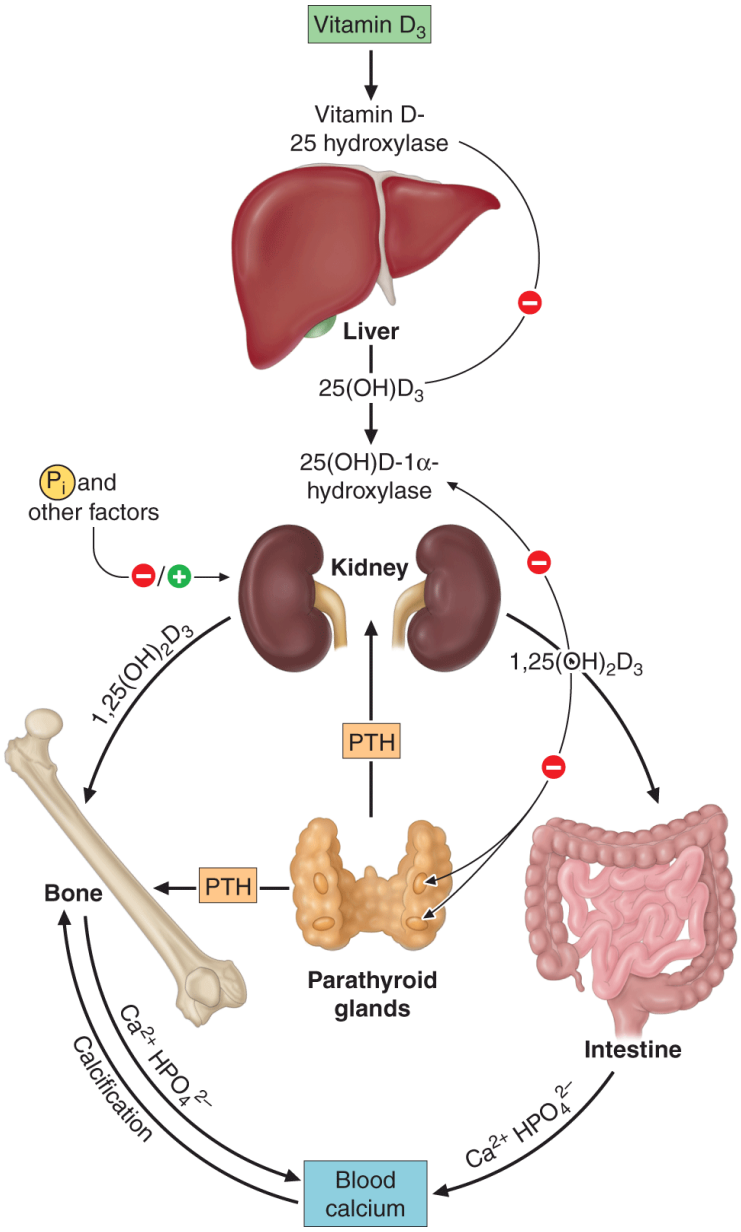


FIGURE 112-1. Schematic representation of the hormonal control loop for vitamin D metabolism and function. A reduction in the serum calcium below approximately 2.2 mmol/L (8.8 mg/dL) prompts a proportional increase in the secretion of parathyroid hormone (PTH) and so mobilizes additional calcium from the bone. PTH promotes the synthesis of $1,25(OH)_2D$ in the kidney, which in turn stimulates the mobilization of calcium from bone and intestine and regulates the synthesis of PTH by negative feedback. (From Bringhurst FR, Demay MB, Krane SM, Kronenberg HM. Bone and mineral metabolism in health and disease. In: Kasper DL, Braunwald E, Fauci AS, et al., eds. *Harrison's Principles of Internal Medicine*. 19th ed. New York, NY: McGraw-Hill; 2015.)

1. Renal: PTH decreases urinary excretion of calcium and increases urinary excretion of phosphate. This increase in urinary phosphate excretion serves to mitigate the increase in serum phosphate levels that results from increased intestinal absorption and release from the bone matrix in response to PTH (below). However, the amount of phosphate excreted in the urine often exceeds the amount of phosphate absorbed in the intestine and released from bone, which can result in hypophosphatemia. PTH also stimulates the 1α-hydroxylase enzyme in the kidney (and other nonrenal tissues) to increase production of 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D (25-OHD). This may result in 1,25-dihydroxyvitamin D levels that are in the upper part of the normal range or slightly elevated, at the expense of 25-hydroxyvitamin D, which is often deficient in primary hyperparathyroidism. 1,25-dihydroxyvitamin D also stimulates 24-hydroxylase, which degrades both vitamin D metabolites, contributing to the 25-hydroxyvitamin D deficiency seen in primary hyperparathyroidism.
2. Bone: PTH has direct effects on many bone cells in order to mobilize calcium and phosphate from their skeletal reservoir. PTH acts, in part, through direct stimulation of osteoblasts in bone which then express receptor activator of nuclear factor κB ligand (RANKL). RANKL stimulates osteoclastic bone resorption to release calcium and phosphate into the blood from the bone matrix.
3. Gastrointestinal (via 1,25-dihydroxyvitamin D): 1,25- Dihydroxyvitamin D increases intestinal absorption of calcium and phosphorous.

In primary hyperparathyroidism, the relationship between the serum calcium level and PTH release is disturbed: PTH secretion persists despite a high level of serum calcium. This results in sustained hypercalcemia. Thus, in hyperparathyroidism levels of PTH are inappropriately elevated. Whereas PTH levels should be low in the presence of hypercalcemia, in hyperparathyroidism the level of PTH is in the upper part of the usual normal range or is frankly elevated—the cardinal diagnostic feature of the disease. There is also a tendency for hypophosphatemia and deficiency of 25-OHD.

Signs and Symptoms

Now that hypercalcemia is being identified with routine laboratories, hyperparathyroidism is detected at an earlier stage and patients present more commonly without symptoms. In fact, approximately 80% of patients with primary hyperparathyroidism in the United States have no signs or symptoms that are referable to their disease. However, in older adults, “asymptomatic” patients may suffer subtle effects of the disease such as decreased functional capacity and quality of life, possibly in part due to concurrent vitamin D deficiency.

Patients with primary hyperparathyroidism who are clinically affected can present with a spectrum of signs and symptoms. An element of the clinical presentation is due to hypercalcemia. Primary hyperparathyroidism typically develops slowly, thereby allowing adaptation to the hypercalcemia. Thus, symptoms of hypercalcemia are usually of gradual onset and relatively mild, but symptoms can vary depending on the severity and duration of the calcium elevation, ranging from the gradual onset of weakness/fatigue to acute hypercalcemic crisis. Acute hypercalcemic crisis is now a rare form of presentation of primary hyperparathyroidism. Therefore, a patient who presents with profound symptoms (eg, stupor or coma), or with a syndrome of more sudden onset is likely to have developed hypercalcemia more acutely. In those patients, an additional reason for the acute worsening of hypercalcemia (eg, immobilization) or an alternative diagnosis (such as malignancy) should be considered.

In addition to the sequelae of hypercalcemia itself, common symptoms of primary hyperparathyroidism have been characterized by the mnemonic “bones, stones, abdominal moans, and psychiatric overtones.” They can include anorexia, nausea, vomiting, abdominal pain (which is typically nonlocalized and vague), constipation, polyuria, polydipsia, confusion, nephrolithiasis, and fractures. Pancreatitis can also occur with or be exacerbated by hypercalcemia. *Central nervous system* findings include impaired cognition, recent memory loss, anosmia, depression, lethargy, and coma. Thus, hypercalcemia and hyperparathyroidism are rare but important considerations in the differential diagnosis of depression and dementia in older people. *Neuromuscular* disturbances include proximal weakness, more prominent in lower than in upper extremities. Many symptomatic patients complain of malaise and fatigue. In rare cases of severe or prolonged hypercalcemia, pruritus can be caused by calcification in the skin. *Articular* disturbances include pseudogout from calcium pyrophosphate crystal deposition in articular cartilage, calcific tendinitis, and chondrocalcinosis. Cardiovascular features, such as hypertension, were more common with the classic presentation of primary hyperparathyroidism but are rare today. At this time, no additional cardiovascular evaluation is recommended in patients with primary hyperparathyroidism.

Nephrolithiasis occurs in 20% of hyperparathyroid patients. Of patients with kidney stones, approximately 5% have hyperparathyroidism. PTH causes a proximal renal tubular acidosis, increasing bicarbonate loss and decreasing hydrogen ion excretion, as well as lowering the phosphate reabsorption threshold. These changes cause a hyperchloremic metabolic acidosis, and 30% of patients will be hypophosphatemic. Hyperparathyroidism can cause nephrocalcinosis and a subsequent decline in the glomerular filtration rate (GFR). More severe hypercalcemia can lead to nephrogenic diabetes insipidus because the renal tubule becomes unresponsive to the action of antidiuretic hormone. Even asymptomatic patients with primary hyperparathyroidism have defects in their ability to concentrate urine that can result in polyuria and polydipsia with subsequent dehydration if their oral intake is unable to compensate for their urinary losses. Dehydration can result in decreased perfusion of the kidney, thereby decreasing the ability to excrete calcium in the urine and leading to worsening hypercalcemia. The geriatric population may be especially predisposed to this vicious cycle due to baseline renal insufficiency, poor intake or inability to compensate for urinary losses. The importance of adequate hydration in primary hyperparathyroidism should be emphasized in this patient population.

Osteitis fibrosa cystica, with radiographic features of osteopenia, subperiosteal bone resorption (**Figure 112-2**), brown tumors, bone cysts, and “salt and pepper” skull, can be the result of prolonged and more severe hyperparathyroidism and thus is now a rare finding. More commonly, patients may present with low bone mineral density (BMD), particularly at cortical sites (eg, distal one-third radius). Fracture risk in severe primary hyperparathyroidism is increased. However, fracture risk in mild primary hyperparathyroidism is unclear, with possibly an increased risk of fracture at the forearm. The risk of vertebral fracture appears to be increased in those with more symptomatic disease and in those who meet criteria for parathyroidectomy (**Table 112-1**). The FRAX fracture risk calculator may not be accurate in these patients.

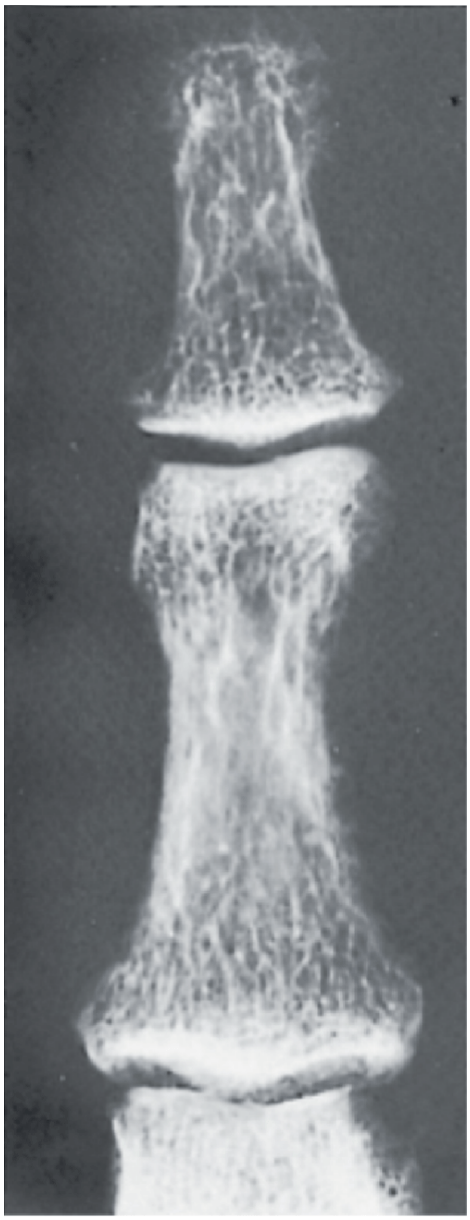


FIGURE 112-2. Subperiosteal resorption. Magnified x-ray of index finger on fine-grain industrial film showing classic subperiosteal resorption in a patient with severe primary hyperparathyroidism. Note the left (radial) surface of the distal phalanx, where the cortex is almost completely resorbed, leaving only fine wisps of cortical bone. (From Shoback D, Sellmeyer D, Bikle DD. Metabolic bone disease. In: Gardner DG, Shoback D, eds. *Greenspan's Basic & Clinical Endocrinology*. 9th ed. New York, NY: McGraw-Hill; 2011. Used with permission from Dr. Harry Genant.)

TABLE 112-1 INDICATIONS FOR PARATHYROIDECTOMY IN PRIMARY HYPERPARATHYROIDISM

Symptoms and/or patient preference
Total serum calcium > 1 mg/dL above the upper limit of normal
Skeletal
• Bone mineral density by DXA: T-score < –2.5 at any site
• Clinical or radiographic evidence of vertebral fracture
Renal
• Creatinine clearance < 60 cc/min
• 24-hour urine calcium > 400 mg/d and increased stone risk by biochemical stone risk analysis
• Radiographic evidence of nephrolithiasis or nephrocalcinosis

Age < 50

Other physical signs are unusual in hyperparathyroidism. Soft tissue calcification can cause pseudogout or cutaneous calcification. When present in the eye, deposits of calcium phosphate crystals can cause conjunctivitis. In the cornea, band keratopathy (lines of calcium phosphate deposition parallel to and within the ocular limbus, usually in the medial and lateral aspects) is best appreciated with a slit-lamp examination. Enlarged parathyroid glands are usually nonpalpable; generally, when a nodule is found in the neck of a hyperparathyroid patient it represents thyroid rather than parathyroid tissue. However, in rare cases a palpable neck mass in a patient with hyperparathyroidism may signal the presence of parathyroid cancer.

Diagnosis

A full list of recommended laboratories and imaging to evaluate patients with asymptomatic primary hyperparathyroidism is presented in **Table 112-2**.

TABLE 112-2 RECOMMENDED EVALUATION OF PATIENTS WITH ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

- Serum laboratories: calcium, phosphate, alkaline phosphatase, BUN, creatinine, 25OHD, PTH (by second- or third-generation immunoassay)
- Three-site bone mineral density by DXA (lumbar spine, total hip, 1/3 distal radius)
- Vertebral spine assessment (x-ray or vertebral fracture assessment by DXA)
- 24-Hour urine for calcium, creatinine, creatinine clearance, and stone risk profile
- Abdominal imaging to assess for nephrolithiasis and nephrocalcinosis (x-ray, CT, or ultrasound)

BUN, blood urea nitrogen; DXA, dual-energy x-ray absorptiometry.

An elevated calcium level should be repeated to rule out a laboratory error. Serum total or ionized calcium levels can be measured. However, each comes with its own caveats. Total calcium is usually an adequate measure of a patient's calcium status. However, in conditions that alter protein levels or acid/base status, consideration should be given to obtaining an ionized calcium level as well.

Serum total calcium measurements Calcium circulates bound to proteins (such as albumin) with only 1% circulating as free (or ionized) calcium in extracellular fluid. Therefore, alterations in total serum calcium can occur with hypo- or hyperalbuminemic states, requiring calculation of serum calcium that has been "corrected" for albumin: Corrected Serum Ca = Total Serum Ca + 0.8 (average normal serum albumin – patient's serum albumin). For instance, a "normal" serum calcium level in a cirrhotic, malnourished or severely ill patient, may be elevated when it is corrected for their hypoalbuminemic state. Gadolinium, administered for magnetic resonance imaging (MRI), can cause spurious hypocalcemia because of altered protein binding of calcium. This is most common within the first 12 hours after gadolinium administration but the susceptible window is longer in those with renal insufficiency. This phenomenon is important for the geriatric population, since they are more likely to have imaging procedures and varying degrees of renal insufficiency.

Serum ionized calcium measurements Ionized calcium can be affected by acid/base disorders. An acidotic serum environment causes calcium to be displaced from its binding sites on albumin by hydrogen ions, thereby resulting in an elevated ionized calcium. Therefore, in cases of acidosis (eg, acute renal failure), ionized calcium can be increased. Conversely, in alkalotic states (eg, fever, hyperventilation), ionized calcium can be reduced. Great care must be taken when collecting serum for an ionized calcium level measurement (including maintaining it anaerobically and analyzing it in the laboratory within 1 hour of it being drawn). Falsely abnormal values can result if specimen collection is not adequate.

When hypercalcemia is confirmed, subsequent evaluation should begin with measurement of PTH (concurrently with calcium) to help establish the etiology. Further laboratory evaluation should depend on these results and the subsequent differential diagnosis. **Figure 112-3** demonstrates the proper evaluation of hypercalcemia. The diagnosis of primary hyperparathyroidism should be strongly suspected in a person with elevated serum calcium and PTH levels that are excessive (in the upper part of the normal range or frankly elevated). A definitive diagnosis of primary hyperparathyroidism can be made after exclusion of other causes of PTH-dependent hypercalcemia (**Table 112-3**).

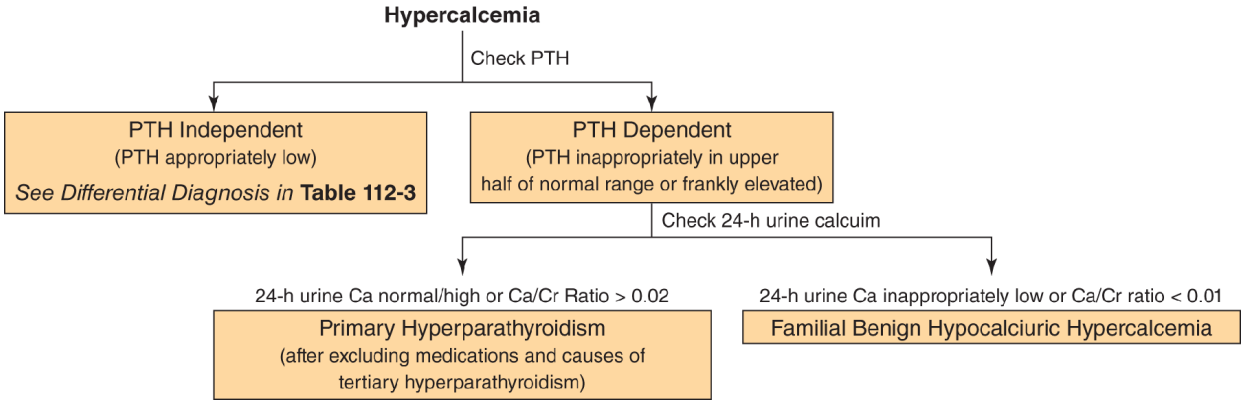


FIGURE 112-3. Suggested algorithm for the evaluation of hypercalcemia. PTH, parathyroid hormone; Ca, calcium; Cr, creatinine.

Serum phosphate levels may be low in hyperparathyroidism but can be normal, especially if there is renal impairment. Although PTH does cause phosphaturia, other factors such as dietary intake and time of day may affect renal phosphate handling. Furthermore, patients with malignancy-associated hypercalcemia can have a decrease in the renal phosphate reabsorption threshold from hypercalcemia per se or from tumor-derived peptides that can produce hypercalcemia. Other serum electrolyte abnormalities, such as elevated chloride, low bicarbonate, and low magnesium levels, are not specific enough to be of diagnostic value. Increased levels of bone turnover markers (eg, alkaline phosphatase) suggest significant skeletal involvement from hyperparathyroidism. Routine use of bone turnover markers in the diagnosis, evaluation, and monitoring of primary hyperparathyroidism is not recommended at this time.

To identify those who may require therapeutic intervention, additional assessment should be performed to assess renal status and bone health. Current guidelines suggest imaging (with abdominal x-ray, ultrasound or computed tomography [CT] scan) to assess for asymptomatic kidney stones and a 24-hour urine collection for a biochemical stone risk profile to identify those who are at increased risk for kidney stones. 24-Hour urine calcium can also aid in distinguishing primary hyperparathyroidism from similar, benign conditions (see Differential Diagnosis of Primary Hyperparathyroidism section later). In primary hyperparathyroidism, the inappropriately elevated PTH stimulates excessive osteoclastic activity and bone resorption, leading to lower BMD over time. Hyperparathyroidism preferentially affects cortical bone. This is in contrast to some other metabolic bone diseases in which changes are most likely at more trabecular measurement sites (eg, glucocorticoid excess preferentially affects trabecular bone, for instance, the lumbar spine). High-resolution quantitative computed tomography (QCT) suggests that trabecular bone is also affected in primary hyperparathyroidism, but cortical bone is more severely affected. For this reason, it is important that bone density evaluations with dual energy x-ray absorptiometry (DXA) include the non-dominant distal one-third radius (a site predominantly composed of cortical bone) in patients with primary hyperparathyroidism.

Differential Diagnosis of Hypercalcemia

Hypercalcemia in an older adult is most commonly due to primary hyperparathyroidism (PTH dependent) or malignancy (PTH independent). These are usually easily differentiated on the basis of history, physical examination, and laboratories. The differential diagnosis for PTH-dependent and PTH-independent hypercalcemia is presented in **Table 112-3**. An algorithm for evaluating hypercalcemia is presented in **Figure 112-3**.

TABLE 112-3 DIFFERENTIAL DIAGNOSIS OF PTH-DEPENDENT AND PTH-INDEPENDENT CAUSES OF HYPERCALCEMIA

PTH INDEPENDENT	PTH DEPENDENT
Malignancy-associated hypercalcemia Local osteolytic hypercalcemia (multiple myeloma, metastases from breast/lung cancer) Humoral hypercalcemia of malignancy (PTH-rp, eg, SCC, renal/breast/bladder/ovarian cancers) $1,25(OH)_2D$-mediated hypercalcemia (lymphoma)	Primary hyperparathyroidism Adenoma(s) Hyperplasia Multiple endocrine neoplasia Parathyroid cancer
Granulomatous disorders	Familial benign hypocalciuric hypercalcemia (FHH)

Sarcoidosis Berylliosis Tuberculosis Histoplasmosis Coccidiomycosis Candidiasis Eosinophilic granuloma Silicone implants	
Medications Thiazide diuretics	Medications Lithium
Endocrinologic disorders Hyperthyroidism Adrenal insufficiency Pheochromocytoma VIPoma	Malignancy with ectopic PTH production (very rare)
Immobilization plus: Malignancy Paget disease of bone	Tertiary hyperparathyroidism Chronic renal failure
Milk-alkali syndrome	
Vitamin A or D intoxication	
Parenteral nutrition	
Hyperproteinemia	
Acute renal failure	

PTH-rp, parathyroid hormone–related peptide; SCC, squamous cell carcinoma.

The most common, and worrisome, cause of PTH-independent hypercalcemia in an older adult is malignancy. The clinical setting must be considered. The most common cause of hypercalcemia in the outpatient setting is primary hyperparathyroidism, as opposed to the inpatient setting when the most common cause is malignancy. Most patients with malignancy-associated hypercalcemia have advanced neoplastic disease that is apparent by physical examination and routine diagnostic work-up. Nevertheless, hypercalcemia can occasionally be a presenting feature of malignancy. Thus, in a patient with PTH-independent hypercalcemia of uncertain etiology, age-appropriate cancer screening, chest x-ray, mammogram, and a serum and urine protein electrophoresis should be performed. Further work-up for malignancy can be directed by history, physical examination, and laboratory/imaging findings. Since primary hyperparathyroidism is a common disease in older women, an older asymptomatic female with hypercalcemia without obvious evidence of malignant disease will be more likely to have primary hyperparathyroidism than occult malignancy.

Other causes of PTH-independent hypercalcemia include vitamin D or A intoxication, granulomatous disease, and other endocrine disorders. In these situations, the PTH level should be low. Hypercalcemia caused by excessive vitamin D (cholecalciferol) intake can be diagnosed by measuring serum 25-hydroxyvitamin D (levels are usually above 120 ng/mL). Hypercalcemia can be found in sarcoidosis, tuberculosis, chronic fungal infections, and other granulomatous disorders. The cause of hypercalcemia in all these granulomatous diseases is believed to be increased production of 1,25-dihydroxyvitamin D by the granulomatous tissue, which increases serum calcium primarily by increasing calcium absorption from the gastrointestinal (GI) tract. Other diseases causing PTH-independent hypercalcemia, such as hyperthyroidism, adrenal insufficiency, and pheochromocytoma can be diagnosed by their historical or clinical features.

In addition to unmasking underlying hyperparathyroidism, hydrochlorothiazide can rarely cause a PTH-independent hypercalcemia. In this case, the PTH would be low and the hypercalcemia should resolve 6 weeks after discontinuation.

Differential Diagnosis of Primary Hyperparathyroidism

Once a PTH-dependent hypercalcemia has been identified the medication list should be examined. Lithium may act, in part, by causing inappropriate PTH secretion, thereby exacerbating or causing PTH excess. Hypercalcemia can occur at any time during lithium treatment and may not resolve with discontinuation of the medication.

Patients who are being evaluated for hyperparathyroidism should have a 24-hour urine calcium and creatinine excretion measured to rule out familial benign hypocalciuric hypercalcemia (FHH). FHH is an inherited condition that results from an inactivating mutation of the CaSR. As a result of this mutation, it takes a higher calcium level to suppress PTH secretion, all four parathyroid glands are either normal in size or slightly enlarged, and there is decreased calcium excretion in the urine (due to the presence of the mutated CaSR in the kidney). This leads to mild, long-standing elevations of calcium (no previous documentation of a normal calcium level), mild PTH elevation, and low urinary calcium. An inappropriately low 24-hour urine calcium value and/or a calcium/creatinine clearance ratio (see equation) less than 0.01 is consistent with FHH.

Calcium/Creatinine Clearance = Urine Calcium × Serum Creatinine Serum Calcium × Urine Creatinine

Patients with FHH typically have a family history of hypercalcemia and perhaps even of "failed parathyroidectomy." It is important to detect FHH since it is a benign condition, and therefore does not require any medical or surgical intervention. Although inherited conditions are typically identified earlier in life, it is important for the geriatrician to be aware of this condition since mild calcium and PTH elevations may have been previously undetected or ignored. Furthermore, it is important for the patient and their family to be aware of the diagnosis to avoid any unnecessary interventions.

PTH-dependent hypercalcemia can also be seen in tertiary hyperparathyroidism. This is typically seen in the setting of chronic renal failure. As kidney function declines, the production of 1,25-dihydroxyvitamin D declines. This results in vitamin D deficiency and subsequently hypocalcemia, which stimulates PTH production (secondary hyperparathyroidism). Over time, this chronic stimulation results in autonomous PTH production (tertiary hyperparathyroidism). The calcium level (normal or low vs high) distinguishes secondary from tertiary hyperparathyroidism.

Normocalcemic hyperparathyroidism Sometimes in the work-up of a patient with mild hypercalcemia, repeat serum calcium may fall within the high normal range, but the PTH level is found to be elevated. An elevated PTH level in the setting of normal serum calcium is sometimes called normocalcemic hyperparathyroidism. There is no clear evidence that the disorder causes end-organ damage and symptoms are variable. There is debate regarding what, if any, intervention is necessary. After causes of secondary hyperparathyroidism have been considered and ruled out, management is similar to that of asymptomatic primary hyperparathyroidism. Observation and monitoring for progression to overt primary hyperparathyroidism may be all that is necessary, particularly in an older adult with other comorbidities.

Conditions that can exacerbate or unmask underlying primary hyperparathyroidism A number of conditions can be superimposed on primary hyperparathyroidism and can worsen hypercalcemia. These include immobilization, malignancy, use of hydrochlorothiazide and excessive calcium intake. These may be particularly relevant for older people who often have comorbid disease, polypharmacy, and are at an increased risk of becoming immobilized.

Treatment

Treatment of hyperparathyroidism depends on the way in which the patient presents to the clinician. Because most cases are asymptomatic, no immediate therapy is usually necessary and a thorough diagnostic evaluation can be undertaken. When the patient presents with more severe or acute symptoms (eg, obtundation), management of the hypercalcemia must take precedence over diagnostic studies. Many of the more severely hypercalcemic patients are dehydrated and may require parenteral fluids to lower the serum calcium. Once hydration has been reestablished and the patient is stable, further decisions about therapy can be made.

All patients with primary hyperparathyroidism should avoid dehydration, thiazide diuretics and immobilization, as these can worsen the hypercalcemia. It may seem logical to stop or decrease calcium and vitamin D intake in those with primary hyperparathyroidism. However, care must be taken as insufficient calcium and vitamin D intake can stimulate additional PTH secretion and therefore should be avoided, as described below. In addition to basic, supportive measures, surgery or prescription medication may be recommended in patients who meet criteria.

Indications for treatment Current guidelines suggest treatment of primary hyperparathyroidism if any of the

following criteria are met (see **Table 112-1**):

- Age: less than 50 years
- Serum calcium greater than 1 mg/dL above the upper limit of normal
- Bone density T-score less than –2.5 at any site *or* clinical or radiographic evidence of vertebral fracture
- Creatinine clearance less than 60 cc/min, 24-hour urine calcium greater than 400 mg/day, and increased renal stone risk, *or* radiographic evidence of nephrolithiasis/nephrocalcinosis.
- Symptoms and/or patient preference.

Surgical management

Preoperative Imaging Neck imaging in primary hyperparathyroidism is used only for preoperative localization of the causative gland(s), and is not useful to establish the diagnosis. Therefore, neck imaging should only be performed after a biochemical diagnosis has been confirmed and the decision has been made to pursue parathyroidectomy.

Neck ultrasound and parathyroid imaging with ^{99m}Tc-sestamibi (single-photon emission CT) are the most sensitive options for localizing abnormal parathyroid tissue in primary hyperparathyroidism. The choice of imaging modality is often dependent on the experience present at the institution. In experienced hands, ultrasound has a sensitivity ranging from 57% to 89% and specificity of 87% to 95%. The technique can be suboptimal in patients with multinodular goiters or ectopic parathyroid glands outside the cervical area. If there is a question as to whether a suspicious nodule is intra- or extrathyroidal, fine-needle aspiration of the nodule with PTH assay on the washout can establish the presence of parathyroid tissue. Sestamibi is only available in centers with expertise in nuclear medicine but has comparable sensitivity (54%–95%) and specificity (91%). It is better than ultrasound for localizing ectopic parathyroid tissue, especially when it is mediastinal, but has lower sensitivity in multigland disease and small adenomas. In the experience of some, false positives can be seen with carcinoid, sarcoidosis, abnormal lymph nodes, and both benign and malignant thyroid nodules. It may be more difficult to use sestamibi in the geriatric population where coexistent thyroid disease is more common. The combination of sestamibi and ultrasound imaging provides the highest sensitivity (91%–95%). Therefore, it is recommended that ultrasound and sestamibi be performed sequentially if glands are difficult to localize. When ultrasound and sestamibi are discordant, multigland disease is more likely and CT or MRI may be useful to improve anatomic discrimination.

Although CT scanning of the neck is relatively insensitive in the detection of abnormal parathyroid glands (sensitivity 40%–60%), it can be used for localization in cases of persistent or recurrent disease, but exposes the patient to more radiation than the other modalities. Parathyroid adenomas may enhance with IV contrast on 4D CT scans making these a popular modality for localization. Normal parathyroid glands are not visible on MRI. However, parathyroid adenomas may appear as soft tissue masses on MRI (sensitivity 40%–85%). On T1-weighted images they will have a low-to-medium signal intensity and a high signal intensity on T2-weighted images. MRI could be used in cases where ultrasound and sestamibi provide conflicting results, for persistent or recurrent hyperparathyroidism and when an ectopic gland is suspected but could not be identified using sestamibi.

Preoperative localization is particularly important to perform in older patients with prior neck surgeries that can make parathyroid identification difficult. Preoperative localization is essential for a minimally invasive surgical approach that targets a specific abnormal gland.

Parathyroidectomy When patients with primary hyperparathyroidism meet criteria for treatment, parathyroidectomy is preferred since 90% to 95% can be cured when an experienced surgeon is available. The favored approach is a bilateral neck exploration (3–6 cm incision) to identify all four parathyroid glands. However, if preoperative localization suggests a single adenoma, multigland disease is unlikely, and intraoperative PTH monitoring is available, a minimally invasive approach (1.5–3-cm incision) that specifically targets the involved gland can be pursued. The minimally invasive approach can be performed under local anesthesia, thereby avoiding the risks of general anesthesia in an older adult population. With intraoperative PTH monitoring, PTH levels should fall by 50% within 10 to 15 minutes of removal of the causative gland(s). When hyperplasia is identified, most surgeons remove 3.5 glands, marking the remaining portion of gland so it can be identified if necessary in the future. Treatment of hyperplasia with total parathyroidectomy and transplantation of some parathyroid tissue into the forearm is used by some surgeons, especially when they anticipate the need for future removal of more tissue should hyperplasia recur.

Hypocalcemia may occur in the immediate postoperative period. It can be transient (due to surgical trauma or prolonged hypercalcemic suppression of remaining normal parathyroid tissue), or prolonged and permanent (if surgical trauma to parathyroid tissue is severe). In the immediate postoperative period, patients should be monitored for

hypocalcemia.

Nervousness, perioral tingling, paresthesias in the distal extremities and a positive Chvostek or Trousseau sign may indicate hypocalcemia, which should be confirmed by laboratory testing. Many patients have transient hypocalcemia, so calcium supplements should be given only if the level is below 8 mg/dL. Calcium gluconate is the preferred form of intravenous calcium and may be given for several days. Persistent hypocalcemia requires oral calcium in a dose of 1000 to 1200 mg daily. If hypocalcemia is severe, 1,25-dihydroxyvitamin D (calcitriol) can be added (0.5–1 μg/day in doses divided every 12 hours). Because calcitriol can cause hypercalcemia and hypercalciuria, serum and urine levels must be monitored.

Rarely, patients may develop hypocalcemia from skeletal uptake of calcium and phosphorus with healing of osteitis fibrosa cystica ("hungry bones"). These patients typically have normal or low serum phosphorus levels. Usually this problem is short lived (days to week), but rarely it can be more prolonged, and treatment with calcium supplements and calcitriol may be necessary for up to 3 months. Preoperative vitamin D supplementation to achieve normal 25-OHD levels can help to prevent the development of hungry bone syndrome and hypocalcemia.

Finally, hyperparathyroid patients can have low serum magnesium levels, another cause of hypocalcemia. Thus, the serum magnesium level should be checked if hypocalcemia develops postoperatively. Intravenous or oral magnesium replacement can be used. However, oral magnesium can cause diarrhea and intravenous magnesium should be infused slowly (over hours) to avoid excessive renal excretion.

Persistent (>6 months) postoperative hypocalcemia with hyperphosphatemia suggests permanent hypoparathyroidism. Permanent hypoparathyroidism is a rare complication of parathyroidectomy (when performed by experienced surgeons). Minimally invasive procedures that target the causative gland and avoid manipulation/biopsy of normal parathyroid tissue further decrease the risk of hypoparathyroidism. Long-term follow-up is required to determine whether parathyroid function returns over time.

Postoperative Course After successful surgery, recovery is rapid. Serum calcium levels normalize within hours to several days. Even in the absence of postoperative complications, serum calcium should be checked 6 months postoperatively to ensure cure.

There is a 90% reduction in the incidence of renal stones in patients with nephrolithiasis. Bone mass usually improves after surgery; some patients gain 12% to 20% of their femoral or lumbar density, respectively in 4 years. Most of the recovery of bone density occurs in the first year after surgery. Neurocognitive impairment may also improve; however, this has not been confirmed in randomized controlled trials of older patients. It is possible that the neurocognitive deficits in geriatric patients are multifactorial. Furthermore, older patients may be more vulnerable to the effects of general anesthesia and the rapid corrections of calcium postoperatively, making symptomatic improvement difficult to assess.

Medical management If treatment of hypercalcemia symptoms would provide therapeutic benefit and improved quality of life, but the patient is unwilling or unable to pursue parathyroidectomy, medications can now be considered as a therapeutic alternative. Medical management can also be pursued for those who did not achieve a cure with prior parathyroidectomy. The choice of which agent(s) to use depends on their mechanisms of action and goals of therapy. If there is not a need to decrease serum calcium or improve BMD, then supportive measures and observation alone may be appropriate.

The frequency of monitoring patients with primary hyperparathyroidism while on medical therapy is not well established. Current guidelines recommend that monitoring should be guided by medical judgment.

Dietary Calcium and Vitamin D in Primary Hyperparathyroidism It is critically important for a patient's bone health that dietary/supplemental calcium not be restricted/stopped in those with primary hyperparathyroidism. Although the exact amount of dietary calcium that is appropriate in individuals with primary hyperparathyroidism has yet to be established, guidelines suggest adherence to the Institute of Medicine's recommendations for the general population (total calcium intake of 1200 mg/day for those 51 years or older). Although the evidence differs with regards to benefits of calcium supplementation in primary hyperparathyroidism (some studies suggest an increase in BMD and others show no difference), dietary calcium is safe in mild primary hyperparathyroidism with periodic monitoring of serum calcium levels.

Since dietary vitamin D intake and the ability to synthesize vitamin D in the skin decrease with age, older people are particularly susceptible to vitamin D deficiency. In primary hyperparathyroidism, 25-OHD deficiency is common, due in part to increased conversion to 1,25-dihydroxyvitamin D (via PTH stimulation of 1α-hydroxylase) and increased degradation by 24-hydroxylase. Vitamin D deficiency exacerbates PTH elevation, increases the risk of bone

loss, and increases the risk for postoperative complications such as hungry bone syndrome and severe hypocalcemia. There are no large, controlled studies demonstrating the benefits of vitamin D repletion in primary hyperparathyroidism. However, due to the known harms of vitamin D deficiency in this setting and the lack of evidence showing risks of supplementation (including lack of worsened hypercalcemia), it is now generally recommended to slowly and carefully provide vitamin D supplementation in patients with low 25-OHD levels. When vitamin D supplementation is used in the presence of hypercalcemia, close monitoring of serum and urine calcium levels is appropriate. Particular caution should be used in those at high risk of nephrolithiasis as vitamin D supplementation can increase urinary calcium excretion and theoretically increase the risk of kidney stones.

Measurement of 25-hydroxyvitamin D is most useful to assess vitamin D status. Although the appropriate target level of 25-OHD is debated, it is now generally recommended to maintain 25-OHD levels of 20 to 30 ng/mL in individuals with primary hyperparathyroidism. About 800 to 1000 IU/day of vitamin D_3 can be used as a starting dose.

Pharmacologic Therapy of Hypercalcemia

CINACALCET Cinacalcet is a calcimimetic commonly used for secondary hyperparathyroidism in chronic renal failure and for parathyroid carcinoma. It increases the CaSR's sensitivity to extracellular calcium to reduce PTH secretion and subsequently serum calcium. It has now been approved by the Food and Drug Administration (FDA) for severe primary hyperparathyroidism in those who are unwilling or unable to undergo parathyroidectomy and in those who fail to achieve cure after previous parathyroidectomy. In primary hyperparathyroidism, cinacalcet can be helpful to achieve control of hypercalcemia but has not proven beneficial in improving bone density.

When used in primary hyperparathyroidism, cinacalcet can result in lowering and even normalization of serum calcium, lowering of PTH, increasing serum phosphorous, decreasing urinary calcium (presumably due to decreased load of calcium filtered by the kidneys), and improving quality of life. However, it does not improve BMD. It is commonly initiated at 30 mg/day, and can be titrated up to 90 mg QID to achieve serum calcium within the normal range. In most studies, the dose required is rarely over 100 mg/day. Although cinacalcet is only FDA approved for severe cases of primary hyperparathyroidism, it is approved and used in Europe for mild cases and there is evidence to suggest that it is safe and effective in these patients as well. In one study, 88% of patients with serum calcium greater than or equal to 12.5 mg/dL had at least a 1 mg/dL decrease in serum calcium with cinacalcet therapy. Normocalcemia was achieved with cinacalcet in 65% with sporadic disease and in 80% with familial disease. Those with familial disease often required higher doses. The PRIMARA study involved a geriatric cohort (median age = 70) in Europe that had mild-to-moderate primary hyperparathyroidism. In that study cinacalcet decreased calcium within 3 months while also decreasing PTH and increasing phosphorous.

Although cinacalcet is generally well tolerated, it has been associated with nausea, vomiting, paresthesias, and falls. This may be of particular concern in the geriatric population where fall risk may already be a concern. Hypocalcemia can rarely occur, mostly in those with lower baseline calcium levels, and resolves when cinacalcet is stopped. There is no long-term data on the safety of cinacalcet in primary hyperparathyroidism or its effectiveness in improving nephrolithiasis or quality of life in these patients. Cinacalcet inhibits CYP P450 2D6. This should be considered when using this medication in the geriatric population in which multiple other medications may be necessary.

When long-term therapy is needed, cinacalcet is not as cost-effective as parathyroidectomy and its long-term safety/efficacy are unknown. However, it may be an acceptable option in those who have symptomatic hypercalcemia but have other comorbidities that limit surgical options and life expectancy.

BISPHOSPHONATES Bisphosphonates are often the first-line medication for osteoporosis (see Chapter 118). They become incorporated into the bone matrix, particularly at sites of active remodeling, and are taken up by osteoclasts, resulting in osteoclast suppression and decreased bone turnover. Alendronate, 70 mg orally every week, is most well studied in primary hyperparathyroidism and although there is no evidence of fracture protection, its use decreases bone turnover markers and increases BMD in women and men. However, reductions in calcium or PTH levels are not consistently observed, and thus its use is less likely to have a positive effect on symptoms of hypercalcemia.

Although alendronate is not directly nephrotoxic, it should be used cautiously in those with renal failure when there is decreased clearance of the medication. It should be avoided in those with a (CrCl < 35 mL/min). Side effects of alendronate include esophagitis. Although rare, bisphosphonates have been associated with osteonecrosis of the jaw and atypical femur fractures. These complications have not been specifically identified in patients with hyperparathyroidism.

COMBINATION MEDICAL TREATMENT Limited data suggest that bisphosphonates and cinacalcet may be used in combination for primary hyperparathyroidism, when the goals of therapy are to both reduce serum calcium and improve bone

health.

OTHER MEDICATIONS If patients requiring treatment are unwilling or unable to undergo parathyroidectomy or take the medications above, other therapeutic agents may be considered. Estrogen therapy can decrease bone resorption. However, there are no data on fracture prevention in this setting, and estrogen use does not consistently affect the biochemical profile of patients with primary hyperparathyroidism. The risks and benefits of estrogen use in postmenopausal women must be weighed prior to instituting it in this setting. There are not enough data regarding the use of raloxifene in primary hyperparathyroidism to make confident recommendations.

Observation In patients with the appropriate indications, parathyroidectomy remains the treatment of choice for primary hyperparathyroidism and is safe and effective in older individuals who have no other contraindications to surgery. However, because many cases of hyperparathyroidism are asymptomatic without complications at diagnosis, immediate surgery is not necessary, and some patients may never need an operation. In the geriatric population, consideration should be given to quality of life, surgical risk, and comorbidities. Primary hyperparathyroidism is often asymptomatic and is unlikely to significantly progress in geriatric patients with other comorbidities. Therefore monitoring may be appropriate.

Observation without active intervention may be preferable in a geriatric population at increased risk of surgical complications and problems related to polypharmacy. If the clinician and patient decide not to operate for hyperparathyroidism, education and long-term follow-up are necessary. Patients with serum calcium levels below 11 mg/dL and no evidence of adverse effects (eg, low bone mass, renal stones) may be safely followed. Patients with asymptomatic hyperparathyroidism require close follow-up (**Table 112-4**) and should be educated about the signs and symptoms of hypercalcemia. The importance of hydration, dietary calcium and vitamin D nutrition, and physical activity to avoid immobilization should be emphasized in all patients who do not receive active treatment. The decision to treat should be reevaluated at each clinic visit. It is not possible to predict who will lose bone, develop nephrolithiasis, or have a decline in GFR rate during observation. The 2014 Endocrine Society Guidelines for Primary Hyperparathyroidism suggest monitoring patients with asymptomatic primary hyperparathyroidism who do not undergo parathyroidectomy with annual serum calcium, creatinine and estimated GFR (eGFR), three-site DXA scanning every 1 to 2 years, and renal evaluation (imaging and 24-hour urine) if nephrolithiasis is suspected (see **Table 112-4**). It is recommended that parathyroidectomy be considered if patients develop any indication for surgery during the monitoring period (see **Table 112-1**). If observation without intervention is chosen, it should be recognized that an older patient who is a surgical candidate at diagnosis may become nonoperable after a period of observation.

TABLE 112-4 RECOMMENDATIONS FOR MONITORING ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM IN THOSE WHO DO NOT RECEIVE SURGICAL OR PHARMACOLOGIC INTERVENTION

Annual serum laboratories
• Total calcium (adjusted for albumin)
• Creatinine with eGFR
Skeletal imaging
• Three-site DXA every 1–2 y
• Spinal imaging if clinical suspicion of vertebral fracture
If kidney stones are suspected:
• 24-hour urine biochemical stone profile
• Renal imaging (x-ray, ultrasound, or CT)

DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate.

PAGET DISEASE OF BONE

Background and Epidemiology

Paget disease of bone, also known as osteitis deformans, is a focal disorder of abnormal osteoclasts that drive excessive bone resorption and subsequent disordered bone formation that results in disorganized, fragile bone. It was

originally described in 1877 by Sir James Paget. In his original description, Paget described six patients with enlarged skulls, hearing loss, bowed extremities, and kyphotic spines. The disease can be monostotic (involving one bone; 40% of cases) or polyostotic (involving more than one bone; 60% of cases).

Paget disease is a chronic disease that predominantly affects Caucasian individuals over the age of 40 and is slightly more common in men. Its prevalence is difficult to determine since the disease is often asymptomatic. Paget disease is most common in North America, Western Europe, Australia, and New Zealand with at least 1% of the population affected. Conversely, Paget disease is very rare (prevalence < 0.01%) in Japan, China, and India. When individuals with low genetic risk move to a region of higher prevalence, they assume the risk of the higher prevalence region, suggesting environmental influences. In the United States it is estimated that 2% to 3% of individuals 55 years or older are affected by Paget disease. Interestingly, the prevalence and severity of Paget disease has been decreasing over the last two decades. A systematic review in New Zealand found a 36% reduction in the prevalence of Paget disease over 8 to 19 years. In addition, in clinics in New Zealand the age at diagnosis increased by 10 years while the proportion of skeletal involvement and degree of alkaline phosphatase elevation at diagnosis decreased. Similar changes in prevalence have also been reported in England and Spain. The reason(s) for these changes in the epidemiology of Paget disease is unknown but the time frame in which the epidemiologic change has occurred is more consistent with differences in environmental, as opposed to genetic, factors.

Etiology

There is evidence to suggest both genetic and environmental influences in Paget disease. There is familial clustering of Paget disease with approximately 33% of patients reporting a first-degree relative with the disease. Mutations in the *SQSTM1* gene have been found in 5% to 10% of sporadic cases and in 25% to 50% of familial cases. In familial cases, the mutations are consistent with an autosomal dominant pattern of inheritance with incomplete penetrance. There may be some genotype-phenotype correlation because individuals with the *SQSTM1* mutations appear to have more extensive and severe disease that presents at an earlier age than those without the mutations. The mechanism by which the *SQSTM1* mutation causes Paget disease is probably related to osteoclast activation. In genome-wide association studies seven other genetic mutations, usually in genes related to osteoclast biology, have been associated with Paget disease but the significance of these mutations is not yet clear.

There is also evidence to suggest a viral etiology of Paget disease. Osteoclasts in Paget disease have virus-like inclusion bodies. Exposure to paramyxoviruses (including measles and canine distemper viruses) has been associated with Paget disease, but no definitive causal link has been established. Measles virus messenger RNA was found in osteoclasts and mononuclear cell progenitors. Transgenic mice with measles virus nucleocapsid protein introduced into osteoclasts develop skeletal lesions similar to those found in patients with Paget disease. However, no virus has been cultured from pagetic cells, and despite use of sensitive techniques, no direct evidence of any type of paramyxovirus RNA or of virus infection has been found. In three other skeletal disorders—osteopetrosis, pyknodysostosis, and osteoclastoma—nuclear inclusion bodies have been identified.

A current hypothesis is that patients in middle to late life who have a genetic predisposition to Paget disease of bone develop a viral infection, which causes the disease to become manifest. It is still unknown why it involves particular areas of the skeleton and why the disease generally presents after the age of 60.

Skeletal Characteristics

Because Paget disease of bone is a localized disorder of accelerated bone remodeling, it is useful to briefly review the normal bone remodeling process (also see Chapter 118). All areas of the skeleton must be remodeled throughout life to maintain extracellular calcium/phosphorous homeostasis, to repair acquired microfractures and to strengthen parts of the skeleton placed under new or increased mechanical loads. The process begins when osteoclasts from bone marrow colony-forming units of the macrophage lineage come to a surface to be remodeled. The osteoclasts excavate a cavity 50 μm in depth over a 2- to 4-week period and then undergo apoptosis. A new series of cells, osteoblasts, derived from bone marrow colony-forming units of fibroblast lineage appear in the resorption cavity and fill it with osteoid tissue. The osteoblasts also stimulate the formation of hydroxyapatite crystals on the collagen, which provides strength to the matrix. The process of bone remodeling is tightly coupled so that increases or decreases in rates of bone resorption are followed by an increase or decrease in bone formation. Through this coupling process, it is possible for most people to maintain their skeleton as a serviceable, lightweight frame throughout life. The coupling process is mediated by cytokines and growth factors released by osteoblasts and osteoclasts, which serve to control the remodeling process. The final common pathway for control of osteoclast differentiation and function is RANK, RANKL, and

osteoprotegerin (OPG). In this pathway interleukin 6 (IL-6) and macrophage colony-stimulating factor are major regulators of osteoclast differentiation and function.

The lytic lesions in Paget disease are the result of abnormal osteoclast activity. Compared to normal osteoclasts, those in Paget disease are increased in size and number and are more active, leading to accelerated bone resorption. A subsequent increase in the number and size of osteoblasts results in disordered bone formation. The newly formed bone is chaotic, lacks the normal lamellar pattern and is enlarged, sclerotic, and structurally weaker than normal bone. Pagetic bone has increased amounts of fibrosis and vascularity as well as enlarged haversian canals. Thus, although the bone can appear denser radiographically, it is more susceptible to fracture. Bones can become bowed with weight bearing and can enlarge as long as the remodeling activity is increased. Eventually, osteoclast and osteoblast activity can decline over time at sites of pagetic involvement and sclerotic bone occurs.

Clinical Manifestations

Any bone can be affected in Paget disease, but it has a predilection for the axial skeleton. The most common skeletal sites involved are the pelvis (70% of cases), lumbar spine (53%), proximal femur (55%), proximal humerus (31%), tibia (32%), or skull (42%). Bones of the hands, feet, and face are rarely affected. The disease will often start in the proximal part of a long bone, advancing distally. Although the activity of the lesion can fluctuate, the disease itself usually does not progress to involve more skeletal sites than those affected at the time of initial diagnosis.

Paget disease of bone is often asymptomatic and is frequently found incidentally either due to an elevated serum alkaline phosphatase level or radiographically on examinations performed for other reasons. However, 30% to 40% of patients are symptomatic at diagnosis and 30% develop complications that cause symptoms. Symptomatology depends on the site affected.

The most common symptom is bone pain. Pagetic bone pain is typically described as a constant, low-grade, deep ache that is worse at night and can be related to activity. Bone pain may also arise from increased vascularity or from stretching of the periosteum caused by the increased amount of new bone from the disorganized bone remodeling. Periarticular pain may be the presenting symptom in 50% of cases. Articular involvement is an important problem because Paget disease commonly affects bone around major joints such as the hip and knee, as well as those of the spine, with narrowing of the joint spaces and formation of osteophytes. Osteoarthritis is thought to occur either due to joint deformities or abnormal force transmission from deformed bone. Degenerative arthritis in joints contiguous with pagetic lesions causes juxta-articular enlargement and altered subchondral bone support. Patients also develop osteoarthritis in unaffected knees as a result of favoring the nonpagetic knee. Protrusio acetabuli occurs in some patients with disease involving the ilium (**Figure 112-4**). Pain in Paget disease can also result from fracture, pseudofracture, spinal stenosis, or skeletal deformities (such as bowing).

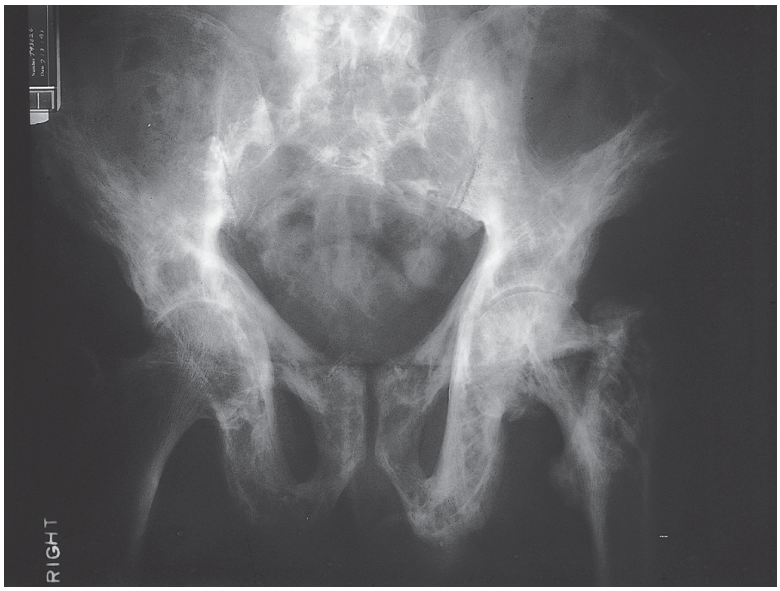


FIGURE 112-4. Anteroposterior pelvis radiograph from a 72-year-old man with Paget disease of bone involving the entire pelvis. Femurs are not involved with Paget disease, but the right side of the pelvis has marked protrusio acetabuli.

Bowing of weight-bearing bone is another common feature, occurring most commonly in the femur, tibia,

humerus, and ulna (**Figure 112-5**). The bowing seen in the femur and tibia is often associated with stress fractures on the convex surface of the bowed bone (**Figure 112-6**). Bone deformity alters force transmission through the adjacent joint causing premature loss of articular cartilage and secondary osteoarthritis especially in the hip and knee. In addition to deformities, the affected bone can enlarge.



FIGURE 112-5. Left anteroposterior tibia and fibula radiograph from a 78-year-old woman with Paget disease of bone involving the tibia. At the proximal portion of the tibia are staples from a failed osteotomy 25 years before. Note the lateral bowing of the tibia. There is the characteristic increase in cortical bone size from the abnormal remodeling process. In the distal portion of the tibia is seen the advancing lytic disease front, sometimes called a blade-of-grass lesion.



FIGURE 112-6. Right proximal femur and pelvis radiograph of a 68-year-old man with Paget disease of bone involving both the femur and ilium. The angle of the femoral neck and femur are decreased as the bone is less strong, a coxa vara deformity. Also note the lateral bowing of the femur with the stress fractures on the convex side of the femur.

Fractures can occur with minimal trauma because pagetic bone is weaker. In addition to incomplete fissure fractures on the convex surfaces of bowed long bones, complete transverse fracture can occur with minimal trauma (**Figure 112-7**). These fractures are called “chalk stick” fractures because the bone breaks evenly as a piece of chalk would, rather than with jagged fragments as normal bone does. Although pagetic fractures often heal normally, such fractures also have a higher rate of nonunion, between 10% and 40%, occurring most commonly in the femur. The bones most commonly fractured in Paget disease include the femur, tibia, humerus, vertebrae, and ribs. Acute focal pain in a pagetic femur or tibia requires urgent x-rays to screen for an extending transverse fracture.

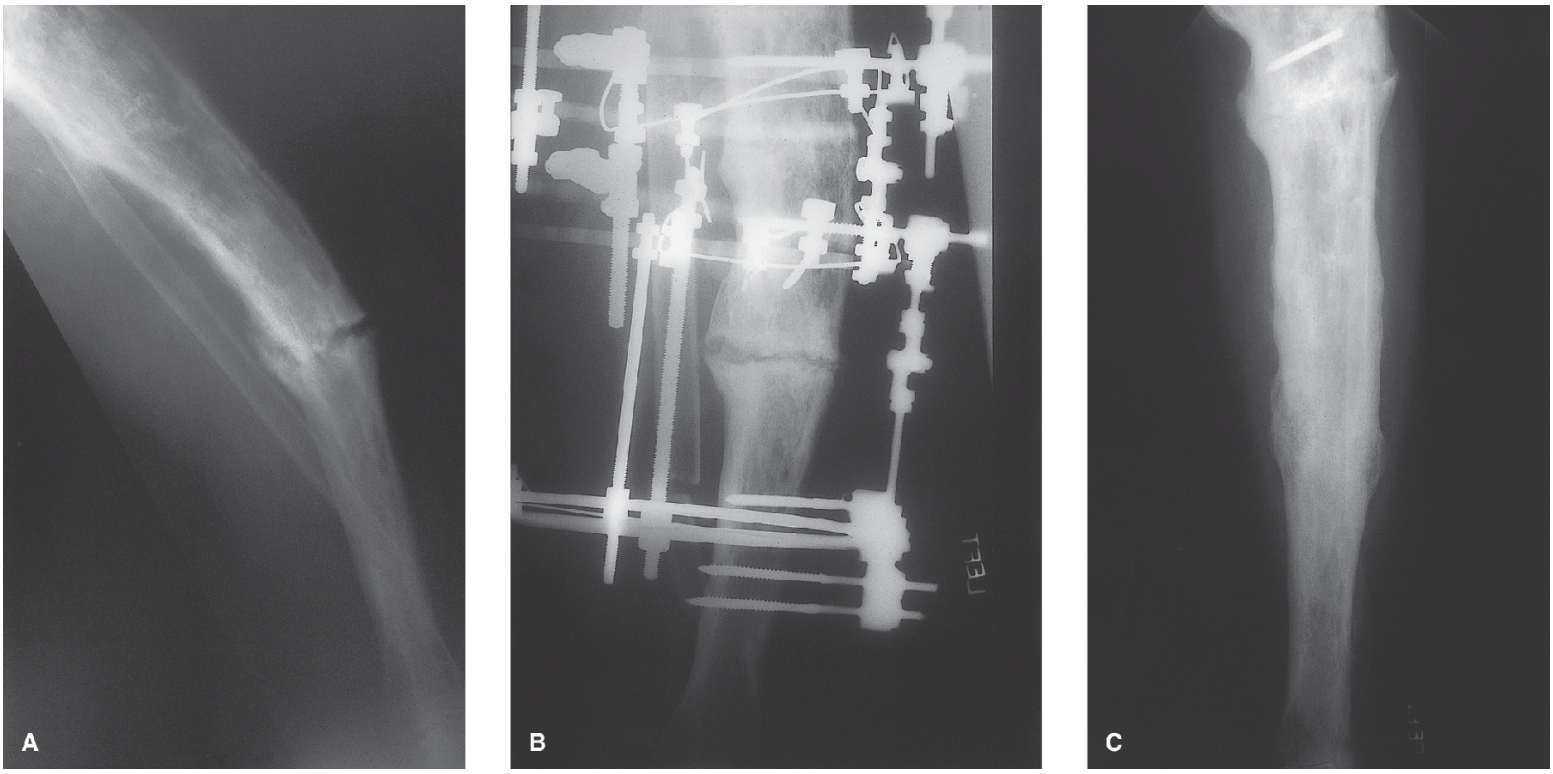


FIGURE 112-7. A series of left anteroposterior tibial radiographs from a 74-year-old man with Paget disease of bone in the left tibia. **A.** The patient's 10th fracture; note chalk stick nature. The fracture did not heal with casting over 6 months. **B.** The patient underwent tibial straightening with two osteotomies. He also wore an Ilizarov external fixation device for 1 year and received 6 months of alendronate 40 mg daily. **C.** The left tibia is much straighter. The patient now walks with a clamshell leg brace.

Pseudofractures are thin, radiolucent bands across the lateral cortex of long, usually weight-bearing bones. They can cause pain or be asymptomatic and either progress to overt fracture, remain stable, or regress spontaneously. Surgical stabilization should be considered when there is increasing pain at the site of a pseudofracture.

Neurologic complications can occur when the skull or vertebrae are affected. Paget disease of the skull can cause headaches, tinnitus, and vertigo, can impact cranial nerves, and can cause hydrocephalus from basilar invagination. Skull deformity may result in enlargement of the cranial vault, with a characteristic appearance particularly of the forehead (frontal bossing) or of the maxilla (leontiasis osseum). Cochlear damage can result in irreversible hearing loss. In the geriatric population, associated dental complications that can occur with an enlarged pagetic jaw (eg, loose teeth, swollen gums) can lead to difficulties with dentures. With involvement of the vertebrae in Paget disease spinal stenosis can occur; however para-/quadriplegia are rare. When paralysis occurs, it is likely due to vascular steal (as opposed to neurologic compromise) and is reversible if treated promptly.

If patients with polyostotic Paget disease become immobilized they can become hypercalcemic. This is most common in the context of other conditions that promote hypercalcemia, and a work-up should be performed to screen for coexistent hypercalcemic disorders such as primary hyperparathyroidism. When severe hypercalcemia occurs, antiresorptive agents must be initiated on an emergent basis to reduce calcium release from overactive bone resorption. With high rates of bone remodeling and skeletal calcium release, patients with Paget disease can develop nephrolithiasis. Hyperuricemia and gout are reported to occur in patients with Paget disease of bone. It is unclear whether abnormal purine metabolism is caused by the elevated bone remodeling or whether gout and Paget disease are just two common diseases occurring in the same patient.

Although rare (< 1%), individuals with Paget disease, especially those with polyostotic disease, are at an increased risk of osteosarcoma. Chondrosarcoma, fibrosarcoma, secondary spread of other cancers to bone and benign giant cell tumors can also occur at pagetic sites. The most common sites for osteosarcoma to develop in Paget disease patients are the femur, humerus, and pelvis. When malignant neoplasms occur, they are very aggressive and unless the neoplasm can be completely removed (usually limb amputation), the disease is rapidly fatal. At present, there is no evidence that treatment of Paget disease reduces the occurrence of malignant neoplasms. Malignant transformation should be considered in the setting of constant and worsening bone pain, an acute fracture or new mass. Radiographic signs of malignancy are nonspecific, and bone biopsy may be necessary to distinguish malignant transformation from the new bone formation seen at pagetic sites.

Due to the accelerated bone turnover and associated increase in blood flow, there is often focal warmth over the area involved. High-output heart failure is an unusual complication but can occur with active, polyostotic disease affecting more than 35% of the skeleton. Other rare complications and associations of Paget disease include aortic stenosis, generalized atherosclerosis, endocardial calcification, increased cerebrospinal fluid pressure, and increased prevalence of fibrosing or inflammatory disorders such as Peyronie disease, Dupuytren contractures, and Hashimoto thyroiditis.

Diagnosis

A thorough history and physical examination should be performed in all patients with Paget disease of bone. Because the diagnosis is made serendipitously in 30% to 70%, it may be necessary to specifically evaluate the patient for symptoms and signs of the disease. Physical examination should assess for the presence of bony deformity, warmth or bruits over affected sites, deafness, neurologic impairment, signs of heart failure, and/or hypercalcemia. Initial laboratory evaluation should include serum calcium, 25-hydroxyvitamin D, albumin, alkaline phosphatase, and liver function tests. Some experts recommend that children of Paget disease patients have an alkaline phosphatase level at the age of 50 or 55 and a total body scan if the marker is elevated. It is not clear how often this screening should be repeated, but such patients should be aware that they have an increased risk of developing the disease.

The diagnosis of Paget disease is primarily radiographic and is supported by history and abnormal levels of bone formation markers. The classic radiographic appearance is a focal lytic area with a coarse trabecular pattern and bone thickening. X-rays of suspected sites should be obtained for initial evaluation. Bone scintigraphy is the most sensitive method for localizing affected areas. Once a diagnostic x-ray has been obtained, bone scintigraphy should be performed to determine the extent of disease. Areas of rapidly remodeling bone will appear as increased uptake and involved areas should then have plain radiographs to confirm the presence of abnormal remodeling. Radiographs of painful or deformed bones are usually diagnostic, showing the characteristic mixed appearance of lytic areas from increased osteoclastic resorption, sclerotic areas from excessive osteoblastic bone formation, and cortical thickening. In the early stages of the disease, the changes may be predominantly lytic with flame-shaped resorption fronts in long bones or osteoporosis circumscripta in the skull. A characteristic radiographic appearance that distinguishes Paget disease from other conditions is the increased size and diameter of affected bones, particularly in the spine or shafts of long bones. If spinal stenosis, hydrocephalus, or brainstem compression from basilar skull invagination is suspected, CT or MRI scans may be necessary to confirm these diagnoses. Bone biopsy is rarely needed for differentiating Paget from other lesions and should be avoided at weight-bearing sites as this may lead to fracture.

After radiographic diagnosis is made, laboratory evaluation with the biochemical marker of choice for Paget disease (alkaline phosphatase) should be performed. Levels are elevated above the normal range in 90% of affected patients. Alkaline phosphatase is located in the plasma membrane of osteoblasts and serum alkaline phosphatase activity reflects the number and functional state of osteoblasts in patients with the disease. The serum level of alkaline phosphatase correlates roughly with the extent of skeletal involvement as established by radionucleotide bone scans. Serial determinations of alkaline phosphatase provide useful, simple, and inexpensive biochemical indices of disease activity. Serum alkaline phosphatase levels vary from day to day, so that the level should increase or decrease by 25% to be clinically significant. Because patients with minimally active, monostotic Paget disease may have normal serum alkaline phosphatase levels, it can be helpful to measure bone-specific alkaline phosphatase (BSAP). This isoenzyme of alkaline phosphatase can be elevated when total alkaline phosphatase levels are normal and can also be useful in patients with coexisting liver disease. Another bone formation marker, procollagen type I N-terminal propeptide (PINP), can also be used for diagnosis and monitoring of disease activity in cases where alkaline phosphatase is not adequate. BSAP is less reliable than PINP because of cross-reactivity with liver alkaline phosphatase antibodies. Measurement of serum osteocalcin level, a vitamin K–dependent protein made by osteoblasts, has not been useful in diagnosing or monitoring Paget disease.

Table 112-5 lists the diseases that should be considered in the differential diagnosis of Paget disease. These diseases can be categorized as either causing an elevated serum alkaline phosphatase level or causing a radiographic lesion similar to Paget disease.

TABLE 112-5 DIFFERENTIAL DIAGNOSIS OF PAGET DISEASE OF BONE

Causes of elevated serum bone alkaline phosphatase level
Metastatic neoplasm to the skeleton

Osteomalacia
Hyperparathyroidism with osteitis fibrosa cystica
Idiopathic hyperphosphatasia
Causes of skeletal lesions with similar radiographic appearance
Vertebral hemangioma
Fibrous dysplasia
Chronic osteomyelitis
Metaphyseal dysplasia (Engelmann disease)
Familial expansile osteolysis
Sternocostal clavicular hyperostosis

Imaging

The three histopathologic stages of Paget disease, some or all of which can be present in different skeletal lesions at the same time in polyostotic disease, correlate well with their radiographic appearances:

Stage 1: Osteolytic phase driven by excessive osteoclast bone resorption. On x-ray this can be seen as areas of bone loss.
Stage 2: Combined lytic/sclerotic phase due to osteoclast-induced activation of osteoblasts. Newly formed bone appears disorganized and structurally weaker. Radiographically, there is thickening of the cortices, exaggerated trabecular markings, and loss of the corticomedullary distinction. These changes are commonly referred to as having a “cotton-wool” or “picture-frame” appearance (for the skull and vertebrae, respectively).
Stage 3: Osteosclerotic “burnt-out” phase due to declining bone turnover. On imaging, bones appear enlarged and dense.

The increased blood flow seen at pagetic sites is seen radiographically as increased uptake on radionuclide bone scans (aka bone scintigraphy). The age of the lesion can affect its appearance. Burnt-out, mature lesions are less likely to be appreciated on scintigraphy but will be easily noted on plain x-ray. Conversely, early symptomatic lesions may appear on scintigraphy prior to being noticeable on plain x-ray.

There is no role for the routine use of CT, MRI, or positron emission tomography (PET) scans in Paget disease. CT scans may be used if plain x-ray is not adequate to assess the affected site (eg, facial bones, middle ear) as lytic lesions enhance with intravenous contrast. MRI can be used in cases of neurologic compromise and to assess for malignant transformation or fracture. Pagetic bone can cause false-positive results on PET scans that use ^{18}F-fluoride since the tracer is taken up at involved sites in proportion to osteoblastic activity.

Treatment

As with any chronic disease, patient education about Paget disease is the first and most important aspect of disease management. The Paget Foundation for Paget’s Disease of Bone and Related Disorders (http://www.paget.org) is helpful in providing information to patients and health care professionals.

Indications for treatment Treatment in Paget disease is not necessary in all patients. In those with asymptomatic, mild disease who are not at risk for secondary complications, observation, adequate calcium and vitamin D, and periodic monitoring may be all that is required. However, treatment is recommended for those with the following indications:

- Active disease at risk for future complications (eg, impending fracture, worsening hearing, paraplegia)
- Prior to elective surgery at or near pagetic sites (eg, total joint replacement, osteotomy to correct deformity, surgical excision of skeletal malignancy)
- Symptoms (eg, bone pain, headache from skull involvement, neurologic symptoms including paraplegia, congestive heart failure)
- Hypercalcemia in the setting of immobilization

Many of the complications of Paget disease (eg, fracture, deformity, malignancy) can take years to develop, and

many studies on Paget disease are of short duration. As a result, there is a lack of long-term event-driven data (eg, fracture prevention, need for joint replacement surgery) for the benefits of treatment in Paget disease of bone. However, trials of bisphosphonate use in Paget disease show decreased levels of bone turnover markers with treatment that parallel improvement in the radiographic appearance of lytic lesions, quality of life, and bone histology. Therefore, bone turnover markers (usually alkaline phosphatase) are typically used as a surrogate end point of effectiveness and anticipated long-term benefit of therapy. The goal of therapy is to target the bone turnover marker (eg, alkaline phosphatase) level in the lower half of the normal range.

Calcium and vitamin D It is recommended that all patients with Paget disease of bone get adequate calcium and vitamin D (25-OHD level > 20–30 ng/mL) to ensure adequate levels for bone formation and reduce the risk of accelerated bone resorption from secondary hyperparathyroidism.

Bisphosphonates Bisphosphonates are the treatment of choice for Paget disease of bone. They are preferentially taken up by active pagetic lesions. When used in Paget disease, bisphosphonates decrease bone turnover and allow for normal lamellar bone to replace the abnormal disorganized bone, thereby decreasing bone pain and improving bone strength. Intravenous infusion of zoledronate 5 mg over 15 minutes is the preferred agent due to its superiority in terms of potency (rapidity of response and degree of suppression of bone turnover markers) and duration of response. Zoledronate is effective even in patients who did not respond to other bisphosphonates such as risedronate and pamidronate. The response to zoledronate is independent of age, gender, baseline alkaline phosphatase level, and previous bisphosphonate therapy. Serum levels of alkaline phosphatase can decrease within 10 days of treatment with zoledronate and continue to fall for 3 to 6 months after the infusion. With zoledronate, alkaline phosphatase levels can remain suppressed for at least 6 years. Symptomatic improvement in bone pain, physical function, and quality of life can occur with zoledronate therapy before normalization of alkaline phosphatase. The therapeutic response can be monitored with serum levels of alkaline phosphatase (or other bone formation marker if alkaline phosphatase cannot be used) or imaging. Bone scintigraphy is more sensitive for assessing response to treatment than plain x-ray. The degree of response to bisphosphonate therapy may not be uniform in all lesions. There is controversy regarding the prophylactic use of zoledronate infusions to reduce the risk of recurrent Paget in patients with quiescent disease.

Zoledronate is generally well tolerated. The most common side effect is a mild-to-moderate transient flu-like reaction characterized by fever, myalgias, bone pain, nausea, and fatigue, in the 24 to 48 hours following an infusion. The reaction can last several days but occurs less frequently with subsequent infusions and if the patient is adequately hydrated prior to the infusion. Rarely, hypocalcemia and a compensatory secondary hyperparathyroidism can occur. Adequate vitamin D nutrition can minimize the risk of hypocalcemia. Complications of bisphosphonates are unusual. Osteonecrosis of the jaw has rarely been reported in Paget disease patients. In all of these cases, the patients received more than the recommended dose to treat their disease. Use of zoledronate is contraindicated in those with a CrCl less than 35 mL/min.

Oral bisphosphonates, such as a 6-month course of alendronate 40 mg/day or a 2-month course of risedronate 30 mg/day, can be used for those with contraindications to zoledronate. Oral bisphosphonates have a lower risk of nephrotoxicity because of their lower peak serum concentrations but are associated with upper gastrointestinal side effects such as esophagitis. Other side effects of oral bisphosphonates are similar to those of zoledronate. Serum alkaline phosphatase levels normalize in over 60% of patients who receive alendronate and 70% of those who receive risedronate. However, the duration of response is shorter than that of zoledronate.

Bisphosphonate therapy can help establish the etiology of pagetic pain. If pain does not respond to bisphosphonate therapy after 3 to 4 months, a non-bone etiology for the pain should be considered.

Bisphosphonate therapy should be administered 1 to 2 months prior to elective surgery in the case of zoledronate and 3 to 4 months preoperatively in the case of oral bisphosphonates.

Bisphosphonate therapy should be considered in cases of ischemia-induced paraplegia associated with Paget disease. The increased blood flow to pagetic lesions can cause decreased blood flow to adjacent tissues, including nerves. Bisphosphonates decrease bone remodeling, thereby decreasing the exaggerated blood flow to pagetic lesions and allowing for normal blood flow to return to adjacent nerves. Symptomatic improvement can be seen within 2 weeks and can continue for several months. When paraplegia is due to a pagetic skeletal deformity, surgery should be considered.

Analgesics Joint pain associated with Paget disease is more likely to respond to analgesic therapy (such as nonsteroidal anti-inflammatories, acetaminophen, aspirin, or antineuropathic medications) than bisphosphonates. In older adults, care should be taken to avoid renal and GI toxicity from nonsteroidal anti-inflammatory drugs (NSAIDs).

Some patients with severe joint destruction from Paget disease who are not candidates for joint replacement may require narcotics to control their pain. Despite a lack of evidence from randomized controlled trials, other therapeutic modalities such as acupuncture, hydrotherapy, transcutaneous electrical nerve stimulation, and physiotherapy have also been used for pain control in Paget disease.

Other agents As a potent inhibitor of osteoclasts, denosumab has the potential to be effective in Paget disease of bone. However, it would likely require more frequent dosing than zoledronate and is not FDA approved for this indication. Denosumab can be considered in those with contraindications to bisphosphonates or impaired renal function. Teriparatide is contraindicated in those with a history of Paget disease due to the potential for an increased risk of osteosarcoma.

Calcitonin has been used for Paget disease of bone and can ameliorate the associated bone pain. However, bisphosphonates are much more effective and have a superior duration of action compared to calcitonin. Furthermore, in the doses required calcitonin commonly causes nausea and flushing. Safety concerns related to a carcinogenic potential have led to the removal of calcitonin from the market in Europe and decreased use for any indication in the United States. Newer agents, such as odanacatib and romosozumab, have not yet been studied in Paget disease of bone. However, since sclerostin inhibitors such as romosozumab primarily work by increasing bone formation, they are unlikely to be of benefit in Paget disease in which excessive bone resorption is the primary abnormality.

Surgical resection is the preferred treatment for osteosarcoma and giant cell tumors arising in Paget disease patients. Adjunctive dexamethasone, denosumab (120 mg subcutaneously every 4 weeks), and radiation have also been used to shrink giant cell tumors.

Monitoring response to treatment and when to retreat Bone resorption markers can be obtained as soon as 10 days after zoledronate infusion to judge the duration of therapeutic response in cases where a rapid response is necessary (ie, paraplegia). Bone resorption markers decrease faster than bone formation markers. The nadir of bone resorption markers occurs approximately 10 days postinfusion whereas the nadir of bone formation markers (eg, alkaline phosphatase) is typically 2 to 3 months postinfusion. In highly active disease, it may take up to 6 months to observe the maximal level of bone turnover suppression. Patients with an alkaline phosphatase level in the lower half of the normal range at 6 months post-zoledronate infusion have less than 10% risk of relapse in 6 years. Therapeutic response should be assessed every 1 to 2 years after zoledronate, or every 6 to 12 months in those receiving less effective medications. Laboratory results (or imaging if laboratory results are consistently normal as in monostotic disease) should be used preferentially over history and physical to indicate relapse. Alkaline phosphatase is the bone turnover marker of choice for monitoring disease, however PINP or BSAP can be used if alkaline phosphatase levels are normal or there is coexistent hepatobiliary disease.

Repeat x-ray of osteolytic sites can be performed approximately 1 year after treatment to assess for efficacy. Additional x-rays may be obtained as needed to assess bone pain and to monitor for resolution of the osteolytic lesion(s). Scintigraphy may be more sensitive than x-ray for monitoring the radiographic response to therapy and serial examinations can be used in cases where bone turnover marker levels are normal.

Retreatment should be considered if patients again meet criteria for treatment such as symptoms or an increase in bone turnover marker level to 20% to 30% above the upper limit of normal.

Supportive measures for deformities and gait disturbances Patients who develop deformities or gait disturbances should be evaluated to correct or improve these impairments. It may be necessary to use supportive measures such as shoe lifts, canes, orthotics, or physical therapy for the skeletal deformities, osteoarthritis, and spinal stenosis. If the patient has a leg-length deformity, it may be beneficial to correct the deformity with a shoe lift to 50% of the leg-length discrepancy over 3 to 4 months. When this has been accomplished, patients may find they ambulate better. Patients with hearing impairments should be referred to an audiologist. The hearing loss is irreversible but the use of cochlear implants is being evaluated. Patients with maxillary or mandibular disease should be evaluated by a dentist. Similar to osteoporosis management, patients with Paget disease should be counseled on fall prevention. Weight management can limit the progression of deformities and osteoarthritis.

When surgery is necessary for conditions associated with Paget disease (eg, neurosurgical intervention for spinal stenosis, tibial osteotomy to realign the knee and decrease mechanical pain, arthroplasty for osteoarthritis), complete immobilization should be avoided so as not to cause hypercalcemia. Preoperative treatment with a bisphosphonate should be considered. When any orthopedic procedure is performed, it is important to maintain the patient on antiresorptive medication after surgery so that prostheses will not loosen with accelerated remodeling or straightened limbs will not rebow.

ACKNOWLEDGMENTS

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Chapter 113

Aging of the Muscles and Joints

Todd M. Manini, David M. Gundermann, Brian C. Clark

Learning Objectives

- Determine the most common age-related changes in key components of the neuromusculoskeletal axis.
- Identify present scoring systems to measure sarcopenia and dynapenia.

Key Clinical Points

1. **Adults over age 50 years, on average, lose 1% to 2% of muscle mass and 3% to 4% of muscle strength per year. This is due to reductions in neuronal, neuromuscular, and muscle function.**
2. **Sarcopenia (age-related muscle atrophy) and dynapenia (age-related muscle weakness) are defined inconsistently among scoring systems and clinical guidelines using aspects of (1) physical function (ie, gait speed), (2) muscle strength, and (3) muscle mass; thus there is no uniform diagnosis accepted for these conditions at the present time. However, if progress is to be made regarding lifestyle and pharmacologic interventions, a uniform definition is essential.**
3. **Age-related changes in cartilage, tendons, and ligaments contribute to common arthritic syndromes (eg, osteoarthritis and a general decline in joint range of motion with age, but the mechanisms that are age) versus disease-related have not been clearly elucidated.**
4. **Intervertebral disk degeneration increases with age, with at least some degree of degeneration universally present by the sixth decade of life. However, the presence of disk degeneration does not correlate well with symptoms of pain, so it is difficult to determine the clinical significance of these findings.**

There are a large number of age-related changes that occur in the tissues that make up the musculoskeletal system. Many of these changes contribute to the most pervasive chronic conditions seen in older adults. In fact, musculoskeletal disorders are the most common cause of chronic disability in late life. This is attributable both to the prevalence of disorders affecting the musculoskeletal system as well as the central role of the musculoskeletal system for daily function for independent living. Despite the prevalence of musculoskeletal disorders, however, there is still much to learn about the pathogenesis of these disorders, including the role of aging, and the interactive role of physical inactivity, in their development.

This chapter reviews aging in each of the major components of the musculoskeletal system including the neuromuscular system, which includes a detailed discussion on sarcopenia (age-related muscle atrophy) and dynapenia (age-related muscle weakness), as well as cartilage, ligaments and tendons, and intervertebral disks (refer to **Table 113-1**). Although bone is a key player in the musculoskeletal system, aging changes in this tissue are discussed in more detail in Chapter 118.

TABLE 113-1 GENERAL MECHANISMS OF MUSCULOSKELETAL TISSUE AGING
Accumulation of modified and degraded extracellular matrix components
Increased collagen cross-linking by advanced glycation end products
Decreased numbers of mesenchymal stem cells to replace lost cells
Decreased tissue regeneration capacity in response to injury
Decreased protein formation in response to systemic growth factors
Imbalance in protein synthesis and degradation
Unregulated apoptosis (cell death)
Impaired coupling of muscle proteins responsible for contraction
Alterations in muscle architecture that promote weakness

AGING OF THE NEUROMUSCULAR SYSTEM

Around 30% of women and 15% of men in the United States over 60 years self-report that they are unable to lift or carry 10 lb, and approximately 50% of women and 40% of men report difficulty in stooping, crouching, or kneeling. Further, more than 40% of seniors have limitations in performing one or more daily tasks (eg, walking two to three blocks, transferring from sitting to standing) that are essential for maintaining physical independence. While many factors contribute to impaired physical function, a major contributor is muscle weakness. In fact, weakness predisposes seniors to a fourfold increase in functional limitations as well as a twofold increase in mortality. It was originally thought that the loss of skeletal muscle mass largely explained the muscle weakness observed in older adults; however, more recent findings suggest that other anatomic and physiologic factors also play an important role in muscle weakness. In general, the mechanisms determining muscle strength or power output arise from two factors: (1) neurological and (2) skeletal muscle properties, as it is well known that the output from these sources control muscle force and power production. These multifactorial mechanisms are outlined in **Figures 113-1** and **113-2**. Specifically, within the neuromuscular system, there are several potential sites likely resulting in weakness, such as reduced excitatory drive to the spinal motor neurons, reductions in motor neuron discharge rates, impairments in neuromuscular transmission, muscle cell death, muscle protein imbalance, reduced repair/regeneration of muscle cells, and impairments in the excitation-contraction (EC) coupling processes. Below we describe the basic neurophysiological and skeletal muscle processes required for muscle contraction followed by an overview of the mechanisms underlying skeletal muscle impairments associated with aging. Lastly, we review the diagnostic considerations of dynapenia and sarcopenia.

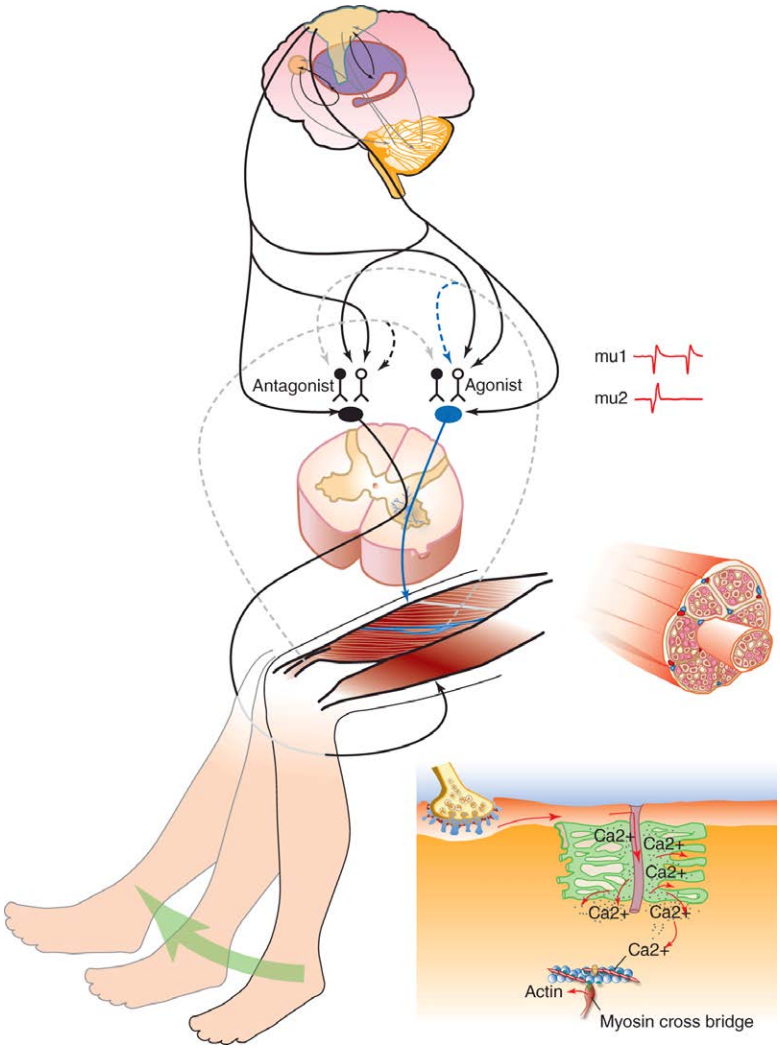


FIGURE 113-1. Theoretical model of the potential neurologic and muscular factors leading to age-related muscle weakness (dynapenia). (From Clark BC, Manini TM. Sarcopenia =/= dynapenia. *J Gerontol A Biol Sci Med Sci*. 2008;63(8):829–834.)

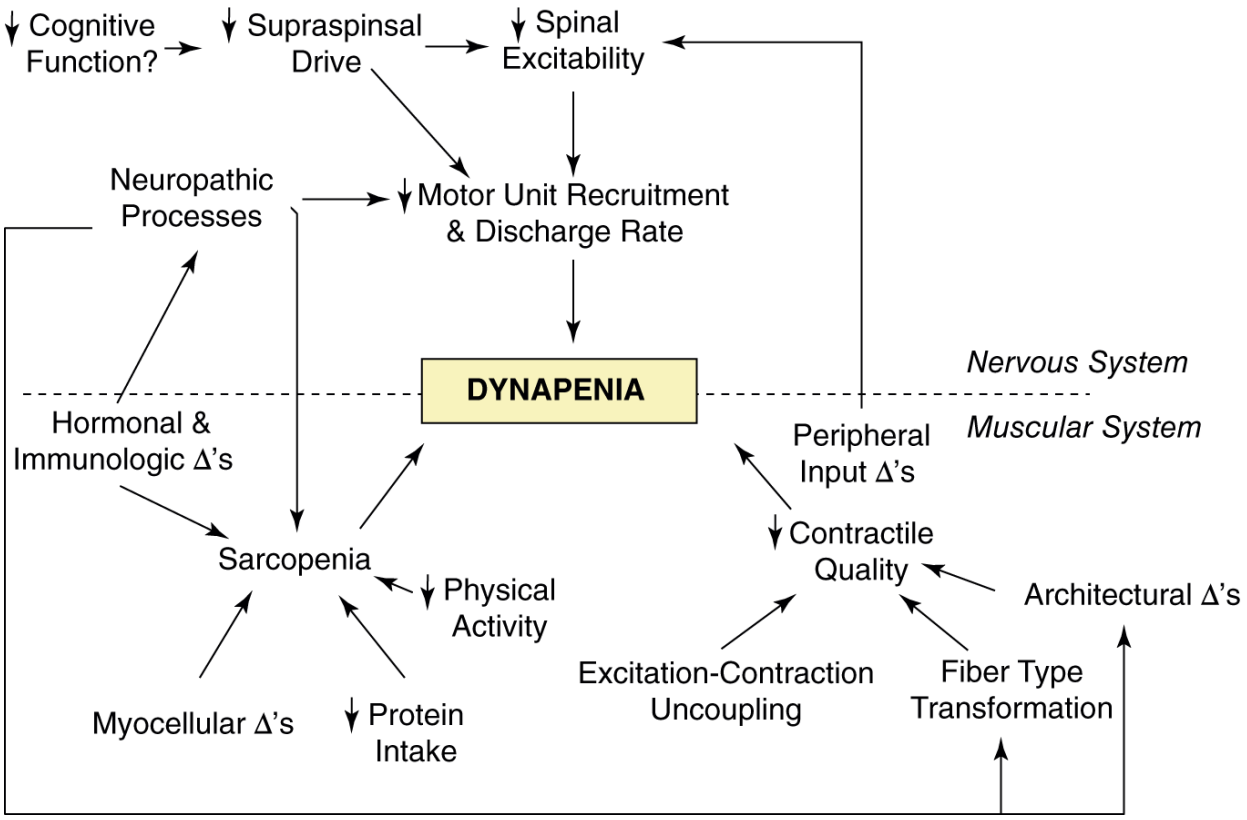


FIGURE 113-2. Potential sites and physiological mechanisms that regulate strength. The neuromuscular system contains several potential sites that can affect voluntary force or power production, such as excitatory drive from supraspinal centers, α-motor neuron excitability, antagonistic muscle activity, motor unit recruitment and rate coding, neuromuscular transmission, muscle mass, excitation-contraction (EC) coupling processes, and muscle morphology and architecture. There is evidence of aging-induced alterations at nearly every denoted site within the system such as, but not limited to, decreased cortical excitability, decreased spinal excitability, decreased maximal motor unit discharge rate, slowed nerve conduction, alterations in muscle architecture, decreased muscle mass, increased myocellular lipid content, and excitation-contraction uncoupling. (From Manini TM, Clark BC. Dynapenia and aging: an update. *J Gerontol A Biol Sci Med Sci*. 2012 Jan;67(1):28–40)

NEURAL CONTROL OF MUSCLE CONTRACTION

"…to move things is all that mankind can do, for such the sole executant is muscle, whether in whispering a syllable or in felling a forest."

Charles Sherrington
1932 Nobel Laureate

The vast range of motions and forces that humans can achieve arises from the activity of more than 600 skeletal muscles, which are under the control of the nervous system. After processing sensory information about the body and its surroundings, the motor centers of the brain and spinal cord generate neural commands that effect coordinated, purposeful movements. The process is complex, as the nervous system is a cellular network of up to 10 billion neurons and 60 trillion synapses communicating together. Each neuron is a component in the system of distinct circuits whose computational processing precision ultimately determines every aspect of behavior. The discharge behavior of these neurons, including the motor neuron, represents a complex interplay between the excitatory and inhibitory synaptic inputs they receive and the cells' intrinsic electrical properties. The patterns of interneuronal connections and communication, as well as the discharge behaviors, are not permanently fixed; they show variability and can be reorganized.

Motor systems are organized hierarchically, with each level concerned with a different decision. The highest and most abstract level, likely requiring the prefrontal cortex, deals with the purpose of a movement. The next level, which is concerned with the formation of a motor plan, involves interactions between the posterior parietal and premotor areas of the cerebral cortex. The premotor cortex conveys the spatial characteristics of a movement based on sensory

information arising from the posterior parietal cortex about the situation (ie, the environment) and about where the body is in space. The lowest level coordinates the space and time details of the muscle contractions needed to execute the planned movement. These supportive motor regions include the contralateral sensorimotor cortex, supplementary motor area, and the cingulate cortex. Control circuits located in the cerebellum and basal ganglia are then initiated to trigger activity in descending motor tracts, which signals the spinal interneurons and lower motor neurons to contract skeletal muscle fibers to produce movement. While this hierarchical view is useful to help us understand the system, it should be noted that there is evidence indicating that many of these processes can occur simultaneously. Understanding the neural control of muscle contraction is not only fundamental in its own right, but it is of further importance in helping us to understand disorders of this system and explore the possibilities for recovery.

Supraspinal Control of Movement

Healthy individuals carry out highly complex and complicated movements without a thought to the actual joint motions or muscle contractions. These neural commands that act on the muscles to cause them to contract and generate movement are commonly known as “motor outputs.” However, for voluntary motor outputs to successfully occur the brain requires a number of steps to convert incoming sensory information into motor outputs (ie, multistage sensorimotor transformations). Sensory representations are the framework that is used for the motor systems to plan, coordinate, and execute the motor programs responsible for purposeful movement. Variability in the inputs and outputs of these transformations, as well the inaccuracies in their representation, underlie the errors and variability in movement. The motor plan typically has to specify both a particular path (where in space to move and what the endpoint is) as well the trajectory (the acceleration and speeds of the movement). Here, we briefly describe the cortical networks that control voluntary movement, particularly the role of the primary motor cortex in the generation of motor commands.

Within the brain, motor functions are localized within the cerebral cortex. Here, distinct sites contain neurons with specific functions, with the most finely controlled body parts (eg, finger and facial muscles) represented on the motor map by disproportionately large areas. This larger area permits for a greater number of neurons, which is needed for fine motor control. The brain control of voluntary behavior is commonly divided into three sequential stages. First, perceptual mechanisms generate a unified sensory representation of the individual and the environment. Next, cognitive processes use this internal model of the world to decide on a course of action, and the selected motor plan is relayed to action systems for implementation. Execution of the motor plan is the final stage. Because several of these stages involve the actual choice of what action to take, it is reasonable to consider these processes as “cognitive” (as opposed to strictly considering them “motor”). Interestingly, a growing body of research indicates that a good predictor of impending cognitive decline in older adults is a slowed and stooped gait, which has been assigned the term “motoric cognitive risk syndrome.”

Several cortical motor regions project in multiple parallel tracts to subcortical areas of the brain as well as the spinal cord. The pyramidal tract, which originates in the deeper structures of the cortex (eg, precentral and parietal cortical areas in layer V), is the best-studied output path. Many of the axons in this tract intersect in the lower medulla (pyramidal decussation) and form the corticospinal tract that projects to the spinal cord. Several cortical areas, including the premotor and parietal areas as well as the primary motor cortex, contribute axons to the corticospinal tract, with many of these axons terminating on spinal interneurons in the intermediate region of the spinal cord. The terminals of some corticospinal axons also extend into the ventral horn of the spinal cord where they branch out and monosynaptically contact the dendrites of spinal motor neurons (these projecting cortical neurons are called corticomotoneurons). A single corticomotoneuron axon often terminates on and excites spinal motor neurons for several different agonist muscles, and can also influence the contractile activity of even more muscles through synapses on spinal interneurons, which can function to indirectly suppress the activity of antagonist muscles. The monosynaptic projection from the primary motor cortex onto spinal motor neurons is greatest for the distal arm, hand, and finger muscles. This arrangement allows for the primary motor cortex to regulate the activity of those muscles directly, in contrast to its indirect regulation of muscles through the reflex and pattern-generating functions of the spinal circuits. **Figure 113-3** illustrates this innervation pattern. The corticospinal tract is not, however, the only pathway for descending control signals to spinal motor circuits, as the spinal cord also receives inputs from the rubrospinal, reticulospinal, and vestibulospinal tracts.

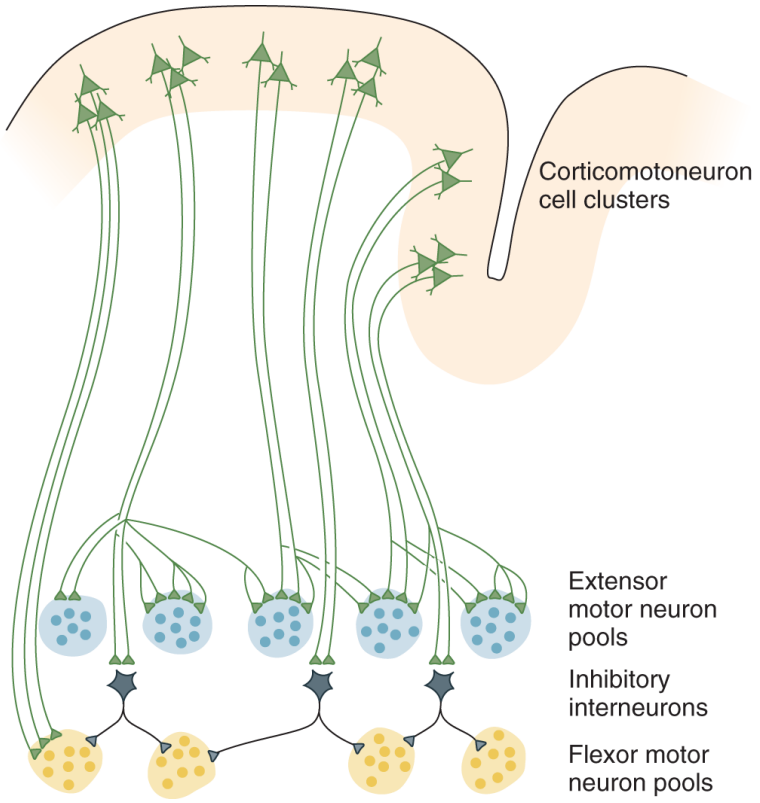


FIGURE 113-3. Different groups of corticomotoneurons in the primary motor cortex terminate on different combinations of spinal interneuron networks and spinal motor neuron pools, thus activating different combinations of agonist and antagonist muscles. Many other corticospinal axons terminate only on spinal interneurons, which are not shown. The figure illustrates corticomotoneuronal projections largely onto extensor motor neuron pools; however, it should be noted that flexor motor pools receive similar complex projections but are not illustrated. (Modified with permission from Cheney PD, Fetz EE, Palmer SS. Patterns of facilitation and suppression of antagonist forelimb muscles from motor cortex sites in the awake monkey. *J Neurophysiol*. 1985. 53:805-820.)

The motor cortex clearly plays a critical role in the control of voluntary movements; however, its neurons do not function like spinal motor neurons whose singular role is to encode muscle activity patterns. Rather, the motor cortex contains different populations of neurons that contribute to the numerous processes required to convert a plan of action into the motor commands that execute the plan. Further, the response properties of the primary motor cortex neurons are not identical in that these neurons seemingly encode the space and time aspects of movement (ie, direction, amplitude, speed, and path aspects, commonly referred to as kinematics) as well as the static and dynamic forces (ie, the magnitude of muscle activity levels, commonly referred to as kinetics). Current evidence suggests that some neurons in the primary motor cortex provide information about force output, whereas the activities of other neurons signal the desired kinematics. The brain is remarkably adaptable and can change its circuitry by learning from experience and storing the acquired knowledge as memories. Accordingly, the motor cortex should be regarded as a dynamic computational map whose internal organization and spinal connections convert central signals about motor intentions and sensory feedback about the current state of the limb into motor output commands, rather than as a static map of specific muscles or movements of body parts.

Spinal Control of Movement

A typical muscle is controlled (innervated) by a several hundred alpha motor neurons; however, wide variability exists between muscles with some muscles having less than 100 and others having more than 4000. The cell bodies of these neurons are located as a collection of cells (motor nucleus) in the spinal cord or brain stem. Each alpha motor neuron axon exits the spinal cord through the ventral root, or through a cranial nerve in the brain stem, and goes to the muscle. Here, the axon branches and innervates the muscle fibers. Each alpha motor neuron will innervate anywhere from a few muscle fibers to several thousand muscle fibers. A motor neuron and the muscle fibers that it innervates is referred to as the “motor unit,” which ultimately represents the elementary unit of motor control as the motor unit represents the final pathway for transmitting the neural signal to skeletal muscle fibers for contraction (**Figure 113-4**). In general, if an action potential is generated in a motor neuron it will transmit this action potential to the muscle fibers that it innervates. Here, acetylcholine is released from the axon ending and attaches to acetylcholine receptors on

the muscle cell membrane, and depolarization occurs and the action potential is generated along the muscle cell membrane. These are the first steps involved in the excitation-contraction coupling process that eventually results in muscle force production and is described in more details later in this chapter. The number of muscle fibers innervated by a motor neuron (innervation number) varies primarily based on the function of a given muscle with muscles responsible for finer control (eg, eye muscles, hand muscles) having a lower innervation number and muscles responsible for higher force and power production (eg, medial gastrocnemius) having a higher innervation number. The number of muscle fibers controlled by a motor neuron is related to the amount of force that is produced by the activation of this motor unit (ie, a motor unit with a lower innervation number will exert a lower amount of force when activated in comparison to a motor unit with a higher innervation number).

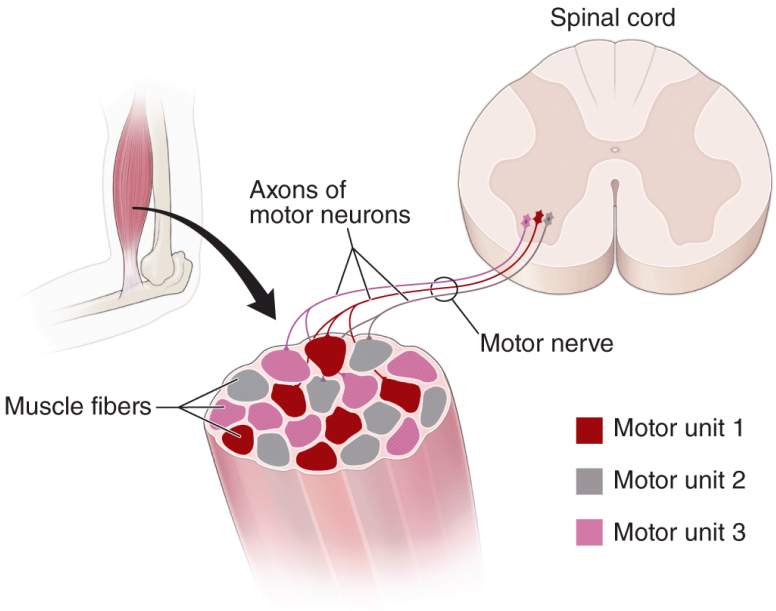


FIGURE 113-4. The motor unit is made up of a motor neuron and the skeletal muscle fibers innervated by that motor neuron. Groups of motor units often work together to coordinate the contractions of a single muscle, with all of the motor units within a muscle commonly referred to as a "motor pool."

Muscle force is primarily controlled by the recruitment and discharge rate of motor units. Here, force can be increased by the activation of additional motor units or firing an active motor unit at a faster rate. For a motor unit to be activated the alpha motor neuron must reach threshold. The recruitment threshold depends on the membrane resistance (a measure of the impediment to the transmembrane flow of ions) of the motor neuron. Specifically, based on Ohm's law, a motor neuron with higher resistance will be activated before a motor neuron with lower resistance. Its surface area determines its membrane resistance, with small diameter motor neurons having higher resistance due to it having fewer parallel ion channels. Stated simply, if a small diameter and a large diameter motor neuron receive the same level of synaptic input current the small diameter motor neuron will have a larger change in its membrane potential and discharge first. This indicates that motor neuron recruitment is determined by spinal mechanisms and not by supraspinal centers (as the brain is unable to selectively activate specific motor units). The phenomenon of motor units being recruited in an orderly manner is commonly referred to as the *size principle of motor neuron recruitment*. The discharge rate of motor neurons depends on the level of net excitatory input to the motor neuron, coupled with its intrinsic membrane properties, which ultimately determine the magnitude of neuronal depolarization. These properties can be dramatically altered by input from monoaminergic neurons in the brain stem. For instance, when the monoamines serotonin and norepinephrine activate L-type Ca^{2+} channels on the dendrites of the motor neurons, the resulting inward Ca^{2+} currents can enhance synaptic currents up to 10-fold. Thus, high levels of monoaminergic drive can result in "self-sustained firing" of the motor neuron (ie, they continue to fire repetitively after being activated by a brief, excitatory synaptic input). It should be noted that not all motor units are the same. That is, motor units vary based on their contraction speed, maximal force, and ability to withstand fatigue. A functional advantage of orderly recruitment is that the slower, lower force generating, and more fatigue-resistant motor units are activated first. Interestingly, physical activity has been shown to modify these motor unit properties with reductions in activity reducing the maximal capacities of all three properties.

Spinal reflexes also contribute to the neural control of muscle contraction. The sensory stimuli for these reflexes arise from a number of receptors, including those in muscles and joints. While the neural circuitry responsible for the motor response is contained in the spinal cord, supraspinal centers play an essential role in modifying and adapting spinal reflexes and can even reverse reflexive movements when appropriate. The stretch reflex (also known as myotatic reflex, deep tendon reflex, or muscle spindle reflex) is a spinal reflex that occurs in response to changes in muscle length. Here, muscle spindles relay sensory information on the length of, and changes in the length of, a muscle to the spinal cord (the anatomic and neural pathways of the stretch reflex are illustrated in **Figure 113-5**). Muscle spindles are collections of specialized muscle fibers (ie, intrafusal muscle fibers) that are not part of the high-force producing muscle mass itself (ie, extrafusal muscle fibers, which are discussed in more detail later, that are innervated by alpha motor neurons). Although intrafusal fibers do not contribute substantially to the force produced during muscle contraction, they do have contractile elements at their ends that are innervated by gamma motor neurons. Muscle spindles reside parallel to extrafusal muscle fibers, stretching alongside these muscle fibers during both active and passive movements. Muscle spindles contain small organelles (nuclear chain and bag fibers) and two different types of sensory nerves (type Ia and II afferents) that convey information about both length and rate of length change in the muscle. The type Ia afferent makes direct excitatory connections with the alpha motor neurons that innervate the extrafusal fibers of the muscle that it resides in. This same afferent axon also connects to interneurons that inhibit the motor neurons that innervate its antagonist muscles. This inhibition prevents muscle contractions that could resist the movement produced by the stretch reflex. Thus, muscle spindles, and stretch reflexes, are used by the central nervous system to sense relative positions of the body segments and modulate the excitability of the alpha motor neurons accordingly. Golgi tendon organs, strands of collagen fibers located in the musculotendinous junction with a type Ib afferent nerve attached, are another sensory receptors in muscle that provide feedback to the nervous system. Tendon organs are most sensitive to changes in muscle tension, with their activation resulting in a spinal reflex that ultimately results in inhibitory input to the agonist muscle (ie, the muscle under tension) and excitatory input to the antagonist muscle.

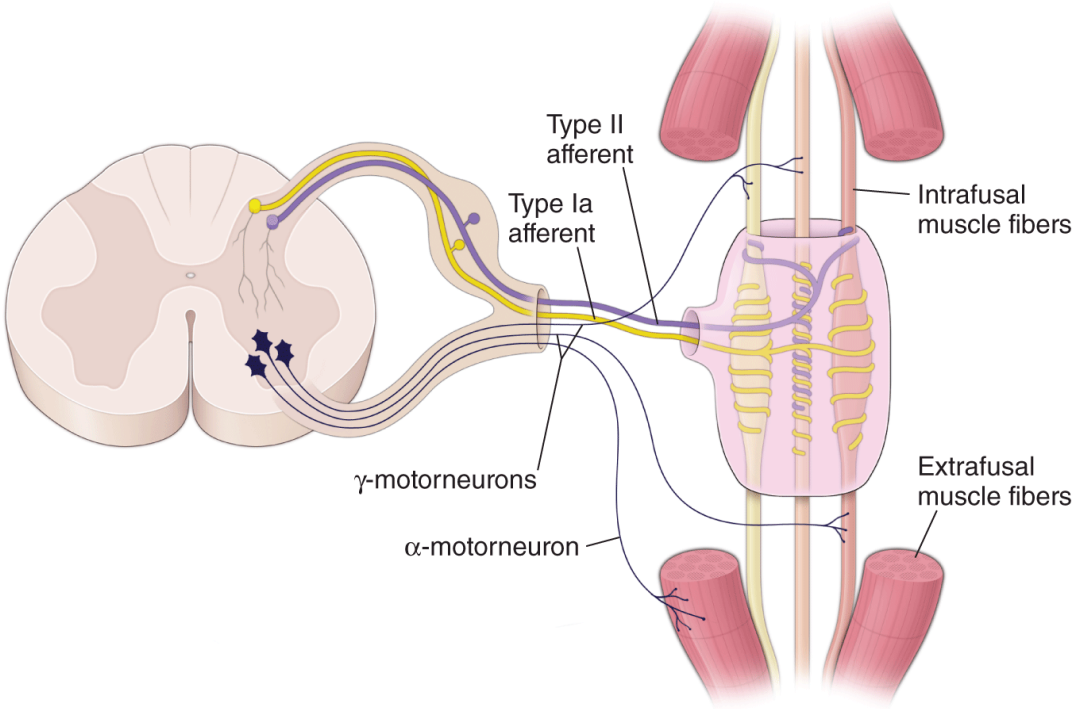


FIGURE 113-5. Anatomic and neural pathways of the muscle spindle. (From Clark BC, Thomas JS, Walkowski SA, Howell JN. The biology of manual therapies. *J Am Osteopath Assoc*. 2012;112(9):617–629.)

The structural and functional behavior of both the supraspinal and spinal control of muscle contraction is considerably more complex than provided herein. We have attempted to simply provide a broad overview of this process. It is our hope that this overview will help you to better appreciate the role the nervous system may play in the losses of physical function (eg, mobility) and muscle function (eg, muscle weakness, motor control) commonly

observed with advancing age.

SKELETAL MUSCLE

Skeletal Muscle Structure and Function

Skeletal muscle is a very important organ playing major roles in metabolism, posture, locomotion, protection, and physical activity. It is comprised of several tissues including muscle fibers, blood vessels, lymphatics, nerves, and connective tissue. The connective tissue merges into stronger structures and connects to the skeleton and the surrounding environment through tendons, aponeuroses, raphes, the reticular layer of dermis, or the periosteum that provide support for muscle insertion and contraction. At the cellular fundamental level, a muscle cell (muscle fiber) functions by shortening its length. The simultaneous shortening of a large number of muscle fibers is the quintessential characteristic of a muscle contraction. The strength of the muscle contraction is then dependent on a number of variables including the number fibers contracting at a time, the types of fibers being stimulated, the frequency of the stimulus to a given muscle fiber, and the muscle architecture, as described further in this section.

Morphologic structure At the most superficial level, skeletal muscle is enclosed by a sheath of connective tissue called the epimysium. Within the epimysium, several muscle fibers are portioned into bundles called fascicles and are surrounded by another layer of connective tissue called the perimysium. A third layer of connective tissue called the endomysium surrounds each muscle fiber encasing multiple myofibrils. Myofibrils are the structures that contain the individual contractile proteins as described in the next section. The particular spatial arrangement of the myofilaments is responsible for the characteristic striation appearance in skeletal muscle.

The architecture at the whole-muscle level and at the fiber level plays a large role in its function. For instance, in most long muscles designed for speed, fibers lie in the longitudinal direction and run from one end to the other. This arrangements increases the number of contractile elements (sarcomeres; further described in the next section) in a series. As the series of sarcomeres is contracting a greater length can shorten in the same period of time and contribute to a higher velocity than shorter muscles. Consequently, the maximum velocity of a contraction partially depends on the number of sarcomeres arranged in series. Conversely, muscles intended for maximal force, are typically thicker and allow for more sarcomeres arranged in parallel. This is because muscle force is equal to the sum of forces produced in parallel. Therefore, increasing the number of sarcomeres in parallel maximizes the force produced. To exploit this feature, the orientation of the fibers relative to the direction of contraction (pennation angle) can also affect force production (**Figure 113-6**). When the pennation angle is greater than zero, the net force of a single fiber is less than the total force the fiber produces. In fact, the transmitted fraction of the force can be calculated as the cosine of the angle of insertion into the tendon. However, the payoff is that significantly more fibers can be arranged in parallel effectively producing a greater force in the same thickness of muscle. A secondary benefit for the existence of a pennation angle is that the distance moved by the central tendon during a contraction is actually greater than the amount of shortening of each muscle fiber. This enables the muscle fibers to enhance function over the optimum length, while the sacrifice of an increased pennation angle is in the velocity of contraction. Therefore, pennation angle varies from muscle to muscle and can also be modified with training.

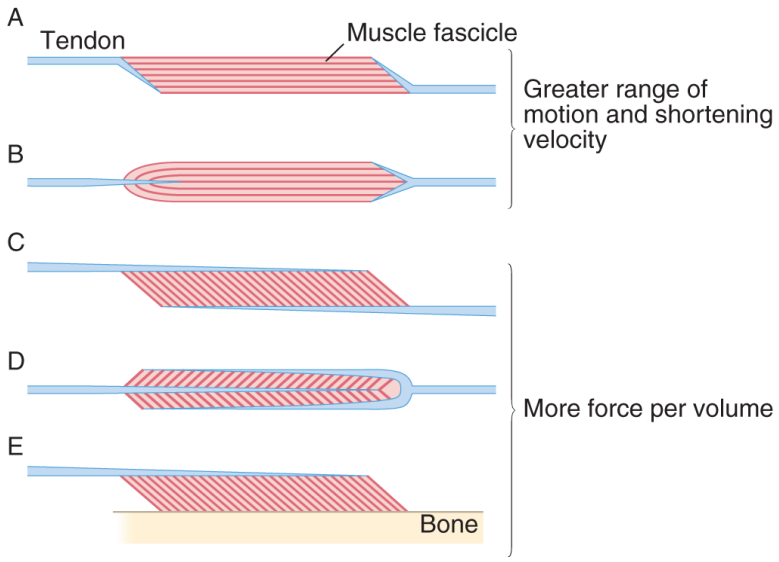


FIGURE 113-6. Five common arrangements of tendon and muscle illustrating the use of pennation. (Reproduced, with permission, from Alexander RM, Ker RF. The architecture of leg muscles. In: Winters JM, Woo SL-Y, eds. *Multiple Muscle Systems: Biomechanics and Movement Organization*. New York: Springer-Verlag; 1990:568–577.)

Muscle contraction The current accepted theory of muscle contraction is the *sliding filament theory*, and it involves two major myofilaments (actin and myosin) along with other regulatory proteins (tropomyosin and troponin), as well as structural supportive proteins (actinin and titin). Actin is a highly abundant cytoskeletal protein that polymerizes in long, thin double helix filaments and is arranged in parallel and in series to each other. Each series of actin filaments represent a sarcomere where the actin filaments are anchored to the z-line via the z-line protein actinin, demarcating the boundaries of each sarcomere (**Figure 113-7**). In essence, the "sliding" of actin filaments (also referred to as thin filaments) along the longitudinal axis, shortening the sarcomere length is the principle behind fiber contraction. Myosin (also referred to as thick filament) is an actin-binding protein composed of a head, neck, and tail domain. The myosin head domain is provided with an actin-binding site where actin and myosin cross-bridges, and a catalytic site that hydrolyzes adenosine triphosphate (ATP) to generate force. The myosin neck domain acts as a linker and lever arm for transducing force allowing the head domain to pivot, pulling the actin filaments, producing the contraction. Myosin filaments are held together and centered in the sarcomere at the tail domain by M-filaments in the M-region. Myosin is also stabilized to the z-lines via titin, which provides some elastic properties. The process of contraction involves a repetitive series of interactions where myosin "walks" along actin. In this process (1) a myosin head finds an available binding site on actin and tightly binds; (2) actin binding initiates the neck region to rotate, contributing to the sliding of actin toward the M-line by approximately 5 nm; (3) energy harvested by ATP hydrolysis is utilized to detach myosin from actin and reset back to its starting configuration; and (4) myosin binds a new site on actin approximately 5 nm down the filament. This cycle repeats continuously as long as the muscle fiber remains stimulated, and ATP levels are maintained.

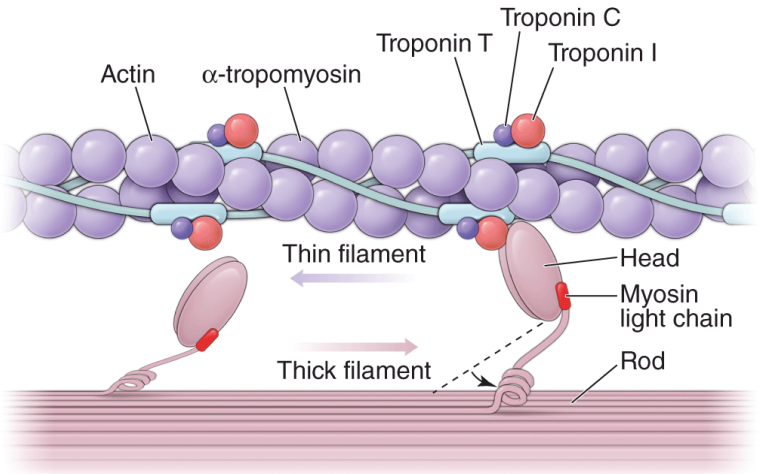


FIGURE 113-7. Interaction of myosin with actin occurs depending on the configuration of troponin. Once bound, the myosin head pivots and produces force to pull on the actin filament.

Skeletal muscle fiber contraction is initiated and maintained by the generation and conduction of action potentials by its motor neuron (as discussed previously in the neural control of muscle contraction section). The action potential propagates throughout the muscle fiber via the sarcolemmal infoldings called the T-tubular system (**Figure 113-8**). Depolarized T tubules activate the voltage-sensitive dihydropyridine receptors (DHPRs), which subsequently opens the ryanodine receptors (RYRs; calcium release channels) (**Figure 113-9**). This releases calcium, from its membranous storage area known as the sarcoplasmic reticulum (SR). An elevation in intracellular calcium concentration is a key event that precedes muscle contraction through the regulatory proteins troponin and tropomyosin.

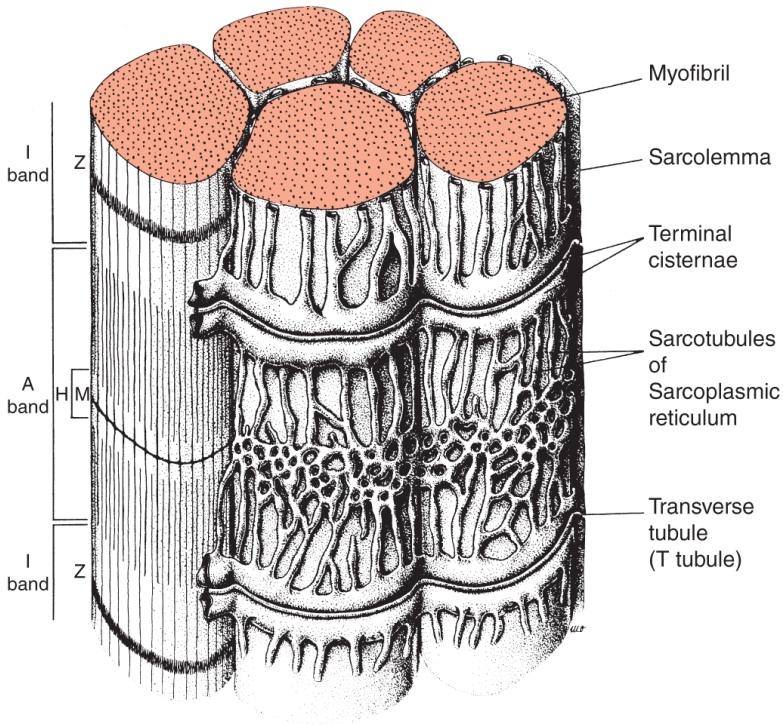


FIGURE 113-8. Diagram of a skeletal muscle fiber illustrating the spatial arrangement of contractile proteins and surrounding membrane system. (Reproduced with permission from Cormack DH. *Ham's Histology*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 1987:402.)

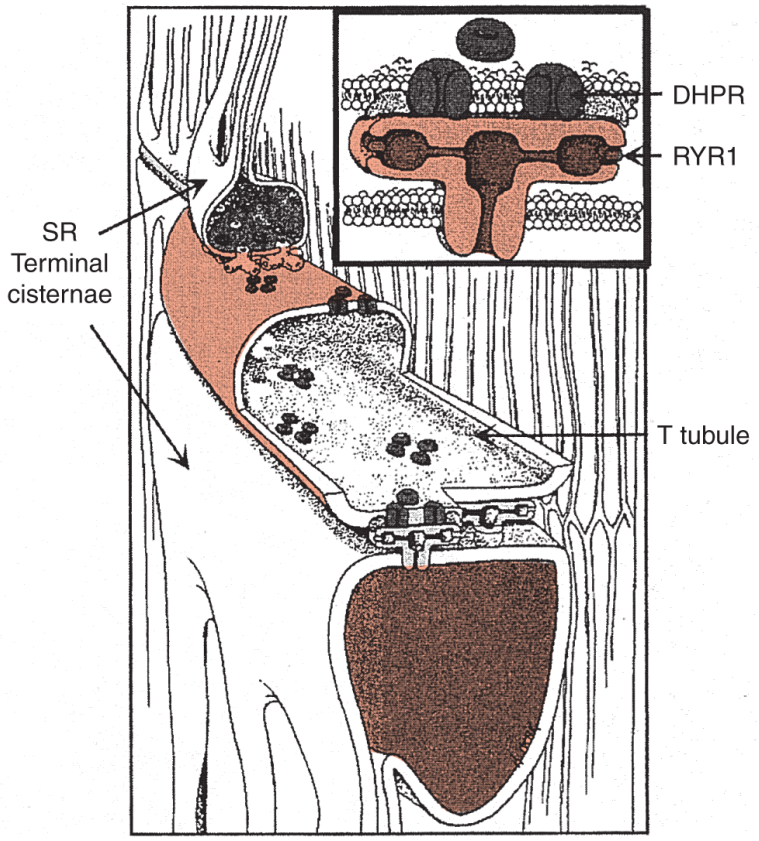


FIGURE 113-9. Schematic of the interaction between the dihydropyridine receptor (DHPR) and ryanodine receptor (RyR1) and their location at the sarcolemmal tubular system and sarcoplasmic reticulum terminal cisternae, respectively. (Redrawn from Block BA, Imagawa T, Campbell KP, Franzini-Armstrong C. Structural evidence for direct interaction between the molecular components of the transverse tubule/sarcoplasmic reticulum junction in skeletal muscle. *J Cell Biol*. 1988 Dec;107(6 Pt 2):2587–2600; Brandt NR, Caswell AH, Wen SR, Talvenheimo JA. Molecular interactions of the junctional foot protein and dihydropyridine receptor in skeletal muscle triads. *J Membr Biol*. 1990 Feb;113(3):237–251; Wagenknecht T, Grassucci R, Frank J, Saito A, Inui M, Fleischer S. Three-dimensional architecture of the calcium channel/foot structure of sarcoplasmic reticulum. *Nature*. 1989 Mar 9;338(6211):167–170.)

Embedded in the actin double helix is a groove where tropomyosin, a long helical protein, resides. Troponin, a protein containing three subunits, is located at regular intervals along tropomyosin. The individual troponin subunits are denoted T, C, and I. Troponin-T is responsible for connecting the other subunits to tropomyosin, while troponin-C contains the binding sites for calcium involved with muscle contraction and finally, troponin-I is a regulatory subunit that physically obstructs the interaction of myosin with actin at rest in the absence of intracellular calcium. The newly released calcium binds to troponin-C, which induces a conformational change in troponin such that troponin-I relocates and exposes the myosin binding sites promoting actin-myosin cross-bridge formation and force production. The calcium is then returned to the SR by the sarcoplasmic reticulum calcium pump (SR-ATPase pump). In the absence of another action potential, the intracellular concentration of calcium diminishes returning troponin to its original configuration with troponin-I obstructing further actin-myosin cross-bridging, quickly relaxing the muscle fiber. This sequence of events resulting from one action potential (stimulus) is called a muscle twitch and results in the generation of a small force. After the fiber has fully relaxed via eliminating the intracellular calcium concentration, a second stimulus can induce another twitch. Although, if a second stimulus is received before the calcium has been fully pumped back into the SR, a higher intracellular calcium concentration will result and induce an increased force (tension) due to additional inhibition of troponin-I, and more actin myosin cross-bridging. Total contractile force depends on the number of cross-bridge interactions. Accordingly, as the stimulus frequency increases, the tension gradually rises until a maximal tension where intracellular calcium concentration is flooded due to the rate calcium release exceeding the rate of resequestering. This maximal tension is called a tetanic contraction or tetanus.

Force, velocity, and power The velocity and extent of muscle shortening independently have inverse relationships with the load applied to the muscle (external force). For example, it is easy to conceive that lifting heavy loads becomes increasingly slower as the load is made larger, even despite maximal muscle stimulation. In addition, the magnitude of the external force also influences the degree of sarcomere shortening, such that a full contraction is gradually reduced with higher external loads. These negative relationships are maintained until the external load

progresses to be equal to the maximal tetanic force exerted by the muscle. It is at this point where the contraction velocity and shortening length both reach zero, resulting in an isometric contraction (ie, a muscle contraction with no change in muscle length).

By definition, muscle power is determined by the product of contraction velocity and external force applied, in which case the power output is zero when there is no load on the muscle or when the load is so heavy that it cannot be moved at all. Therefore, at some intermediate point within that range, power will be the greatest for that given muscle. Maximal force was described in the last section as being dependent on the number of cross-bridge interactions occurring at one time, which can be a result of increased muscle cross-sectional area, or enhanced muscle recruitment. Contraction speed is influenced by the composition of various muscle fiber types within the muscle, as described in the next section. Together, these components can be varied to modify maximum muscular power.

Muscle fiber types Skeletal muscle fibers can be roughly categorized based on their contraction speed, magnitude of force, and resistance to fatigue. For example, slow-twitch (type I) fibers exhibit unloaded twitch durations up to 100 ms, are more economical and are involved in gross and sustained movements. These fibers also have high levels of mitochondria resulting in a great oxidative capacity and reduced fatigability, well suited for long-lasting and repetitive activities like respiration, locomotion, or chewing. On the other hand, fast-twitch (type II) fibers exhibit unloaded twitch duration less than 10 ms, enhanced isometric force per unit cross-sectional area (specific tension), and overall greater power. The trade-off is less mitochondrial content, more fatigable, and thus not suitable for long-duration activities. These fibers are primarily implicated with rapid or powerful movements. Since this initial dichotomization, type II fibers have been further distinguished as IIa and IIx, the latter being the fastest and the former considered to be an intermediate in respect to shortening velocity, although they both produce indistinguishable specific tension. Therefore, the peak power values increase orderly from I < IIa < IIx and it turns out that it is strictly determined by the type of myosin that is present in the fiber.

The discovery that specific myosin heavy chain (MyHC) isoforms correlate with each major muscle fiber type made vast improvements in our understanding of the different fiber types. In addition to the varying contraction speeds, MyHC is the main modulator of ATPase activity, thus contributing to the muscle economy. MyHC-I splits ATP three times slower than type IIx, IIa being intermediate. Since the disparity of specific tension is not as large as the ATPase activity, the tension cost (ATP consumed per unit time and per unit tension) is twofold and threefold lower in type I than in type IIa and IIx fibers, respectively (**Table 113-2**). In humans there are only three distinguishable pure muscle fibers; I, IIa, and IIx, as determined by all the criteria mentioned above. However, this categorization is not as simple as it seems. Muscle commonly contains hybrid fibers with intermediate abilities between the defined muscle types including I-IIa and IIa-IIx. In fact, it can be further argued that varying muscle fiber types fall on a continuum with coexpression of different MyHC isoforms in varying proportions per fiber, with each having unique characteristics of maximum velocity, specific tension, power, economy, fatigability, and so on.

TABLE 113-2 CLASSIFICATION OF MUSCLE FIBERS

	FUNCTIONAL AND HISTOCHEMICAL CHARACTERISTICS			
MUSCLE FIBER SUBTYPES	CONTRACTION VELOCITY	SPECIFIC TENSION	ECONOMY	POWER
Type I	Slow	Low	High	Low
Type IIa	Intermediate	High	Intermediate	Intermediate
Type IIx	Fast	High	Low	High

REGULATION OF SKELETAL MUSCLE PROTEIN METABOLISM

Besides its obvious mechanical roles as discussed in the prior sections, skeletal muscle has a metabolic role as it serves as a constant amino acid source for the whole body's protein needs and backup energy supply. On a continuous level, every tissue in the body is under constant remodeling; that is to say proteins are regularly being degraded and resynthesized from an amino acid pool maintained in the blood stream. Considering that humans do not constantly ingest the necessary amino acids to adequately maintain plasma amino acid concentrations for this purpose, the pool is maintained primarily by the tight regulation of skeletal muscle degradation in the postabsorptive state. Therefore, the

maintenance of skeletal muscle is crucial to the survival of an individual.

The term *muscle metabolism* is the combination of muscle anabolism (muscle building) and catabolism (muscle breakdown); a process that is under tight regulation to maintain muscle mass while still maintaining the plasma amino acid concentration. Skeletal muscle is typically maintained through the ingestion of a diet containing high-quality protein that ultimately causes a transient increase in muscle protein synthesis. Thus, skeletal muscle is in dynamic equilibrium as a result of anabolism after a meal and catabolism during the postabsorptive state. In order to maintain muscle mass, the amount of muscle anabolism must on average equal the amount of muscle catabolism; a concept referred as net balance. This concept is important when considering a variety of conditions such as infections, diseases, burns, injuries, and cancer. In such cases, the demand of amino to produce immunoglobulins, and other proteins involved with wound healing, significantly increase. Likewise, muscle catabolism concomitantly rises to provide the additional amino acids, resulting in a negative muscle net balance. For example, burns can increase muscle protein breakdown at such a rate to cause significant and sometimes lethal levels of muscle loss. Alternatively, conditions such as malnutrition, starvation, immobilization, bed rest or generalized inactivity, decrease muscle anabolism and also results in a negative muscle net balance. Depending on the severity and duration, all of these conditions can potentially be fatal as the catabolic condition continues to degrade muscle until insufficient mass is left to maintain the cellular functions of the other tissues. Therefore muscle loss can be viewed as the most life-threatening condition when combined with another illness. The regulation of skeletal muscle protein synthesis is also complex and under tight regulation.

Protein synthesis requires transcription of the mRNA that carries the message necessary for the synthesis of a particular protein and translation of that mRNA into protein. Studies have failed to show a consistent correlation between changes in the amount of mRNA and the rate of protein synthesis for a given protein. This is because the amount of mRNA only provides information regarding the potential for protein synthesis while it is the process of translation that is directly related to the rate of protein synthesis. Specifically, the regulation of translation initiation and elongation seem to be the rate limiting step in protein synthesis.

Translation initiation involves a series of events necessary for ribosomal complex assembly and binding of the target mRNA. A plethora of initiation factors and signaling molecules regulate the formation of the translational apparatus, thus implicating tight levels of control of the synthesis of new proteins, which can occur within minutes of a particular stimulus. The mechanistic target of rapamycin (mTOR) is a key regulator of translational control. Nutrient, hormonal, and contractile stimuli often converge at this regulator, suggesting that mTOR is an important modulator of protein synthesis. mTOR, once activated, has the ability to phosphorylate two main downstream effectors, eukaryotic initiation factor 4E binding protein (4E-BP1) and p70 ribosomal S6 kinase 1 (S6K1), both of which have independent roles in translation initiation and elongation. 4E-BP1 phosphorylation specifically regulates the assembly of the translation initiation complex. The amount of phosphorylated S6K1 has repeatedly been shown to correlate with the rates of protein synthesis and long-term increases in muscle mass. Thus, quantification of phosphorylated S6K1 is a common surrogate indicator for the potential of an anabolic stimulus to induce an increase in protein synthesis (**Figure 113-10**).

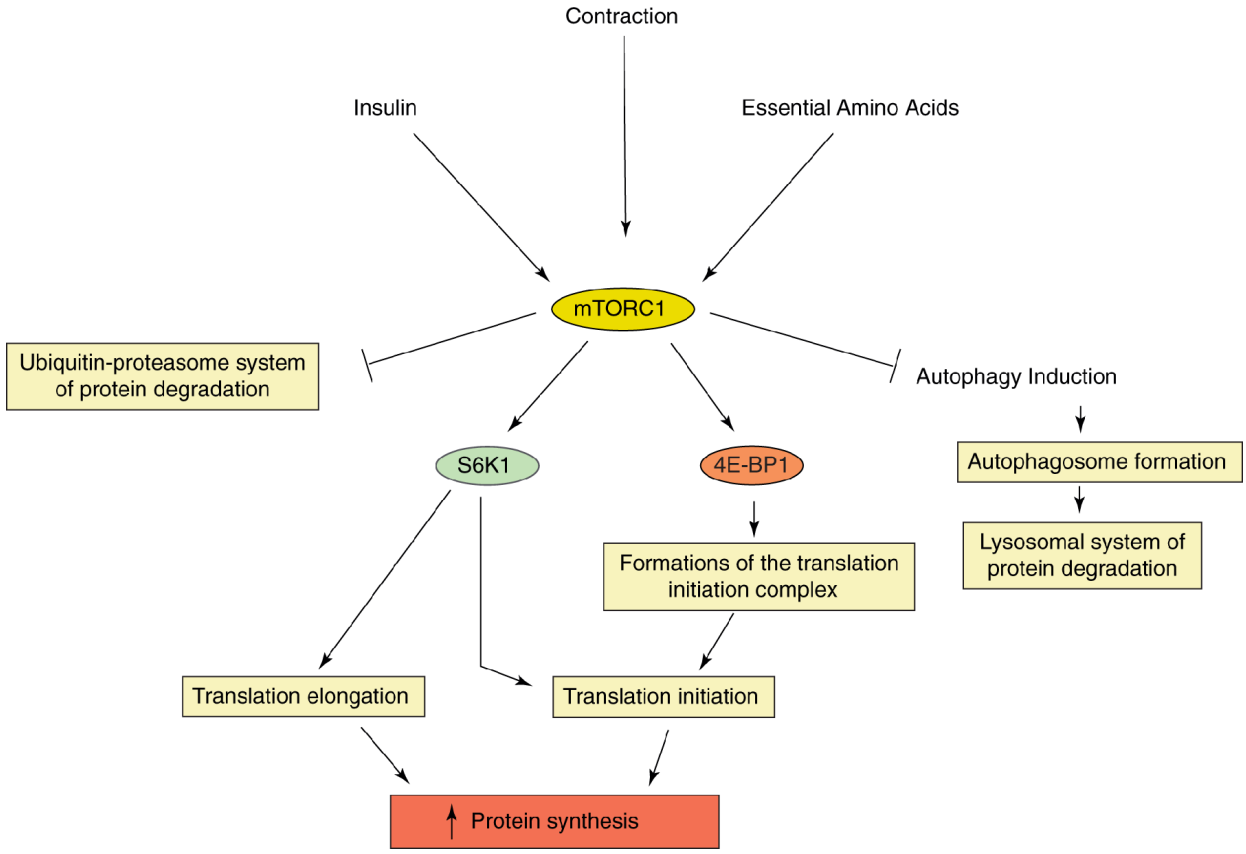


FIGURE 113-10. Simplified signaling pathway of anabolic stimuli inducing an increase in protein synthesis.

MECHANISMS UNDERLYING SKELETAL MUSCLE ATROPHY AND WEAKNESS IN OLD AGE

Over the past two decades the scientific and medical communities have recognized that skeletal muscle dysfunction (eg, muscle weakness, muscle atrophy, poor muscle coordination) is debilitating and it has been considered a life-threatening condition in older persons. For example, the age-associated loss of muscle strength is highly associated with both mortality and physical disability, and maintenance of muscle mass with advancing age is critical because it serves as a metabolic reservoir that is needed to effectively withstand disease. Moreover, the health care costs associated with lost physical function due to muscle impairments are expected to rise sharply in the coming decades considering that the total number of persons over 65 years is expected to double over the next 25 years.

Adults tend to lose muscle mass at a rate of 1% to 2% per year after the age of 50 years. However, it is important to note that adults lose muscle strength at a much faster rate—approximately 3% to 4% year. Therefore, while muscle atrophy and weakness are certainly correlated, the former cannot fully explain lost muscle strength in late life. Additionally, while behaviors like exercise are important for maintaining a healthy lifestyle, they do not completely stop the rate of decline in muscle with aging. In fact, there is some evidence that those adults who exercise on a regular basis experience a faster rate of decline because they tend to have a high level of fitness in early life.

Despite the importance of muscle weakness in contributing to physical impairment, the biological and physiological mechanisms responsible for these phenomena are poorly understood yet are known to be multifactorial. In a general sense they originate from internal muscle and upstream neural factors that control muscle output. The sections that follow will describe the biological and physiological mechanisms from a muscle and neural perspective.

Neural Mechanisms of Skeletal Muscle Impairment With Aging

There is clear evidence that alterations in nervous system form and function contribute to declines in skeletal muscle impairment (namely muscle weakness and diminished motor control) with age. Conceptually, a breakdown in any of the processes described in the “Neural Control of Muscle Contraction” section detailed above could lead to skeletal muscle impairments.

"Voluntary activation" (also referred to as "central activation") is a term commonly used to describe the nervous systems overall ability to fully activate skeletal muscle (ie, the ability to optimally recruit and discharge motor units). There are a number of methodological approaches to quantify voluntary activation such as amplitude measures of the voluntary electromyogram signal as well as by comparing voluntary and electrically stimulated muscle forces. While these approaches do not give insight about where in the nervous system impairment may occur, they do provide insight into whether the nervous system may have a global involvement in weakness. Over the past several decades, numerous studies have investigated the following question "Does voluntary activation become impaired with advancing age?" These studies largely report discrepant findings, but a critical examination indicates several notable observations: (1) many older people, particularly those who are healthy and physically active, *do not* exhibit impairments in voluntary activation; (2) weaker older people as well as the oldest old *do* exhibit impairments in voluntary activation; and (3) impairments in voluntary activation vary from muscle group to muscle group, with the muscle groups that have higher motor unit discharge rates (eg, the quadriceps) being more affected than the muscles with lower motor unit discharge rates (eg, tibialis anterior). Thus, it appears that many older people are indeed able to preserve their nervous systems ability to optimally activate their motor units and musculature while many are not. In the following sections we will briefly discuss more specific neural mechanisms that may underlie muscle weakness in many older people. By and large the evidence indicating causality is limited, and considerable work is still required to identify the precise neural mechanisms of muscle weakness in older people.

Age-related changes in supraspinal properties There are a large number of aging-related changes that are observed in motor cortex morphology, neurochemistry, and excitability. There are an overwhelming number of morphometric changes in the motor cortex that occur in with normal aging. For example, cadaveric studies suggest that individuals over 65 years of age exhibit a greater than 40% volumetric reduction in the premotor cortex neuronal cell body size in comparison to adults younger than 45 years, and in vivo imaging-based studies have corroborated these findings suggesting that cortical thinning occurs by middle age, and that areas near the primary motor cortex demonstrate prominent atrophy. In addition to changes in the overall size of the motor cortex there is also evidence to suggest that age-related differences exist in white matter mass and length of myelinated nerve fibers. While these observations have not been causally linked to muscle weakness per se, it seems likely they would affect the connectivity of the cortex with itself as well as the rest of the central nervous system, which could have functional implications.

In addition to morphometric changes, there has long been interest regarding the neurochemical changes within the basal ganglia that can be attributed to aging. This interest was largely driven by the hypothesis that changes in neurotransmitters and their receptors may be attributed to decreases in cognitive as well as motor functions. Certainly, it has been shown that impaired neurotransmission is responsible for at least some age-related behavioral abnormalities, including the serotonergic, cholinergic, adrenergic, dopaminergic, GABAergic, and glutamatergic systems. Reductions in neurotrophic factors have been shown within the motor cortex as well. Age-related changes in the dopaminergic system are perhaps the best understood from work on different neurological conditions such as Parkinson disease. Older adults have been reported to exhibit reduced dopamine transporter availability, and animal findings show that older rodents have decreased dopamine (D2) receptors.

Aging also affects motor cortical properties at the systems level. Specifically, aging has been shown to result in decreased cortical excitability and interhemispheric inhibition, both of which have been associated with weakness. Additionally, aging has been shown to result in increased activation in areas of sensorimotor processing and integration, and result in reduced cortical plasticity. Collectively, these findings suggest that aging results in cortical atrophy, altered neurochemistry, and alterations in motor cortical excitability and plasticity, all of which could be mechanistically link to impairments in voluntary activation capacity and contribute to age-related reductions in muscle performance.

Age-related changes in spinal properties and the neuromuscular junction Motor units demonstrate numerous age-related adaptations, including changes in morphology, behavior, and electrophysiology. With regard to changes in morphology, advancing age is thought to result in a reduced motor unit number as well as an increased number of fibers per motor unit (increased innervation number) due to the compensatory collateral sprouting by surviving neurons (**Figure 113-11**). More specifically, age-related remodeling of motor units appears to involve denervation of fast muscle fibers with reinnervation by axonal sprouting from slow motor neurons. Therefore, motor unit remodeling leads to changes in fiber-type distribution toward a predominantly slow muscle fiber phenotype. Reinnervation of muscle fibers tends to compensate for denervation; however, a net loss of fibers across age has been detected. This obviously occurs when the rate of muscle fiber denervation surpasses the rate of axonal sprouting and reinnervation. Recent work

has suggested that lifelong high-intensity physical activity, such as running, may minimize the loss of motor units associated with aging. Additionally, some of the latest findings also suggest that weaker older adults exhibit a lower number of functioning motor units in comparison to stronger older adults.

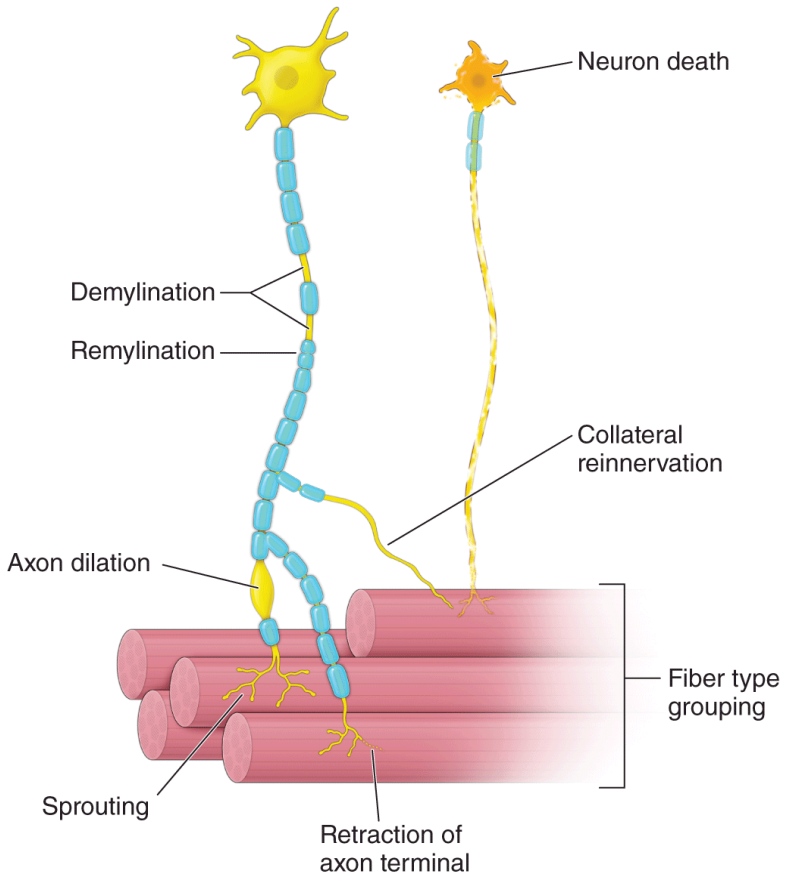


FIGURE 113-11. Overview of the age-related changes that may occur in the motor innervation of older adults' skeletal muscle fibers.

Aging has also been shown to result in changes in spinal excitability, with the current literature indicating that there is a general decrease in the excitability of spinal reflexes. Whether alpha motor neuron excitability itself is altered with advancing age is still yet to be determined. There is growing evidence that the behavioral discharge properties of motor units are altered with age. For instance, older adults have been reported to exhibit mean motor unit firing rates of the tibialis anterior across a variety of contraction intensities that are approximately 30% to 35% lower than young adults, and the maximum motor unit firing rate of an intrinsic hand muscle is also comparably reduced. These lower firing rates appear to be largely interrelated to the longer twitch contraction durations in older muscle, which further illustrates the critical integrative control processes involved between the nervous and muscular systems as it relates to overall neuromuscular function. More recent evidence suggests that more subtle age-related differences exist in motor unit behavior. Specifically, older adults have been reported to exhibit a greater variability in motor unit discharge rates that appears to largely influence their ability to maintain steady forces, and the occurrence of motor unit doublet discharges is lower in older adults.

Aging also elicits remodeling of the neuromuscular junctions endplate. Specifically, aged neuromuscular junctions exhibit elevations in presynaptic nerve terminal branching, and in the postsynaptic distribution of receptor sites for neurotransmitter. Disuse further compounds these age-associated changes as muscle unloading causing significant remodeling of aged rodents neuromuscular junction, but not in those of young, healthy rodents. Collectively, these findings suggest that aging results in morphologic changes in motor units, including an actual reduction in functional motor units. A change of this nature (ie, loss of motor units resulting in some muscle fibers not undergoing reinnervation) would theoretically result in weakness. Additionally, age-related changes in spinal properties and the neuromuscular junction, such as decreased spinal excitability and a reduction in maximal motor unit discharge rates, may contribute to impairments in voluntary activation capacity and thus weakness.

Muscular Mechanisms of Skeletal Muscle Impairment With Aging

Changes in systemic and cellular properties contribute to muscle atrophy with aging. Systemically, increased proinflammatory cytokine production, catabolic hormones (eg, cortisol) and decreases in production of anabolic hormones, such as testosterone, are commonly noted as contributory factors to muscle atrophy. Within the muscle, cell death signaling, altered protein synthesis and/or turnover, and impaired satellite cell function contribute to atrophy. It is well know that the systemic factors are a major influence in activating pathways for atrophy within the muscle cell (eg, proteolytic signaling). For example, tumor necrosis factor alpha (TNF-α) can either stimulate proteolysis through the ubiquitin-proteasome system or induce apoptosis via the cell death-receptor pathway. It should be noted that other morphologic changes occur during the atrophy process including increased variability in fiber size, accumulation of nongrouping, scattered and angulated fibers, expansion of extracellular space, and deposition of protein aggregates within the interstitial matrix. Additionally, changes to the excitation-contraction process that is independent of muscle atrophy can be influential for explaining age-related muscle weakness. Below we provide a broad overview of some, but not all, of the factors potentially causing age-related muscle atrophy as well as impaired muscle contractile output.

Muscular Mechanisms of Skeletal Muscle Atrophy With Aging

Increased myocyte apoptosis (cell death) Several reports indicate that enhanced activation of apoptosis occurs in aged skeletal muscle, likely contributing to the development of muscle atrophy. Apoptosis is an evolutionarily conserved process of programmed cell death that is necessary to clear damaged muscle cells—also known as myocytes. However, left unregulated, apoptosis can result in the elimination of individual myonuclei (myonuclear apoptosis) and the surrounding portion of cell.

There are multiple ways for activation of apoptosis. One is through a protein cascade involving caspases, which are cysteine-dependent, aspartate-specific proteases. Another path is through a caspase-independent pathway. The three pathways that regulate activation of caspase originate from: mitochondria, endoplasmic reticulum, and cytokine receptor. However, it should be noted that because muscle fibers are multinucleated, a proapoptotic event may not result in cell removal or complete fiber death. The process may simply remove individual myonuclei leaving the existing myonuclei to increase the size of domain under control. Such a process, might lead fiber atrophy rather than complete cell death. In addition, proapoptotic signaling may stimulate protein degradation that is independent of myonuclei removal or cell death.

With regard to age-related muscle atrophy there has been much focus on the mitochondrial-mediated pathways. Mitochondria are the main source of cellular ATP, carry out various biochemical reactions, and contain critical intracellular signaling molecules that could determine the cell's normal function as well as its existence. In general, aging increases mitochondrial dysfunction and increases proapoptotic signaling through an imbalance of mitochondria mediated pro- and antiapoptotic pathways. The ratio of pro- to antiapoptotic proteins regulates myonuclei integrity and cell survival by controlling mitochondrial membrane permeability and activation of caspases. Thus, poorly functioning mitochondria can release their internal "machinery" into the cytosol, which then forms a complex that activates caspase. Apoptosis can also be initiated without caspase through the mitochondrial release of factors that directly cause large scale DNA fragmentation and eventual cell death.

Aside from mitochondria-mediated apoptosis, other pathways of myonuclear apoptosis may occur with advancing age. In particular, the death receptor-mediated pathway, triggered by an inflammatory factor such as TNF-α. There is an abundance of data that inflammation is higher in older adults and rodents suggesting that this might be a viable pathway. Additionally, inflammatory factors can induce protein breakdown in skeletal myocytes without activating apoptosis and directly through the ubiquitin-proteasome pathway. The temporal relation between the initiation of apoptosis and the induction of proteolysis as well as the relative magnitude of the two processes during age-related muscle wasting is still unclear. However, it is known that apoptotic signaling is required for, and precedes, protein degradation during muscle atrophy.

Imbalance in muscle protein turnover There is imbalance between protein synthesis and breakdown that appears to contribute to muscle atrophy with aging. However, this imbalance is not seen at the basal state, but rather following an anabolic stimulus (eg, a blunted response following exercise or protein intake). This appears to be caused by an age-related state of insulin resistance, independent of diabetes mellitus, and to reduced or slowed responsiveness of the aged muscle to the stimulatory effect of amino acids. Additionally, low-grade chronic inflammation, which is highly prevalent among older persons, may also directly impair protein synthesis.

Muscle proteolysis is controlled through a well-described pathway involving the ubiquitin-proteasome and proinflammatory cytokines, in particular TNF-α, are potent stimulators of this process. This pathway is responsible for

the bulk of muscle proteolysis, but there is not clear and consistent evidence to suggest that activation and regulation of the ubiquitin-proteasome pathway may be altered with age. The evidence that exists suggests expression of muscle-specific ubiquitin factors is higher in the tibialis anterior muscle of old rodents, concomitant with increased TNF-α expression. Similarly, protein levels of proteolytic factors not related to TNF-α expression are reportedly increased with aging. In addition to proinflammatory cytokines, glucocorticoids are potent triggers of muscular protein catabolism. For example, cortisol antagonizes common growth pathways, blocks production of IGF1, and upregulates proteolysis via the ubiquitin-proteolytic system. Although a comprehensive understanding of how glucocorticoids upregulate proteolysis is undetermined, researchers have shown that glucocorticoids are capable of inducing expression factors known to regulate protein degradation. In addition, glucocorticoids appear to inhibit synthesis of proteins in muscle. In support of the involvement of glucocorticoids in muscle atrophy, older adults with low muscle mass are more likely to have elevated cortisol levels compared to those older adults with normal muscle mass.

Impaired satellite cell (eg, stem cell) function and regeneration The muscle's ability to repair and regenerate itself, through satellite cell repair and regeneration, is another critical component in the maintenance of muscle mass. Satellite cells are precursors to muscle cells and are largely *quiescent*, which means they neither form into a muscle cell nor undergo cell division unless activated. Satellite cells are located between the basal lamina and the sarcolemma and are required for the regeneration and hypertrophy of muscle cells. In response to mechanical or pathological stimuli, satellite cells are activated, proliferate and subsequently fuse to existing muscle fibers and/or to one another, forming myotubes and eventually mature myocytes. Studies in experimental animals showed age-dependent decreases in satellite cells number and proliferative capacity. Similarly, researchers reported reduced satellite cells number in older persons compared to younger individuals. Interestingly, this reduction appears to preferentially affect type II fibers (ie, fast twitch fibers), thus providing a further explanation for the higher degree of age-related atrophy suffered by fast-twitch muscles.

The age-dependent decline in satellite cells number and proliferative capacity are not completely understood. One thought is that impaired proliferative potential of satellite cells is largely due to replicative senescence (ie, a finite number of times that a cell can replicate). However, this mechanism may not be relevant to human muscle atrophy, since the proliferative potential of satellite cells remains substantially stable over time after childhood. Alternatively, satellite cells isolated from skeletal muscle of old rodents exhibited decreased differentiation as well as reduced expression of proteins and markers of muscle mass compared to satellite cells from young animals. Moreover, satellite cells cultured from aged cell give rise to less organized and more fragile myotubes. In addition, satellite cells from old rodents display a greater susceptibility to apoptosis than those from young rodents. Despite the mixed knowledge about the number of satellite cells, it is clear there are defects in intrinsic satellite cell properties with increased age.

Reduction in growth factors Insulin-like growth factor-1 (IGF-1) is a peptide structurally related to proinsulin, which has a primary role in promoting skeletal muscle differentiation and growth. In skeletal muscle, IGF-1 potentiates calcium current to adult muscle fibers but not in muscles from aging mammals, probably because there is IGF-1 resistance. Using a transgenic mouse model overexpressing IGF-1 in skeletal muscle, increases in the number of DHPRs have been reported. IGF-1 also has an effect on muscle mass, inducing hypertrophy in transgenic models or preventing atrophy in aging rodents. Virally mediated overexpression of IGF-1 in muscle prevents the age-related loss in type IIB fibers and contractile force in rodents. IGF-1 also promotes excitation contraction coupling, improves fiber type composition, and increases absolute and specific muscle force. In healthy individuals, deficiency with aging in spontaneous and stimulated growth hormone secretion, as well as circulating IGF-1 and IGF-binding protein-3 levels, is associated with decreased lean body mass, decreased protein synthesis, and increased percent body fat. Administration of recombinant human growth hormone or growth hormone secretagogues improves nitrogen balance, increases lean body mass, and decreases body fat in older people with low IGF-1 levels. Unfortunately, the effects on muscle strength do not seem to be proportional to the improvement in muscle mass with such replacements. Despite initially promising results, there are issues with IGF-1 administration, as with any growth factor, that include promoting growth of abnormal cells (eg, cancer cell proliferation) and there is no clear delivery strategy that can be sustained indefinitely.

Testosterone is a steroid hormone that has a wide array of effects on most tissues of the body after binding to its androgen receptor. Serum testosterone concentration declines 1.6% per year and tends to accelerate after 40 years of age. This decline is associated with reductions in muscle mass and increases in fat mass, diminished energy, muscle strength, cognition, sexual function, and depressed mood. Supplementation of testosterone started soon after it's synthesis in the mid-1930s and there have been hundreds of trials to demonstrate its efficacy for increasing skeletal muscle mass and maximal voluntary strength in healthy, androgen-deficient and eugonadal young and older men, and

in men with many chronic disorders. However, wide acceptance of supplementation has not been universally accepted because of a variety of side-effects especially risk to the cardiovascular system and prostate cancer. For example, a trial on hypogonadal older men with mobility limitation was terminated because during the course of the study the testosterone group had higher rates of cardiac, respiratory, and dermatologic events compared to the placebo group. However, despite these findings, there are significant efforts being placed into Selective Androgen Receptor Modulators (SARMs) that mimic the chemical structure of testosterone (or other androgen) that binds to an androgen receptor and activates muscle protein synthesis. Additionally, there are other compounds, such as monoclonal antibodies like myostatin and activin receptor inhibitors, that are in active clinical trial testing to determine their efficacy at enhancing muscle mass and function in older people.

Mass Independent Muscular Mechanisms of Skeletal Muscle Impairment With Aging

Impaired excitation-contraction coupling Excitation-contraction coupling converts the neural signal for muscle activation (muscle action potential) into muscle contraction and force development. The actin and myosin proteins produce force, but the transmission of this force is dependent on an array of cytoskeletal proteins. Impairments in the excitation and coupling of myosin proteins and connecting cytoskeletal proteins are not independent of the mass of the muscle, but can have dramatic effects on the muscle force output. Specifically, impairments in sarcoplasmic reticulum Ca^{2+} release might explain deficits in specific contractile force (force normalized to muscle cross-sectional area) in aging skeletal muscle. There appears to be an excitation-calcium release uncoupling in single fibers from aged human muscles. The cause of this is not completely understood, but DHPRs, which function to open the ryanodine receptors for Ca^{2+} release is a primary target of the study. There also appears to be an age-related reduction in DHPRs that causes a reduced Ca^{2+} release. Interestingly, ryanodine receptor expression is unaltered with increased age. Further, there is evidence that a particular subunit of the DHPR that regulates the Ca^{2+} current is overexpressed in aged muscle. This results in dysregulation of Ca^{2+} causing a decline in muscle specific force. While the effect of increased age on excitation-contraction coupling is not completely understood, it is currently a major area of research to explain muscle weakness that is not related to atrophy of the muscle.

Muscle architecture Other morphologic changes, beyond simply a reduction in muscle size, such as specific changes in muscle architecture may directly contribute to skeletal muscle impairments in older people. The architecture of the muscle is described by the arrangement of muscle fibers and the connective tissue that binds these fibers into a muscle-tendon complex. This architecture is a major determinant of the mechanical behavior and force potential (force-length and force-velocity relations as well as maximal isometric force) of a particular muscle. The volume of muscle tracks closely with muscle and fascicle length. Older adults have shorter fascicle lengths and smaller pennation angles suggesting that there is not only a loss in sarcomeres in series, but also in parallel. As a result, the muscle produces less force. For example, the medial head of the gastrocnemius muscle of older adults has a shorter fascicle and muscle length that results in a lower force/power producing potential. However, these results are not universal across all muscle groups because those that are heavily pennated are most susceptible. The soleus muscle retains a high-force potential with aging and does not exhibit changes in fascicle or muscle lengths.

Diagnosing Sarcopenia and Dynapenia

Sarcopenia and dynapenia are common, and are associated with a variety of health outcomes in elders. To become recognized as a clinical condition, and for the development of pharmaceutical interventions, an agreed upon diagnosis is needed. In recent years there has been a growing effort to develop criteria/criterion for the diagnosis of clinically significant sarcopenia and dynapenia. **Table 113-3** shows the latest definitions and criteria being proposed for diagnosis. Importantly, the definitions differ in their use of physical performance as a screening or diagnostic tool for identifying sarcopenic or dynapenic older adults. Additionally, the condition has become akin to the frailty syndrome that involves multiple factors for diagnosis. For example, the European Working Group on Sarcopenia in Older People incorporates aspects of (1) physical function (ie, gait speed), (2) muscle strength, and (3) muscle mass. Other criteria, namely, those by the Foundation for the National Institutes of Health's Sarcopenia Working Group, attempted to define low muscle mass and muscle weakness independently using a data driven approach in pooled sample of 26,635 older adults. Presently, scientists disagree on whether sarcopenia refers only to age-related muscle atrophy as it was originally proposed, or whether muscle function (ie, strength and endurance) and physical function should be included as part of the definition. Muscle function is clearly the critical step that links sarcopenia to functional disability, but the degree to which remains unclear. Although there is significant effort being put forth by both researchers and

practitioners, it is important to note there is no established agreed upon definition for these common conditions.

TABLE 113-3 SARCOPENIA DEFINITIONS

ORGANIZATION OR SOCIETY	DESCRIPTION	PHYSICAL FUNCTION	LEAN MASS
International Academy on Nutrition and Aging Society of Sarcopenia, Cachexia and Wasting Disorders	Sarcopenia with limited mobility	6 min walk < 400 m or gait speed < 1.0 m/s	Low appendicular lean mass (< 7.23 kg/m^2 in men; < 5.67 kg/m^2 in women)
European Working Group on Sarcopenia in Older People	Sarcopenia	Gait speed < 0.80 m/s OR grip strength: men < 30 kg; women < 20 kg	Low appendicular lean mass (< 7.23 kg/m^2 in men; < 5.67 kg/m^2 in women)
European Working Group on Sarcopenia in Older People	Severe sarcopenia	Gait speed < 0.80 m/s AND grip strength: men < 30 kg; women < 20 kg	Low appendicular lean mass (< 7.23 kg/m^2 in men; < 5.67 kg/m^2 in women)
Foundation for National Institutes of Health Sarcopenia Project	Muscle weakness and low lean mass	Grip strength: men < 26 kg; women < 16 kg	Appendicular lean mass/body mass index Men: < 0.789 Women: < 0.512
Foundation for National Institutes of Health Sarcopenia Project	Slow walking speed with muscle weakness and low lean mass	Grip strength: men < 26 kg; women < 16 kg; and gait speed < 0.80 m/s	Appendicular lean mass/body mass index Men: < 0.789 Women: < 0.512

Body mass index = body weight (kg) / height^2 in meters.

AGING OF THE JOINTS

One of the most prevalent conditions in the United States is joint pain, as more than 70 million adults (~1 out of 3) report joint pain. The economic burden of joint pain has been estimated to be greater than $70 million. The prevalence of joint pain increases with advancing age with osteoarthritis (OA) being the most common type of joint problem in older people, with rheumatoid arthritis being the second most common type of chronic arthritis. Other common types of joint problems include those affecting the soft tissues like muscles, tendons, and ligaments, which include, but are not limited to, rotator cuff injuries, tendonitis, frozen shoulders, carpal tunnel syndrome, and bursitis. In this section we provide an overview of the normal structure and function of articular cartilage followed by a discussion on the age-related changes in cartilage. Subsequently, a brief review of tendons and ligaments as well as intervertebral discs is provided.

ARTICULAR CARTILAGE

Normal Structure and Function

Articular cartilage is the tissue present on the ends of bones that comprise diarthrodial joints. This cartilage serves to provide a smooth surface with a very low coefficient of friction necessary for rapid, painless, and smooth joint motion. During joint motion, the opposing cartilage surfaces, separated by a thin layer of viscous and slippery synovial fluid, easily glide over each other. In addition to providing a form of lubrication for the joint surface, the synovial fluid also provides a large portion of the nutrition for the articular cartilage, which is an avascular and aneural tissue.

When a load is placed across the joint surface, such as occurs in the knee joint during ambulation, the thin gel-like cartilage is compressed. Compression of the cartilage helps to distribute the load evenly to the underlying bone, where force can be absorbed. Cartilage is too thin to absorb any substantial amount of force itself. Rather, the force of joint

loading is absorbed by the muscle and bone associated with the loaded joint. This concept is relevant to the pathogenesis of diseases occurring in weight-bearing joints. If changes occur in muscle or bone that limit their ability to absorb mechanical loads, then the articular cartilage may experience abnormal stresses, which could adversely affect the tissue. Loading of the articular cartilage in the knee is also modulated by the presence of the medial and lateral menisci, which absorb approximately 50% of the load placed on the tibiofemoral regions. Damage to a meniscus can therefore significantly increase the load placed on the cartilage.

Complete compression of cartilage during joint motion is resisted by forces within the tissue generated primarily by the highly negatively charged proteoglycans. Proteoglycans are composed of a core protein to which are attached chains of glycosaminoglycans containing negatively charged sulfate groups. In articular cartilage, a large proteoglycan called aggrecan is present. Aggrecan is bound at its amino-terminus to a long strand of hyaluronic acid. Many aggrecan molecules are bound to a single strand of hyaluronic acid to form a large complex that is quite hydrophilic. Cartilage is approximately 70% to 75% water, and much of this water is bound to the negatively charged groups on proteoglycans, forming a gel-like substance. Water is partially extruded from the cartilage matrix during compression, resulting in exposure of negative charges that, as they are brought closer together, resist further compression. As the force is released, the proteoglycans reexpand, and water is drawn back into the cartilage bringing along nutrients from the synovial fluid. The role of joint motion in providing cartilage nutrition may be very relevant to changes occurring in cartilage with disuse.

In addition to proteoglycans, a number of other matrix proteins are responsible for the physical properties of cartilage, including several types of collagen (predominantly types II, VI, IX, and XI) and glycoproteins (including fibronectin and cartilage oligomeric protein). Collagen is quite abundant in cartilage, comprising about half of the dry weight of the tissue. The majority of the collagen in cartilage is type II collagen. Type II collagen forms long fibrils that provide the tensile strength of the tissue, while the proteoglycans provide the resiliency. The collagen fibers appear to hold aggrecan complexes in place and prevent the proteoglycan gel from complete expansion, which results in the generation of swelling or osmotic pressure within the tissue. Thus, in normal cartilage, the osmotic pressure generated by proteoglycans is balanced by the tensile force provided by the collagen fibrils. The nonfibrillar collagens and the other matrix proteins in cartilage are thought to be involved in the organization and maintenance of the collagen fibrillar network, in structural interactions between collagen and proteoglycans, and in mediating interactions between the chondrocytes and the extracellular matrix (ECM).

Regulation of Cartilage Matrix Turnover

Chondrocytes, the only cells present in cartilage, control the composition and organization of the cartilaginous matrix through the synthesis and degradation of selected ECM components. Together, the processes of synthesis and degradation result in ECM repair and remodeling. From studies performed in a number of tissues, including cartilage, it is becoming clear that ECM proteins can bind to cell surface receptors such as the integrin family of receptors, which, along with growth factors and cytokines, send signals to the cell to regulate matrix synthesis and degradation.

Several different types of enzymes capable of degrading cartilage ECM proteins are produced by chondrocytes, including the metalloproteinases, serine proteases such as elastase, and the cathepsins. The matrix metalloproteinases (MMPs) are prominent players in mediating cartilage catabolism. These include collagenases (MMP-1, MMP-8, and MMP-13), which cleave fibrillar collagens, the gelatinases (MMP-2 and MMP-9), which degrade denatured collagen, and stromelysin (MMP-3), which degrades proteoglycans. Other important MMPs in cartilage are the membrane-type (MTMMPs), the ADAMs (a disintegrin and a metalloproteinase) and the ADAMTSs (a disintegrin and a metalloproteinase with a thrombospondin motif). The MT-MMPs are bound to the chondrocyte surface through transmembrane domains and can serve to activate other MMPs at the cell surface. An ADAM found in cartilage is ADAM-17, also known as tumor necrosis factor-α-converting enzyme, which functions to cleave TNF-α to an active form. The ADAMTSs use the thrombospondin motif to interact with proteoglycans that can serve as substrates for these enzymes. ADAMTS-4 and ADAMTS-5 are aggrecanases that cleave the large proteoglycan aggrecan. The activity of the MMPs in cartilage is controlled in part by proteins called tissue inhibitors of metalloproteinase (TIMP). There is evidence for a reduction in the levels of TIMPs relative to the increased levels of MMPs in osteoarthritic (OA) cartilage.

A number of growth factors and cytokines are present in cartilage. These serve to regulate anabolic and catabolic processes involved in repair and remodeling (**Table 113-4**). In general, growth factors stimulate matrix synthesis, whereas the inflammatory cytokines inhibit synthesis and stimulate degradation. Insulin-like growth factor-1 (IGF-1), transforming growth factor-β (TGF-β), and osteogenic protein-1 (OP-1) appear to play a prominent role in regulating

adult articular cartilage metabolism. They are expressed in cartilage and act in a paracrine and autocrine fashion to stimulate cartilage matrix synthesis as well as inhibit cytokine-stimulated matrix degradation. IGF-1 also appears to promote chondrocyte survival in conjunction with signals from the matrix. As discussed later in this chapter, there is growing evidence that chondrocytes from older individuals are less responsive to growth factor stimulation than those from younger persons. This could contribute to aging-related changes in the tissue, as well as to disease progression with age.

TABLE 113-4 MAJOR GROWTH FACTORS AND CYTOKINES ACTIVE IN CARTILAGE

GROWTH FACTORS/CYTOKINES	ACTIVE
IGF-I	Promotes cell survival, stimulates matrix synthesis
OP-1 (BMP-7)	Stimulates matrix synthesis, inhibits some catabolic pathways
TGF-β	Mitogenic, stimulates matrix synthesis, stimulates chondro-osteophyte production
bFGF	Mitogenic, stimulates matrix synthesis, potentiates IL-1–induced protease release, may be more important in fetal and growth plate cartilage than adult
IL-1β	Inhibits matrix synthesis and stimulates matrix degradation
TNF-α	Similar to IL-1β
LIF	Stimulates matrix degradation
IL-6	Inhibits proteoglycan synthesis
IL-8	Neutrophil chemoattractant
MCP-1	Monocyte chemoattractant; stimulates MMP production

bFGF, basic fibroblast growth factor; BMP-7, bone morphogenic protein-7; IGF-1, insulin-like growth factor-1; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; LIF, leukemia inhibitory factor; MCP-1, monocyte chemotactic protein-1; MMP, matrix metalloproteinase; OP-1, osteogenic protein-1; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β.

The mitogenic properties of growth factors noted in cell culture studies may not be relevant to normal adult cartilage homeostasis in vivo. In the normal tissue, adult articular chondrocytes do not appear to proliferate or do so at such low rates that proliferating cells are not detected. Chondrocytes, however, are not postmitotic cells. When removed from cartilage by enzymatic digestion of the tissue and placed in cell culture, human chondrocytes can proliferate. Proliferation of chondrocytes in situ occurs during the development of OA, when the presence of clusters or “clones” of chondrocytes is a common pathologic finding. These clusters of cells are thought to represent an attempt at repair of damaged and lost tissue (**Figure 113-12**).

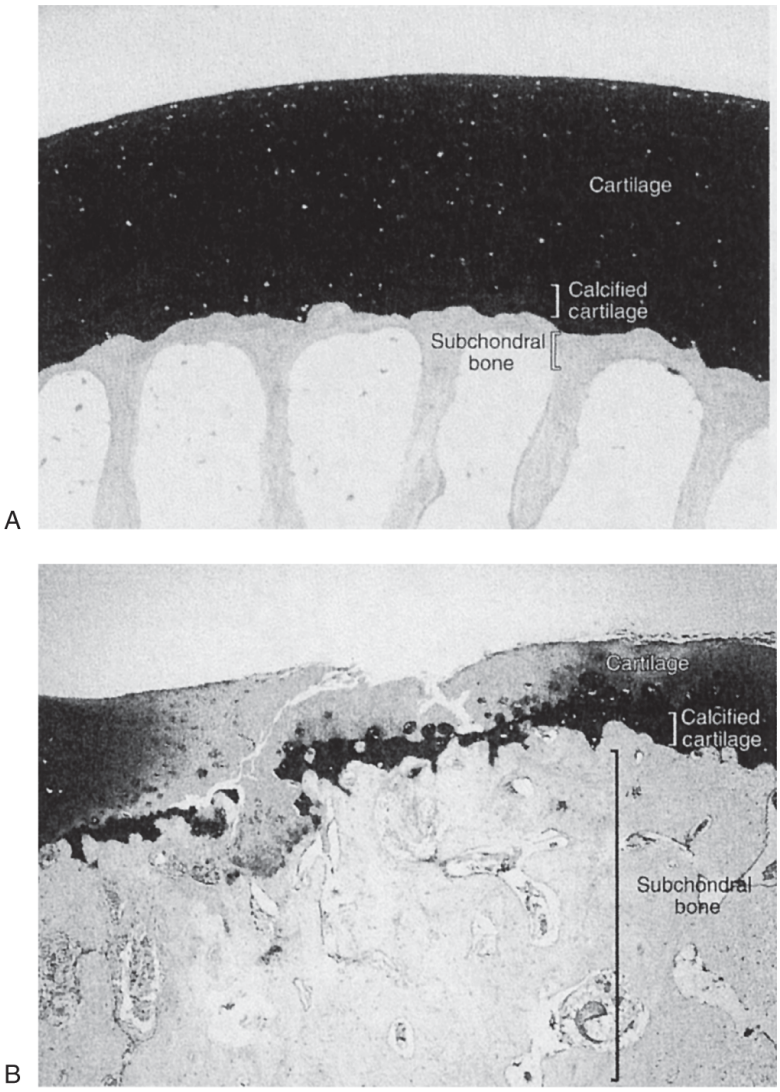


FIGURE 113-12. Normal (**A**) and osteoarthritic (**B**) cartilage. These sections from monkey knee joints are stained with toluidine blue, which binds to the negatively charged proteoglycans that are abundant in cartilage. In the osteoarthritic tissue, there is a loss of cartilage matrix staining, resulting from loss of proteoglycans. Other changes include fibrillation and cleft formation, presence of chondrocyte clusters, and a marked thickening of the subchondral bone. (Photographs are courtesy of Dr. Cathy S. Carlson.)

Normal articular cartilage in the adult contains fully differentiated cells and does not appear to contain its own source of undifferentiated mesenchymal cells available to repair or replace damaged or lost tissue. However, mesenchymal stem cells capable of differentiating into chondrocytes are present in the bone marrow, synovium, adipose tissue and periosteum. Current research is trying to use these cells for repair of cartilaginous lesions because endogenous repair responses in cartilage are inadequate to replace significant amounts of lost matrix, particularly after damage to the collagen network has occurred. The potential role of aging in the failed repair response in cartilage is discussed in the following sections.

AGE-RELATED CHANGES IN CARTILAGE

Cartilage Structure and Matrix Composition

A number of studies have examined age-related changes in articular cartilage by using tissue collected from various animal species or human tissues obtained either at autopsy or from surgical specimens. When surgical specimens are studied, they usually are obtained from subjects undergoing hip or knee replacement surgery for arthritis, in which case the tissue is taken from grossly normal appearing areas but may not be truly normal. Tissues have also been obtained during hip replacement surgery after femoral neck fracture, which is usually associated with osteoporosis. In these cases, the cartilage is more likely to be normal because osteoporosis and osteoarthritis tend to occur in different patient populations, although this is not always true. A theoretical model for pathways leading to cartilage destruction

and eventual osteoarthritis are illustrated in **Figure 113-13**.

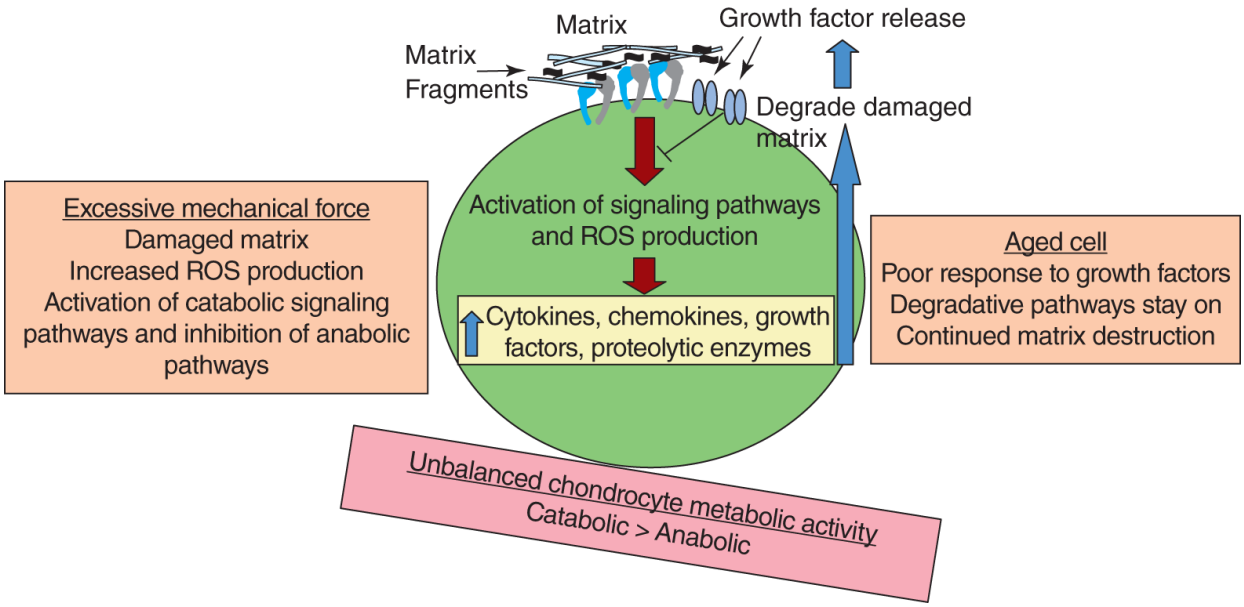


FIGURE 113-13. Theoretical model for pathways involved in cartilage destruction during the development of osteoarthritis. Excessive mechanical forces stimulate the chondrocyte directly or indirectly through signals generated by matrix damage including generation of matrix fragments. The resultant activation of signaling pathways, including ROS generation, results in increased production of cytokines, chemokines, and proteolytic enzymes. This catabolic response to injury serves to degrade the damaged matrix. Matrix degradation results in release of growth factors stored in the matrix, which would normally feed back on the cell and shut down the catabolic pathways. But aged chondrocytes have an insufficient response to growth factor stimulation, resulting in continued matrix destruction from unbalanced catabolic and anabolic activity. (Reproduced with permission from Loeser RF. Molecular mechanisms of cartilage destruction: mechanics, inflammatory mediators and aging collide. *Arthritis Rheum*. 2006;54:1357.)

Problems in interpreting the results of cartilage aging studies include translating the biology from lower species of animals to humans and separating disease effects from aging effects. In addition, a number of changes have been reported to occur in cartilage when comparing immature versus middle-aged animals. These changes are probably best considered to be developmentally related rather than aging-related. With the above caveats in mind, there do appear to be a number of changes occurring in cartilage that can be related to aging and, importantly, many of the aging-related changes can be contrasted to changes seen in disease (**Table 113-5**).

TABLE 113-5 CONTRASTING DIFFERENCES BETWEEN AGING AND OSTEOARTHRITIS

AGING	OSTEOARTHRITIS
Decreased cartilage hydration	Increased cartilage hydration
Proteoglycans	Proteoglycans
Normal quantity	Decreased quantity
Smaller size	Smaller size
Ratio of CS 4/6[a] decreased	Ratio of CS 4/6[a] increased
Collagen	Collagen
Normal quantity	Decreased quantity
Increased stiffness	Decreased stiffness
Increased cross-linking	Cross-links lost during degradation
Chondrocytes	Chondrocytes
No or reduced proliferation	Increased proliferation
Reduced metabolic activity	Increased metabolic activity
No change in subchondral bone	Increased subchondral bone thinkness

[a] Ratio of CS 4/6 is the ratio of chondroitin sulfate containing sulfate groups on either the fourth or sixth carbon.

Source: Data from Bottinelli R, Reggiani C. Human skeletal muscle fibres: molecular and functional diversity. Prog Biophys Mol Biol. 2000;73:195.

Cartilage from older individuals has been noted to have microcracks in the calcified layer and be thinner suggesting a gradual loss of cartilage matrix. The significance of these cracks is not clear, but if they extend to the underlying subchondral bone, they could provide a mechanism for the exchange of cytokines and growth factors between the two tissues; and if vascular invasion occurs, they could mediate remodeling of subchondral bone, which is a characteristic feature of OA. A consistent biochemical finding in cartilage is an age-related decrease in hydration. A decrease in hydration could explain evidence obtained from magnetic resonance imaging of knee joints showing that some thinning of knee cartilage occurs with age, particularly at the femoral surface, which is more evident in women than men. The decrease in cartilage hydration is likely related to changes with age in the proteoglycans that bind the majority of the water in cartilage. The total proteoglycan content does not appear to change significantly. Instead changes in proteoglycan structure have been reported that could affect its biophysical properties. Aggrecan molecules become smaller with age and are structurally altered as the result of proteolytic modification in the core protein as well as changes in the length and abundance of the attached glycosaminoglycan chains. Hyaluronic acid, to which the aggrecan molecules bind to form large aggregates, is also decreased in size with age. In addition, proteolysis of the aggrecan core protein between the G1 and G2 domains results in increased levels of molecules bound to hyaluronic acid that contain only the G1 region and therefore lack the remainder of the aggrecan molecule necessary for normal function. The half-life for the free binding region is calculated to be as long as 25 years, consistent with its accumulation in cartilage with aging. By occupying and competing for space on the hyaluronic acid strands, the bound G1 domains may reduce the number of newly synthesized aggrecan molecules bound to hyaluronic acid.

As with proteoglycans, there does not appear to be a significant reduction in the total amount of collagen present in cartilage with age. However, important changes in collagen structure and function have been noted. The collagen network appears to become stiffer with age. The increased collagen stiffness is thought to be a result of increased collagen cross-linking. There is evidence for nonenzymatic glycosylation in cartilage from older adults that result in the formation of pentosidine residues that can cross-link collagen molecules. An age-related accumulation of advanced glycation end products (AGEs) has been noted in cartilage (**Figure 113-14**). Pentosidine and other AGEs have been found in collagen, as well as in aggrecan. The accumulation of pentosidine is reported to be greater in collagen than aggrecan because of the exceptionally long half-life of collagen in cartilage, which is calculated to be approximately 117 years.

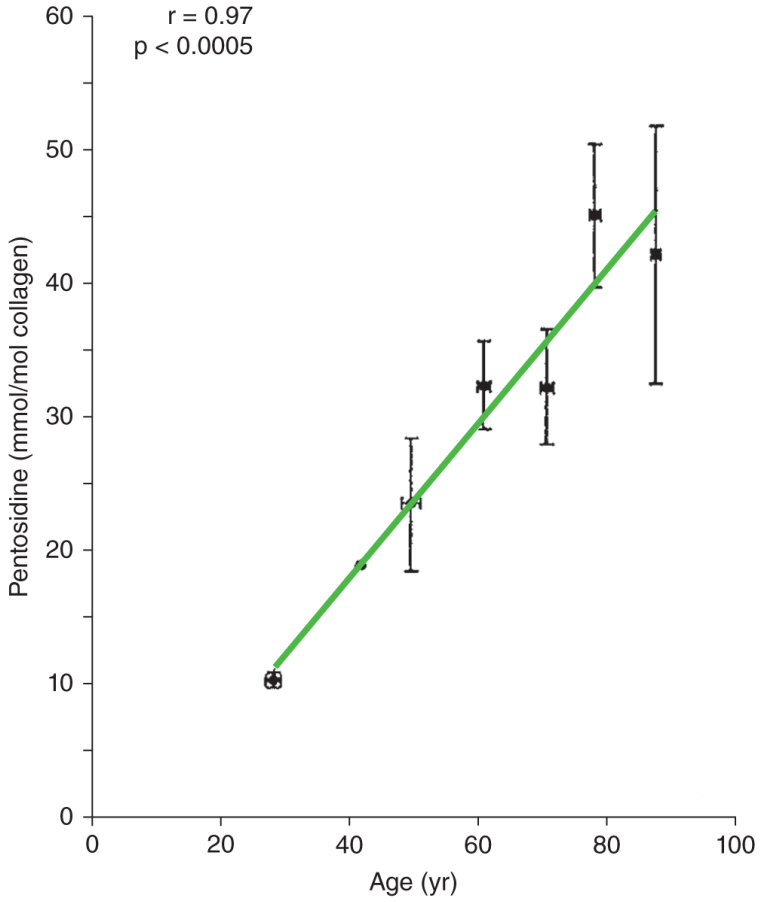


FIGURE 113-14. Age-related accumulation of advanced glycation end-products in cartilage. Pentosidine levels were measured in cartilage samples from 36 donors clustered into 10-year age intervals. Results shown are mean ± SEM (standard error of mean). (Reproduced with permission from DeGroot J, Verzijl N, Bank RA, Lafeber FP, Bijlsma JW, TeKoppele JM. Age-related decrease in proteoglycan synthesis of human articular chondrocytes: the role of nonenzymatic glycation. *Arthritis Rheum*. 1999;42:1003.)

In addition to increased cross-linking from the accumulation of AGEs, collagen fibril diameter tends to increase with age, and this may also contribute to changes in collagen stiffness. Increased collagen network stiffness could contribute to the decrease in hydration, as stiffer collagen would tend to cause greater proteoglycan compression and thereby push out more water from the matrix. Biomechanical studies suggest that the stiffer network is more prone to fatigue failure. With age there is a decrease in the tensile strength of cartilage as well as a decrease in overall tensile stiffness. Therefore, age-related changes in the overall composition of the cartilage matrix result in a tissue that is less capable of handling mechanical stress.

In addition to changes in type II collagen and aggrecan, age-related changes in several of the other less-abundant cartilage matrix proteins have been reported. These include a decrease in type IX collagen, a protein that may be important in holding together adjacent collagen fibers and an increase in link protein, the protein that helps bind aggrecan molecules to hyaluronic acid. While link protein is increased with age, it also appears to undergo proteolytic modification with age that could affect its function.

An age-related finding in cartilage, which is also observed in many other soft tissues, is an increased prevalence of crystals and calcification. It is difficult to determine the relative effects of age and disease on cartilage calcification. Calcification or crystal formation within cartilage is a common feature of OA, particularly in advanced disease and, like OA, age is the strongest risk factor for the development of crystal-associated arthritis. Cartilage from older individuals often contains crystals composed of calcium pyrophosphate dihydrate or hydroxyapatite. Studies with animal tissues show that the increase in the formation of calcium pyrophosphate crystals may be caused by an age-related increase in the activity of transglutaminase, an enzyme that is involved in the biomineralization process. Also chondrocytes from older individuals produce more inorganic pyrophosphate in response to TGF-β stimulation, despite a decreased proliferative response to this and other growth factors.

Chondrocyte Function

There appears to be a slight decline in the number of chondrocytes present in cartilage with age. Early studies of cartilage from the femoral head noted a 30% fall in cell density between the ages of 30 and 100 years. Although, recent studies of knee joints have noted much lower cell loss with normal aging in the range of 1% to 2%, possibly attributed to chondrocyte death and/or apoptosis. Age-related changes inside chondrocytes including cellular senescence, reduced responsiveness to growth factors and extracellular factors work together to disrupt cartilage homeostasis.

There is evidence that HMGB2, an important chondrocyte survival protein, is involved with this progression since HMGB2 expression declines with age and this decline is strongly associated with increased chondrocyte death. Furthermore, changes in the proliferative and synthetic capacity of chondrocytes with age have been noted. There is evidence for an age-related decreased mitogenic response to serum and growth factor stimulation. For example, during aging, chondrocytes exhibit reduced responsiveness to growth factors, such as insulin-like growth factor-1 (IGF-1), osteogenic protein-1 (OP-1) or bone morphogenic protein-7, and transforming growth factor-β (TGF-β). These findings suggest that the chondrocyte catabolism may be driven by the decline in anabolism.

In chondrocytes, AGEs can increase the production of inflammatory cytokine TNF-α, inflammatory mediator prostaglandin E2, and nitric oxide. It can also suppress the production of type II collagen and stimulate the expression of degradative enzyme MMPs and ADAMTS. AGEs accumulation also has adverse effects on the cartilage extracellular matrix. AGEs increase collagen cross-linking, which enhances tissue stiffness, making cartilage more brittle and susceptible to mechanical failure.

There is also evidence for telomere shortening in chondrocytes isolated from older adults but it is not clear if telomere dysfunction is the cause of the reduced mitogenic response. In addition, a reduction in proteoglycan and protein synthesis in response to growth factor stimulation has been in seen in cartilage from older animals, including nonhuman primates. Likewise, decreased proteoglycan synthesis in response to serum stimulation has been noted in human cartilage from older adults. In the human samples, the decreased serum response correlated with the presence of AGEs. Other studies also suggest that a decline in cell signaling in response to growth factors is responsible for the decreased mitogenic and synthetic responses.

A reduction in response to growth factor stimulation with age, disease, or both, could be significant in the development of OA, where catabolic processes are greater than anabolic. In addition, there appears to be an age-related increase in the ability of catabolic factors, including the cytokine interleukin-1β (IL-1β) and a fibronectin matrix fragment, to stimulate MMP production by chondrocytes. These age-related changes could contribute to the anabolic-catabolic imbalance that has been observed in OA (see Chapter 117).

TENDONS AND LIGAMENTS

Tendons and ligaments are composed of dense connective tissue that has a high content of fibrillar collagen to provide tensile strength. Tendons attach muscle to bone, while ligaments attach bone to bone. The integrity of these attachments is important for normal joint function. Ligaments serve to stabilize the joints, and tendons transmit the forces of muscle contraction to bone. There appears to be a general decline in joint range of motion with age that may be related, at least in part, to changes in tendons and ligaments.

The percent reduction in range of motion varies with the joint studied and is greatly influenced by both disuse and disease. In general, declines in the range of 20% to 25% have been reported. In addition to effects on joint motion, aging-related changes in tendons and ligaments may contribute to the development of injuries to these structures, resulting in conditions ranging from tendonitis to tendon and ligament tears or rupture. Although these injuries certainly occur in younger individuals, the amount of trauma required to produce them is reduced with age. In addition, ligamentous ruptures from injuries in younger individuals can predispose the affected joint to the development of OA later in life as a result from joint instability, altering joint biomechanics.

Biomechanical studies reveal that the strength of tendons and ligaments and their insertions to bone are reduced with age. In one study, it took approximately one-third less loading to cause failure of the anterior cruciate ligament attachment in cadaver knees from individuals aged 60 to 97 years, as compared with a younger group individuals aged 22 to 35 years. A twofold decrease in the strength of the anterior longitudinal ligament of the spine has also been noted in subjects between the ages of 21 and 79 years in cadaver studies.

Shoulder problems are quite common in older adults and may be related to aging changes in the rotator cuff tendons. Changes with age including calcification, microtears, and fibrovascular proliferation have been reported in the

region where the tendons attach to bone. These changes would result in a weakening in the attachment, predisposing the tissue to injury after minor trauma.

Biochemical studies of aging in tendons and ligaments have been limited but have shown changes with age, some of which are similar to changes noted in cartilage. Like cartilage, the tensile strength of these tissues depends on the collagen fibers, although the primary fibrillar collagen is type I rather than the type II found in cartilage. There is no clear evidence that collagen content in ligaments or tendons changes with age, but changes in cross-linking have been reported with the appearance of nonreducible cross-links with age, including cross-links formed by nonenzymatic glycation. Increased cross-linking may cause increased stiffness of the collagen and make it more prone to fatigue failure. Like cartilage, there appears to be a decrease in the water content of tendons and ligaments with age, but there is little information on changes in proteoglycans that, if altered, could explain the reduced water content as discussed earlier with respect to cartilage proteoglycans.

INTERVERTEBRAL DISKS

Imaging studies of normal subjects without recent back pain, as well as morphologic studies of autopsy material, show that disk degeneration increases with age, with at least some degree of degeneration universally present by the sixth decade of life. Because the presence of disk degeneration does not correlate well with symptoms of pain, it is often difficult to determine the clinical significance of these findings. Magnetic resonance imaging evidence of disk bulging and herniation increases with age but is often asymptomatic. On the other hand, disk herniation associated with extrusion of disk material is more likely to be associated with symptoms, particularly if the disk material extends beyond the posterior longitudinal ligament. It is also generally agreed that degenerative changes in the intervertebral disks likely contribute to a variety of conditions seen in older adults, including osteoarthritis, spondylosis, and spinal stenosis.

The intervertebral disks consist of an outer fibrous ring of dense connective tissue referred to as the annulus fibrosus and an inner gel-like material called the nucleus pulposus. The annulus fibrosus is composed of approximately 70% collagen by dry weight, whereas the nucleus pulposus is approximately 20% collagen and 50% proteoglycan. The superior and inferior boundaries of the disks are formed by end-plates consisting of a thin layer of cortical bone covered by hyaline cartilage that directly connects with the vertebral bodies. Age-related changes occur within all these regions but are probably most pronounced in the nucleus pulposus.

The most common age-related change in the disk is dehydration. There is a marked decrease in water content, particularly in the nucleus pulposus, which becomes fibrotic, and, starting in young adults, contains fissures and cracks. Tears also become common in the outer annulus in young adults. These can lead to disk herniation, which has a peak incidence at about 40 to 50 years of age. With advancing age, the nucleus pulposus becomes more dehydrated and less likely to herniate. The decrease in water content is likely related to a decrease in proteoglycans in the nucleus pulposus as well as an increase in collagen cross-linking which, by making the collagen network stiffer, allows for less expansion of the proteoglycans. Similar to articular cartilage, there is evidence that increased collagen cross-linking with age is caused by the accumulation of AGEs.

Many of the age-related changes noted in intervertebral disks are thought to be attributable to a decline in the diffusion of nutrients to the disc cells. Cells in the nucleus pulposus derive their nutrition by diffusion from vessels in the outside layers of the annulus and from the vertebral end plates. There appears to be a decline in the number of vessels in these regions with age, a disease that can be made worse by conditions including atherosclerotic vascular diseases and diabetes. There is also a dramatic decline in the number of viable cells in the nucleus pulposus with age. This is associated with evidence of apoptotic cell death, likely because of the lack of nutrients.

Apoptotic cell death has also been noted in the end-plates. These structures become increasingly calcified with age. This contributes to the development of sclerosis. Because the facet joints of the spine are intimately linked with the end-plates and the disks, the age-related changes in these structures contribute significantly to the development of osteoarthritic changes in the spine. Degenerative disk disease accompanied by vertebral osteophytosis results in spondylosis, which, when severe, can cause spinal stenosis.

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Chapter 114

Biomechanics of Mobility

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Learning Objectives

- Identify the biomechanical factors that affect mobility.
- Recognize the factors that determine the performance of mobility tasks.
- Determine the biomechanical factors that are amenable to intervention.

Key Clinical Points

1. **Patients need to know they should avoid falling directly onto their greater trochanter—it is a major cause of hip fracture on a hard surface.**
2. **Maintenance of adequate muscle strength reserve, and, at times, the ability to deploy this strength rapidly enough are crucial for many mobility tasks.**
3. **Walking speed is a powerful predictor of patient outcomes.**

PREVALENCE OF MOBILITY PROBLEMS AMONG OLDER ADULTS

Problems with mobility in older adults are common. In the United States, among noninstitutionalized persons 65 years and older, approximately 13% have difficulty in performing activities of daily living. Approximately 9% have difficulty with bathing, 8% have difficulty with walking, and 6% have difficulty with bed or chair transfers. The rate at which these problems occur increases progressively after the age of 65 years and climbs sharply after the age of 80 years, so that, for example, more than 34% of noninstitutionalized persons who are 85 years or older have mobility problems.

AGE AND SEX DIFFERENCES IN FALLS AND FALL-RELATED INJURY RATES

Perhaps the most serious problem of mobility impairment is the tendency of older adults to fall and to be injured by falls. Death rates from falls per 100,000 persons in 1999 were 9.1 for those between 65 and 74 years, 31.7 for those between 75 and 84 years, and 109.7 for those 85 years or older. For comparison, in those aged 75 years and older, the death rate from falls (67.9 per 100,000) is more than double that from motor vehicle accidents (29.8 per 100,000). Falls and fall injuries are of substantial concern because of their frequency and because of their physical, psychological, and social consequences. Even a fall that does not result in injury can have a substantially adverse effect on an older person's self-confidence, mobility, and independence. Indeed, fear of falling, which can accompany decreased mobility, can lead to decreased physical activity outside and avoidance of social activities because of the possibility of embarrassment as well as injury in connection with a fall.

Older females are substantially more prone to fall and to be injured in a fall than are older males. Three studies of rates of falls, involving more than 4500 adults ages 65 years or older, found those rates to range from 137 to 690 falls per 1000 persons per year, with older females falling from 1.3 to 2.2 times more often than older males. Three studies of rates of fall injuries requiring medical attention, involving more than 38,000 adults, found that fall injuries leading

to hospital admission or death occurred in males and females at rates per 1000 persons per year of 1.88 and 0.83, respectively, for those aged 20 to 29 years and increased steadily with age to 6.97 and 15.58, respectively, for those aged 70 to 79 years. Correspondingly, female-to-male ratios of these serious fall injury rates increased with age from 0.44 to 2.24.

In 1996, there were 340,000 hip fractures requiring hospital admission. The direct medical and other costs for the injury have been estimated as being at least $16,300 in the first year following the injury. With current trends, approximately 500,000 hip fractures are expected to occur in the year 2040, with an associated total annual cost of $240 billion. Most hip fractures occur in old adults, and more than 95% of those hip fractures result from a fall; the remainder fracture spontaneously during a physically stressful activity or prior to the fall.

Hip fractures can be devastating, particularly in older women. In 1998, there were 863 hip fractures per 100,000 adults older than 65 years (1056 and 593 per 100,000 in women and men, respectively), with the highest rate in white women 85 years and older (2690 hip fractures per 100,000). Approximately 20% of women who fracture their hip do not survive the first year after fracture, and another 20% do not regain the ability to walk unassisted. The incidence of hip fractures rises much faster with age than that of falls. This increase in hip fractures with age is not fully accounted for by increases in the number of falls or decreases in bone mass of the hip with age. Therefore, other factors must increase susceptibility to hip fractures. The biomechanics of the fall arrest responses are likely to be among these factors. More than 85% of wrist fractures involve falls. The incidence of wrist fractures rises from the age of 50 to 65 years and then reaches a plateau after the age of 65 years, but why this occurs is not yet known.

Most falls (78.3%) in those 65 years and older occur in or within the immediate vicinity of the home. Much is known about the epidemiology of falls, but little is known about the mechanisms responsible for the remarkable increase with aging in falls and fall-related injury rates. Diagnosis of specific diseases does not discriminate older fallers from older nonfallers. Individual risk factors for falls may be grouped into intrinsic and extrinsic factors. Intrinsic factors include decreased level of physical activity, cognitive impairment, depression, visual deficits, sensory and strength deficits in the lower limbs, previous stroke, dizziness, medications, abnormal balance and gait, use of assistive devices, and age more than 80 years. Extrinsic factors include environmental factors including stairs and obstacles in the gait path that can cause trips or slips. The presence of multiple risk factors substantially increases the risk of a fall. Relatively little is known about the changes with age in impending fall response biomechanics that must, in part, be responsible for the rate changes. For example, tripping is commonly self-reported by older persons as a cause of falls. In a 1-year study of 1042 persons greater than 65 years of age, tripping was reported to be the cause of the fall in 53% of the 356 falls that were documented. Whatever the underlying neurological and physiological mechanisms, responses to trips are ultimately expressed in terms of biomechanical factors.

Fall-Related Injury Biomechanics

There probably are a number of factors that determine whether a fall will result in an injury: the initial conditions under which the fall begins, the biomechanics of the response during the fall, the passive and active mechanisms for dissipating energy on impact with the ground or other surfaces, and the proneness to injury of the hard and soft tissues that are impacted. Over the past decade the biomechanics of fall arrests and of fall-related injuries have received increasing attention because insights will improve assessments of risk and programs for both intervention and prevention.

The Biomechanics of Hip Fractures

The risk of bony fracture has been defined by Hayes and colleagues as the ratio of the magnitude of the force applied to the bone divided by the force necessary to cause fracture. A fall from standing height directly onto the greater trochanter carries a 21-fold higher risk for hip fracture than landing on another body part. This is because the loss in potential energy associated with such a fall is an order of magnitude greater than the average energy required to fracture the proximal femur in older cadaver specimens. Hence, falls in a lateral direction, which carry a higher risk for landing directly on the hip than other directions, must be avoided if possible. The fact that this is still unrecognized by older people represents a missed self-help opportunity because “forewarned is forearmed.” Knowing that risk ahead of time can allow at least some individuals to arrange to land on an alternative structure, such as a buttock rather than a hip, for example, as we have shown using computer simulations. A fall directly onto the hip is particularly devastating for the individual with reduced bone mineral density and reduced body mass index. Reductions in the latter are associated with less soft tissue over the hip to dissipate the impact energy. Hip pad protectors can be effective in reducing the risk of hip fracture in frail ambulatory older people. By diverting the impact energy to adjacent tissues, the

impact force on the hip may be more than halved. However, patient compliance has been problematic because the pads are uncomfortable to sleep with and the garment in which they are located can impede dressing and undressing. Alternate approaches have included the use of compliant flooring materials to reduce the impact force in the event of a fall. However, the expense of such installations has kept them from widespread adoption.

The Biomechanics of Wrist Fracture

Once a fall is initiated, fall arrests have two postinitiation phases: a preimpact phase and an impact phase. In a fall from standing height, the preimpact phase lasts approximately 0.7 seconds as the body falls to the ground. The impact phase lasts only tens of milliseconds for structures near the impact site (**Figure 114-1**) to a few tenths of a second at more proximal body sites further from impact. Thus, for structures near the impact site, like the hands and elbows in a forward fall, short- and long-loop neuromuscular reflexes are simply too long to be able to alter the fall arrest strategy if they are initiated during the impact phase.

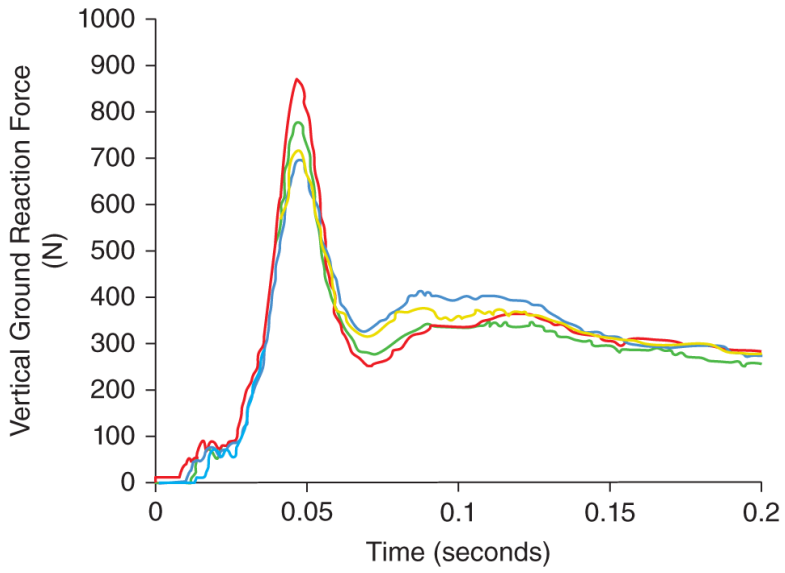


FIGURE 114-1. Example of the measured wrist impact force plotted versus time for one hand in four consecutive forward falls onto both arms for a young subject weighing 620 N. The subject fell onto a lightly padded surface from a shoulder height of 1 m. Note that (1) the time-to-peak force is less than any upper extremity neuromuscular reflex, rendering reflexes unable to protect the wrist, and (2) the magnitude of the peak impact force on one hand exceeds as much as one body weight for a brief time in two of the four trials, mainly as a result of the ground arresting the downward momentum of the upper extremity over a relatively short distance. (Data from DeGoede KM, Ashton-Miller JA. Fall arrest strategy affects peak hand impact force in a forward fall. *J Biomech*. 2002;35:843.)

The hands and arms are commonly used to protect the head and torso during a fall. The factors that determine the risk of Colles fracture, the most common upper extremity fall-related injury, are the height of the fall and the compliance of the surface. Moreover, at impact, the relative velocity of the hand as it strikes the surface, the elbow flexion angle, the angle of the lower arm with respect to the ground, and, of course, forearm bone mineral density status play a role. There is almost always time for older women or men to deploy their upper extremities in the event of a fall. But our research shows that a fall by an older woman from 25 cm or more onto a stiff surface, when landing with a straight arm, will almost certainly break the wrist. However, falling onto a slightly flexed arm will reduce this risk, although triceps and shoulder muscle strength is required to prevent the elbow from buckling. If the elbow buckles then the head, face, and cervical spine are placed at risk of injury. This justifies encouraging older people to maintain extensor muscle strength in the upper extremities so that they can better protect themselves in a fall. Our research suggests that the ability to perform even a single push-up provides useful capacity for handling the dynamics of such falls during impact with the ground.

AGE CHANGES IN COMPONENTS OF BIOMECHANICAL CAPABILITY

The biomechanical factors that underlie mobility impairments among older adults in general, and falling and fall injuries in particular, are not well understood. To come to that understanding, examination of the changes in

biomechanical capabilities that occur with natural aging and with disease is merited. This section discusses the changes that occur in myoelectric latencies, reaction times, proprioception, joint ranges of motion (ROM), and muscular strengths and the rapid development of those strengths.

Myoelectric Latencies

The myoelectric latency or premotor time is the delay from a test stimulus cue to the onset of the first measurable change in myoelectric activity in a muscle. Myoelectric activity refers to the electrical signals sent through the nerves to initiate or modify the muscle contraction process. At the latency time, the muscle will not have yet developed any significant contractile force or, if already contracted, changed that force. Myoelectric latencies typically range from 30 to 50 milliseconds for myotatic reflexes involving the muscle spindles, 50 to 80 milliseconds when cerebellar or cortex neural pathways are involved, 80 to 120 milliseconds when afferent receptors and higher motor centers are involved, and 120 to 180 milliseconds for volitional actions.

Reaction Times

The term “reaction time” refers to the delay from a stimulus signaling a needed reaction to making a movement or developing a force. Reaction time is longer than myoelectric latency because it includes both the myoelectric latency and the finite time required for a muscle to develop or change its force magnitude after myoelectric activity begins. This additional time interval is called the motor time.

Researchers define reaction time in different ways. For example, in studies of postural control, reaction time is often defined as the delay between stimulus onset and the first measurable change in the forces exerted by the feet on the floor support. This reaction force is usually measured with an instrumented force plate. This force development reaction time incorporates the myoelectric latency and the motor time required for the muscles to contract in order to alter the body configuration enough to change the support force. This happens with little discernible foot movement or limb-segment acceleration. Reaction time has also been defined to be the delay from stimulus onset until the first detectable acceleration of a body segment. This might be termed segment acceleration reaction time. Reaction time has also been defined as the delay from stimulus onset until a limb has been moved to a target. This movement-to-target reaction time incorporates myoelectric latencies, body-segment acceleration reaction times, and body-segment movement times. Movement reaction times depend on how far body segments have to be moved. Reaction times also depend on how many choices a subject has in responding to a cue. Simple reaction times are those exhibited when no choices are given to the subject. Choice reaction times are those exhibited when the subject must decide between two or more courses of action, depending on which of two or more cues is presented. Choice reaction time increases in proportion to the logarithm of the number of choices to be made. Choice reaction times are, therefore, considerably longer than simple reaction times. A speed-accuracy tradeoff is also found in reaction time measurements. As the accuracy requirement of the task is increased, reaction time increases. These differing definitions of reaction time and differing circumstances in which it is measured make it difficult to compare results from different studies of reaction times. Meaningful data on group differences in reaction times seem best obtained by comparing those times among different groups performing the same task, with the reaction time measure defined in the same way among the different groups. A method for reliably measuring simple and choice reaction times in the clinic has been developed by Eckner and coworkers.

Age and Sex Group Differences in Latencies and Reaction Times

Many studies report age differences, but not sex differences, among healthy adults in myoelectric latencies. Myoelectric latencies are typically 10 to 20 milliseconds longer in healthy old than in young adults.

Age systematically increases force development reaction times. Older, compared with younger, adults require perhaps 10 to 30 milliseconds longer to volitionally develop from rest modest levels of ankle torque or to begin to take a step upon loss of balance. Systematic age differences in movement-to-target reaction times are often found. These increase on the order of 2 milliseconds per age decade between the second and 10th decades. Age differences increase when subjects are not warned several seconds in advance of the cue that it is imminent. Much larger increases with age occur in choice reaction times than in simple reaction times. For example, in 10-choice button pushing tasks, where choices were identified by letter or color or both, choice reaction times increased 27% to 86% more in subjects aged 65 to 72 years compared with those aged 18 to 33 years. No notable sex differences in reaction times have been reported.

Biomechanical Effects of Age Differences in Latencies and Reaction Times Are Minor

Despite these age differences of 10 to 20 milliseconds in latencies and of 15 to 30 milliseconds in some reaction times, they seem seldom critical to mobility function. Even rapid responses in time-critical situations take place during perhaps 200 to 500 milliseconds, so these age-related latency and reaction time differences compared with the task execution times are not large. For example, among healthy older adults, the time required to fully contract a muscle is on the order of 400 milliseconds. The time to lift a foot in order to take a quick step is on the order of 200 to 400 milliseconds. Adults need warning times on the order of 400 to 500 milliseconds to be able to stop before reaching or to turn away from obstacles that come suddenly to attention.

Reaction times, which include muscle latencies, are task and strategy dependent. These are modifiable by central command. Reaction times of older adults are not always slower than those of young. Moreover, reaction times do not necessarily predict performance on complex mobility tasks. For example, one of our studies found that simple reaction times in lifting a foot immediately upon a visual cue did not predict how well the same young or older subjects could avoid stepping on a suddenly appearing obstacle during level gait. In fact, age-group differences in simple reaction times were substantially larger than age-group differences in the response times needed to avoid the obstacles successfully.

Proprioception

Proprioception describes awareness of body-segment positions and orientations. Relatively few studies have examined changes with aging in proprioception. One study found joint position sense in the knee to deteriorate with age. Joint angles could be reproduced to within 2 degrees by 20-year-olds, but only to within 6 degrees by 80-year-olds. Twenty-year-olds could detect passive joint motions of 4 degrees, but 80-year-olds could detect only motions larger than 7 degrees. Other studies have found no major decline with age in motion perception in finger and toe joints but have found declines with aging in sensing vibration. Proprioceptive acuity at a joint is better when muscles at the joint are active than when these are passive. Proprioceptive thresholds during weight bearing are at least an order of magnitude lower than those typically reported during non-weight-bearing tests. Healthy adults can sense quite small ankle rotations in the sagittal and frontal planes under the weight-bearing conditions of upright stance. The probability of successful detection of rotation increases with increasing magnitude and speed of imposed foot rotation. A 10-fold reduction in the angular threshold was observed on increasing the speed of rotation from 0.1 to 2.5 degrees per second, but thresholds did not further reduce at higher speeds. In healthy adults between the third and eighth decades, age, rotation angle, and rotation speed also affect the threshold for sensing the direction of foot rotation. Threshold angles were three to four times larger in older females than in younger females.

Individuals with central or peripheral proprioceptive impairments can exhibit articular pathology. Examples include Charcot changes occurring in the upper or lower extremities owing to central nervous system damage by syringeomyelia over several levels of the spinal cord and changes in the foot or ankle owing to lower extremity peripheral neuropathy often associated with diabetes. Indeed it is prudent to warn older diabetic patients planning an exercise program about the risk of developing Charcot foot if they try to return to activities requiring the foot to impact the ground in order to abruptly change direction (ie, racquet sports or running), since they simply may not feel compression fractures of the bones comprising the arches of the feet. These can lead to skin breakdown, thereby increasing the risk for serious infection and even amputation.

Peripheral neuropathy increases the proprioceptive threshold at the ankle nearly fivefold compared with age-matched healthy controls. This increased threshold, which correlates well with fibular nerve amplitude on electrodiagnostic testing, adversely affects postural stability and raises the risk of obstacle contact during gait, suggesting one mechanism that might underlie the 20-fold increase in fall risk and the sixfold increase in fall-induced fractures that these patients have. Furthermore, when loss of ankle proprioception is combined with poor hip adductor muscle strength, there is a particularly high risk of falls and fall-related injuries. So maintenance of good hip muscle strength would seem important in these patients.

Joint ROM

Body joint ROM has generally been found to diminish with age, but not all findings are consistent. For example, there is approximately a 20% decline between ages 45 and 70 years in hip rotation, but only 10% declines in wrist and shoulder ROM. Comparisons of the ROM of lower extremity joints for young and middle-aged adults with those for older adults showed declines ranging from negligible to 57%. At the age of 79 years, one-fifth of a large group of

subjects had restricted knee joint motion and two-thirds had restricted hip joint motion. Among more than 3000 blue-collar workers with ages ranging from 20 to 60 years, a 25% decline with age was found in ability to bend to the side and a 45% decline in shoulder motion. Declines of 25% to 50% have been found in various ROM of the lumbar spine between ages of 20 to 80 years. However, a comparison between two groups with mean ages of approximately 65 and 80 years found no significant differences in 28 different joint ROM. At least one study suggests that passive or active stretching exercises can increase hip extension ROM in young adults by 8 to 17 degrees, and another study suggested that exercises with a focus on stretching improve spine flexibility in older adults.

The effects of decreased ROM on abilities to perform activities of daily living are not well understood in young or old adults. One study of adults with arthritis found that the ability to move around in one's environment correlated well with ROM in knee flexion, the ability to bend down correlated with hip flexion ROM, and the abilities in activities requiring use of hands and arms correlated well with ROM of the upper extremities. Another study found that restricted knee motion in 79-year-olds correlated with disability in entering public transport vehicles but that ROM impairment did not generally associate with need for institutional care. A third study found the majority of a group of 134 people aged 79 years to have enough spinal mobility to perform common activities of daily living.

Muscle Strength and Power

There is loss of strength with age, even in healthy and physically active older adults (**Table 114-1**). Isometric strengths peak at approximately the age of 25 years and then decline. The loss is approximately one-third by the age of 65 years. Isometric strength is more reliably measured, and considerably greater values are recorded, when the patient exerts force on a fixed force transducer, rather than one held by an examiner. To express the strength developed about the joint in units of torque, the force (in newtons) developed by the limb segment against a force-measuring transducer is multiplied by its lever arm (in meters) about the joint being tested. Muscle strength about a joint is, therefore, expressed in torque units (ie, Nm), and these torque units can be normalized by body size (ie, body height * body weight) to facilitate sex or age comparisons. Dominant limb strengths are typically approximately 10% greater than nondominant strengths. Mean strengths of female adults of any age are on the order of one-third lower than those of male adults (see **Table 114-1**). However, when those strengths are normalized by body size, then the difference may no longer be significant. Reports of strength values vary widely because these depend on many factors, for example, substantially on whether subjects have impairments or experience pain or discomfort during testing, at which joint angles, whether under isometric or constant velocity conditions, and, at constant velocity, whether muscle shortening or lengthening is occurring. As an example, maximum knee extensor torque in healthy individuals decreases by 14%, 23%, 41%, and 53% of isometric values at joint rotation speeds of 30, 60, 90, and 180 degrees per second, respectively. Isokinetic dynamometers do not measure maximum torque or power accurately at speeds above 180 degrees per second because of substantial measurement artifacts.

TABLE 114-1 LITERATURE VALUES FOR JOINT TORQUE STRENGTHS (UNLESS OTHERWISE NOTED, MEAN VALUES IN NM)

	HEALTHY YOUNG ADULTS[a]		HEALTHY OLDER ADULTS[b]	
DATA SOURCE	FEMALES	MALES	FEMALES	MALES
Toe flexors	14	24	11	16
Ankle dorsiflexors				
Sepic et al.	44	78	46	74
Thelen et al.	28	43	22	37
Ankle plantarflexors				
Sepic et al.	100	129	82	131
Thelen et al.	130	181	88	137
Knee flexors				
Borges	100	155	65	109
Knee extensors				
Borges	183	289	128	188

Hip flexors Cahalan et al.	66	108	51	89
Hip extensors Cahalan et al.	126	204	110	203
Hip abductors Cahalan et al.	90	108	55	72
Shoulder flexors[c] Hughes et al.	32	58	16	38
Shoulder extensors[c] Hughes et al.	40	72	22	40
Cervical spine extensors Jordan et al.	33	65	37	45
Grip strength[c] (N) Mathiowetz et al.	272	466	185	289

Most values quoted are for isometric strengths, but a few are for low-rate isokinetic strengths.

[a] Mean ages approximately 25–30 yr.

[b] Mean ages approximately 60–80 yr.

[c] Nondominant limb.

Modified from Schultz AB. Mobility impairment in the elderly: challenges for biomechanics research. J Biomech. 1992;25:519.

The strength capacity needed at the very start of a recovery movement can best be measured by isometric strength because it is what is needed to initiate limb acceleration. For the hip flexor muscles, which are needed to recover balance after tripping by swinging a leg forward rapidly and placing the foot on the ground ahead of the center of gravity, maximum hip flexor torque decreases linearly with increasing hip flexion angle, as a result of muscle shortening, and additionally with increasing hip flexion speed. So, given the typical bell-shaped hip flexion angular velocity versus time curve for a recovery step, it is the maximum power developed about the relevant joint that best predicts the fastest velocity that can be achieved mid-swing and, therefore, length of the recovery step. Since power at a joint is defined as the product of the torque developed at that joint times the joint angular velocity, large hip flexion power values would be attained by being able to develop a large torque about the joint at a high rotational velocity. Maximum power usually occurs in a shortening muscle at approximately one-third of the maximum movement velocity. The steady loss of power in older people is caused by the age-related loss of type II fast-twitch motor units, this leads to slowing of the muscle because of the reinnervation of the denervated type II fibers by slow-twitch motor units.

A prevalent casual belief is that many of the mobility impairments that arise in older people are caused by declines in muscular strength. This belief warrants careful consideration. In fact, the joint torques needed to maintain postural balance and even to rise from a chair are often well below the joint torque strengths that healthy older adults have available.

The decline with aging in the ability of muscles to produce power is illustrated by records of elite athletic performances. In short-distance races, male elite runners more than 70 years old run approximately one-third slower than do elite young adult male athletes. In long-distance races, male elite runners more than 70 years old run approximately half as fast as elite young adult male athletes. By that age the maximum extensor muscle power that can be developed about the knee, for example, has declined by approximately 40%. It is this drastic loss of power that underlies the age-related slowing of older people's ability to make rapid movements.

Age-related changes in muscle morphology and physiology help to explain these changes (see Chapter 113). Older adults are particularly prone to loss of isometric strength as well as torque at high velocities because of the irreversible loss of the largest (and fastest) motor units with age. Fast/slow muscle fiber innervation ratios also seem to change with age. By contrast, the maximum speed of unloaded shortening for specific muscle fiber types does not decrease significantly with aging. The reduction in muscle power reduction with age may also be caused by systemic factors, such as declines in cardiopulmonary function. It is thus likely that, in order to maintain muscle function in older adults, the focus should be on the assessment and training of both muscle power and strength.

What is the biomechanical stimulus for improving strength capacity? In one study with muscle biopsies, a 16-week

progressive resistance training regimen resulted in a 10% increase in type II muscle hypertrophy. This effect was similar in young and old whether, for the same number of repetitions, subjects used traditional weights moved slowly, or lighter weights moved 3 times faster. Interestingly, both resulted in a 50% increase in strength, presumably due to improved neural coordination. But the biomechanical explanation for why moving lighter weights faster can have the same training effect as moving heavier weights slowly is that the muscle is required to develop a similar maximum force in both cases. In the former case, the muscle must develop a moderate force to lift the weight and significant additional force to accelerate it to the higher speed; in the latter case, the muscle must develop a large force to lift the weight, but little additional force to accelerate it to the slower speed.

Rapid Development of Joint Torque Strengths

Upon a substantial perturbation of standing balance, as already noted, fewer than 500 milliseconds are often available for the critical initial phase of balance restoration, yet 300 to 400 milliseconds can be required to develop maximum joint torques. Even older adults who are healthy and physically active have diminished abilities to develop large joint torques rapidly, compared with young adults. Moreover, older females have lower torque development rates than do older males. For example, in one study, the mean total time required to develop 60 Nm of ankle plantarflexion torque, when subjects were asked to develop maximum torque as fast as possible, was 311 milliseconds in young adult females and 472 milliseconds, or 161 milliseconds (52%) longer in older females. Corresponding times for males were 270 and 313 milliseconds (16% longer), respectively (**Figure 114-2**). Maximum rate of torque development tends to correlate highly with maximum voluntary torque strength, with correlation coefficients on the order of 0.8. Owing to slowing in peak rate of joint torque development abilities, capacities of even healthy old adults to recover balance or to carry out other time-critical actions that require moderate-to-substantial strengths, such as those required to avoid obstacles that come suddenly to attention, may be considerably reduced.

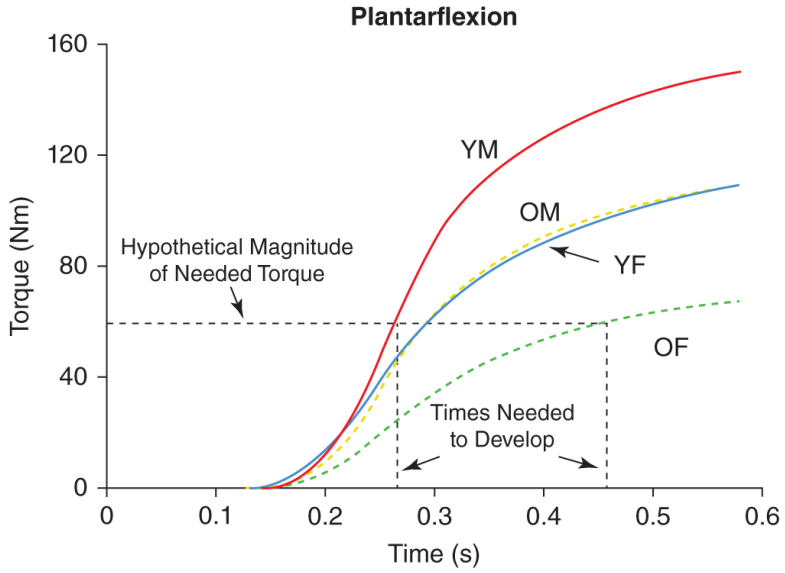


FIGURE 114-2. Age and sex differences in rapid development of ankle plantarflexor torque. The subjects tested were healthy young and older (Y, O) females and males (F, M). Time is measured from a light flash cue signaling the subjects to push against a pedal as hard and as fast as possible. The four subject groups exhibited nearly the same mean reaction times, approximately 160 milliseconds. However, the mean time needed to develop a given magnitude of torque varied substantially among the four age/sex groups. For example, if a plantarflexion torque of 60 Nm was required to regain balance upon the initiation of a fall, YM would need approximately 275 milliseconds to develop that torque, and OF would need approximately 475 milliseconds. (Data from Thelen DG et al: Effects of age on rapid ankle torque development. *J Gerontol Med Sci*. 1996;51A:M226.)

Source of Age Differences in Rapid Strength Development

Measurements of myoelectric signals in ankle dorsiflexor and plantarflexor muscles during rapid isometric and isokinetic exertions have been used to explore the extent to which this age-related slowing in rapid torque development might be attributed to neural factors, that is, those processes that precede the initiation of muscle contraction. In one study, latency times, muscle activation rates, and myoelectric activity levels of agonistic and antagonistic muscles were quantified. There were few marked age differences in the latencies or in the onset rates or

magnitudes of agonistic or antagonistic muscles activities during maximum isometric and during isokinetic exertions. Myoelectric latency times were statistically associated with age, but, in the mean, these were only approximately 10 to 25 milliseconds longer in the old. Given the outcomes of this study, the differences observed in rapid torque development abilities in healthy older compared with healthy young adults seem largely because of differences in muscle contraction mechanisms once contraction is initiated; this contrasts with differences in the speeds of stimulus sensing or central processing of motor commands, and differences in the muscle recruitment decisions that precede contraction initiation, which appear minor.

AGE DIFFERENCES IN PERFORMANCE OF SIMPLE MOBILITY TASKS

To reach a better understanding of the biomechanical mechanisms that underlie mobility impairments in general, and falling and fall injuries in particular, attention to how the changes in biomechanical capabilities that occur with natural aging and with disease affect the performance of individual mobility tasks is merited. This section discusses age differences in performance of common mobility tasks, such as walking; turning, rising from chairs, beds, and floors; and regaining standing balance when it is disturbed.

Age-related declines in mobility task performances are seen in tasks that are physically and/or cognitively very challenging long before any declines are seen in tasks easily performed. Physical and cognitive capacities can decrease substantially without leading to any impairment if task performance demands are modest because these do not tax the functional reserve. Once capacity falls to a point at which task demand begins to equal capacity, performance ability begins to decline substantially. In healthy adults, the consequences of a decrement in capacity are unlikely to be seen in performances of easy tasks but are likely to be seen in performances of demanding tasks, accompanied, perhaps, by compensatory changes in performance strategies.

Assessment of Mobility Function

Mobility does associate with decrements in biomechanical variables. For example, in a study of community-dwelling older adults, self-reported difficulty with chair rise, ascending and descending stairs, and fast walking was associated with a reduction of isometric knee extensor strength capacity below 3 Nm/kg body weight. A number of performance-based test batteries have been developed to globally assess a patient's mobility function, including that in changing positions, controlling upright posture, and walking. These batteries are designed to detect clinically significant changes that might, for example, place an individual at risk of falls or of developing mobility disability. Not all of these batteries are sensitive to the subtle age-related changes in performance found among healthy adults. Some do not include tasks that are sufficiently demanding. Others use rating systems that are not quantitative enough. These involve low-tech measures, quick to administer and requiring at most a stop watch for timing, and are used for screening and to track progress in response to interventions. Such batteries serve well for assessing more impaired older adults. For example, the Performance-Oriented Mobility Assessment—also known as the Tinetti Balance and Gait Scale, is often used in clinical settings; however, in community-dwelling populations there is concern about ceiling effects and low sensitivity to change. Perhaps the simplest battery in the clinical setting is the Timed Up and Go (TUG), a timed sequence of rising from a chair, walking 3 m, turning, and returning to sit in the chair. One study suggests a TUG score of greater than or equal to 14 seconds as an indicator of fall risk but many older adults can perform the task more quickly. Other investigators have found limitations in TUG in the presence of cognitive impairment and difficulty in completing the test because of immobility, safety concerns, or refusal. Of increasing use in research is the Short Physical Performance Battery, which includes two tests perhaps more sensitive to age-related changes, gait speed and multiple rises from a chair. Also increasingly used in research are measures of walking endurance, the 6-minute walk test, long the foundation of functional cardiopulmonary assessment, and the 400-m walk test, considered a marker of major mobility disability that responded to a physical activity intervention in a clinical trial of at-risk older adults. In terms of studying mobility and falls outside the clinic or laboratory, a classic study was conducted by Robinovitch and colleagues who gained permission to use multiple security video cameras in order to identify the circumstances leading to falls in the nursing home. Most were due to incorrect weight shifting, followed by trips and stumbles but very few slips. The advent of inexpensive miniature inertial measurement units that can be mounted unobtrusively on more than one body segment is allowing mobility to be assessed over long periods in the home and community. As these sensors improve, along with the software required to analyze the prodigious amounts of data they generate, we should obtain valuable insights into the assessment of mobility, how mobility varies with time and disease, and the detailed circumstances leading to falls and fall-related injuries whenever and wherever they might occur.

Ascribing Functional Decline Fully to Insufficient Motivation, Activity, or Training Is Questionable

Performance records of elite older athletes suggest that physical inactivity, lack of motivation, and lack of training cannot fully explain functional decline in healthy older adults. Declines with age in physical performance abilities can be seen among even highly trained and highly motivated athletes. As already noted, top running speeds of short- and long-distance older elite runners are lower than those of young adult elite runners.

Gait

Hippocrates once said that walking is man's best medicine. We now know that gait speed is a powerful predictor of outcomes, including disease activity, mobility and activity of daily living disabilities, institutionalization, and mortality. In older adults free of overt neurologic, musculoskeletal, cardiorespiratory, or cognitive problems, comfortable gait speed declines minimally until approximately the age of 60 years and then declines by 1% to 2% per year through the age of 80 years; however, there is substantial variability among studies of age changes in comfortable gait speed (**Figure 114-3**). A pooled analysis of nine cohort studies of community-dwelling older adult found that usual gait speed predicted 5 and 10 year survival as accurately as a number of other important clinical variables such as age and chronic conditions. The likelihood of poor health and function increases at usual walking speed cutoffs of 0.8 or 1.0 m/s and particularly below 0.6 m/s; speeds above 1.0 m/s and perhaps 1.2 m/s are associated with better functional outcomes and increased life expectancy. Particularly slow speeds are seen in clinical settings, such as the acute care, subacute care, and ambulatory settings, with estimates of 0.46, 0.53, and 0.74 m/s, respectively. Changes in gait speed are increasingly used to evaluate intervention outcomes. The extent to which a change in gait-related performance, such as gait speed, is clinically meaningful is being investigated. For example, in cohorts that include mobility-impaired individuals, estimates range from 0.05 to 0.10 m/s for small and substantial change, respectively. Using even a 0.10 m/s cutoff, however, may not coincide with perceived change in mobility in certain patient populations, such as in patients post-hip fracture.

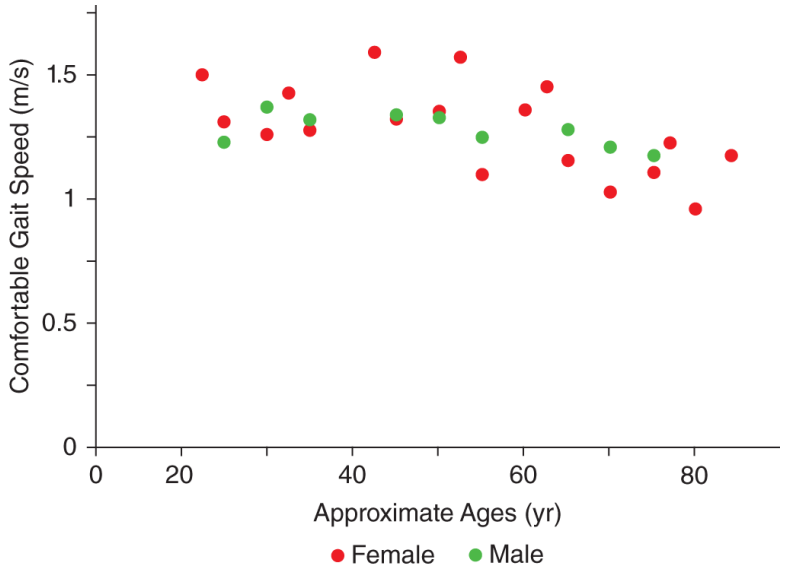


FIGURE 114-3. Age and sex differences in self-selected comfortable gait speeds. These data are graphed using those abstracted by Bohannon et al. (1996) from seven earlier literature reports. The mean speeds reported vary substantially. Nonetheless, the general trend is for comfortable gait speed to decline minimally until approximately the age of 60 years and then to decline by 1% to 2% per year through the age of 80 years.

The causes of gait slowing with age are a subject of controversy and may be multifactorial. They include subtle age-related changes in joint stiffness, leg strength, standing balance and energy conservation strategies. Other contributing factors are commonly disease associated (eg, cardiopulmonary or musculoskeletal disease, pain) and include vision, aerobic function, physical activity, as well as previous falls and fear of falling. Multiple organ system changes appear to contribute to age-related changes in gait speed, but no single system is primarily associated with this decline. Combining factors can result in an effect greater than the sum of the single impairments (as when combining balance and strength impairments). Independently of age, comfortable walking speed associates nonlinearly with

muscle strength (**Figure 114-4**) and maximum aerobic power.

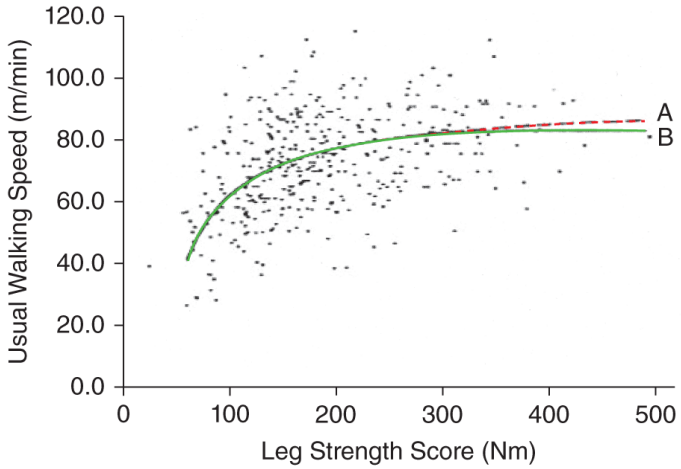


FIGURE 114-4. Comfortable gait speed is nonlinearly related to leg muscle strength score in a population-based sample of over 400 adults between the age of 60 and 96 years. The strength score was formed from the summed isokinetic right knee and ankle flexor and extensor muscle strengths. The regression curve represents the fit for an average age of 76 years. (Data from Buchner DM et al: Evidence for a nonlinear relationship between leg strength and gait speed. *Age Ageing*. 1996;25:390.)

Much of the decline in speed has been attributed to reductions in step length. The earliest studies of gait in older adults found that men in their sixties demonstrated shorter step and stride lengths and decreased ankle extension and pelvic rotation compared with younger males. More recent studies have confirmed those findings, but not without exception. One found no significant age-group differences in step and stride lengths, velocity, or movements of the ankles, pelvis, and total body mass center. Another concluded that increased variability in gait should not be regarded as a normal concomitant of old age. Still another found that among older adults, more than 40% of the variance in normal walking speed can be accounted for by differences in height, calf muscle strength, and the presence of health problems such as leg pain. In a prospective study, older women with the poorest knee strength and balance scores were five times more likely to develop severe walking disability than those with normal function. The association between age-related reductions in stride length and gait speed and a tendency to fall is unclear. Fall risk may increase not just with slow gait but very rapid gait (> 1.3 m/s), with slow walkers more likely to fall indoors and fast walkers more likely to fall outdoors.

There are age- and disease-associated deficits in the ability to walk and perform a simultaneous cognitive task ("dual tasking," such as talking while walking). These deficits have been linked to increased fall risk, and include gait speed changes as well as gait variability. However, dual task changes in gait speed as well as variability may be equivalent to single task changes in discriminating fallers from nonfallers even when considering those who walk more slowly or who are cognitively impaired. The dual task effect may thus be most clinically useful in very high risk groups who require extensive attentional resources to maintain safe gait. While slower gait speed can predict decreased cognition in healthy older adults, the opposite is true as well, namely that decreased cognitive function, in multiple domains including executive function, is associated with slower speed.

Rising From Chairs, Beds, and Floors

The biomechanical demand of rising from a regular chair imposes the largest strength demands on the knee and hip extensor muscles: healthy older individuals are required to develop approximately 30% and 25% of their maximum knee and hip extensor strengths, respectively. It is instructive to think about how disease or impairments that affect muscle strength can affect the ability to rise from a chair. With bilateral symmetry in function and their young adult body weight, knee strength would have to be reduced by 70% before becoming inadequate. Thus, healthy older people have considerable functional reserve. However, if their body weight has doubled from their young adult weight, the older individual's knee strength would only have to fall 35% below age norms before knee extensor strength is inadequate to rise from a chair without arms. Likewise, a complete unilateral loss in knee extensor strength would mean that a healthy older individual could only tolerate a 35% loss in remaining knee strength before it becomes inadequate. In general, healthy older adults do rise more slowly than young adults, but the time differences for bed and

chair rises are 2 seconds or less. When rising from the floor, age differences are larger, with older adults tending to take twice as long as young. Characteristic age-related changes in trunk, arm, and leg motions used to rise may account for these differences.

When rising from a chair, particularly without the use of hands for assistance, healthy old people flex their necks, trunks, and legs and extend their thighs more than the young, resulting in a more anterior placement of their floor reaction force than young adults demonstrate. In one study of graded difficulty chair rise tasks, healthy young and older adults did not differ in the leg joint torques that they used to perform the series of tasks. Both young and older adults had enough strength to perform even the most challenging task. However, the older people generally used a greater percentage of their available knee strength to rise from a chair, using near-maximum levels in challenging situations. Some of the older adults failed to rise when their postural control was challenged by a lowered seat and by a narrow foot support base. So, there are situations where older adults have adequate strength to rise from a chair but are limited by other factors, such as difficulty with postural control.

While rising from a bed, older adults, compared with young adults, tend to lengthen the time of contact of their arm with the bed surface. They are more likely to rotate and laterally flex their trunks, bear weight on their hip/gluteal area, and use their elbow to help pivot while rising. Declining trunk strength may account for some of these findings.

Many healthy older adults are unable to sit up in bed without the use of their hands. When rising from the floor, older adults tend to use key intermediate positions, such as getting to an all-fours position, in order to reduce the strength requirements and to enhance postural stability. In general, intermediate postures that reduce physical demands (eg, knee extensor strength required) can be used as part of task-specific exercises to improve the ability to rise from the floor. Improvements as a result of these interventions, quantifiable biomechanically (such as increased momentum during the rise) and clinically (such as in time), are modest.

Turning in a Confined Space

In bathrooms and kitchens it is often necessary to use the feet to turn through angles as much as 180 degrees as one moves from one point to another. Falling while walking and turning has been shown to be 7.9 times more likely to result in hip fracture than falling while walking straight. In an effort to understand why turning is linked to such a high rate of injury, we have studied how age affects the kinematics of foot placement during turning by healthy young and older women. We found that subjects generally have a preferred direction of turning and that, in older women, the minimum foot separation distance during the turn was less when turning in the nonpreferred direction than in the preferred direction, raising the probability of foot-foot collisions, and hence a trip. The minimum foot separation distance during the turns was generally 55% more variable in the healthy older women than in young controls, despite the fact that they turned 20% more slowly.

Walking on Irregular Surfaces

There is often a need to cross irregular or uneven surfaces outside. Walking on an uneven or bumpy surface can pose a considerable challenge to an older person, as is evidenced by the fact that it is one of the two most frequent causes of falls in community-dwelling individuals. One of the first studies of gait on uneven surfaces compared subjects with age-related maculopathy against controls while walking across level, compliant, and uneven surfaces. An irregular surface increases step width variability in healthy young and old controls and step time in peripheral neuropathic subjects who had to slow significantly on such surfaces. The irregular surface discriminated age and disease group differences in stepping pattern, as well as faller versus nonfaller group differences better than did similar tests on a level surface. Application of bilateral ankle braces or use of a cane improved the step width variability in neuropathic patients walking on uneven surfaces.

Restoration of Standing Posture After Modest Disturbance

There is evidence of deterioration in many of the sensorimotor systems underlying postural control, even in older populations without obvious signs of disease. However, aging alone does not account for the heterogeneity of postural control problems in older people. Moreover, responses to postural perturbations are task and perturbation specific, so that a single assessment technique may not serve as a true indicator of the overall integrity of the balance control system.

Sway while standing generally increases with age during adulthood, but not without exception. Age-related changes in postural control in healthy adults are minimal through the age of 70 years under situations of low task

demand. Examples of low-demand tasks are standing on two feet with eyes open, or maintaining stance when it is perturbed by modest movements of the support surface or by gentle backward pushes. When task demand increases, age-group differences in postural control abilities become more apparent. For example, when a sway response no longer suffices to recover balance in the face of a perturbation, young adults tend to resort to a single step, whereas older adults tend to employ multiple steps in order to recover their balance. Task demand can be increased by decreasing visual input, by reducing the width of the base of support, for example, by narrowing stance or balancing one foot, or by making the support surface more compliant. The most striking age-related differences often occur when several different demands are increased simultaneously. When both the support surface and the visual surround were rotated in phase with body sway, 50% of older adults lost their balance on their first attempt to maintain stance, compared with 9% of younger controls. The timed ability to balance on one leg is a simple yet challenging balance test that is popular in the clinic. Often the data are censored by terminating the test after a set time of, say, 30 seconds or 1 minute. When they are not censored in this way, the mean time for standing on one leg with eyes open before losing balance for 20- to 29-year-olds was at least 3 times as long as that for 70- to 79-year-olds and over 5 times longer with eyes closed (**Figure 114-5**).

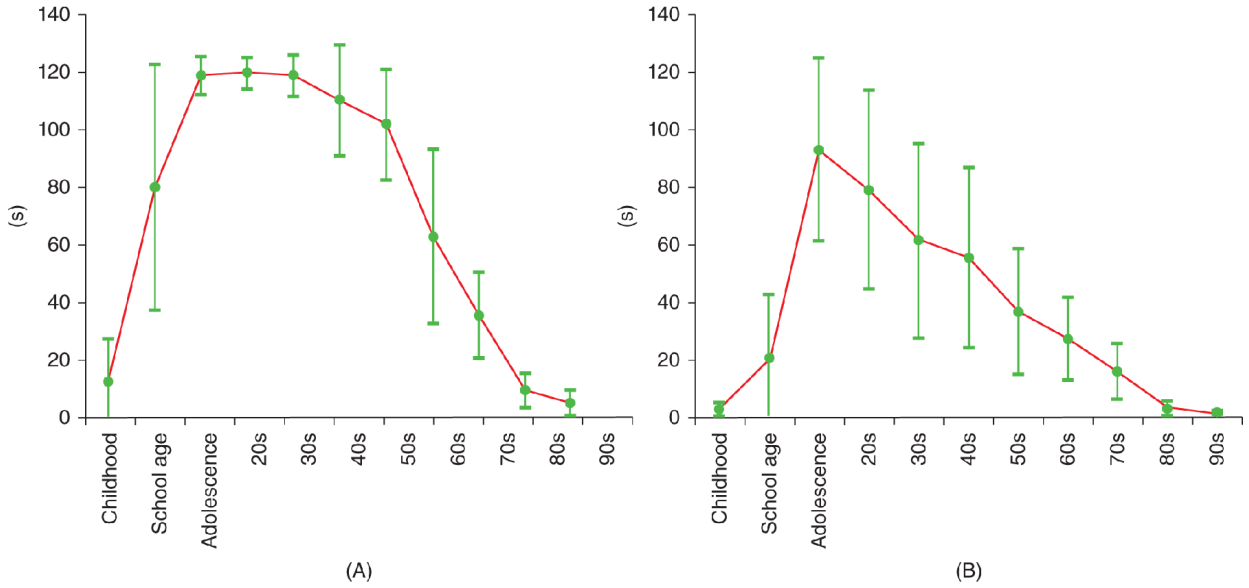


FIGURE 114-5. Effect of age on the mean (SD) maximum one leg balance times measured with eyes open (**A**) and eyes closed (**B**). The data are from 1241 community-dwelling individuals in Japan from 2 to 92 years of age without musculoskeletal impairments. (Reproduced from Morioka S et al. Changes in the equilibrium of standing on one leg at various life stages. *Curr Gerontol Geriatr Res*. 2012;2012:516283.)

It is not known why these changes with age occur in postural control abilities. One-leg stance time differences might result from reduced muscle strength or endurance, increased muscle latency times, decreased cutaneous or joint proprioception, or decreased willingness to allow the center of the floor reaction to deviate from the center of the foot support area. Only a few studies to date have analyzed the body-segment motions or joint torques developed. Ongoing theoretical studies in our laboratory suggest that hip muscle strength may be a limiting factor.

Cognitive and Other Psychological Factors

Cognitive demand relative to cognitive capacity substantially influences physical task performance. As mobility task complexity increases, so do the cognitive demands placed on the individual. The need to perform two tasks simultaneously or to divide attention degrades performances of healthy older people more than for healthy young. For example, in a study of abilities to step over suddenly appearing obstacles while walking, the attention of groups of healthy young and older adults was divided by having them simultaneously respond in two reaction time tasks. Both young and old adults had an increased risk of obstacle contact while negotiating obstacles when their attention was divided, but attention division diminished obstacle avoidance abilities of the older people more than it did in the young. These results suggest that diminished abilities to respond to physical hazards present in the environment when attention is directed elsewhere may partially account for high rates of falls among older people. As an example, relative to controls, fallers tend to prematurely transfer their gaze from an obstacle that they are about to cross.

In our studies of relationships between neuropsychological status and physical performance, relatively minimal

associations have been found in performance of simple tasks, such as in assessments of proprioception, joint ROM, and strengths. With tasks of increasing complexity, such as in chair rise, ambulation, and postural maintenance, visual attention abilities, and psychomotor speed were good predictors of performance. In performance of mobility tasks of substantial complexity, such as avoiding obstacles when attention is divided or stepping accurately under adverse conditions, measures of problem-solving ability and mental flexibility, along with psychomotor speed and attention, become performance predictors. These capacities include elements of executive control, an area of cognitive function increasingly recognized as critical to control of gait and fall avoidance. We have found that when embedding aspects of executive control into a walking task, such as the trails tests of visuomotor processing, older adults, particularly those with executive function impairment, perform more poorly.

Difficulties in walking seem to relate to cognitive impairment. Demented older adults have shorter step lengths, lower frequencies of stepping, more step-to-step variability, and lower gait speed. Gait abnormalities in nondemented older adults can predict future occurrence of dementia, particularly vascular dementia. Difficulties in concurrent performance of cognitive and mobility tasks, such as a verbal task while walking, have been proposed as risk factors for falls. An extreme example, when the individual stops walking while talking, appears relevant only in those with significantly impaired gait or cognition. These findings reflect the inherent underlying cognitive demand in walking, particularly in those with already impaired gait. A geriatric rehabilitation program led to greater gains in walking speed in subjects with normal cognition than in those with impaired cognition. Moreover, walking speed appeared to be closely related to the ability to rise from a chair and to be a powerful predictor of patient placement upon discharge from the rehabilitation program. Of 116 older adults studied, none were able to live alone or even in a rest home if they were discharged with a walking speed of less than 0.15 m/s. Many frail older people are aware of the difficulty of dividing one's attention while walking, as demonstrated by the ability of the simple but effective "Stops Walking When Talking Test" to predict impending falls in these patients.

AGE DIFFERENCES IN PERFORMANCE OF TIME-CRITICAL MOBILITY TASKS

Times Needed for Quick Responses to Maintain or Recover Balance

As already noted, the time available in which to recover from a substantial disturbance of upright balance or to safely arrest a fall is often less than 1 second. For example, when walking forward at a speed of 1.3 m/s, the comfortable walking speed typically self-selected by healthy young and old adults, only 200 to 300 milliseconds may be available in which to make initial responses appropriate for balance recovery when tripping over an obstacle. If a large obstacle in the gait path, such as a moving vehicle, suddenly comes to attention 1 m ahead while walking at this speed, then turning away from the obstacle or stopping before reaching it would have to be accomplished within approximately 750 milliseconds. The term "time critical" is used here to refer to such situations. Differences in abilities to respond appropriately in at least some time-critical situations (**Figure 114-6**) may help explain age and sex differences in rates of falls and fall-related injuries.

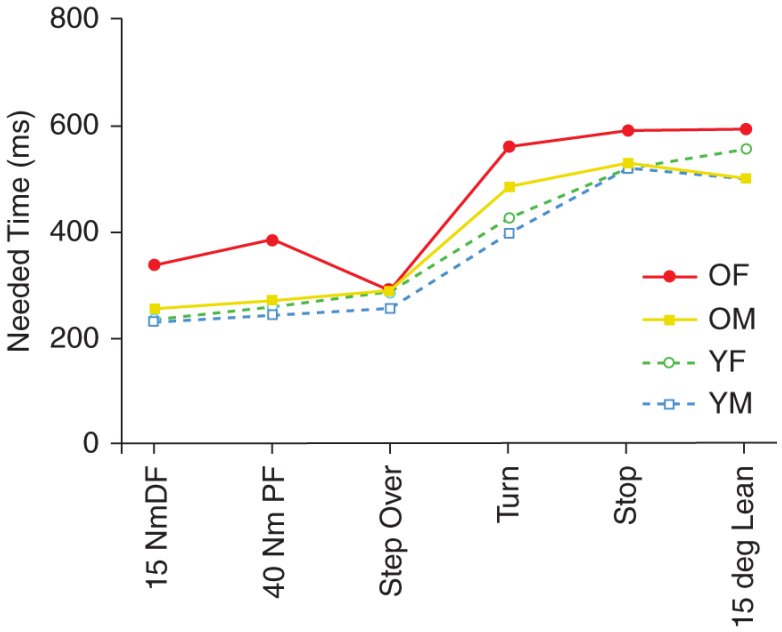


FIGURE 114-6. Summary of age and sex differences in times needed for various quick responses. Mean values across groups of healthy older females (OF), older males (OM), young females (YF), and young males (YM) of the times required for six different responses are shown. The responses are indicated by the horizontal axis labels. Each of the situations being responded to is further described in the text of this chapter. From left to right, the responses are the development of, respectively, (1) 15 Nm of ankle dorsiflexor (DF) torque or (2) 40 Nm of ankle plantarflexor (PF) torque, as fast as possible; the achievement of a 50% rate of success in avoiding suddenly appearing obstacles by, respectively, (3) stepping over the obstacle, (4) turning away before reaching the obstacle, or (5) stopping before reaching the obstacle; and (6) the replacement of the stepped foot on the ground when recovering balance by taking a single step up on sudden release from a 15-degree whole-body forward lean. The data points are connected by lines only to help distinguish the four subject groups.

Studies of Time-Critical Obstacle Avoidance Tasks Avoiding Obstacles by Stepping Over Them

The abilities of healthy and physically active young and older adults, who were walking forward at a speed of approximately 1.3 m/s, to step over an obstacle that suddenly appeared at seemingly random times and locations in front of them have been examined. The appearance of this obstacle was arranged to give the subjects available response times that varied from 200 to 450 milliseconds before they would have stepped on it. This task is a time-critical one, but because avoidance requires relatively minor changes in stepping pattern and relatively minor redistributions among segments of kinetic energies and forward momenta, the strength requirements of the task likely are modest. Few young or old people could avoid obstacles if only 200 milliseconds were available. Most young and old people reliably avoided obstacles that appeared so as to give 450 milliseconds warning time. Over all available response times used, the older people had lower avoidance success rates than the young, but, in biomechanical terms, it was estimated that they would have needed only 30 milliseconds more warning time to have the same success rates as the young. No significant sex differences in avoidance abilities were found.

Avoiding obstacles by turning away before reaching them In a study of abilities to make sudden turns to avoid previously unseen obstacles, healthy old adults were substantially less successful than young when available response times were short. For example, for an available response time of 450 milliseconds, mean success rates in completing the turn without colliding with the obstacle were 68% in young and 27% in older adults. Moreover, males had substantially better success rates for given available response times than did females in corresponding age groups. This task is a time-critical one. Avoidance requires complete arrest of forward momenta and quick development of lateral momentum, but relatively minor redistributions among segments of kinetic energies. Therefore, the strength requirements of the task likely are moderate.

Avoiding obstacles by stopping before reaching them In a similar study of abilities to make sudden stops to avoid previously unseen obstacles, healthy old adults again were substantially less successful than young when available response times were short. For example, for an available response time of 525 milliseconds, mean success rates in stopping before passing forward of the obstacle were 58% for young females and male adults and 51% for older males, but only 23% for older females. This task is also a time-critical one. Avoidance requires complete arrest of forward momenta and total dissipation of body kinetic energy. Thus, the strength requirements of the task likely are

substantial.

Studies of Time-Critical Balance Recovery Tasks

Once a fall begins as a result of a trip, quick recovery of balance may be needed to avoid injury. In one set of studies by Grabiner and coworkers, forward falls were induced in healthy older adults by an unexpected trip or backward movement of the support surface. Factors associated with a failure to recover balance were one or more of the following: too short a recovery step, slower response time, greater trunk flexion angle at toe-off, greater trunk flexion velocity at recovery foot contact with the ground, and buckling of the recovery limb. In the case of an unexpected trip, there are two basic recovery strategies: a so-called "elevating" strategy and a "lowering" strategy. In the elevating strategy, the swing foot that is obstructed by the obstacle is directly lifted up and over the obstacle and then swung forward as quickly as possible as a (slightly delayed) recovery step. If it should prove difficult to disentangle the foot from the obstacle (thereby obviating use of the elevating strategy), then the subject can switch to a lowering strategy: the swing foot that is impeded by the obstacle is immediately placed onto the ground behind the obstacle to become the stance limb, as the contralateral foot is lifted up and over the obstacle and used for the recovery step. A computer simulation of a simple inverted pendulum model to represent the forward fall of the body following the trip demonstrated that the recovery foot placement must occur before the inclination of the center of mass exceeds a critical angle of from 23 to 26 degrees from the vertical. In modeling studies, a faster response time has been predicted to be more useful than a slower walking speed.

There is evidence for two distinct phases of recovery from a trip in healthy adults: an early response and a later response. In the early response, a powerful stance limb plantarflexion moment and knee extensor and hip extensor moment are used to slow the forward angular momentum (and rotation) of the whole body around the point of obstacle contact, as well as torso flexion about the hip joint. The powerful plantarflexion moment helps to achieve this by orienting the ground reaction force in front of the whole-body center of mass. The resultant slowing of forward angular momentum allows more time for the necessary second part of the response: the powerful hip and knee flexor moment required to swing the recovery limb forward fast enough and far enough to land its foot in front of the onward traveling whole-body center of mass. Finally, as the recovery limb impacts the ground, sufficient resistance must be generated by its knee and hip extensor muscles to resist flexion buckling of the knee as the residual forward angular momentum of the body is attenuated. This resistance to buckling of the knee must come from the resistance of the knee extensor muscles to being forcibly lengthened. In other words, the knee extensor muscles must first be adequately activated, and then there must be sufficient knee extensor muscle mass to generate adequate elastic and viscous resistance to the sudden stretch of the knee extensor muscles. Inadequate activation or inadequate knee extensor muscle mass will mean that the task demands will exceed the capacity of the knee muscles to handle the challenge, the knee will then buckle and its owner will fall as the limb buckles under his/her weight.

Pijnappels and coworkers have shown that despite initial reactions not meaningfully slower, age adversely affects the ability of healthy individuals to generate an adequate stance limb ankle plantarflexor recovery response. This caused an age-related increase in failure to recover from a trip.

We have also studied the effect of age on the ability to recover from a forward fall by rapid step taking. Subjects were released from a forward-leaning position and instructed to regain standing balance by taking a single step forward. Lean angle was successively increased until a subject failed to regain balance as instructed. This task is a time-critical one, likely requiring the use of maximum strengths. The mean maximum lean angle from which older males could recover balance as instructed, 23.9 degrees, was smaller than that for the young males, 32.5 degrees. Corresponding angles for the females were 16.2 and 30.7 degrees, but those numbers do not include five of the 10 older females who could not recover balance from even the smallest lean angle at which they were tested, approximately 13 degrees. Maximum lean angles were well correlated with the average forward step velocity and inversely correlated with the time required to unload the stepping foot, but were unrelated to myoelectric response latencies of approximately 70 milliseconds in both young and older people. A sex difference has been found in torques used for recovery of balance. None of the males needed to use their maximum ankle, knee, or hip torque capacities; but the young females used maximal hip flexion torques, and the older females used maximum plantarflexor, knee flexion, hip flexion, and extension torques. Carty and coworkers showed that the effect of weak hip flexor and knee extensor muscles forced older subjects to take multiple steps rather than a single rapid step to recover their balance at larger lean angles.

The results suggest that reduced abilities of healthy older adults to recover from forward falls result from an inability to generate adequate stance limb torques and sufficiently rapid body-segment movements, rather than from

delayed initiation of response. This means that future interventions should target hip, knee, and ankle muscle strengths and powers in order to help the subject to maintain the agility needed to make sufficiently rapid recovery movements.

Recovery From a Slip

An unexpected slip can be particularly challenging to recover from during gait. Healthy young subjects walking onto a level slippery floor attempt to correct an ongoing slip between 25% and 45% of stance phase (190–350 milliseconds after heel contact). In healthy young adults, the initial response to an unexpected slip is an early flexor synergy (starting at 146 milliseconds) in the muscles of the perturbed limb, presumably serving to limit how far the slipping foot slips; bilateral shoulder muscle activation (143 milliseconds) serving to produce bilateral arm elevation after approximately 288 milliseconds; and rapid protraction of the trailing swing foot onto the ground in order to rapidly enlarge the base of support rearward so as to be able to prevent a backward fall. This slows the acceleration of the whole-body center of mass by employing a flexor synergy in the trailing leg and decelerating the center of mass by using an extensor synergy of the leading leg. The trailing leg is rapidly placed back on the ground in order to provide a larger rearward base of support to decelerate the descending center of mass. Arm elevation movements help to dissipate forward momentum. After the first slip, healthy subjects exposed to successive slipping trials showed very rapid adaptation, with much less arm movement and more muscle cocontraction, often adopting a proactive “surfing” response whereby they slid forward on both feet.

The physical characteristics determining the potential for a slip as well as the required coefficient of friction (ratio of the shear to the normal foot forces) on slippery surfaces have been reviewed. Redfern and coworkers have demonstrated on level floors and descending ramps that healthy subjects make proactive changes in gait (shorter stance phase duration, shorter normalized step lengths, and slower foot strike velocities) when anticipating the possibility for a slip. Properly corrected vision and good lighting can help foster such proactive strategies by older people.

Mechanisms Underlying Age and Sex Differences in Performance of Time-Critical Tasks With High Strength Demands

The source of both age and sex differences in performance of tasks that both are time critical and have high strength requirements appears to lie primarily in strengths and speeds of muscle contraction, rather than in sensory processing or motor planning abilities. As pointed out earlier in this chapter, there are no detectable sex group differences in myoelectric latencies for rapid ankle torque development. There are age-group differences, but the differences in the mean latencies were only approximately 10 to 20 milliseconds, whereas the total times needed to develop near-maximum torques were on the order of 400 to 600 milliseconds. In addition, age-group differences in the use of cocontraction were not responsible for the age-group differences in torque development rates. Furthermore, age-group differences in mean reaction times were only approximately 10 to 20 milliseconds, whereas the total response times ranged approximately from 400 to 800 milliseconds. No substantial sex differences were found in those reaction times. These findings suggests that, among healthy older compared with young adults and among females compared with males, differences in rapid torque development abilities, noted earlier in this chapter, and differences in performance of tasks that are both time critical and have high-strength requirements seem largely because of differences in strengths and speeds of muscle contraction once contraction is initiated, rather than because of delays in initiating contraction.

These studies suggest that healthy older compared with young adults, and healthy older females compared with older males, are more at risk of injury in tasks that both are time critical and have high-strength requirements. Time-critical obstacle avoidance tasks involve rapid visual processing, rapid triggering of preplanned strategies, and rapid execution of movements, during which whole-body balance must be maintained. Among healthy adults, the times needed for the visual processing and response triggering phases are a few hundredths of a second longer for older people than for young. In contrast, the times needed for movement execution are a few tenths of a second longer for older people than for young. Almost exclusively because of these longer movement execution times, the warning times that older compared with younger adults need to perform successfully time-critical tasks with high-strength requirements are a few tenths of a second longer. Although differences of a few tenths of a second in abilities to respond are not usually important, circumstances leading to needs for time-critical, high-strength responses probably combine at random. Sometimes the consequence of needing a few tenths of a second longer to execute avoidance or recovery maneuvers may not be small, and that need, when circumstances combine unfavorably, may substantially lower the probability of regaining balance or avoiding a fall-related injury. The ability to perform these avoidance and recovery maneuvers usually involves stepping, and well-established clinical tests of these time-critical stepping responses do not yet exist. Tests of voluntary maximal distance and high-speed stepping are being evaluated.

CONCLUSION

Research findings to date regarding the biomechanics of mobility among healthy older adults suggest the following:

1. In activities such as ambulation, chair and bed rise, and postural responses to small perturbations, performances of healthy older adults are often remarkably similar to those of the young. Age-group differences among healthy adults that seem biomechanically significant have been found in only certain kinds of tasks.
2. Age differences in performances of many tasks apparently seldom arise from limitations in joint ROM. Only a few physical tasks present substantial joint ROM requirements.
3. Similarly, those performance differences apparently arise only in some circumstances from limitations in joint torque strengths. The strength requirements of many daily tasks, excluding time-critical tasks requiring high strengths and certain kinds of transferring tasks, are modest compared with the available strengths of healthy old adults.
4. There are substantial age and sex differences in abilities to develop joint torques rapidly, but these differences generally seem to be of importance chiefly in performing time-critical tasks requiring high strengths and/or powers.
5. When age differences in responses have been found, those differences appear to seldom depend in major ways on age differences in latencies or reaction times. Under many circumstances, the age differences that do exist in sensing and neural processing times are small compared with total response times.
6. In performing time-critical tasks requiring high strengths, for which major age differences arise, these presumably arise because of age differences in the muscle contraction physiology underlying the biomechanical response execution.
7. Cognitive and other psychological factors, such as risk-taking preferences, have a substantial role in mobility task performance.
8. Age-related declines in mobility function appear during performances of tasks that are physically and/or cognitively very challenging at much younger ages than these appear in tasks that are easily performed.
9. Gait tests performed on an irregular surface appear to discriminate age and disease effects better than gait tests conducted on a flat surface.
10. The advent of miniature inertial measurement units is allowing studies of older adult mobility and falls to be conducted at home and in the community over long periods of time. These should bring valuable new insights into mobility problems of older adults.

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Chapter 115

Exercise: Physiologic and Functional Effects

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Learning Objectives

- Describe the changes in endurance exercise capacity and in skeletal muscle strength and power that occur with aging.
- Describe the effects of aerobic and resistance exercise training on endurance exercise capacity, skeletal muscle strength and power, and physical function in older adults.
- Identify common geriatric disorders for which exercise may be beneficial for prevention or treatment.

Key Clinical Points

1. **The physiologic responses to aerobic and resistance training on endurance exercise capacity and muscle strength and power are preserved in older adults.**
2. **Because the relation between physiologic impairment and functional limitations is nonlinear, older adults with little or no physiologic reserve may realize large functional improvements with exercise.**
3. **Older adults can safely engage in even high-intensity exercise; exercise and physical activity recommendations should be specific and tailored to the individual to enhance long-term adherence.**

AGING, DISUSE, AND DISEASE

A common belief among the lay public, as well as among many health care professionals, is that much of the disease and loss of function that accompanies aging is inevitable and a result of the "aging process" itself. However, much of the physical decline and reduced physiologic reserve previously blamed on aging is, in fact, caused by complex interactions of true genetically determined aging, disease (often subtle or subclinical), disuse, and environmental exposure.

The myriad of possible interrelationships among these factors makes it difficult to ascribe specific causality for the loss of physical vigor or function. Thus, for example, preconceived societal notions about aging may predispose to greatly reduced expectations with regard to physical as well as mental performance. Such preconceptions may promote inactivity and disuse in women at an even earlier age than in men. With years of ensuing inactivity, disuse not only exaggerates and enhances any true age-related loss of endurance, strength, and flexibility, leading to further inactivity and disuse, but may also exacerbate previously subtle or subclinical conditions such as intra-abdominal obesity, glucose intolerance, osteopenia, hypertension, dyslipidemia, and coronary artery disease. These physiologic disorders, the drugs used in their treatments, and the associated functional impairments and disability can, in turn, further limit activity and continue a vicious downhill spiral.

Physical activity level (and measured fitness) appears to be inversely related to the risk of mortality and is associated with a greater average lifespan. An inverse dose–response relationship has also been noted between physical activity and the risk of developing many chronic diseases including cardiovascular disease (CVD), stroke,

hypertension, type 2 diabetes, osteoporosis, obesity, colon and breast cancer, depression, and dementia. Many of these reports included older adults. Despite the clear advantages to physical activity, only 35% of persons more than 60 years of age meet the Centers for Disease Control and Prevention recommendations for physical activity (ie, 150 min/week of moderate-intensity or 75 min/week of vigorous-intensity aerobic activity, and muscle-strengthening activities for 2 or more days/week), and this percentage falls significantly further in older age groups.

This chapter reviews the physiologic effects of aging and exercise training on endurance or maximal aerobic exercise capacity, and on skeletal muscle strength and power. Next, it discusses the theoretical relationship between fitness and functional status, reviewing the available data on the effects of increased activity on functional performance. The chapter also reviews the effects of aging and physical activity on chronic conditions commonly observed in geriatric patients. Last, the risks associated with exercising are discussed, and some suggestions are made with respect to prescribing an exercise program for older individuals.

Although exercise training is associated with many health benefits, it is now abundantly clear that many health benefits can be accrued simply through a more active (nonsedentary) lifestyle in the absence of formal "exercise training." This concept may be especially helpful in trying to encourage older individuals who feel unable or unwilling to engage in formal exercise training, but who can and will increase their physical activity.

SEDENTARY BEHAVIOR AND HEALTH IN OLDER ADULTS

Time spent engaged in sedentary behaviors is associated with markers of CVD, and with increased risk of weight gain, metabolic syndrome, type 2 diabetes, and increased all-cause and CVD mortality. Importantly, these associations remain even after considering the amount of physical activity performed, suggesting that sedentary behavior is an independent risk factor for chronic disease. Although there is no universally accepted definition of sedentary behavior, it is commonly defined as activities that require an energy expenditure of less than or equal to 1.5 times resting energy expenditure, and encompasses activities such as sitting, watching TV, using a computer, reclining, or lying down during waking hours.

The impact of sedentary behavior on older adults is of particular concern, as objective measurements of sedentary time in the National Health and Nutrition Examination Survey indicate that adults aged more than or equal to 60 years spend more time engaged in sedentary behaviors (~8–9 h/day, or 60% of their waking time) than any other segment of the population. Nonetheless, in older adults, sedentary behavior has been associated with increased risk of sarcopenia, and inversely associated with physical function. Sedentary time is also associated with functional limitations in older adults, even in those that achieve the recommended amount of moderate to vigorous physical activity (MVPA). In older women, more time spent in sedentary behavior is associated with lower bone mineral density (BMD) of the femur and hip, independent of time spent in physical activity.

It appears that prolonged periods of sedentary behavior are particularly deleterious, particularly for metabolic health. Longer durations of sedentary time are accompanied by low levels of energy expenditure and muscle activity, leading to reductions in glucose clearance and lipoprotein lipase activity. In younger adults, postprandial glucose and triglyceride concentrations are reduced when intermittent short bouts of activity (5–10 minutes) are performed compared to continuous periods of sitting (6–8 hours). Although similar studies have not yet been performed in older adults, it is reasonable to expect that such an intervention would be as effective or perhaps more effective. In older adults, the number of breaks in sedentary time is associated with higher levels of physical function, independent of MVPA.

Changing sedentary behavior may have an immediate impact on the health of older adults. In one study, older adults who reduced their sedentary time over a 2-year period had a lower risk of all-cause mortality compared to those who either increased or did not change their sedentary time. However, much of the data available on sedentary behavior and health in older adults has been derived from cross-sectional or observational studies. Thus, reverse causality (ie, poor health and/or function causing sedentary behavior, rather than sedentary behavior causing poor health and/or function) cannot be ruled out. Nonetheless, the growing body of evidence demonstrating improvements in CVD risk factors with acute interventions warrants consideration of sedentary behavior and physical activity as distinct behaviors, each an important target for health promotion and disease prevention in older adults. It is also advisable to consider the type of sedentary behavior. For example, in a sample of older Japanese adults, passive sedentary time (TV viewing, talking while sitting, sitting around) was associated with lower levels of MVPA and a higher risk of being overweight, whereas mentally active sedentary time (computer use, reading) was associated with higher levels of MVPA.

Because of their reduced physical capacity and functional reserve, sedentary older adults may prefer performing several short bouts of exercise throughout the day to a single bout of continuous exercise. Indeed, in one study in older adults reductions in objectively measured sedentary time were achieved with a single goal-setting session and a follow-up mailing. However, this intervention was only performed over 1 week, so it is not known if these behavioral changes can be sustained, and if not, whether repeated follow-up would be beneficial. Additionally, the determinants of sedentary behavior in older adults remain unknown. Are older adults more sedentary simply because they are unaware of how long they spend sedentary, and lack an understanding of the dangers of prolonged sitting? Is it related to the increased leisure time available with retirement? Or do factors such as fatigue, joint pain, or decreases in functional reserve and self-efficacy contribute to sedentary behavior? Understanding the social and environmental factors that influence sedentary behavior in older adults, as well as identifying barriers to modifying sedentary behavior, will be important for developing effective and lasting strategies to reduce and interrupt sedentary behavior.

AGING AND EXERCISE

Endurance (Aerobic) Exercise Capacity

Age-associated changes in endurance exercise capacity One of the key physiologic changes that occurs with aging and contributes to the decline in physical function and loss of independence is a decline in endurance exercise capacity. The best physiologic measure of endurance exercise capacity is the amount of oxygen consumed at maximal or peak exercise (maximal or peak aerobic power; VO_{2max} or VO_{2peak}). Longitudinal data acquired in healthy sedentary men and women aged 21 to 87 years over a median follow-up period of 7 years indicate that the longitudinal rate of decline in VO_{2peak} is not linear across the age-span (as suggested in cross-sectional data), but rather accelerates markedly with each successive decade. Although both cross-sectional and longitudinal data show approximately a 5% decline per decade in VO_{2peak} starting at age 30 years, the longitudinal declines in peak VO_2 per decade are two- to threefold larger than the cross-sectional analyses in the same subjects from the 50s onward, and accelerate to more than 20% per decade from the 70s onward (**Figure 115-1**). The rate of decline in VO_2 peak per decade is similar between men and women up until approximately age 40; thereafter the rate of decline steepens more in men than women, independent of changes in physical activity levels and body composition. The reasons for this sex difference remain unclear.

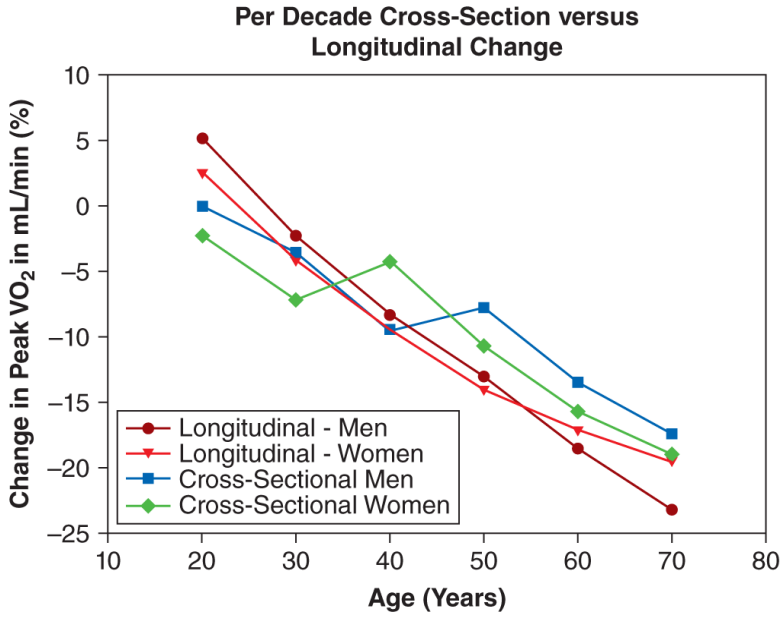


FIGURE 115-1. Per-decade percent cross-sectional and longitudinal changes in peak VO_2 by gender and age decade. (Reproduced with permission from Fleg JL, et al. *Circulation*. 2005;112:677.)

In all age groups, endurance-trained adults have a higher VO_{2max} than their age-matched sedentary peers, suggesting that participation in habitual endurance exercise may attenuate the age-related decline in VO_{2max}. However cross-sectional comparisons of younger and older endurance trained and sedentary adults report that endurance-trained

men and women have a greater absolute (mL/kg/min per decade) rate of decline in VO_{2max} compared to sedentary adults. In contrast, when the rate of decline is expressed as a percent decrease from early adulthood, the age-associated rate of decline in VO_{2max} is similar between older endurance-trained and sedentary men and women. Longitudinal studies of endurance-trained and sedentary women followed for 7 years, and men followed for 10 to 22 years, confirm these observations of a greater absolute rate of decline in VO_{2max} in endurance-trained men and women compared to sedentary controls. The greater rate of decline in endurance-trained individuals appears to be mediated by their higher "initial" baseline values during young adulthood. Reductions in training volume also appear to contribute. When characterized by the volume of exercise training they maintained, endurance-trained men and women demonstrate a decline of 0.3% per year in those who trained vigorously, 2.6% per year in those who trained moderately, and 4.6% per year in the low-training group. Importantly, even in the low-training group, VO_{2max} remained higher at follow-up (33.8 mL/min/kg; age 74 years) than in the sedentary individuals (25.8 mL/min/kg; age 70 years), which may afford protection later in life by allowing them to remain above the threshold of exercise capacity necessary to remain functionally active and independent.

Age-Associated Changes in Central and Peripheral Components of Aerobic Exercise Capacity

The age-associated decline in VO_{2max} can be attributed to alterations in both central (cardiovascular) and peripheral components that are determinants of exercise capacity. Based on the Fick equation, VO_{2max} is equal to the product of maximal heart rate, maximal stroke volume (ie, maximal cardiac output, Q_{max}) and the maximal ability of muscle to extract oxygen from the blood: the arteriovenous (a-v) O_2 difference. It appears that reductions in Q_{max} with advancing age in healthy endurance-trained and sedentary adults are proportionate to the decline in VO_{2max}. This age-related decline in Q_{max} appears to be mediated predominantly by reductions in maximal heart rate, independent of sex and training status. The reduction in maximal heart rate is largely explained by reductions in intrinsic heart rate (ie, heart rate observed in the absence of autonomic nervous system influences), as well as by reduced chronotropic responsiveness to β-adrenergic stimulation. Reductions in maximal heart rate appear to be a consequence of aging, and thus, may not be modifiable. With regard to maximal stroke volume, the data are inconsistent. Some studies report that maximal stroke volume is reduced with aging, whereas others report no change and even increases in maximal stroke volume. The latter is thought to off-set the age-associated reduction in maximal heart rate, to maintain Q_{max}. It is has also been suggested that maximal stroke volume declines with aging up until middle aged, and thereafter ceases to decline. The mechanisms mediating the changes in maximal stroke volume with aging are unclear but may be related to age-related changes in left ventricular filling (preload), vascular compliance (afterload) and/or contractility of the heart (see Chapter 75).

In contrast to Q_{max}, maximal a-v O_2 difference has been shown to consistently decline with advancing age. The rate of decline in maximal a-v O_2 difference is greater in men than women, but is similar between sedentary and endurance-trained people (~ 5–10% over 30 years). The decline in maximal a-v O_2 difference in sedentary adults has been attributed to reductions in oxygen extraction by the active muscles due in part to reduced capillary density and mitochondrial enzyme activities. However, because capillary density and mitochondrial enzyme activities are similar between young and old endurance-trained people, oxygen extraction does not appear to be a contributing factor for the age-associated decline in maximal a-v O_2 difference. Rather, it is more likely that maximal oxygen delivery contributes substantially to the age-associated reduction in maximal a-v O_2 difference in endurance-trained adults. Another factor that could be contributing to the decline in maximal a-v O_2 difference with aging is body composition changes, specifically reductions in muscle mass. Aging is associated with increases in fat mass and decreases in fat-free mass (FFM) or lean body mass (LBM). Furthermore, with aging, muscle mass comprises a lesser percentage of what is usually measured as FFM. In a cross-sectional study of very healthy men and women, muscle mass, as reflected by 24-hour creatinine excretion, was found to decline 23% between ages 30 and 70 years. When VO_{2max} was normalized for this reduction in muscle mass, the slope of the decline in VO_{2max} with age was attenuated. The predicted age-related decline in VO_{2max} between the ages of 30 and 70 years was reduced in both men (39% vs 18%) and women (30% vs 14%). Thus, approximately half of the original age-related decline in VO_{2max} could be explained by the age-associated loss of muscle mass.

Endurance Exercise Training Effects on Physiologic Function

Effects on VO_{2max} As discussed in the previous section, even though VO_{2max} declines with aging in endurance-trained individuals, master athletes can still maintain a high level of endurance exercise capacity into old age. The fitness response to an endurance exercise training program in previously sedentary, healthy older adults is comparable

to that observed in younger subjects. The magnitude of improvement in VO_{2max} has been reported to be between 6% and 30% depending on the type of exercise and the duration of the exercise program employed, with similar adaptations between men and women. Significant improvements in VO_{2max} can be observed in as little as 3 weeks, and can continue to improve with incremental exercise training. Moreover, when young and older subjects are trained at the same relative intensity, the relative increments in VO_{2max} are similar. Thus, implementing endurance exercise training programs even in older adults can be done safely and can improve overall physiologic function.

What is the optimal dose of endurance exercise needed to improve aerobic exercise capacity in older adults? In general, higher intensity exercise training programs elicit greater improvements in Vo_{2max}. Healthy older individuals can tolerate endurance training with acceptable attrition rates and rare, if any, significant injuries even at relatively high intensity levels (eg, 85% of heart rate reserve; HRR = 0.85) where HRR = (HR max – HR rest)/HR rest. However, few older individuals choose to maintain such a strenuous training intensity on their own. It appears that cardiovascular improvement can be obtained with low-to moderate-intensity programs, where subjects train at approximately 50% of HRR. Importantly, some studies have reported no differences in the magnitude of improvement in VO_{2max} between lower and higher intensity training programs, or between continuous versus intermittent exercise training when the total amount of work performed (ie, total energy expenditure) is the same. Thus, safe and effective exercise training programs involving low-to-moderate intensity exercise and/or multiple short (10 minute) bouts can be prescribed to achieve a certain level of total energy expenditure that will improve aerobic exercise capacity in older adults.

Circuit training has been used to target improvements in both endurance exercise capacity and muscular strength. Circuit training involves performing various resistance and cardiovascular exercises (8–15) in a “circuit” with minimal rest periods (< 30 seconds) between each exercise. Each exercise typically targets different muscle groups and is performed in 12 to 15 repetitions, at 40% to 60% of one repetition maximum (1RM). The circuit is completed 1 to 3 times. Circuit training programs with 8 to 12 exercises at intensities of 40% to 60% 1RM, 3 days/week for 12 to 24 weeks can increase VO_{2max} by 15% to 19% in older adults.

Effects on central and peripheral components The increase in VO_{2max} in response to endurance exercise training is mediated by both central and peripheral adaptations. The involvement of each component in the adaptive response of VO_{2max} is different between older and young adults, and between older men and women. For example, in older men, the incremental improvements in VO_{2max} are primarily (~2/3) mediated by central adaptations, specifically increases in Q_{max}, and approximately 1/3 from peripheral adaptations (widened a-v O_2 difference). The central and peripheral adaptations occur within 3 weeks and continue to improve throughout the training program. In contrast, in young men early improvements in VO_{2max} are largely driven by a widened maximal a-v O_2 difference, after which further improvements with continued exercise training are driven by increases in Q_{max}. In young women, improvements in VO_{2max} with endurance exercise training are associated with improvements in Q_{max}; however, in older women the improvements in VO_{2max} are attributed solely to a greater maximal a-v O_2 difference as Q_{max} remains unchanged with exercise training. The reasons for this sex difference are unclear, but raise the question of whether estrogens are important for exercise training cardiac performance adaptations in women, as has been observed for vascular adaptations. The role that estrogens play in cardiovascular adaptations to exercise, therefore, remains uncertain.

In both older and young individuals, maximal heart rate does not change in response to endurance exercise training programs; thus, the increase in Q_{max} in men and young women are explained primarily by increases in maximal stroke volume. The improvements in maximal stroke volume with endurance exercise training are attributed to enhance left ventricular filling and/or left ventricular contractility. The latter may be related to training-induced increases in left ventricular mass, and or improved β-adrenergic sensitivity. A vigorous exercise training program improved left ventricular systolic and diastolic function in older men. There is some evidence for a sex- and age-specific difference in the left ventricular response to endurance training, with an improvement in diastolic function demonstrated in young and older men and possibly only in young women. Peripheral adaptations with exercise training are attributed to increased capillarization and mitochondrial enzymatic activity, augmented type IIa muscle fibers, and improved microvascular blood flow. The improvement in VO_{2max} with resistance training is attributed to improved oxygen transport and utilization due to increases in capillary density per muscle fiber and mitochondrial enzyme oxidative capacity of the muscle.

SKELETAL MUSCLE STRENGTH AND POWER

Skeletal muscle strength is defined as the maximum force exerted by a muscle, and power is the rate of force development by the muscle. Strength and power are determined by muscle mass and also by neurologic function. As noted above and in Chapter 113, aging is associated with a significant loss in skeletal muscle mass, and consequently in muscle strength and power. Importantly, strength and power can be increased by improving muscular function (eg, muscle cell hypertrophy) or by improving neurologic function (eg, learning).

Strength assessment depends on the conditions of measurement, specifically the speed of muscular contraction, whether the muscle is shortening (concentric) or lengthening (eccentric) during the contraction, and the conditions of mechanical leverage. Muscle strength can be measured during isometric, isotonic, or isokinetic contractile activity. Isometric strength is the force generated against a fixed object, and isotonic strength is the force generated against a moving object (ie, free weights and most resistance-exercise machines). Isokinetic strength also involves generating force against a moving object but in this case, the speed of movement is controlled and constant. Muscle power can be determined simultaneously with the assessment of either isotonic or isokinetic strength by measuring the speed of movement.

Age-Associated Changes in Muscle Strength and Power

Aging is associated with a loss of skeletal muscle strength and power in both men and women, independent of physical activity status (some have termed this dynapenia). The loss of muscle strength and power is associated with both mortality and physical disability in older adults. Peak strength is reached around the age of 40 years. Thereafter, muscle strength declines such that by age 80, strength is approximately 30% to 40% of peak. However, similar to endurance exercise capacity, the true rate of decline may be underestimated by cross-sectional data. For example, a longitudinal study estimated a 60% loss of handgrip strength between 30 and 80 years of age, whereas cross-sectional analysis of the same cohort estimated the loss at only 40%. Longitudinal studies also show that the loss in muscle strength is more rapid at older ages, as indicated by a decline in quadriceps strength of approximately 10% to 25% within 5 to 7 years in 70-year-old adults.

Although the majority of these studies did not measure muscle power, the rate of decline in muscle power appears to be even greater than the decline in strength. Measurements of muscle strength and power for more than 10 years in the Baltimore Longitudinal Study on Aging indicated that the decline in muscle power was approximately 10% greater than the decline in strength. This may be clinically important because the decline in muscle power is a stronger determinant of physical function in old age than muscle strength. Leg muscle power was reduced in older women prone to falling, as compared with nonfallers, and was a stronger predictor of self-reported functional status in older women than strength. These findings suggest that intervention strategies should be aimed not only at preserving muscle strength with aging, but also muscle power.

To prescribe appropriate intervention strategies, one needs to understand the potential mechanisms underlying the decline in muscle strength and power in older adults. The evidence that muscle mass decreases with aging is unequivocal, and originally it was thought that the loss of muscle mass was the primary determinant of the decline in muscle strength in older adults. However, other factors (ie, muscle quality) independent of muscle mass may be just as, or more important in the loss of muscle strength and power in older adults. The Health, Aging and Body Composition (ABC) Study measured strength and muscle mass over a 3-year follow-up period. Although the loss of muscle mass was associated with the decline in muscle strength in older adults in Health ABC, the decline in muscle strength was more rapid (3 times greater) than the parallel rate of decline in muscle mass. Muscle strength declined approximately 3.6% in men and 2.8% in women, whereas the decline in leg muscle mass was approximately 1% per year. Moreover, maintaining or increasing muscle mass did not prevent the age-related decline in muscle strength. Other factors that contribute to the decline in muscle strength and power in older adults include age-related changes in muscle fiber type/size, neural innervation, motor unit recruitment and intermuscular coordination, and muscle quality.

The concept of “muscle quality” has been used to describe the relation between muscle strength/power and muscle mass (ie, muscle strength/power relative to muscle size). In general, muscle quality declines at a rate of approximately 2.5% per year, whereas muscle cross-sectional area declines at a rate of approximately 1% per year. Although there is no general consensus regarding the factors that determine muscle quality or how it should be measured, “muscle quality” may encompass many factors including structural composition, innervation, contractility, capillary density, fatigability, intramuscular fat content, protein metabolism, mitochondrial function, oxidative damage, and glucose metabolism. There is an age-related deterioration in most of these factors that are thought to influence muscle quality. However, whether these are inevitable consequences of aging is not clear, as almost all respond favorably to increased physical activity.

Physical Inactivity Versus Aging

Are the age-related changes in muscle strength and power immutable, or are they attributable to a sedentary, low physical activity lifestyle? Bed rest studies demonstrate a rapid, dramatic loss of strength—estimated as high as 1% to 5% per day. Prolonged unweighting using unilateral lower limb suspension is also associated with significant losses in strength and muscle characteristics (eg, size, neural function). Regular physical activity may prevent or attenuate some of the age-related loss in strength. A cross-sectional study of workers at a machine shop showed no decline in grip strength between the ages of 20 and 60 years. In master athletes who maintain a high level of fitness and compete in his or her sporting event, age-associated muscle atrophy, weakness and fatigability can be slowed, but are not entirely prevented. Importantly, vigorous strengthening exercise (discussed below) can produce substantial gains in strength in older adults.

Resistance Training Effects on Skeletal Muscle Strength and Power

Resistance (strength) training can be done in several ways, but there is no consensus on a "best" approach. In general, resistance training programs involve performing a certain number of sets (usually one to three) of several exercises targeting different muscle groups, with a specific number of repetitions in each set. The number of repetitions that are performed depends on the relative intensity of each repetition, which is usually based on the maximal weight that the subject can lift one time (the one-repetition maximum or 1RM). Once an individual can complete the prescribed number of repetitions in each set, a new prescription is written, based on a newly determined (higher) 1RM. Because the neuromuscular adaptations with resistance training can impact older individuals' ability to perform activities of daily life more independently and safely, resistance training is recommended for all older adults. Current recommendations from the American College of Sports Medicine and the American Heart Association suggest that older adults perform 8 to 12 repetitions (moderate to vigorous intensity) of 8 to 10 strengthening activities involving the major muscle groups at least 2 nonconsecutive days per week.

Muscle strength Large positive effects on muscle strength have been consistently demonstrated in trials of resistance training in older adults, although the variability among studies is large. Strength training can also be done safely and effectively in frail, very old adults. One study randomized 40 nonagenarian nursing home residents to thrice weekly 45 to 50 minute resistance exercise training sessions or usual care (mobility exercise) for 8 weeks. Resistance exercises included leg press, biceps curls, arm extension, arm side lifts, shoulder elevations, seated bench press, and calf raises. Intensity started at 30% of 1RM and progressed to 70%. Leg press strength improved on average 17% with resistance training while controls tended to lose strength. Over a 4-week detraining period, these gains were diminished, but still 9% higher than baseline. Several meta-analyses have reported a dose response with higher intensity training associated with greater improvements in strength. With respect to volume and frequency of resistance training, performing 1 to 3 sets of each exercise is sufficient to increase strength, and training appears most effective at increasing strength when performed 2 to 3 times per week.

Power As noted, muscle power may be a more important determinant of function in older adults than strength. While increases in power can be achieved with traditional progressive resistance training (ie, progressive increase in intensity to moderate to high levels), exercises done at a lower intensity (40%–60% of 1RM) but at a high velocity (resulting in explosive concentric contractions) produce greater increases in power. This type of exercise, termed power training, may be more effective at improving functional end points than traditional resistance training. One study in older (mean age 78 years), mobility-impaired adults compared power training at either a low (40% of 1RM) or high (70% of 1 RM) resistance. After 16 weeks, both groups had similar improvements in muscle power (26%–42%) and clinically significant improvements in function as measured by the Short Physical Performance Battery. Of note, the low-resistance exercise was associated with lower rates of perceived exertion and lower workloads, which may be more appealing for frail, older people. Importantly, in a *supervised* setting and with careful pre-exercise medical screening, adverse event rates have been comparable to that of traditional strength training regimes.

Physiologic Mechanisms Explaining Gains in Strength With Exercise

Resistance exercise results in muscle hypertrophy, and older adults appear to achieve increases in muscle fiber size and cross-sectional area that are comparable to those in younger adults. The degree of muscle hypertrophy is similar with both traditional strength training and high-velocity power training. One study of resistance training in older adults found increases in both type 1 and type 2 muscle fibers (~60% and ~70%, respectively) after 30 weeks. There may be

gender differences in responses; in one study comparing the effects of 9 weeks of heavy resistance strength training among younger and older men and women, younger and older individuals achieved comparable increases in muscle volume, but men in both groups had greater increases than women. During a subsequent detraining period, men lost more muscle volume than women.

Even modest increases in muscle fiber size or cross-sectional area are accompanied by much greater increases in strength, suggesting involvement of other mechanisms. In addition to learning effects from improvements in motor skill coordination, a number of neural adaptations have been proposed to account for the increases in strength observed with resistance training. One is voluntary muscle activation, reflecting recruitment, firing, and synchronization of motor units. A meta-analysis found that exercise-induced increases in voluntary activation of knee extensors and plantar flexors were related to increases in lower-extremity strength in older adults, with the largest gains tending to occur in individuals with the lowest levels of activation at baseline.

Another potential mechanism underlying the significant gains in strength with resistance training is better coordination of synergistic and antagonist muscle cocontraction. Increased coactivation of antagonist muscles, observed in older adults, may promote joint stabilization and thus protect against postural instability, but excessive activation of antagonist muscles can decrease the force generated by the agonist muscle. However, better coordination of synergistic and antagonist muscle cocontraction has not yet been convincingly demonstrated during resistance training in older adults.

Exercise, Physical Activity, and Functional Limitations

The question of whether regular physical activity can prevent and/or reverse functional limitations and disability in older adults is of great public health importance. In discussing this question, we adopt the terminology and framework of the Nagi model of disablement (**Figure 115-2**). In this model, etiologic factors (risk factors) include genetic, behavioral, and environmental factors. The effects of these factors on the disabling process can be measured at four distinct levels:

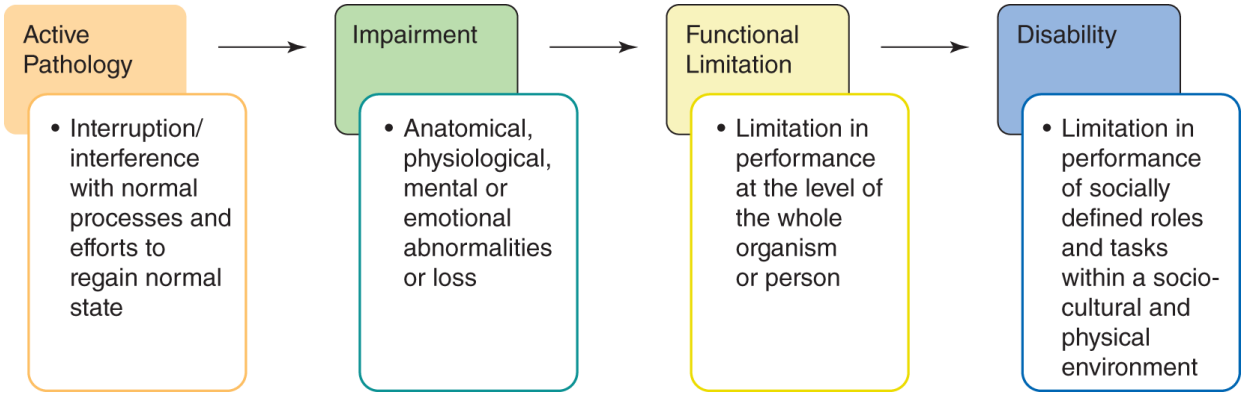


FIGURE 115-2. The Nagi model of disablement. (Reproduced with permission from Jette AM, et al. *Med Care*. 1997; 35:JS30.)

1. Measurements of disease or pathology are made at the cell and tissue level.
2. Measurements of physiologic impairment (eg, muscle strength and VO_{2max}) are made at the organ and organ system level.
3. Measurements of functional limitations are made at the behavioral, whole organism level. Measures of functional limitations range from assessing simple movements (eg, pushing with the foot) to more complicated movements (eg, ability to walk as measured by gait speed) and to sequences of movement (eg, ability to stand, walk, turn, and sit down).
4. Measurements of disability are made at the level of the interaction of the whole organism with the physical and social environment. For example, a person using a wheelchair has disabilities if stairs are the only means of getting inside and does not have disabilities if there is a ramp.

In this framework, risk factors cause disease, which causes physiologic impairment, which causes functional limitations, which causes disability. The model also includes the possibility of feedback loops and more complicated causal pathways.

The discussion also makes a distinction between physical activity and exercise. Physical activity can be defined as any movement of the body produced by skeletal muscles that causes energy expenditure. Exercise is a subset of physical activity and can be defined as planned, structured, and repetitive body movement done specifically to improve fitness.

Evidence That Exercise Improves Functional Limitations

It is intuitive that adults who remain physically active are less likely to experience problems in performing activities of daily life, such as climbing stairs, walking, gardening, and housework. In the framework of the Nagi model, physical inactivity (risk factor) causes muscle weakness, low VO_{2max} and other physiologic impairments, which then cause functional limitations.

This intuition regarding the importance of physical activity in helping to maintain activities of daily life is supported by a number of important epidemiological studies. For example, in the Established Populations for Epidemiologic Studies of the older people, older adults who were physically active at the baseline examination were less likely to experience mobility impairments during several years of follow-up. But the crucial issue is whether increasing physical activity levels in normally inactive older adults achieves the same health benefits found in naturally active older adults. While there is consensus that exercise improves functional limitations in older adults, not all well-designed randomized trials have shown a beneficial effect of exercise. One study of adults aged more than 75 years that compared resistance and balance training found that balance training, but not resistance training, improved functional balance tasks. Another study that compared strength, aerobic, and combined training found no effects of exercise on functional limitations. In a study of adults aged 68 to 85 years, walking exercise improved gait speed and physical health (Short Form-36 Health Survey), while aerobic movement and cycling exercises did not. In a study of older adults with knee osteoarthritis, both aerobic and strengthening exercise caused similar, modest improvements in functional limitations for more than 18 months. Also, few studies have assessed whether regular physical activity (as opposed to exercise) affects functional limitations. This is important, as most adults who are sufficiently active according to public health guidelines do not also participate in regular, structured exercise programs. Finally, most intervention studies have used laboratory measures of physical function. However, how changes in these laboratory measures translate into behavior, that is, what older people are really doing in their daily lives is unknown. Improvements in function, particularly lower extremity function, are associated with changes in objectively measured physical activity. However, the impact of improving function on sedentary behavior and other activities performed in community-dwelling older adults is largely unknown.

It is plausible that the effects of exercise on functional limitations will differ according to (1) type, frequency, duration, and intensity of exercise; (2) the functional limitations of interest; (3) the method of measuring limitations; and (4) the target population. In particular, the effects of exercise on functional limitations should differ by target population because of a complicated, nonlinear relationship between physiologic impairment and functional limitation.

As noted above, high-velocity training (power training) results in greater functional improvements than low-velocity strength training in older adults. End points have included comprehensive performance-based functional assessment tests as well as tests of functional fitness. Power training also improves balance and slows contraction velocity at baseline, leading to balance improvement following the intervention.

Nonlinear Relationship Between Physiologic Impairment and Functional Limitation

Nonlinear relationships and thresholds are implicit in the Nagi model. Healthy humans have excess physiologic capacity not tapped during most daily activities and can thus lose a fair amount of physiologic reserve before functional limitations occur. Indeed, the relationship between leg strength and walking speed is nonlinear. This nonlinear relationship is actually intuitive. After all, if strength was linearly related to walking speed, highly trained weight lifters would walk ridiculously fast (16–30 km/h) because they are several times as strong as normal adults, who walk at around 5 to 8 km/h. That is, above a certain threshold level of adequate physiologic reserve, function is normal; below the threshold, function is impaired (**Figure 115-3**). The exact shape of the curve depends on the task and the physiologic capacity of interest. The figure may oversimplify the situation because most tasks have multiple physiologic determinants that may interact to affect behavioral ability.

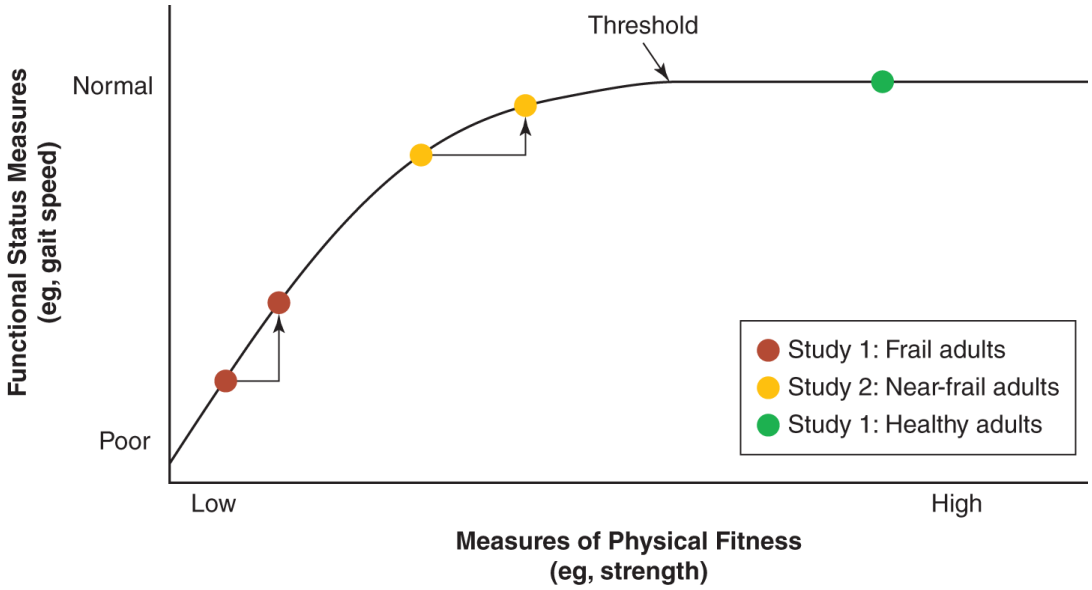


FIGURE 115-3. Theoretical relationship between physical fitness and functional status. The curvilinear relationship shows a threshold effect: above the threshold level of fitness, functional status is normal; below it, function is impaired. A curvilinear relationship implies that the benefit from exercise depends on the target group. Three hypothetical exercise studies are shown. Each study produces the same absolute improvement in fitness. In the frail adults of study 1, exercise produces a large improvement in functional status. In the healthy adults of study 3, no benefit is seen. Study 2 shows intermediate benefits. (Data from Buchner DM, et al. Evidence for a non-linear relationship between leg strength and gait speed. *Age Ageing*. 1996;25:386.)

To illustrate the concept of thresholds, consider that in steady-state measures of oxygen consumption, walking on a level grade at 5 km/h requires 3.2 METs (1 MET = 3.5 mL O_2/kg/min). With illness or inactivity, aerobic capacity falls below the level required for daily tasks. Because exercise can increase aerobic capacity, it should improve functional status when aerobic capacity is below the threshold needed for normal daily function. However, aerobic exercise would not affect ability to walk at 5 km/h in adults whose aerobic capacity already greatly exceeds 3.2 METs.

The implication of this model is that the effect of exercise on functional limitations depends on the target group. In frail adults with little or no physiologic reserve, exercise theoretically produces a large improvement in function. In general, well-designed studies of exercise in frail adults report improvements in functional limitations with exercise. A randomized trial of 3 months of weight lifting in frail, very old nursing home residents found improvements in gait velocity and stair climbing. Even a 3-month supervised low-intensity exercise program produced a small improvement in physical performance in a group of frail older adults when compared to home-based flexibility training. Similarly, a 3-month task-specific resistance training program improved both the ability and the speed of bed and chair rises in a group of older patients living in a congregate care setting. A large study of frail older adults (70–89 years), the Lifestyle Interventions and Independence for Elders (LIFE), demonstrated that a structured moderate-intensity physical activity intervention reduced these vulnerable adults' risk of mobility disability. The LIFE intervention was a structured, moderate-intensity physical activity program (including aerobic, resistance and flexibility training, ~150 min/week) which was compared to a control health education program. During 2.6 years of follow-up, the odds of incident mobility disability, defined as the inability to walk 400 m in less than 15 minutes, and persistent mobility disability were reduced in the structured exercise group by approximately 20% to 30%. The greatest risk reduction (HR = 0.75) was observed in older adults with lower physical function at baseline, compared to those with moderate functional impairments at baseline (HR = 0.95).

The presence of comorbidities exacerbates the declines in physical function that occur with aging. For example, older adults with type 2 diabetes have an increased risk of disability and impairments in physical function, and the risk is increased further with obesity. Exercise and weight loss may have substantial effects on physical function in older adults with type 2 diabetes. In a secondary analysis from results of the Look AHEAD (Action for Health in Diabetes) study, a large multicenter trial examining the effects of intensive lifestyle intervention (ILI) on cardiovascular events in type 2 diabetes, older adults (> 58 years old), had greater improvements in physical function (as measured by the physical function subscale of the Short Form-36) compared to their younger counterparts. Moreover, the decline in function over 8 years was lower in older adults receiving the ILI compared to older adults randomized to a control group (diabetes and support education). However, in this trial the ILI was comprised of a program designed to both increase physical activity (to 175 minutes of moderate-intensity physical activity) and induce weight loss (target 7%)

via caloric restriction. Thus, it is unclear if the improvements in function were due to weight loss, increased physical activity, or the combination. However, another study of frail older, obese adults (without diabetes) demonstrated that both weight loss and exercise (without weight loss) improved self-reported functional status (4%–5%) and measured physical function (12%–15%). Importantly, the combination of weight loss and exercise provided greater improvements in both of these outcomes (10% and 20%, respectively) than either intervention alone.

In contrast, exercise would be expected to have much smaller effects on functional limitations in healthy older adults, at least in basic activities of daily life. Indeed, well-designed studies that did not detect an effect of exercise training on functional limitations generally enrolled relatively healthy older adults. It follows that if exercise has effects on functional limitations in healthy adults, effects will mainly occur with more difficult tasks, and a sensitive measurement tool may be required to ascertain the effects. One randomized trial of general exercise in healthy older adults suggests that this conclusion is true. The measurement used, the Continuous-Scale Physical Functional Performance Test, is sensitive to changes in functional limitations over a range of difficult tasks. In this study, there was an improvement in function noted in generally healthy older individuals following mixed endurance and strength exercise training.

EXERCISE AND COMMON GERIATRIC DISORDERS

Cardiovascular Diseases

Although the mortality rates attributable to cardiovascular diseases (CVD) have declined, the burden from CVD remains elevated, particularly in older adults. There is a consistent, independent inverse relationship between aerobic fitness and physical activity levels and reduced risk for CVD and all-cause mortality. Expending more than 1000 kcal per week in physical activity assessed as blocks walked, flights climbed and participation in sports or recreational activities was associated with a 20% reduction in the risk for coronary heart disease (CHD) in middle-aged and older men participating in the Harvard Alumni Study. Importantly, among men with several CHD risk factors, those expending 1000 kcal/week had a lower CHD risk compared to those expending less than 1000 kcal/week. Moreover, accumulating the physical activity either in shorter bouts or in one longer continuous session of physical activity appeared to be equally effective for reducing CHD risk, as long as the total energy expended was similar. Even low-to-moderate intensity physical activity can reduce risk for CVD and all-cause mortality, with no additional protection from participating in more vigorous activities. Although most of the observational studies assessing the protection of activity against CVD and overall mortality have been completed in male populations, similar observations have now been reported in women. A 7-year follow-up of more than 40,000 postmenopausal women (ages 55–69 years at baseline) reported that regular physical activity was associated with reduced relative risk of death (0.77) compared to those who reported no regular physical activity. A dose-response effect was reported for increasing frequency of moderate activity and reduced CVD risk, but moderate activity as little as once per week was also protective. Similar to physical activity, fitness has been reported as being at least as good a predictor of both overall and CVD-related death as blood pressure, obesity, smoking, or diabetes. In a 20-year prospective follow-up study of older male veterans, impaired aerobic exercise capacity was inversely related to all-cause mortality. Moreover, unfit veterans who improved their fitness status had a 35% lower mortality risk than those who remained unfit. All of the above studies involved endurance exercise; the association between CVD or all-cause mortality and strength training is still unexplored.

Because of the reported benefit of increasing physical activity and fitness levels on CVD risk, exercise training in older adults with CVD is typically prescribed as part of a comprehensive cardiac rehabilitation program to increase aerobic capacity, improve CVD risk factors, prevent disease progression, and reduce the risk for future cardiovascular events and death. A meta-analysis involving 8440 patients with coronary artery disease (CAD) reported reductions in CVD and total mortality risk of 31% and 27%, respectively, as a result of exercise training interventions. In a randomized controlled trial comparing 1 year of exercise training (20 min/day, cycle ergometer) with percutaneous coronary intervention (PCI), those individuals randomized to exercise training improved their aerobic capacity and had a higher event free survival than those receiving PCI. The greater survival was attributed to reduced repeat revascularization and hospitalization.

Exercise training is also beneficial in improving exercise tolerance and improving quality of life in other CVD patient populations including heart failure and peripheral arterial disease (PAD). The Exercise Training Meta-Analysis of Trials in Patients with Chronic Heart Failure (ExTraMATCH) Study concluded that supervised aerobic exercise

training reduced mortality (35%) and hospital readmission (28%) compared to control. In contrast, in the prospective endurance exercise training HF-ACTION trial no reduction in all-cause mortality or hospitalization was detected. However, the lack of statistical significance in mortality was attributed to poor compliance to the prescribed exercise program. A subsequent meta-analysis reported a dose-response between exercise training intensity (MET-h per week) and reduced all-cause and CVD mortality or hospitalization.

With regards to PAD, one prospective study found that patients who were limited by intermittent claudication who participated in any physical activity greater than light intensity at baseline had a lower mortality than those who were sedentary and who performed either no physical activity or only light-intensity activities. In general, walking is the exercise of choice for older adults with PAD and is effective in improving the absolute claudication distance (ACD). Most exercise training studies in PAD have used walking claudication pain—either onset of pain, or mild to moderate or maximal level tolerable—for prescribing exercise intensity. Other modes of exercise including cycle ergometer, stairclimbing, arm cranking, and resistance exercise also improve ACD from 33% to 151% in various studies. However, the data are insufficient, particularly with regard to resistance training, to make any clinical recommendations. Thus, there is a need for further definitive, large clinical trials of alternative or complementary exercise interventions and guidelines for PAD.

Exercise training programs in CVD patients have numerous physiologic effects on the cardiovascular system and CVD risk factors. Improvements in VO_{2max} of 15% to 25% are driven by either central and/or peripheral adaptations, depending on the population. One year of intense exercise training 60 minutes a day at 70% to 90% VO_{2max}, 5 days/week improved myocardial oxygenation, enhanced left ventricular function, and improved glucose and insulin sensitivity in stable coronary artery disease (CAD) patients. Importantly, these exercise training effects were maintained 6 years later. Similarly, patients with CAD who underwent a 1-year exercise training program demonstrated improvements in left ventricular systolic reserve and ventricular-vascular coupling. However, only those patients who had normal left ventricular function to begin with demonstrated cardiac adaptations. Those patients with depressed left ventricular function demonstrated no cardiac adaptations and had more cardiac events 7 years later. Similarly in heart failure patients with left ventricular diastolic dysfunction, exercise training improves VO_{2max} without changes in left ventricular systolic or diastolic function or Q_{max}. Rather, the improvements in VO_{2max} are largely attributed to improvements in maximal a-v O_2 difference due to improved mitochondrial oxidative enzymatic capacity.

Besides improving multiple CVD risk factors, exercise training programs in CVD patients also benefit vascular endothelial function which is important for overall vascular homeostasis. The vascular endothelium plays a key role in the maintenance of vascular health, through the production of factors that regulate vascular tone, inflammation, cellular adhesion, coagulation, and smooth muscle cell proliferation. The loss of normal endothelial function is thought to contribute to the initiation and progression of atherosclerotic disease and future clinical manifestations and events. Endothelial dysfunction is characterized by reduced endothelial-dependent vasodilation due to reduced nitric oxide (NO) bioavailability and is a hallmark of aging and CVD. Indeed reduced endothelial-dependent vasodilation is a significant predictor of cardiovascular events. In general, aerobic exercise training programs improve endothelial vasodilatory function in older adults independent of disease state. However, there are noted sex differences between the magnitude of improvement with exercise training:near restoration of endothelial function to youthful levels in healthy older men, but attenuated or minimal improvements in estrogen-deficient postmenopausal women. The effects of aerobic exercise training on endothelial function in patients with CVD have been tested mostly in men. For example, 4 weeks of supervised aerobic exercise training (3 times daily for 10 minutes on rowing ergometer and 3 times daily for 10 minutes on bicycle ergometer) in men with stable CAD resulted in improvements in endothelial-dependent vasodilation in epicardial coronary vessels and in the left internal mammary artery compared to inactive controls. The improvements in endothelial function with exercise training were attributed to an increase in NO bioavailability due to a decrease in reactive oxygen species, which can inactivate NO. Exercise training also increased circulating bone marrow derived endothelial progenitor cells (EPC) and improved EPC function. EPCs facilitate vascular repair and vasculogenesis, and are reduced in CVD patients. Other potential mechanisms of exercise training on CVD could be related to regression of coronary artery stenosis and formation of collateral vessels, resulting in enhanced myocardial perfusion.

Although exercise training is beneficial overall for CVD patients, there are a few conditions in which exercise may not be as beneficial and actually contraindicated. These conditions include unstable angina, uncontrolled hypertension, uncontrolled cardiac arrhythmias, recent myocardial infarction, severe aortic stenosis and other valvular diseases, acute pericarditis and decompensated heart failure.

Hypertension

As described in Chapter 82, the prevalence of hypertension increases with advancing age in both men and women. More than 80% of adults greater than or equal to 60 years of age with hypertension are treated with antihypertensive therapies; more than 30% of adults greater than or equal to 80 years are taking three or more classes of antihypertensive medications. Although antihypertensive medications produce long-term benefit, these medications have numerous side-effects, especially in older patients. Thus, using nonpharmacologic treatments (eg, weight loss, low-sodium diet, and exercise), is appealing, especially in older adults with mild-to-moderate hypertension.

There is an independent, inverse, graded association for both leisure-time activity and aerobic exercise capacity (ie, VO_{2max}) and risk for hypertension, with the lowest risk for hypertension in the most active and fit groups. In one population-based study of nearly 3000 middle-aged men and women, the relative risk of developing hypertension during the 10-year follow-up period was 1.7 in the least active group compared to the most active group of men. A quantitatively similar trend was noted for women. A 25-year prospective study of men born in Malmo, Sweden, in 1914, found that hypertensive men who regularly exercised vigorously had an adjusted relative risk of 0.43 for total mortality and 0.33 for cardiovascular mortality. Given the apparent benefits of increased physical activity on endurance exercise capacity and reduced hypertension risk, the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) recommends increased physical activity designed to enhance aerobic exercise capacity as initial therapy to prevent, treat, and control hypertension.

Endurance exercise training programs effectively lower blood pressure in older adults with mild to moderate hypertension. The consensus of several meta-analyses is that endurance exercise training programs or increasing physical activity of moderate intensity and of adequate volume result in a 4 to 10 mm Hg decline in systolic blood pressure and a 3 to 8 mm Hg decline in diastolic blood pressure in individuals with stage 1 hypertension, regardless of age or sex. The effects of endurance exercise training in older adults with stage 2 hypertension, or those with resistant hypertension are less clear. One study reported a decrease in blood pressure in male veterans with stage 2 hypertension after 16 weeks of moderate-intensity exercise training. A more pronounced effect was observed after 32 weeks of exercise, even with a 33% reduction in antihypertensive medications. In contrast, individuals randomized to the nonexercise control group had substantial increases in blood pressure. In resistant hypertension, moderate-intensity exercise training reduced 24-hour ambulatory blood pressure similarly to that reported for mild to moderate hypertensives. Although there are limited data comparing different exercise intensities, low- to moderate-intensity exercise may be more effective at lowering blood pressure than more vigorous exercise. Indeed, even light Tai Chi exercise or increasing daily walking can reduce and even normalize blood pressure in sedentary older hypertensive patients.

There is limited and inconsistent data on the effect of strength training on blood pressure in older hypertensive adults. Excessive blood pressure elevations can occur during high-intensity resistance training, especially if associated with Valsalva. However, with low- to moderate-intensity strength training and proper breathing techniques, this is not a concern. Meta-analyses of randomized controlled trials of progressive resistance training effects on resting blood pressure revealed a 3 mm Hg decrease in both systolic and diastolic blood pressure. However, when the data are broken down by age group ($\leq$ 50 years and $>$ 50 years) and blood pressure status (normotensive, borderline-hypertensive, and hypertensive), the effect of resistance training on systolic blood pressure in adults older than 50 years and on systolic and diastolic blood pressures in hypertensives are diminished and are not significant. Given the small number of studies available in hypertensive older adults, additional research is warranted to provide recommendations on the effect of resistance training for blood pressure reduction in hypertensive older adults.

The mechanisms underlying the blood pressure lowering effects of exercise in hypertensive adults are not completely understood, although changes in body composition, sympathetic nervous system activity, peripheral vascular resistance, and insulin levels have all been postulated. For example, weight loss alone or combined with exercise provides a greater blood pressure lowering effect than exercise alone. Endurance exercise training has been shown to decrease arterial stiffness and improve endothelial function in hypertensive adults. However, whether the decreases in blood pressure with exercise are due to improvements in arterial stiffness and endothelial function, or vice versa, are unclear. Although age-associated arterial stiffening and endothelial dysfunction can lead to the development of high blood pressure, high blood pressure can also lead to arterial stiffening and endothelial dysfunction.

Obesity

As described in Chapter 34, obesity is associated with increased morbidity and mortality from multiple medical complications, and has been consistently correlated with mobility impairment and poor physical function. Over 70% of

US adults older than 60 years are overweight or obese, an epidemic that affects both men and women in all racial and ethnic groups. There are also profound changes in body composition with aging, and older adults preferentially accumulate fat centrally, a pattern of adiposity that is strongly associated with multiple cardio-metabolic risk factors.

While weight loss alone can improve cardio-metabolic risk factors, fitness, function and quality of life in obese older adults, it is also associated with loss of fat-free mass (FFM) and decreases in BMD. These potential harms, coupled with the fact that the majority of weight loss studies have been conducted in middle-aged and not older adults, has resulted in considerable clinical uncertainty about how to treat geriatric obesity. There is general agreement, however, that exercise should be a component of any weight loss intervention, given the need to minimize loss of muscle and bone with weight loss in older obese adults.

Several large trials have demonstrated improvements in multiple cardio-metabolic and functional outcomes with diet plus exercise interventions in older adults, although an effect on cardiovascular events or mortality has not been demonstrated yet. In the Diabetes Prevention Program, the lifestyle intervention of moderate-intensity exercise and modest weight loss (7%) was more effective in preventing diabetes in the older (60–85 years) than in the younger participants, due to both greater weight loss and physical activity in this group. Older participants had greater reductions in waist circumference and lost more weight; they also reported more physical activity and were more likely to achieve the goal of at least 150 minutes of exercise per week.

The Look AHEAD study compared a weight loss diet and physical activity intervention with support and education in more than 5000 overweight or obese adults with type 2 diabetes (mean age 58 years). The lifestyle intervention was associated with a 5% increase in fitness, as well as increased function and decreased cardio-metabolic risk factors compared to controls. Improvements were related to both weight loss (8% at one year and 5% at 4 years) and increased fitness.

Perhaps the most compelling evidence for including exercise in any weight loss intervention in older obese adults comes from Villareal et al's randomized, controlled trial comparing 52 weeks of weight loss diet, exercise (aerobic and strength training) or both in more than 100 older obese adults with mild to moderate functional impairment. Participants receiving the diet intervention lost weight (10% and 9% for diet only and diet plus exercise, respectively), whereas weight remained stable in the exercise only group. Physical function improved in all groups, but was greatest in the diet plus exercise group (21% vs 15% exercise only and 12% diet only). Weight loss diet alone was associated with significant declines in FFM (5%) and BMD (3%), whereas these measures increased in the exercise only group (2% and 2%, respectively). Decreases in FFM and BMD with weight loss were attenuated in the diet plus exercise group (3% and 1%, respectively), but not completely reversed.

Because the negative effects of weight loss on body composition and BMD in older obese adults are not fully offset by exercise, an important question is whether weight loss per se is necessary, or whether exercise alone can confer most of the benefits without the associated risks of weight loss in this population. Another area that has yet to be addressed is the role of weight history. The age of onset, and possibly the duration of obesity, may be important determinants of obesity-associated morbidity and mortality and may thus warrant different approaches to treatment.

Diabetes Mellitus

Exercise is routinely recommended for patients with a diagnosis of type 2 diabetes. The joint position statement by the American College of Sports Medicine and American Diabetes Association describes the role of exercise in the treatment of type 2 diabetes, with both aerobic and resistance exercise associated with improvements in insulin resistance and blood glucose control.

The role of exercise in the prevention of type 2 diabetes in at-risk individuals is critical. Several large, long-term prospective studies have demonstrated striking reductions in the incidence of type 2 diabetes in high-risk populations with lifestyle interventions (diet and exercise). The Diabetes Prevention Program, described above, randomized over 3000 nondiabetic adults with impaired glucose tolerance to a lifestyle intervention, metformin treatment, or placebo. After an average of 3 years, the rate of developing type 2 diabetes was 56% lower in the lifestyle group than in the placebo group and 39% lower than in the metformin group. These benefits have persisted, with 15-year follow-up showing a 27% reduction in the incidence of type 2 diabetes among participants originally randomized to the lifestyle group compared to placebo, even though all participants were offered the lifestyle intervention after the initial treatment phase of the study.

Exercise appears to also have beneficial effects on glucose homeostasis in nondiabetic older adults. Middle aged and older athletes are more insulin sensitive and have increased rates of glucose disposal compared to age-matched sedentary controls, even after controlling for body fat. In healthy 60- to 80-year-old men and women with normal

glucose tolerance, 12 weeks of exercise (upper body calisthenics and aerobic exercise) improved insulin sensitivity approximately 13%. Another study reported a 36% improvement in insulin sensitivity in healthy older men (mean age 69 years) after 6 months of intensive endurance exercise training. Improvements in insulin sensitivity were also seen with 9 months of either moderate- or high-intensity aerobic exercise in sedentary older women (mean age 73 years), over half of whom met the criteria for impaired glucose tolerance. In sum, aerobic exercise training can result in improvements in insulin sensitivity in older adults, but the responses to exercise may be attenuated compared to younger individuals. Resistance exercise may also improve insulin sensitivity and glucose tolerance.

Dyslipidemia

The benefits of exercise on cardiovascular disease risk are thought to be due at least in part to improvements in lipid profiles. Higher levels of physical activity are associated with less atherogenic lipoprotein profiles in young and middle-aged individuals. Reduced plasma triglyceride (TG), very-low-density lipoprotein triglyceride concentrations, and higher high-density lipoprotein (HDL)-C, HDL2-C, and apolipoprotein A-I levels are consistently observed in trained subjects compared to sedentary controls.

The most consistent change in lipid profiles with exercise appears to be increases ranging from 4% to 18% in HDL-C. In older adults (50–75 years), 6 months of endurance exercise training positively affected HDL-C concentrations and particle size independent of baseline or change in body fat. While HDL-C is responsive to moderate-intensity exercise, higher intensity exercise may be required to affect LDL-C and TG levels, although there is little data in people over age 65. There is no consistent effect of resistance training on lipoproteins.

It is unclear whether the effect of training on plasma lipoproteins differs between men and women, and few studies have directly addressed this question. A large population-based cohort study in middle-aged adults (30–60 years) found that increases in self-reported physical activity over a 5-year period were associated with improvements in HDL-C only in men. In contrast, in an older population (mean age ~65 years) with coronary artery disease, 12 weeks of cardiac rehabilitation was associated with greater increases in HDL-C among women than men. In women, improvements in HDL-C were independent of baseline levels, whereas only men with low baseline HDL-C had an increase.

Arthritis

Arthritis is major contributor to pain and functional impairment in older adults. A description of age-related changes in joint function and the impact of arthritis on function in older adults is given in Chapter 117. The benefits of exercise on pain and functional status in arthritis are well-established, and exercise forms the cornerstone of treatment for patients across the range of disease severity.

Exercise trials in arthritis patients consistently report improvement in outcomes including gait speed, physical function performance, depression, and pain. The majority of the data are from trials in osteoarthritis of the knee, although there is a beneficial effect of exercise on pain and functional status in osteoarthritis of the hip and in rheumatoid arthritis.

Multiple land and water-based exercise modalities appear to be effective, and there is not one approach that is superior. Muscle strengthening is generally included in exercise programs for patients with arthritis, although improvements in pain, disability and function have been demonstrated with aerobic exercise alone. The slow continuous movements and focus on balance and flexibility as well as strength make Tai Chi an appealing form of exercise for many older adults with arthritis. Few trials to date have rigorously studied Tai Chi, but the limited data suggest it may also improve pain and function in arthritis.

Importantly, the improvements in pain and functional status from exercise are generally not maintained after about 6 months postintervention. “Booster” sessions, however, may provide greater persistence in improvements, emphasizing the importance of developing effective strategies to promote long-term adherence.

Osteoporosis

The decline in BMD with age is well recognized (see Chapter 118), and there is an epidemic of osteoporotic fractures that affects women more than men and that primarily involves hip, vertebral, and wrist fractures. Mechanical loads are critical to skeletal integrity. Animal studies confirm the importance of mechanical strain to bone modeling and remodeling. They have also identified that (1) the osteogenic response to mechanical loading is optimized with relatively few repetitions of high-magnitude forces; (2) the application of force must be in a dynamic, rather than

static, fashion; and (3) fast strain rates are more osteogenic than slow strain rates. Furthermore, the osteogenic response to mechanical loading is mediated locally in skeletal regions subjected to the strain, highlighting the need for exercises to specifically target regions of the skeleton at risk of fracture. It appears that bone cells lose sensitivity to mechanical loading after relatively few loading cycles. For example, four sets of 90 load applications per day was more osteogenic than one set of 360 loading cycles, and interposing an 8-hour recovery period between loading sessions resulted in a greater osteogenic response than when the recovery period was 0.5 hour. These concepts have not been rigorously evaluated in humans, but they suggest that multiple short bouts of exercise per day may be more effective in preserving bone health than a single, longer daily session. The concept of allowing bone to "rest" between loading cycles may also have implications for resistance training. For example, if the intent is to perform three sets of eight repetitions of several exercises, it might be of greater benefit to bone to perform one set of each exercise and then cycle back through for the second and third sets, rather than doing three consecutive sets of each exercise.

The effects of exercise on bone mass have been estimated by comparing athletes who participate in different sports or physically active versus sedentary people. For example, the humerus in the dominant arm of tennis players had approximately 30% greater cortical bone thickness when compared to the nondominant arm. Athletes who participate in muscle-building activities (eg, weight lifting and body building) and in activities that involve jumping or vaulting (eg, volleyball and gymnastics) also tend to have elevated BMD. These data suggest that exercise in younger individuals may increase peak bone mass—an important protective factor for reducing osteopenia later in life. In contrast, the primary benefit of physical activity in older adults may be to preserve, rather than increase, bone mass.

Although both weight-bearing endurance exercise and resistance exercise can increase bone mass in older women and men, increases in BMD appear to require a vigorous level of exercise, which supports the contention that the osteogenic response to exercise is attenuated with aging. In postmenopausal women, exercise may increase BMD by up to 5%, as compared to no-exercise controls, but average increases generally are only 1% to 3%. These modest increases may reflect difficulty reaching the strain threshold needed for bone remodeling to occur due to decreased muscle mass and strength, declines in hormones and growth factors that affect the sensitivity of bone to strain, and/or insufficient calcium and vitamin D.

Although it might be expected that the rate of osteoporosis will decline in the future with the epidemic of obesity in the United States and other countries, there are reasons why this may not occur. First, while low body weight is a risk factor for osteoporosis, increased body weight is not necessarily protective. In studies of overweight and mildly obese postmenopausal women, approximately one-third had osteopenia or osteoporosis. Second, the increased prevalence of overweight and obesity is likely to be accompanied by an increased prevalence of weight cycling (ie, multiple cycles of weight loss and gain). Women with a history of weight cycling have lower BMD levels than noncyclers. In addition, BMD decreases in response to modest weight loss (~ 5%) in postmenopausal women, even when calcium supplementation is provided and even when the weight loss is mediated by moderate-intensity exercise. Furthermore, BMD is not fully restored with weight regain. The Villareal et al study described above showed that exercise may attenuate, but not completely offset, losses in BMD with weight loss in older obese adults.

There is also evidence that exercise can prevent fractures. Results from prospective cohort studies, such as the Nurses' Health Study and the Study of Osteoporotic Fractures, suggest that the risk for hip fracture is reduced by approximately 50% in the most physically active quintile of the population. In evaluating the potential benefit of simple walking activity, the Nurses' Health Study found a dose-response benefit for both duration and speed of walking, such that more hours per week spent walking and fast walking speed conferred reduced fracture risk. Even hours per week spent standing was inversely related to hip fracture incidence. Perhaps most importantly, changes in physical activity for several years were related to hip fracture incidence in the expected manner: decreases in physical activity were associated increased risk and vice versa. Such findings suggest that any type of ambulatory physical activity may confer skeletal benefits and that increased physical activity should be advocated at any age as a strategy to reduce fracture risk.

The low frequency of fractures makes well-designed, adequately powered randomized controlled trials extremely expensive. Very few exercise trials have included fractures as an outcome, or reported fractures as an observation. Analysis of 11 exercise intervention studies that reported fractures found that exercise reduced the risk of overall fracture by approximately 50% and vertebral fracture by approximately 40% compared to controls, although the authors urged caution due to the strong likelihood of publication bias. The Erlangen Fitness and Osteoporosis Prevention Study compared fracture incidence among 137 postmenopausal osteopenic women either participating in a supervised exercise intervention (two group and two home session per week), or a sedentary control group for 12 years. Although fewer fractures occurred in the exercise group, the difference between groups did not reach statistical significance.

Important areas for future research include determining the effects of age and sex in the response of bone to exercise. In addition, new methods such as peripheral quantitative computed tomography may provide important information on bone quality (eg, strength and geometry) in response to exercise.

Falls

Both group and home-based exercise interventions have consistently demonstrated a potent effect on fall reduction in community-dwelling older adults. Importantly, exercise also reduces injuries from falls. Meta-analysis of 17 trials estimated reductions of 37% for all injurious falls, 43% for falls resulting in serious injury, and 61% for falls resulting in fracture. Exercise may help to prevent fractures both by preserving bone mass and strength and by reducing the incidence of injurious falls. Multicomponent interventions that include strength and endurance and that also emphasize balance appear to be more effective than single component interventions.

Of course, many factors contribute to risk for falling, including some that would be expected to improve in response to exercise (eg, poor muscle strength) and some that would not (eg, poor vision). Falls among nursing home residents are particularly likely to have diverse and multiple causes. This may explain the lack of data supporting the effectiveness of exercise alone in this population.

Cancer

Data from cohort and case control studies consistently support an inverse relation between physical activity and overall cancer incidence and mortality. Among 17 observational studies of leisure or occupational physical activity, 16 reported a protective effect. The effects appeared to be stronger in men than in women. However, only 7 of the studies included women. Overall, occupational and leisure physical activity were associated with a 30% independent protective effect on overall cancer risk in men, and men who engaged in regular vigorous activities had a 20% reduction in cancer risk compared to sedentary men. Analysis of more than 15,000 cancer deaths over 12 years in the NIH-AARP Diet and Health Study found that compared to those who reported rarely or never engaging in moderate to vigorous physical activity, those who reported more than 7 h/week had a lower risk of cancer mortality (HR = 0.89).

In persons diagnosed with cancer, exercise is associated with improved surgical outcomes, decreased symptoms and side effects of treatment, improved physical function and psychological health. Participation in exercise post cancer diagnosis has been estimated to increase cancer survivorship by 50% to 60%.

To date, the most compelling data involve the relationship between activity and risk of colon or breast cancer. A reduced risk of colon cancer (relative risk, 0.4–0.9) has been found in groups with high physical activity levels compared to those with low levels. In general, controlling for other cancer risks including tobacco, alcohol, age, obesity, and diet does not diminish the relationships, and this finding has been demonstrated in men and women of different racial and ethnic groups. Among patients with colon cancer, any prediagnosis physical activity was associated with a 25% reduction in colon-cancer mortality, and a 26% reduction in all-cause mortality compared to patients who reported no physical activity prior to diagnosis. Moderate to high levels of postdiagnosis physical activity were also associated with reductions in all-cause mortality ranging from 24% to 39%.

Physical activity reduces the risk of breast cancer overall by 15% to 20%. The strongest effect appears to be in postmenopausal breast cancer, where the risk reduction ranges from 20% to 80% when comparing the most active to the least active groups. These associations remain even after adjusting for potential confounding factors such as age, BMI, reproductive history, tobacco use, and diet. There appears to be a dose response, with higher levels of activity associated with greater risk reduction. As with colon cancer, exercise in breast cancer patients is associated with better physical function and fewer treatment-related side effects.

Mood

Subjects who exercise regularly consistently report an improved sense of well-being and reduced tension and anxiety. Large epidemiological studies have demonstrated an association between low levels of physical activity and depressive symptoms. These studies have also shown physical activity to be an independent predictor of the development of depressive symptoms. In the National Health and Nutrition Education Survey I Epidemiologic Follow-Up Study, low levels of physical activity predicted depressive symptoms 8 years later in white women, with those reporting little to no physical activity twice as likely to develop depressive symptoms as those reporting moderate to high levels.

As for treatment for clinical depression, structured, mixed exercise programs result in a modest reduction in symptom severity. The effects of exercise appear to be comparable to those of behavioral or pharmacologic therapy.

Proposed mechanisms for the effects of exercise on mood include increases in endorphin and monoamine levels, as well as social engagement and improvements in self-efficacy and self-esteem.

Cognition

There may be a positive effect of exercise on cognition. Numerous cross-sectional and longitudinal studies including the Nurse's Health Study and the Mayo Clinic Study on Aging have found an association between higher levels of physical activity and both better cognitive test scores and reduced risk of cognitive impairment and dementia. Among 16 longitudinal epidemiologic studies, 11 reported a significant inverse association between physical activity and risk of dementia. Among 1200 older adults in the Framingham Study, a hazard ratio of 0.55 was found for incident all-cause dementia after 10 years of follow-up in participants reporting moderate to heavy physical activity compared to less active participants. Among those in the lowest quintile of physical activity, the hazard ratio for incident dementia was 1.45.

Results from exercise intervention studies have been mixed, although the balance of evidence supports moderate positive effects of exercise training on cognition in both cognitively normal and cognitively impaired individuals. A meta-analysis of 16 trials in older patients with dementia found a significant positive effect on cognitive function with exercise training, although the authors emphasized caution given the substantial heterogeneity between trials. In older adults without known cognitive impairment, 8 of 11 studies using aerobic exercise interventions found positive effects on cognitive function that coincided with improvements in maximal oxygen uptake (VO_{2max}).

Some studies have also reported cognitive benefits with resistance training alone. One meta-analysis found the greatest cognitive effects with mixed training paradigms. Exercise appears to improve function in multiple cognitive domains, with the strongest effects in executive control functions. Important areas for further study include determining the duration and intensity of exercise needed to realize cognitive benefits, and potential sex differences in the cognitive responses to exercise.

The bases for the exercise-associated improvements in cognition are presently an active area of investigation. Animal studies support a neuro-protective effect of exercise through promotion of neuroplasticity, increases in brain-derived neurotrophic factor and enhanced neurogenesis. Other work is investigating the vascular contributions to cognitive impairment and the role of obesity, insulin resistance and type 2 diabetes.

Sleep

Sleep quality progressively decreases with increasing age (see Chapter 49). The most profound changes with aging are in non-REM sleep, with decreased slow wave sleep (SWS), and more awakenings in stage 1 sleep. Indeed, sleep disturbance (inability to fall asleep or maintain sleep; more nighttime awakenings) is the most common complaint in older adults. These sleep disturbances are of concern, as chronic sleep problems in older adults are associated with impaired cognitive function, decreased quality of life, reduced physical function, and increased morbidity and mortality.

It is generally accepted that physical activity and regular exercise are beneficial for sleep in older adults. Higher levels of cardiorespiratory fitness and physical activity in older adults are associated with better self-reported sleep quality. For instance, objectively measured indices of sleep quality (eg, sleep onset latency, wake time after sleep onset, sleep efficiency) are better in physically fit older men compared to sedentary controls, and higher levels of physical activity are protective against insomnia in older adults. Although few longitudinal exercise studies have specifically focused on older adults, a systematic review and meta-analysis of 6 studies in adults over 40 years old demonstrated that 10 to 16 weeks of aerobic exercise has positive effects on self-reported sleep quality measured using the Pittsburgh Sleep Quality Index.

It appears that SWS, which plays a role in the restorative functions of sleep, is particularly sensitive to exercise training. Older physically fit men have more SWS than sedentary older men, and exercise training increases SWS in older men and women. One longer term study (12 months) demonstrated that in older adults with mild to moderate sleep problems, exercise was associated with decreases in stage 1 sleep, increases in stage 2 sleep, and fewer awakenings.

The mechanisms by which physical activity improves sleep quality are not entirely understood. Homeostatic sleep drive or pressure increases during periods of wakefulness; the longer we remain awake, the stronger the desire and need to sleep become. Endogenous substances, such as adenosine (which increases as a result of increased energy expenditure), build up during the day and increase the pressure to sleep, particularly SWS sleep. However, it has also been posited that any increase in neural activity during the day is compensated by proportional increases in SWS.

There remain many questions regarding the effects of exercise on sleep in older adults. For example, most studies in older adults have examined the effects of aerobic training, but at least one study has shown that progressive resistance training can improve subjective measures of sleep quality. It is not known if aerobic, resistance, or a combination is most effective for improving sleep. The effects of exercise intensity have not been established, but lower intensity activities such as yoga and Tai Chi also improve self-reported measures of sleep quality, and one study reported that Tai Chi was more beneficial than traditional aerobic exercise. Similarly, lower intensity exercise (eg, stretching and flexibility) was associated with greater improvements in self-reported sleep quality than higher intensity exercise performed at 60% to 75% of maximal heart rate. The effects of frequency of exercise have also not been defined, but a study in older men (~ 64 years) showed that after a 16-week exercise training period, SWS increased on a day when exercise was performed, but not on a sedentary day. These findings suggest that physical activity should be done on most days of the week to maximize the benefits on sleep. Whether exercise has different effects in men and women is not known. Since older women tend to be less physically active and report more sleep problems than men, increasing physical activity to improve sleep may be particularly effective in older women. Finally, the effects of extended periods of sedentary behavior on sleep quality in older adults are not known. However, there is reason to believe that sedentary behavior could impact sleep parameters as well; for example, immobilizing the arm during the day elicited reductions in SWS during the subsequent sleep period. Considering the previously mentioned improvements in sleep quality with stretching and flexibility exercises, it may be that reducing sedentary time with short bouts of low-intensity activity will improve sleep quality in older adults with sleep problems. This would also be consistent with the hypothesized effect of neural activation on homeostatic sleep drive.

It should also be recognized that there may be a reciprocal relationship: poor sleep is associated with lower levels of physical activity. For example, in sample of subjects from the Healthy Women Study (~ 73 years), greater self-reported sleep efficiency and less sleep fragmentation were associated with higher physical activity levels the following day. Thus, there appears to be a circular association whereby increased physical activity improves sleep, and improved sleep facilitates greater physical activity levels.

Parkinson Disease

Exercise is associated with reduced mortality rate, and with improvements in functional mobility and activities of daily living in individuals with Parkinson disease. The majority of studies to date have examined the effects of physical therapy. While studies of physical therapy interventions clearly suggest benefit, there is currently no consensus on “best practice” approaches in Parkinson disease. Modalities are variable and often target broad goals such as posture, balance and mobility. Though data are limited, controlled trials of both resistance and endurance training in individuals with Parkinson disease have demonstrated improvements in mobility, gait, and quality of life. The intensity of exercise required to realize benefits in Parkinson disease is an area of active investigation, as some studies have found greater improvements with a higher dose of exercise, while others have not.

Despite impaired force production and increased fatigability, individuals with Parkinson disease are able to participate safely and effectively in high-intensity resistance exercise, and appear to derive benefits similar to those in neurologically healthy adults. In one study, 12 weeks of high-force eccentric resistance training in adults with Parkinson disease was associated with a 6% increase in muscle hypertrophy, a 24% increase in torque, and an 18% improvement in 6-minute walk time compared to a standard exercise program. Aerobic exercise interventions—mainly treadmill exercise—consistently improve gait, mobility, and quality of life. One ongoing multisite study will compare the effects of 6 months of moderate-intensity (60%–65% of maximal heart rate) or high-intensity (80%–85% of maximal heart rate) treadmill training on symptoms in individuals with de novo Parkinson disease.

The mechanisms by which exercise may be beneficial in Parkinson disease are not known. Animal studies have demonstrated increased neurogenesis and reduced neurodegeneration in response to high-intensity exercise, and these effects have been attributed to increased expression of multiple neurotrophic factors. These mechanisms have not been examined in humans, although one study reported normalization of corticomotor excitability in early Parkinson disease with 8 weeks of high-intensity treadmill training.

Other Chronic Disorders

In addition to the common geriatric disorders discussed above, exercise also has a role in the prevention and treatment of other chronic disorders frequently present in the older population.

Chronic obstructive pulmonary disease Exercise is a key component of pulmonary rehabilitation programs, which

also generally include education and nutritional counseling. Numerous trials of pulmonary rehabilitation have demonstrated benefits in patients across all stages of disease. Improvements in exercise capacity, symptoms of breathlessness, anxiety and depression, and health-related quality of life have all been associated with pulmonary rehabilitation. In addition, pulmonary rehabilitation reduces hospitalizations and increases survival in patients with chronic obstructive pulmonary disease (COPD). Programs typically last from 4 to 10 weeks and vary in frequency, duration and intensity of exercise. Longer programs appear to produce greater effects than shorter programs. The benefits of pulmonary rehabilitation can be sustained, but tend to wane after the completion of formal rehabilitation. Thus, methods to encourage patients to continue exercise after discharge from the program are important.

Stroke Stroke is a leading cause of disability in older adults, with 20% to 25% of stroke survivors requiring at least some assistance with activities of daily living. These functional deficits predispose patients to a sedentary lifestyle, further increasing the risk of stroke and cardiovascular disease, the leading causes of death among stroke survivors. Physical rehabilitation in stroke patients has traditionally focused on the first few months after the event, as prevailing wisdom held that further functional improvements were unlikely after this time. However, improvements in aerobic capacity and sensorimotor function can be achieved with continued rehabilitation. Physical activity and exercise recommendations for stroke survivors from the American Heart Association identify three primary goals: (1) preventing complications from prolonged inactivity; (2) decreasing the risk of recurrent stroke and cardiovascular events; and (3) increasing aerobic fitness. Specific recommendations for aerobic exercise and strength training are similar to those recommended for all adults. In addition, incorporation of stretching and balance/coordination activities is recommended to prevent muscle contractures, and to improve the ability to safely perform activities of daily living.

Constipation A sedentary lifestyle is associated with chronic constipation. Increasing physical activity is one of the standard nonpharmacologic approaches to treating this disorder, although data supporting this recommendation are limited. One study of 43 middle age adults (> 45 years) with chronic idiopathic constipation found that 12 weeks of exercise (30 minutes of brisk walking at least twice weekly and 11 minutes of strength/flexibility exercises daily) improved symptoms of constipation and increased colonic transit time compared to controls. These improvements occurred even though the training produced no change in either VO_{2max} or maximal workload. However another study of eight adults (mean age 50 years) found no change in transit time or constipation symptoms with 4 weeks of regular moderate physical activity.

RISKS ASSOCIATED WITH EXERCISE

Despite the overwhelming evidence that exercise confers multiple benefits and can be performed safely even in frail older adults, concerns about potential injury and other adverse events are common among patients and health care providers. These fears may prevent patients from engaging in the amount and intensity of exercise needed to realize health benefits, thus presenting a potential barrier to increasing physical activity levels.

"Overuse" injuries involving soft tissues are by far the most common, and are likely to increase with advancing age. Eccentric exercise (eg, lowering a weight that has been lifted) may predispose to excess muscle injury. Appropriate warm-up and cool-down periods, as well as emphasis on stretching and flexibility, are likely to be especially important in reducing soft-tissue injury in an older population.

The prevalence of asymptomatic coronary artery disease is higher in older compared to younger adults, and there is a transient increase in the risk of sudden death occurring during a bout of vigorous exercise, especially in previously sedentary individuals. However, the small increased risk of a cardiovascular event with exercise is clearly outweighed by the reduction in risk during the nonexercising period of the day. Thus, the overall risk of sudden death in active men is only 30% of that in sedentary men. Furthermore there is lower cardiovascular-related and overall mortality in active individuals.

In older patients with diabetes mellitus, careful attention to the possibility of exercise-induced hypoglycemia is critical because of the sustained improvement in insulin sensitivity for 24 to 48 hours following vigorous exercise. Meticulous foot care and supportive, well-fitted shoes are also important for the exercising diabetic patient. Patients with proliferative retinopathy should avoid anaerobic (specifically isometric) exercise, such as power lifting, because of the increased ocular and systemic pressure occurring with the Valsalva maneuver.

In the past a pre-exercise assessment, including a complete history and physical examination, and an exercise stress test were recommended by most experts for adults older than 60 years before vigorous exercise. Such an evaluation is expensive and could present a significant barrier to exercise. Furthermore, there are little data to

substantiate this recommendation. Current recommendations suggest that asymptomatic individuals who plan to exercise at moderate intensity do not need screening before initiating an activity program. The geriatric medicine axiom of "start low and go slow" should be applied to beginning a safe physical activity program. It is appropriate for patients to notify their health care providers of their intent to begin an exercise program, because adjustments in medications or dosages may be necessary. The health care provider can also work with the individual to tailor the exercise program to the individual's abilities and be a source of ongoing support and encouragement.

RECOMMENDATIONS

There is now ample evidence that older adults can safely engage in both endurance and resistance exercise training, and that exercise has beneficial effects on numerous important health-related end points in this population. Despite these acknowledged benefits, however, older adults are the least physically active age group. Potential barriers to exercise in older adults include perceptions of safety, chronic conditions and physical limitations, and access to exercise programs or facilities.

Consensus recommendations for physical activity in older adults were published by the American College of Sports Medicine and the American Heart Association in 2007 (**Table 115-1**), and are consistent with the first-time national physical activity guidelines published by the Department of Health and Human Services (DHHS) in 2008. The DHHS guidelines stress the importance of avoiding sedentary behavior, and that any amount of physical activity provides some health benefits. The specific modifications for older adults include: (1) being as physically active as their conditions allow if the target of 150 min/week is not possible because of chronic conditions; (2) engaging in balance exercises for individuals at risk of falling; (3) determining the level of effort for physical activity relative to level of fitness; and (4) understanding how chronic conditions may affect the ability to safely engage in regular physical activity. Key to recommendations for exercise in older adults is the need to individualize the program of physical activity. While there is a dose-response relationship between the intensity of exercise and the improvement in most outcome measures, significant cardiovascular and metabolic improvements can be obtained when less intense exercise is maintained over sufficiently long periods of time. Less intense exercise regimens may be more acceptable to some older individuals and appear to make long-term compliance more likely. Low-intensity programs may be necessary in frail populations, such as those with stroke, heart failure, and chronic lung disease, in which more intensive exercise is not tolerated. While multiple short bouts of exercise (at least 10 minutes each) may be effective in improving certain outcome measures, longer sessions remain preferable if these can be tolerated.

TABLE 115-1 ■ SUMMARY OF PHYSICAL ACTIVITY RECOMMENDATIONS FOR OLDER ADULTS

- Perform (1) moderate-intensity endurance activities at least 30 min/d in bouts of at least 10 min each to total 150–300 min/wk; (2) at least 20–30 min/d or more of vigorous-intensity endurance activities to total 75–150 min/wk; or (3) an equivalent combination of moderate and vigorous activity.
- Perform 8–10 strengthening activities involving the major muscle groups between moderate and vigorous intensity (8–12 repetitions) at least 2 d/wk.
- Perform flexibility exercises that use sustained stretches involving the major muscle groups with static movements at moderate intensity at least 2 d/wk.
- For frequent fallers or individuals with mobility problems, perform balance exercises including (1) progressively difficult postures that gradually reduce the base of support (eg, two-legged stand, semitandem stand, tandem stand, one-legged stand), (2) dynamic movements that perturb the center of gravity (eg, tandem walk, circle turns); (3) stressing postural muscle groups (eg, heel stands, toe stands); or (4) reducing sensory input (eg, standing with eyes closed).
- The intensity and duration of physical activity should be low at the outset for older adults who are highly deconditioned, functionally limited, or have chronic conditions that affect their ability to perform physical tasks. The progression of activities should be individual and tailored to tolerance and preference. Muscle strengthening activities and/or balance training may need to precede aerobic training activities among very frail individuals. Older adults should exceed the recommended minimum amounts of physical activity if they desire to improve their fitness. If chronic conditions preclude activity at the recommended minimum amount, older adults should perform physical activities as tolerated so as to avoid being sedentary.

Data from American College of Sports Medicine, Chodzko-Zajko WJ, Proctor DN, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc. 2009;41(7):1510–1530.

Because the physical activity goals may seem daunting, especially for inactive older adults, specific instructions are more helpful than general advice to "increase physical activity." Provision of written exercise prescriptions from health care providers increases activity levels among previously sedentary adults. In addition, an increasing array of technologies allows individuals to set activity goals and to monitor and track activity in real time.

Changes in lifestyle are difficult to maintain at any age, and recidivism rates for exercise programs are high. This problem may be reduced by: (1) careful attention to warm-up periods and slow progression in an effort to reduce early injuries; (2) enthusiastic leadership; (3) regular assessment of improvement with personalized feedback and praise; (4) spousal and family support for participation; (5) flexible goals (time rather than distance) set by the participant; and (6) use of distraction techniques such as music.

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Chapter 116

Mobility

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Learning Objectives

- Describe the prevalence and consequences of mobility disorders in older people.
- Identify strategies to detect and evaluate mobility disorders.
- Characterize approaches to the management of mobility disorders.

Key Clinical Points

1. **Loss of mobility is a major cause of disability in older people but is rarely assessed in typical clinical practice.**
2. **The assessment of mobility involves taking a history and performing a physical examination that identifies cardiopulmonary, musculoskeletal, and neurologic contributors.**
3. **Mobility can be assessed by a number of simple performance tests including gait speed, the short physical performance battery, and the get up and go test.**
4. **Interventions to promote mobility include addressing underlying impairments, therapeutic exercise, assistive devices, home adaptations, and caregiver training.**

INTRODUCTION

Mobility problems are pervasive in older adults. Mobility limitations affect personal independence, need for human help, and quality of life. Limited mobility predicts future health, function, and survival. Like other geriatric syndromes, mobility disorders are often caused by diseases and impairments across many organ systems, so evaluation and management require multiple perspectives and disciplines. Health care providers should be able to assess and treat mobility problems. They should be able to measure and interpret clinical indicators of mobility such as gait speed, the short physical performance battery, and the performance-oriented mobility assessment. They should know the physiologic and biomechanical mechanisms underlying normal and abnormal mobility, the differential diagnosis of the causes of mobility disorders, and the approaches to management of mobility problems.

DEFINITIONS AND METHODS OF CLASSIFICATION

Defining Mobility

Mobility is the ability to move one's own body through space. Mobility requires force production and feedback control systems to navigate the mass of the body through a three-dimensional environment. Walking is the fundamental mobility task for human life. Mobility also includes a wide range of other important activities that require moving one's body, from turning over in bed to climbing stairs. Mobility tasks have an inherent hierarchical order based on the biomechanical and physiologic demands made on the body. This orderedness is apparent in the developmental tasks of infancy and childhood, when mobility independence is first achieved. The simplest and first mobility task is turning

over in bed, followed by sitting upright, transfers from lying to sitting and from sitting to standing, locomotion with an increased base of support (like crawling or using a walker), to independent two-legged walking, then more challenging tasks like ascending and descending stairs, running, climbing ladders, and sports.

Mobility disability is best defined within a conceptual framework such as that of disablement (**Table 116-1**). Disability is caused by pathologic processes that lead to organ system impairments and functional limitations. Disability causes handicap by limiting life roles such as work or caregiving. Disability in mobility occurs at the level of the whole person and is manifested by the inability to carry out normal mobility activities like bathing or shopping. Mobility disability is caused by functional limitations in walking, transferring, or climbing stairs, which are, in turn, caused by problems with strength, endurance, coordination, balance, and range of motion. These functional limitations can be caused by numerous pathologic processes. Disablement can be modified by psychological, social, and environmental factors. Mobility disability can precipitate a cycle of negative consequences because it often leads to decreased activity, which in turn worsens functional limitations and causes organ system deconditioning, including muscle weakness, loss of joint range of motion, and poor cardiovascular endurance.

TABLE 116-1 ■ MOBILITY DISABILITY AND THE DISABLEMENT PROCESS

COMPONENT OF THE DISABLEMENT PROCESS	EXAMPLES RELATED TO MOBILITY DISABILITY
Pathologic processes	Cardiopulmonary, neurologic, and musculoskeletal conditions
Organ system impairments	Losses of strength, endurance, coordination, balance, and range of motion
Functional limitations	Problems with transfers, walking, and climbing stairs
Mobility disability	Dependence or difficulty with activities of daily living such as bathing or shopping
Handicap	Limitations in work, care giving

Classification Methods for Mobility

Mobility classification is often driven by a tacit assumption of orderedness. No single current instrument assesses the full range of mobility from the lowest levels of rolling over in bed to the highest levels of endurance and coordination required for athletics or dance. Mobility assessment tools for older adults generally address one or more of the following three mobility levels: nonambulatory, ambulatory, and vigorous, corresponding broadly to Tinetti's levels of frail, transitional, and vigorous mobility status. Mobility levels are surprisingly stable. While day-to-day variability does occur, people in general tend to remain in one level or decline very gradually unless a major event has occurred. Within the nonambulatory level, there are important mobility skills that affect independence in personal care activities, care needs, and demand for human help; these activities include bed mobility, self-transfer skills, and wheelchair mobility. Within the vigorous mobility level, the degree of fitness, as represented by the ability to perform demanding or challenging mobility activities, may be a useful indicator of the extent of "successful aging" and "physiologic reserve." As an indicator of the extent of physiologic reserve, vigorous mobility status may be a marker of ability to tolerate physiologic stressors such as acute illness, surgery, or periods of reduced activity.

Mobility can be assessed by self-report, professional observation, or direct measurement. Instruments to assess mobility from all three perspectives have been developed (**Table 116-2**). Each has advantages and disadvantages. These tools have been used to estimate the population incidence and prevalence of mobility disorders, predict the consequences of mobility problems, screen patient populations, determine care needs, and reimburse services in rehabilitation settings. More detailed instruments have been developed specifically for sorting out causes and mechanisms. Detailed instruments will be discussed separately in the section on causes of mobility limitations. Mobility measures have varying strengths and limitations, depending on characteristics such as reliability and validity, respondent burden, feasibility and convenience of use, and assessor skill required.

TABLE 116-2 ■ INSTRUMENTS USED TO SCREEN AND CLASSIFY MOBILITY

INSTRUMENT TYPE	INSTRUMENT NAME	ITEMS	RANGE	COMMENTS
Self-report	Rosow-Breslau	Walk ½ or ¼ mile and climb stairs	Ambulatory to vigorous	Used as single items
	SF-36 physical function	10 items, many directly related to mobility, from walk across a room to walk 1 mile	Ambulatory to vigorous	Score 0–100 US adult mean 84.2 Older adult mean 52.0 Insensitive at lower levels of mobility
	Long-term care survey	Walking inside and bed/chair transfers	Nonambulatory to ambulatory	Used as single items
	Mobility modifications	Self-report of changing the way one walks 1/2 mile or climbs stairs	Ambulatory	Used as single items
	Avlund mobility	Fatigue and need for help in six mobility activities from transfer to stairs and walking outside	Nonambulatory, ambulatory, and vigorous	Scores 0–6
Professional assessment	Barthel mobility items	Walking (or wheeling), transfers, and stairs	Nonambulatory, ambulatory, and vigorous	Mobility items integrated into total score
	Functional independence measure (FIM)	Transfers and locomotion (walk, wheelchair, and stairs)	Nonambulatory, ambulatory, and vigorous	Seven-level scoring of need for assistance with mobility items Mobility items are integrated into total score
	Minimum data set (MDS)	Bed mobility, transfers, locomotion (includes wheelchair mobility), and walking	Nonambulatory to ambulatory	Used as single items
Performance	Short physical performance battery (SPPB)	Timed walk, chair rises, and tandem stands	Ambulatory	Score 0–12 Scores of 10–12, 7–9, and 4–6 associated with increasing risk of poor outcomes
	Gait speed	Timed walk, varying distances, instructions, and procedures	Ambulatory	Healthy older adult > 1.0 m/s Slow < 0.6 m/s Very slow < 0.4 m/s
	Timed up and go	Time to rise from chair, walk 10 feet, turn, walk back, and sit down	Ambulatory	< 10 s—normal < 20 s—able to move in community > 30 s—needs assistance for mobility
	6-min walk	Distance covered in 6 min	Ambulatory to vigorous	Healthy older adult mean > 500 m Older adults in assisted living < 300 m
	Health ABC	Walking endurance: 400 m walk time, distance in 2 min Expanded SPPB: longer tandem stands, one foot stand, and narrow walk time	Ambulatory to vigorous	Supplements SPPB by increasing discrimination among healthy older adults. Useful for persons with scores of 10–12 on SPPB score range 0–4

Self-report measures are the easiest type of measure to obtain when gathering data from large populations. Self-report measures have high face validity in that they reflect the opinion of the person themselves. Since self-report measures usually ask about a period of time, such as recent weeks or months, they can identify fluctuating ability over time. Self-report measures can be limited by problems with reliability, accuracy, and nonresponse. Because these are usually ordinal scales, they lack ability to discriminate small but important differences.

Professional report measures reflect the opinion of an experienced assessor, can integrate over time, and may be more feasible when an individual is considered an unreliable informant or is unable to cooperate with testing. Professional report is limited by the need for assessor experience and training and can be vulnerable to problems with interassessor reliability unless extensive efforts to standardize assessment are made. Since professional reports are usually based on ordinal scales, ability to discriminate small but important differences might be limited.

Performance measures are more independent of opinion. Performance testing can produce quantitative results, which discriminate small but important or subclinical differences. Performance measures are limited in that they require direct observation, subject cooperation, and standardization of instructions and procedures. These measure capability rather than actual daily mobility activities. The need for subject cooperation can lead to problems with nonresponse. Performance measures do not account well for short-term fluctuations over hours to weeks. Despite these limitations, performance testing may have direct application in clinical settings because it can provide useful information and is brief and quantitative.

Psychological aspects of fear, mobility confidence, and activity avoidance can have great effect on mobility disability, separately or in combination with observable mobility limitations. Several instruments to assess psychological factors related to mobility disability have been developed (**Table 116-3**). Items from these scales might have use in the clinical setting.

TABLE 116-3 INSTRUMENTS TO ASSESS PSYCHOLOGICAL FACTORS RELATED TO MOBILITY

CONSTRUCT	INSTRUMENT/QUESTION	# ITEMS	POPULATION
Fear	Survey of Activities and Fear of Falling in the Elderly (SAFFE)	33	Community dwelling
	Fear	11	
	Activity	11	
	Activity restriction	11	
	Are you afraid of falling? (yes/no)	1	Community and LTC
	How would you rate your fear of falling? (five-point numerical rating 0–4)	1	
Self-efficacy/confidence	Falls Efficacy Scale (FES)[a]	10	Community dwelling, inpatients, and LTC
	Activities-Specific Balance and Confidence Scale (ABC)	16	Community dwelling and patients
Avoidance	Has fear of falling made you avoid activities? (yes/no)	1	Community dwelling and LTC
	Modified SAFFE (mSAFFE)	17	Community dwelling

[a] Several modified versions exist (revised FES, adapted FES, modified FES, and FES United Kingdom).

EPIDEMIOLOGY

Prevalence

The epidemiology of mobility can be considered from the perspective of basic or higher-level mobility. Examples of basic mobility problems are getting around inside the house and transfer from bed or chair. Examples of higher-level mobility problems are getting around outside the house, ability to walk one-quarter or one-half mile, and ability to climb stairs. Basic mobility problems are uncommon in community-dwelling older persons but are very frequent in institutionalized older people. Among community-dwelling persons aged 65 years and older, approximately 5% are dependent in getting in and out of a chair or bed and 7.5% are dependent in getting around inside. Among institutionalized persons older than 65 years, approximately 80% are dependent in getting in and out of a chair or bed and getting around inside.

Mobility disability increases dramatically with age; dependence in getting around inside increases from 5% of persons aged 65 to 74 years to 30% of persons aged 85 years or more. Women tend to have higher rates of mobility disability than men and nonwhites higher than whites. In the past decade basic mobility problems have decreased in prevalence for those older than 85 years, while remaining stable for those aged 65 to 84 years old. The decline in prevalence observed in the oldest old may be due to decreasing rates of disability in some chronic diseases in late life; for example, arthritis and heart disease, the two diseases that have been most commonly associated with increased disability, have become less disabling. With advances in the management of these conditions, progression is delayed, consequently the disabling effect on mobility is reduced. At the same time, there has been an increase in the incidence of obesity and sedentary life style in middle age and among young old: these are also major contributing factors to disability, and these trends may explain why there is not a reduction in disability among the younger old.

Approximately 13% of Americans older than 60 years report higher-level mobility problems in that they have difficulty going outside the home alone. There is a marked increase with age. There is also geographic variation; self-reported difficulty going outside the home alone is more common among older adults in the southern United States. Higher-level mobility problems, defined as difficulty walking a quarter mile or climbing stairs, increase with age, are more common in women than in men, and appear to be decreasing.

Risk of Adverse Consequences Associated With Mobility Status

Mobility problems have serious consequences. Mobility status predicts mortality. Older people with difficulty walking

2 km or climbing one flight of stairs are twice as likely to die during the next 8 years compared to those with no difficulty. Mortality risk is even higher among those who have mobility difficulty and are also physically inactive. Poor mobility performance, even in the absence of self-reported mobility limitations, is an independent predictor of death and nursing home placement. Among persons who report no mobility problems, gait speed less than 1.0 m/s is associated with an increased risk of death. Older persons who have a 0.1 m/s decline in gait speed over 1 year have a double risk of dying during the subsequent 5 years, whereas older persons who have a 0.1 m/s improvement in gait speed over 1 year have a 40% decreased risk of dying in the following 8 years. In a pooled analysis of over 30,000 community-dwelling older adults, each 0.1 m/s faster gait speed was associated with a 13% reduction in risk of mortality.

Poor mobility performance is an independent predictor of future self-care difficulty and mobility disability. Among community-dwelling persons older than 70 years without disability, baseline physical performance score was a powerful predictor of incident disability in both activities of daily living and in higher-level mobility disability. Mobility self-report and performance have been shown to predict disability and mortality in older populations from numerous countries and cultures, including Mexican American, British, Italian, French, Dutch, Spanish, Scandinavian, Australian, Japanese, and Chinese.

Poor mobility performance is also an independent predictor of hospitalization and nursing home placement. In a population-based study of nondisabled older adults, poor baseline physical performance score was associated with a twofold increased risk of hospitalization and more days in the hospital over the following 4 years, independent of baseline health status. The risk was mostly associated with hospitalization for dementia, pressure ulcer, hip fractures, other fracture, pneumonia, and dehydration.

Mobility may be part of an underlying constellation of core factors that link multiple outcomes associated with aging. Poor mobility as measured by timed chair stands is one of four factors proposed to be common risk factors for geriatric syndromes, including incontinence, falls, and functional decline. Conversely, good mobility, along with good cognition and nutritional status, is an independent predictor of recovery of independence after a period of disability. Abnormalities of gait and slow gait speed have been found to precede the onset of cognitive decline and dementia, especially vascular dementia. Among older adults, simultaneous abnormalities of mobility, cognition, and mood are more common than would be expected by chance, perhaps implying potential common underlying causes.

Severe mobility disability, sometimes called immobility, has widespread and devastating consequences. It accelerates impairments in multiple organ systems, including bone, muscle, heart, circulation, lung, skin, blood, bowel, kidney, nutrition, and metabolism. Loss of organ system function can be rapid and severe; muscle strength can decline by 1% to 5% per day of enforced bed rest. Skin breakdown and pressure ulcers start to occur after only hours of persistent and unrelieved pressure. Major consequences of clinical significance include decreased plasma volume, orthostatic hypotension, accelerated loss of bone density, muscle weakness, decreased pulmonary ventilation, and constipation leading to fecal impaction. When even temporary bed rest is combined with the increased vulnerability of aging and acute illness, there is a marked increased risk of death, disability, and institutionalization.

PATHOPHYSIOLOGY

The causes of mobility problems are complex. Unique and complementary etiologic perspectives can all contribute to a better understanding of mobility. Three perspectives are described here: epidemiologic, biomechanical, and biomedical. Each has advantages and disadvantages.

Epidemiologic Perspective: Risk Factors

Epidemiologic risk factors for the onset of higher-level mobility disability include demographics, health behaviors, psychological factors, and diseases. Among the demographic factors associated with increased risk, advancing age has the strongest effect, with lower income, and lower educational level also playing a role. Behavior-related risk factors include current smoking, alcohol abstention, low physical activity, high body mass index, and high waist circumference. Exposure to some of these factors as early as in mid-life can have an effect on development of disability later in life. Physical activity, a health behavior that is a key to mobility, is influenced by multiple psychological, social, and environmental factors. Common reasons given by older adults for limiting or avoiding physical activity include lack of an exercise companion, lack of interest, fatigue, fear of falling, weather, and safety. Self-reported conditions identified as major barriers to physical activity by older adults include arthritis and past injury. Psychological factors that influence mobility include negative attitudes toward aging, fear of falling, and poor

emotional vitality. Self-reported conditions associated with increased risk of new higher-level mobility disability include baseline and incident heart attack and stroke, baseline hypertension, diabetes, angina, dyspnea, exertional leg pain and incident cancer, and hip fracture.

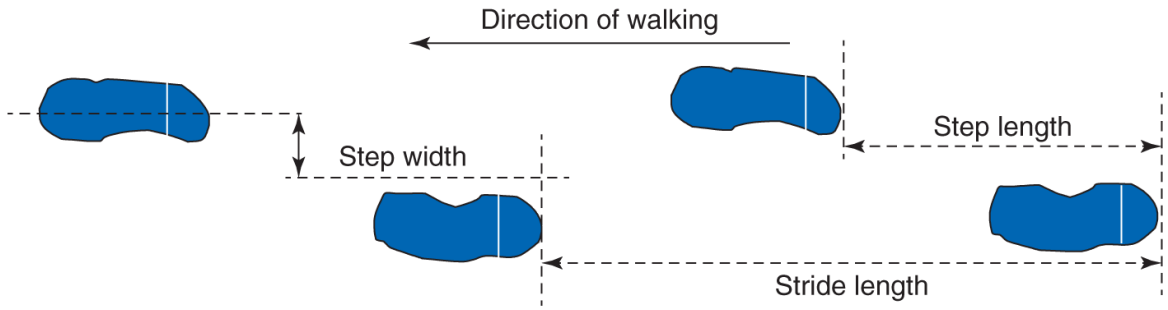
Biomechanical Perspective: Direct Assessment of the Body in Motion

Age affects the biomechanics of walking (also see Chapter 114). Normal gait can be defined in terms of the gait cycle with two main phases: stance and swing (**Figure 116-1**). A normal cycle begins with a push off from the forefoot, then a swing through and heel strike, timed tightly to be followed by the push off of the other leg. Normal gait has highly characteristic patterns of foot, ankle, knee, hip, pelvis, trunk, and arm motion. Gait biomechanics can also be viewed from the perspective of the pattern of steps (footprints) (**Figure 116-2**). Step length is the forward distance between two foot falls. Stride length is the distance covered by one foot until it falls again. Stride length is, therefore, twice the step length, assuming the step lengths are the same on both sides. Step width is the lateral distance between two foot falls. With age, gait speed slows, step length decreases, and the proportion of the gait cycle when both feet are in contact with the ground (double support time) increases. During gait, older people compared to young adults tend to have more thoracic kyphosis, more anterior pelvic tilt, increased hip flexion, and greater external rotation of the foot. Older people tend to generate less power about the ankle and use hip flexion to compensate more than young adults. Normal gait has a very regular spatial and temporal pattern. An irregular gait can be either regularly irregular, like a limp, or irregularly irregular, with no pattern at all (**Figure 116-3**). Irregularly irregular gait, often called gait variability, predicts falls and mobility disability.

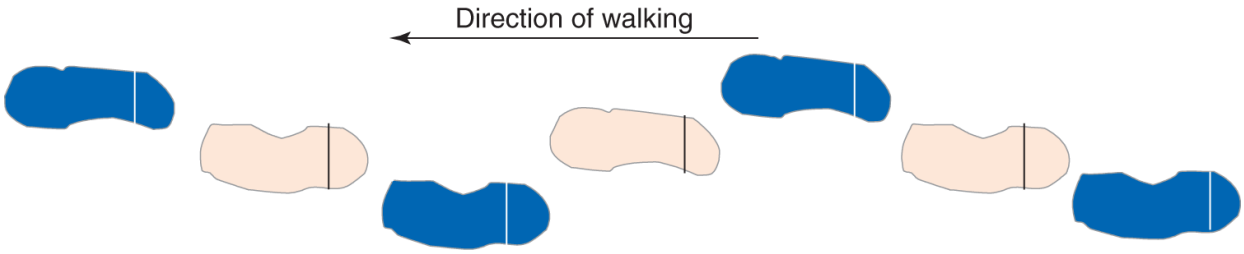
				
Right Lower Extremity (LE)	**Heel strike**	**Stance**	**Toe off**	**Swing**
Ankle Joint:	Neutral position (90°)	Neutral position (90°)	Plantar flexion for push off	Dorsiflexion for foot clearance
Muscles:	Ankle dorsiflexors active to support position of ankle	Plantar flexor torque drives foot into floor, ankle dorsiflexors eccentrically active to slow foot	Plantar flexors active	
	Weight rolls from heel to toe			
Knee Joint:	Extended to prepare for weight bearing	Slight knee flexion (shock absorbing) progressing to full extension for stable weight bearing	Extension progressing to passive knee flexion to prepare for swing	Knee flexion for foot clearance progressing to passive extension for limb advancement
Muscles:	Initially, knee extensors (quadriceps) active then both quadriceps and hamstrings active for knee stabilization	Quadriceps eccentrically active to decelerate knee flexion		Hamstrings and gastrocnemius active for knee flexion, relax for knee extension
Hip Joint:	Hip flexed ~30°	Progressive hip extension	Hyperextension of the hip progressing to hip flexion	Hip flexing to advance limb
Muscles:	Hip extensors active for stability	Hip extensors active initially; Hip abductors active to keep pelvis neutral	Hip flexion initiated by hip abductors and hip flexors	Hip adductors and flexors active for swing, hamstrings active to terminate swing
Left LE*	Toe off	Swing	Heel strike	Stance
SUPPORT	Double support	Single support (right)	Double support	Single support (left)

*Note: When the right LE is at heel strike, the left LE is approaching toe off and vice versa. When the right LE is in stance the left LE is in swing and vice versa.

FIGURE 116-1. Human walking.



Step length = the distance between two consecutive footprints on opposite sides of the body.
Stride length = the distance between two consecutive footprints on the same side of the body.
Step width = the distance between the inner most borders of two consecutive footprints.



Dark-colored footprints represent foot placement during walking.
Quick clinical inspection for approximation of normal gait:
Step length = 1 step length between right and left steps (light-colored footprint).
Step width = 1 foot width (light-colored footprint) between right and left steps

FIGURE 116-2. Step patterns in human walking.

A. Usual gait: right and left step lengths approximately equal.



B. Asymmetric gait (limp): right step length consistently shorter than left step length. All left step lengths approximately equal and all right step length approximately equal



C. Variable gait: inconsistent right and left step lengths.



Blue = left foot prints, Grey = right foot prints

FIGURE 116-3. Gait patterns.

Normal walking maximizes energy efficiency. When walking changes owing to biomechanical alterations caused by disease or aging, walking becomes more energy demanding. Normal walking also requires excellent control of balance and timing. When problems develop with balance and timing, the priority for safe walking may be to increase stability and support at the expense of losses of energy efficiency. Thus, many changes with aging increase the energy cost of walking and decrease gait efficiency.

A biomechanical perspective can be applied broadly to mobility and balance, based on the increasing biomechanical demand placed on the body in motion. Typically, tasks are considered more challenging as the base of support narrows and transfers of mass over the base become more demanding. Thus, difficulty increases from sitting to standing to walking, to climbing stairs, walking a line, or running. A biomechanical approach to postural alterations and body-segment movement abnormalities can be useful for identifying causes of, and solutions to, mobility problems. Specific abnormalities can be addressed by targeting rehabilitative programs, the type of assistive devices, or the design of environmental adaptations.

Physiologic Perspective: Using Organ System Impairment to Link Function and Disease

The causes of mobility limitation can be assessed from a physiologic perspective. There are three main physiologic components of mobility: balance control (neurologic system), force production (cardiopulmonary and muscular systems), and structural support (skeletal system—bone and joints). Ferrucci has created a framework that identifies six main physiologic subsystems of the ability to walk: central nervous system, perceptual system, peripheral nervous system, muscles, bones and joints, and energy production. Another way of organizing the systems that affect walking is to consider inputs and outputs. In this approach, the physiologic elements of mobility can be assigned to three main components based on a sequence of information from sensory inputs to central processing to effector factors that carry out instructions from the brain. Sensory inputs include vision, vestibular function, and peripheral sensation. Central processing includes level of consciousness, integration of sensory inputs, coordinated timing of multiple segmental body motions, and postural reflexes. Effector-related factors include generation of muscle strength and power, endurance, pain, speed of reaction, and flexibility. There are several important emerging areas of knowledge related to our understanding of the physiologic contributors to walking. Brain abnormalities found on magnetic resonance imaging (MRI) are associated with alterations in central processing and abnormal gait. Small vessel cerebrovascular disease in the absence of stroke and MRI findings of “white matter disease” or focal grey matter atrophy are associated with slower gait speed, even among high-functioning older adults. These MRI findings predict the onset of mobility disability. Such brain abnormalities appear to be most pronounced in the frontal areas, in regions that are most vulnerable to changes in cerebral perfusion with older age. These areas have been found to concurrently affect mobility, cognition, and mood and may suggest a shared underlying cerebrovascular process. Another emerging area of knowledge is related to subclinical losses of dopaminergic transmission in the brain in the aged. These losses of dopaminergic function also contribute to altered mobility and may present clinically in patterns that differ from traditional Parkinson disease. Dopamine deficiency in the aged may be related to cerebrovascular disease. Loss of oxygen-carrying capacity because of anemia has been recognized as a potential contributor to mobility limitations, especially in Caucasians, perhaps owing to decreased endurance but also possibly because of chronic subclinical ischemic effects on the brain. Research on the links among cardiovascular risk factors, brain structural abnormalities, mobility, cognition, and mood is developing rapidly. In the future, it may be possible to refine these observations into diagnosable and possibly treatable disorders. It is possible that attention to cardiovascular risk factors might reduce the risk of developing some of these brain abnormalities and thus potentially reduce the incidence of mobility problems.

A physiologic perspective on mobility helps define organ system impairments, which can be linked to treatable diseases, conditions, and pathologic processes, as described by the disablement process in **Table 116-1**. A physiologic perspective is also helpful when accounting for the multiple interacting health problems of many older adults. When more than one organ system that is important for mobility is impaired, the risk of mobility problems increases. Thus, mobility can be affected when one system is severely disrupted, when several are modestly disrupted or when many are mildly disrupted. A physiologic perspective also helps account for the phenomenon of stress-induced disability. Organ systems have excess capacity, called physiologic reserve. Losses of organ system function can be clinically unapparent because these are losses of unused reserve or because one system is compensating for another. Many subclinical physiologic losses may not be recognized until stress is placed on the system by further physiologic decline or by an unexpected high demand on the system. When sufficient reserve is lost or a compensating organ system fails, mobility disability becomes overt. For example, when persons with many subclinical physiologic losses face an

unexpected mobility demand, such as walking on ice at night, they may face a demand that is greater than their mobility capacity. Mobility reserve can now be assessed. One way to challenge reserve is to perform simultaneous physical and cognitive tasks. Described as “dual tasks,” older individuals may deteriorate significantly when asked to walk and talk or walk and perform a mental calculation. Mobility tests that incorporate obstacles also assess reserve. Tests of gait variability may be another way to detect subclinical change in mobility.

A physiologic perspective can help define interventions, based on the disablement structure described in **Table 116-1**. Treatments could be aimed at managing the underlying pathologic conditions that are causing the impairment (eg, improving cardiac ejection fraction through treatment of congestive heart failure), treating the impairments themselves (eg, strength training), or creating compensations and adaptations at the level of functional limitations (such as using a cane). A physiologic approach offers a constructive way to connect biomechanical and clinical mobility assessment to a biomedical model of diagnosis and treatment.

Gait Speed as an Integrator of Multiple Approaches

Walking is the foundation of mobility, is influenced by biomechanical and physiologic processes, and is a major driver of disability. Walking speed could be considered a “vital sign” in older adults. While there are several influences on measures of gait speed such as leg length, gender, or periods of acceleration and deceleration, in general gait speed can be interpreted clinically. Normal usual walking speed in the older adult should be at least 1 m/s. When measuring a fixed walk distance, this means that the time should be less than the distance in meters. For example, a 4-m walk time should be less than 4 seconds. When measuring a fixed time, this means that the distance should be more than the time in seconds. For example, the distance walked in a 6-minute walk (360 seconds) should be more than 360 m. The normal step frequency of walking (called the cadence) is a little more than two steps per second or somewhat more than 120 steps per minute. With approximately two steps per second at a normal pace of 1 m/s, there is approximately 0.5 m or 20 in in a step. Clinically, this translates into approximately two shoe-lengths per step, or an imaginary “shoe” in between each step (see **Figure 116-2**).

As a general rule, there are links among walking speed, energy expenditure, and disability. Energy expenditure can be measured in metabolic equivalents (METs). One MET is the energy requirement for lying in bed. Two METs is twice the energy requirement for lying in bed and is approximately the energy requirement for self-care activities. The usual energy cost in METs of walking at various speeds has been reported in relationship to miles per hour, and walking speed can be translated directly between meters per second and miles per hour. Therefore, the energy requirements in METS and the expected activity level can be associated with gait speed, as described in **Table 116-4**. This conversion table allows clinicians and researchers to approximate the functional status of individuals or populations based on any measure of gait speed. Using METS as a basis for function, a sequence of mobility capacities is described in **Table 116-5**.

TABLE 116-4 TRANSLATING WALKING SPEED: WALKING SPEED, METS, AND FUNCTION

WALKING SPEED			METs	FUNCTION
M/S	MPH	6-MIN WALK DISTANCE (M)		
0.67	1.5	240	< 2	Self-care
0.89	2.0	320	2.5	Household activities
1.0	2.2	360	2.7	
1.11	2.5	400	3.0	Carry groceries and light yard work
1.33	3.0	480	3.5	Climb several flights of stairs

METS, metabolic equivalents.

TABLE 116-5 EXAMPLE OF A SEVEN-LEVEL CLASSIFICATION OF MOBILITY BASED ON ENERGY EXPENDITURE

Level 1	Able to perform sustained physical activity for at least 30 min at a vigorous pace like running, jogging, and tennis. Greater than 4 METs, sustained activity
Level 2	Able to perform sustained physical activity for at least 60 min at a usual pace like walking one or more

	miles. 3.5–4 METs, sustained activity
Level 3	Able to perform physical activity at a usual pace for at least 15 min like walking one-half mile. 2.5–3.5 METs, limited duration of activity
Level 4	Physical activity limited. Able to walk one block. May have slowed gait speed. May use an assistive device like a cane to walk. 2.0–2.5 METs
Level 5	Physical activity limited. May have difficulty walking one block but able to walk across a room. May use assistive device like a cane or a walker. < 2 METs
Level 6	Mobility severely limited. Requires wheelchair for indoor mobility. Transfers independently. 1.5 METs
Level 7	Mobility profoundly limited; requires assistance with transfers from chair or bed. 1 MET

METS, metabolic equivalents.

EVALUATION

Strategy for the Clinical Encounter

There are no established standards for the overall evaluation and treatment of mobility problems in older adults. Currently, the best approach is similar to the ones used for other geriatric syndromes. These approaches are all based on a biopsychosocial model that incorporates biomedical, rehabilitative, and psychosocial elements and a multidisciplinary team. The initial goal of assessment is to classify the mobility problem into one of three large groups: **nonambulatory, ambulatory, or vigorous**. For the person who presents in a wheelchair or bed, one can screen for ability to stand or walk with assistance. For ambulatory individuals, a quick sorting strategy is to observe gait. Since most gait parameters are highly interrelated, abnormal gait can be grossly distinguished from normal by a few simple characteristics like use of a gait aid, gait speed less than 1 m/s (or step length less than twice foot length), or step asymmetry. Persons with normal gait can be assessed for higher level fitness by use of one or more screening tests for higher level abilities such as single foot stand for 30 seconds, ability to tandem walk or ability to walk more than 450 to 500 m in 6 minutes. Persons with normal walking but inability to perform higher level tasks might be good candidates for exercise programs for well elders or for further evaluation if the mobility change is recent or causing problems.

Further assessment of the nonambulatory or for those with abnormal gait depends in part on the treatment goals. The team can select a basic strategy; either to try to improve mobility or to compensate for irreversible mobility loss (**Figure 116-4**). This decision is based on the time course of the mobility loss, the potential to reverse impairments, the ability of the patient to participate in treatment, and preferences of the patient. For example, a person with severe cognitive deficits or severe irreversible motor paralysis might be considered more appropriate for compensation than for interventions to improve mobility. Planning for compensation might target mobility care needs and resources. For the person considered to have potential for improving mobility, the major decisions are the timing and value of interventions directly on mobility (usually through exercise and rehabilitation) and on underlying impairments (usually through medical team care). In primary care, the provider can offer a screening and triage function by recognizing mobility disorders and assessing potential for intervention. **Table 116-6** gives examples of a quick system of assessment for symptoms and clinical findings based on the three main involved organ systems. The primary provider can identify and treat overt clinical impairments that can be detected quickly in the clinic, like weight-bearing pain caused by osteoarthritis, or dyspnea caused by congestive heart failure. When the cause of the mobility problem is less obvious, a referral to multidisciplinary team for comprehensive mobility assessment can be considered. Since the potential causes range across many organ systems, this strategy might be more efficient than referral to several organ system–based specialists. Since research into mobility problems is an active and high-priority area in aging, in the future, efficient clinical practice and referral may be better informed by evidence.

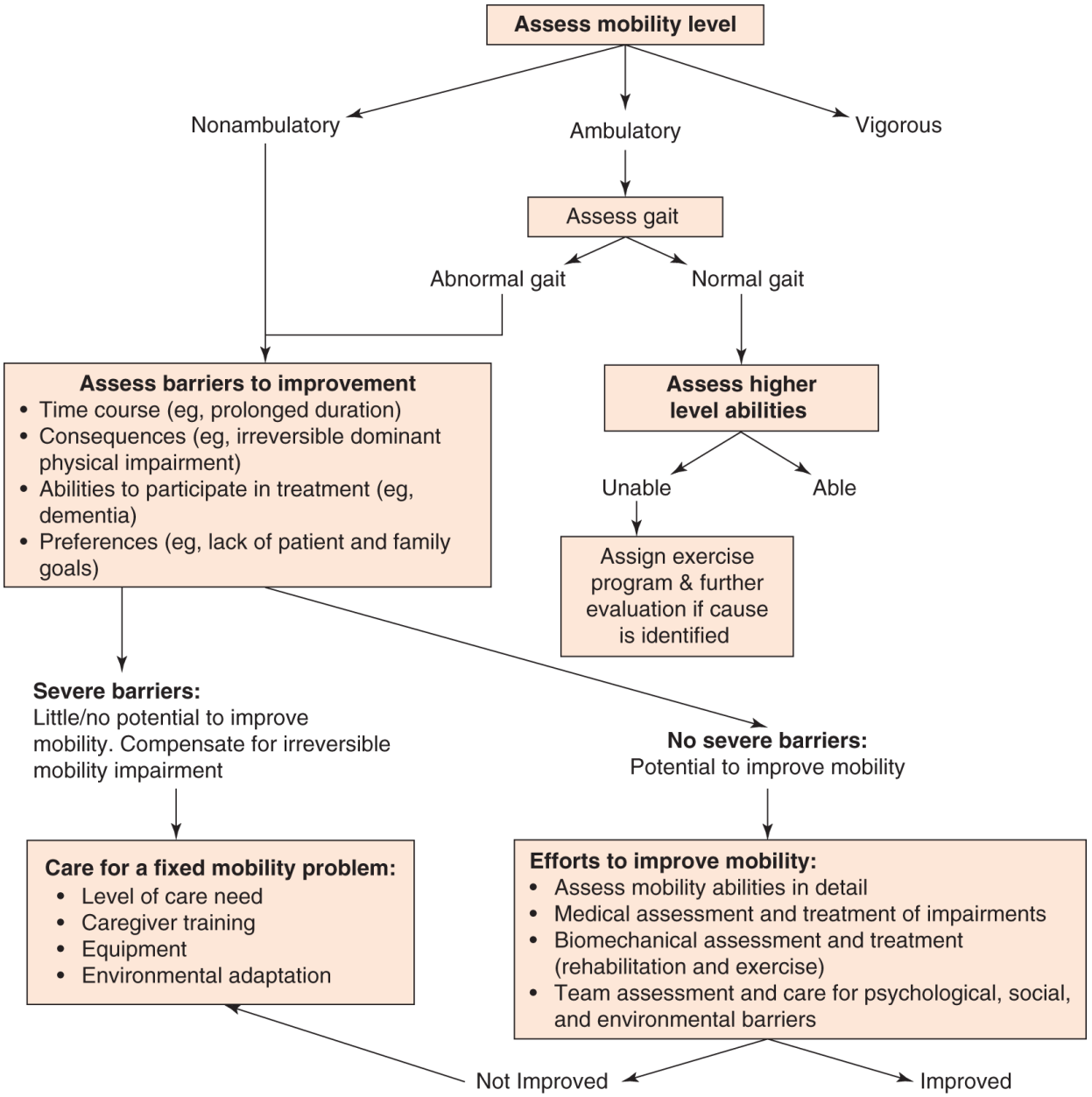


FIGURE 116-4. A clinical strategy for assessment and management of mobility problems.

TABLE 116-6 ■ BRIEF EVALUATION OF MOBILITY PROBLEMS FOR USE IN PRIMARY CARE

SYSTEM	SYMPTOMS LIMITING WALKING	CLINICAL FINDINGS
Cardiopulmonary (lung, heart, and blood)	Dyspnea and fatigue	FEV_1, O_2 saturation with activity, hemoglobin, and ejection fraction
Neurologic (frontal, motor, extrapyramidal, and peripheral)	Unsteady and hesitant	Tone, timed tapping, executive cognitive function, and peripheral sensation
Musculoskeletal (bones and joints, muscles)	Pain and stiffness	Knee, hip, low back range of motion, and pain Manual muscle tests and chair rise

The comprehensive approach to the clinical assessment of treatable causes of mobility is currently a specialized referral function that is resource intensive. Evaluation starts with the clinical assessment of the severity, course and consequences of mobility limitation, and the determination of potential to improve mobility. Mobility performance is assessed in more detail, including biomechanical aspects of functional limitations during movement. Potential contributing factors are identified based on physiologic impairments, and evidence is sought for psychosocial and

environmental influences.

Clinical Assessment of Mobility Performance

In ambulatory patients, simple assessment of gait speed is a useful place to start. The gait speed can be used to estimate function as described above. Gait can be assessed in more detail from a biomechanical perspective (**Table 116-7**). Gait can be examined for general characteristics like path deviations, irregular or variable stepping, or a widened base of support and for altered motion of the component parts: trunk, arms, hip, knee, ankle, and foot. Mobility tasks can be examined for performance difficulty or altered movement patterns as task demands increase. Sometimes, the finding of an abnormal body-segment movement or gait characteristic suggests a specific impairment or disease. More often, the abnormality is nonspecific but is amenable to direct intervention in rehabilitation. A clinical gait assessment that captures many of these biomechanical elements (eg, variable stepping, path deviation, hip range of motion, arm swing) is the modified Gait Abnormality Rating Scale.

TABLE 116-7 EXAMPLES OF A BIOMECHANICAL ASSESSMENT OF COMMON GAIT ABNORMALITIES AND POSSIBLE CAUSES

GAIT ELEMENT	GAIT ABNORMALITY	POSSIBLE CAUSES
Body segments		
Ankle and foot	Forefoot strikes floor simultaneously with initial heel contact (foot slap)	Weak ankle dorsiflexors and decreased proprioception
	Initial contact is by forefoot	Leg length discrepancy, plantar flexion contracture, and painful heel
	Heel and toe leave floor together during push off	Fixed ankle, weak plantar flexors, and painful forefoot
	Forefoot drags during swing (foot drop)	Weak ankle dorsiflexors
	Tendency to roll from plantar to medial surface of the foot while walking	Weak lateral ankle stabilizers and varus knee deformity
Knee	Knee flexed at initial contact	Painful knee, weak knee extensors, leg length discrepancy, and knee flexion contracture
	Decreased knee extension during swing	Knee pain or decreased range
	Hyperextension of the knee in stance	Weak knee extensors
Hip	Decreased hip flexion at initial contact	Weak hip flexors and decreased range of motion
	Increased hip flexion during swing (steppage gait)	Compensation for foot drop
	Decreased hip extension during late stance	Hip flexion contracture
	Hip circumduction with lateral movement of entire limb	Weak hip flexors and inability to flex leg
	Pelvis drops on one side, lateral instability when walking	Contralateral hip abductor or gluteus weakness
	Excessive elevation of the ipsilateral side of the pelvis during swing (hip/pelvic hiking)	Inadequate hip or knee flexion or excessive plantar flexion
Gait pattern		
Gait initiation	Hesitation	Parkinson disease, frontal lobe disorders, and normal pressure hydrocephalus
Stance width	Increased	Cerebellar disorders and peripheral neuropathy

Path	Weaving	Vestibular disorders
	Scissoring (steps cross over laterally)	CNS disorders
	Increased variability	CNS disorders (eg, white matter hyperdensities and lacunar infarcts)

Mobility assessment scales usually have a functional rather than a biomedical perspective and are not designed to detect specific impairments. These scales can be used to identify areas for task practice or adaptation in rehabilitation and to assess the effects of treatment. When selecting an assessment tool, level of mobility of the patient should be considered. For nonambulatory patients, assessments should focus on bed mobility and transfers. The Hierarchical Assessment of Balance and Mobility assesses mobility, transfers, and balance and detects multiple levels within the bed and chair. For ambulatory patients, assessments should focus on walking including unchallenged (straight path walking) and some challenged walking. For patients with vigorous mobility, assessments should focus on more challenging walking tasks such as uneven surfaces, obstacles, curved paths, dual task, and walking for longer distances. Some clinical measures focus on one mobility group (ie, nonambulatory) but many clinical assessments of mobility are based on a hierarchy of task difficulty and will span the various mobility groups. One such measure, the Berg Balance Scale, assesses 14 tasks of progressive difficulty from sitting balance to one leg standing and rising onto a step. The Physical Disability Index has eight mobility tasks including six items for nonambulatory persons. The Activity Measure for Post-Acute Care (AM-PAC) was developed specifically for use across post-acute care settings (from inpatient to outpatient settings) and can also capture a range of mobility. The AM-PAC is based on patient responses and clinician observation, and captures three domains: basic mobility, daily activities, and applied cognitive. The Dynamic Gait Index, which includes eight challenging gait items such as changing gait speed, walking with head turns, and stepping over an obstacle, may be appropriate for patients with higher level (ie, vigorous) mobility.

Differential Diagnosis Based on a Physiologic Perspective

A clinical schema for the comprehensive evaluation of mobility that is derived from Ferrucci, Tinetti, and the authors' own work is proposed in **Table 116-8**. Many impairments are detectable through the usual geriatric clinical history and physical examination. Some sensory systems are amenable to clinical evaluation. Some impairments are hard to detect in the clinic and require further testing. Vestibular testing may be helpful when there is unsteadiness that is not well explained by other impairments or when specific vestibular symptoms are present. Electrodiagnostic testing of nerve conduction velocity or abnormal muscle activity may be indicated when neurologic findings are suspicious. Exertional chest pain or dyspnea requires appropriate cardiac and pulmonary testing and a screen for anemia. Leg pain on exertion suggests testing for peripheral vascular disease or lumbar stenosis.

TABLE 116-8 ASSESSMENT AND TREATMENT OF ORGAN OR SYSTEM IMPAIRMENTS THAT CAUSE MOBILITY PROBLEMS

FUNCTIONAL DOMAIN	ORGAN SYSTEM	IMPAIRMENT	ASSESSMENT	RELATED CAUSES	TREATMENT
Sensory	Eye	Acuity	Near and far by Snellen chart	Presbyopia and cataracts	Lenses and surgery
	Eye	Peripheral vision	Confrontation	Glaucoma and stroke	Prisms
	Eye	Depth	Depth testing	Monocular	Lighting, contrast, and avoid multifocal lens while walking
	Eye	Dark adaptation	Self-report	Miotic agents for glaucoma	Change medications and lighting
	Vestibular	Otoliths	Ability to perceive vertical	Benign positional vertigo	Eppley maneuver and vestibular rehabilitation
	Vestibular	Semicircular canals	Ability to perceive rotation and acceleration	Ménière disease	Medications and vestibular rehabilitation
	Peripheral nerve	Neuropathy	Filaments and vibratory sense	Diabetes and peripheral vascular disease	Haptic enhancement (see text) and footwear
Central	Circulation	Decreased brain perfusion	Hypotension and orthostasis	Medications, arrythmias, postprandial	Change medications, antiarrythmics, or pace-

				hypotension, and dehydration	maker; increase fluid intake
	Brain	Motor processing	Level of consciousness, digit symbol substitution test, and trail making B test	Medications and CNS disorders (white matter hyperdensities, focal atrophy, and brain infarcts)	Change medication and blood pressure control
	Brain	Postural reflexes	Righting reflexes	Parkinson disease and other CNS disorders diseases	Trial of anti-Parkinson medications
Effector	Muscle	Strength	Manual muscle tests and strength-based motions (chair rise and squat)	Multiple neurologic conditions and inactivity	Exercise, bracing, and medication adjustment
	Musculoskeletal	Flexibility	Contractures and range of motion (ROM)	Injury, arthritis, and inactivity	Active and passive ROM and orthotics
	Heart endurance	Cardiomyopathy	Dyspnea at rest or on exertion, fluid retention, and echocardiogram	Systolic or diastolic dysfunction	Standard care for systolic and diastolic dysfunction
	Lung endurance	Hypoxia or reduced air flow	Dyspnea rest or on exertion, hypoxia, and decreased peak flow	Chronic obstructive pulmonary disease, asthma, and other lung	Standard pulmonary care and oxygen
	Circulation endurance	Peripheral vasculature	Leg pain on exertion, decreased pulses, and bruits	Arteriosclerosis and venous insufficiency	Medical and surgical, and exercise
	Hematologic endurance	Anemia	Dyspnea or fatigue on exertion	Multiple causes	Treat based on cause and transfusion for severe
	Muscle endurance	Sarcopenia	Leg fatigue on exertion	Inactivity	Exercise and possibly trophic agents in the future
	Musculoskeletal pain	Bone and joint deficits	Weight-bearing pain	Osteoarthritis, osteoporotic fractures, periarticular conditions, and foot problems	Pain medications, injections, assistive devices, and orthoses
	Neurologic pain	Spinal cord, roots, and nerves	Leg and back pain with activity	Spinal stenosis, radiculopathies, peripheral neuropathies, and CNS disorders	Injections, surgery, and medications

Psychosocial and Environmental Assessment

Mobility limitations are influenced by psychological, social, and environmental factors (**Table 116-9**). Depression can have a powerful effect on the desire to be mobile. Fear of falling, lack of confidence, and low self-efficacy can also adversely influence a person's mobility. Screens for these conditions can include a single question or multiple questions (see **Table 116-3**) and should be part of a comprehensive mobility assessment. Apathy and lack of motivation are a common concern in geriatric rehabilitation. Formal and informal social support resources can be critical for the person with mobility limitations. Cultural and financial factors can influence attitudes toward disability and resources for addressing the problem. The safety and accessibility of the living environment can be a barrier or facilitator for persons with mobility problems. A home visit for assessment can offer many opportunities for creative problem solving.

TABLE 116-9 PSYCHOSOCIAL AND ENVIRONMENTAL ASSESSMENT AND MANAGEMENT OF MOBILITY

AREA	TYPE	ASSESSMENT	MANAGEMENT
Psychological	Depression	Standard screen (see Chapter	Antidepressants and counseling

		71)	
	Self-efficacy	Interview	Counseling
	Apathy	Interview and observation	Stimulants and social therapies
Social	Emotional and instrumental supports	Interview	Community programs and family engagement
	Culture	Interview	Cultural consultation
	Finances	Interview	Community resources
Environment	Physical barriers	Home visit	Environmental adaptations
	Access	Interview and home visit	Community programs

MANAGEMENT

Intervening Directly on Mobility

Interventions directed at functional limitations are often rehabilitative in nature and involve exercise, adaptive equipment, and environmental modifications. Mobility limitations can be addressed through mobility task practice and exercise to improve specific impairments in strength, balance, endurance, and/or flexibility. Since deconditioning is almost always present as a direct consequence of reduced mobility and inactivity, and deconditioning has been found to be treatable in many older adults who are sick or frail, general conditioning programs of exercise are frequently indicated. Assistive and orthotic devices can improve stability and reduce weight-bearing pain. The evidence for the effectiveness of rehabilitation and exercise interventions is growing and has been examined in older adults with varying levels of mobility limitations. In general, increasing the amount of time spent walking, even at moderate pace and in the absence of direct cardiovascular beneficial effects, can be beneficial to improve mobility and reduce disability. Recent studies suggest that a focus on neural control of walking through the development of progressively more complex motor skills may be especially effective in improving walking speed and the energy efficiency of walking. Chapter 29 on rehabilitation and Chapter 115 on exercise present these interventions in more detail.

Treating Impairments

Some impairments can be linked to diseases and pathologic processes that are amenable to treatment, and some impairments can be improved directly regardless of pathologic cause (see **Table 116-8**). Peripheral sensory disorders are often not correctable, but compensation can be achieved through the use of lighting to improve visual information and use of a cane to enhance haptic perception. Haptic perception is demonstrated by the remarkable decrease in sway with eyes closed, seen in persons with peripheral sensory or vestibular disorders, when they are allowed even minimal, nonsupporting contact with a stable surface such as a table or wall. Haptic sensation implies that another sensory input source can be used by the brain to provide information about body position when information from the feet is lost. When a cane is used to promote haptic sensation, it is providing information to the hand about body position and is not used as a weight-bearing device. Shoe inserts that increase sensory feedback are in development. The slowed gait of Parkinson disease can be responsive to medication although the balance disorder is not. Parkinson patients may move faster and thus increase their risk of fall injury when medications are initiated.

Attention to Factors That Modify Behavior and Environment

The modifiable psychosocial factors that influence physical activity may offer opportunities to intervene (see **Table 116-9**). Depression can be managed medically or with psychotherapy. In post-acute care settings, methylphenidate has been used for short term to treat apathy. Social support and encouragement can be promoted through group activities. Exercise (ie, balance, strength training, Tai Chi/dance) may reduce fear of falling without increasing the risk or frequency of falls. Physical environmental adaptations in the home include ramps and railings, bathroom modifications, proper lighting, and strategic placement of stable furniture items. Further modifications are often indicated in institutional settings.

Care for the Immobile Person

Interventions to reduce the consequences of immobility include determining the level of care need and living setting,

training others to properly position and move the patient, implementing a mobilization plan, use of pressure-reducing devices to prevent pressure ulcer, and, sometimes, using equipment to aid in transfers (see Chapter 52). Persons who are responsible for carrying out transfers of immobile patients, including health aides and family caregivers, need training in proper techniques that reduce injury to the patient and the assistant. Absolute bed rest is almost never indicated and should be discouraged in all settings. Mobilization, including walking, has been shown to be feasible even in the intensive care setting. An exception to routine mobilization might be for humanitarian reasons when an individual is actively dying, where routine mobilization might cause suffering without associated benefit. Mobilization rather than bed rest during hospitalization for acute illness has been one of the most consistent interventions in acute care of the elderly units.

SUMMARY

Mobility disorders are widespread in older adults. Mobility limitations constrain many functions required for independent living and are powerful indicators of future problems. Mobility can be classified using simple screening. Evaluation starts with a triage function or simple measures like gait speed. Many common contributors to mobility limitations can be managed in the primary care setting. A comprehensive mobility evaluation is resource intensive and requires a multidisciplinary team. Evaluation and management include a biomechanical approach to function, a biomedical approach to the physiologic components of mobility, and a psychosocial and environmental approach to modifying factors.

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Chapter 117

Osteoarthritis

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Learning Objectives

- To be aware of potential causes and risk factors for developing osteoarthritis (OA).
- To learn how to diagnose OA based on patient clinical presentation, imaging tests, and other diagnostic tools.
- To be familiar with nonpharmacologic, pharmacologic, and surgical treatments available for patients with OA.

Key Clinical Points

1. **OA is a prevalent and disabling disease, especially among older adults.**
2. **Joint pain and self-limited morning stiffness are characteristic symptoms of the disease.**
3. **OA may be diagnosed based on patient-reported symptoms and physical examination findings (eg, Heberden nodes). Radiographic imaging can help confirm the diagnosis.**
4. **Various nonpharmacologic and pharmacologic therapies can be used to treat patients with OA.**
5. **Joint replacement surgery and other surgical options may be considered when conservative therapies fail.**

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent and disabling disease. Nearly 27 million US adults have clinical OA, the most common form of arthritis. This number is also expected to rise with longer life expectancies and the worsening obesity epidemic. Lifetime risk of symptomatic knee OA is 1 in 2 overall. OA is also the third leading cause of years lived with a disability in the United States and is the most common cause of mobility limitation. Finally, the economic burden associated with OA is highly significant due to direct medical costs and indirect costs (eg, lost wages, home care).

EPIDEMIOLOGY, CAUSES, AND PREDISPOSING FACTORS

Age, Sex, and Race

Age is the strongest risk factor for developing OA. The prevalence of the disease increases with increasing age. Among adults over 60, approximately 80% have radiographic evidence of hand OA while 37% have evidence of knee OA. Symptomatic OA is less prevalent, with 7% of all adults having symptomatic hand OA and 12% of those aged 60 years or more with symptomatic knee OA. Among adults aged 45 years or more, 27% have radiographic and 9% have symptomatic hip OA.

Women are more likely than men to be affected by hand and knee OA. This higher prevalence of OA is most prominent among perimenopausal women. Such epidemiologic observations suggest that sex hormones are possible factors in the development of OA. The prevalence of OA may also vary by race and ethnicity. OA of the knee is more common in African-Americans than in non-Hispanic whites or Mexican-Americans. OA of the hip is more common in

people of European descent compared to those of Asian or African descent. Compared to older whites in the United States, older Chinese subjects have higher prevalence of knee OA but lower prevalence of hip and hand OA.

Obesity

Obesity is the strongest modifiable factor for the development of OA. It is estimated that the odds of developing radiographic and symptomatic knee OA is nine times higher among those with the highest compared to those with the lowest body mass index (BMI) tertile. Increased waist circumference and waist-to-hip ratio may also be associated with increased risk of radiographic knee OA, but this increased risk is no longer relevant after adjusting for BMI. Obesity is also associated with having increased risk of developing hand OA. However, there is less consistent data supporting the relationship between hip OA and obesity

Occupation, Sports, and Joint Trauma

OA has also been linked to certain occupations. Working as a farmer or as a construction worker/laborer increases the risk of developing knee and hip OA, especially among those who are overweight. Specific occupational activities such as more than 30 minutes of squatting, more than 30 minutes of kneeling, and climbing more than 10 flights of stairs per day increase the risk of developing radiographic knee OA. Among older adults, recreational walking, jogging, and other recreational activities do not seem to increase the risk of developing knee OA. However, certain sports are associated with increased risk of OA in certain specific joints: American football (knees, feet, ankles); baseball (shoulders, elbows); soccer (knees, hips, ankles); ice hockey (knee); and boxing (carpometacarpal), for instance. This often accounts for the development of OA at joints not usually affected by OA.

The increased risk of OA from occupational and sports activities is likely due to the occurrence of injury rather than participation in these activities. Hip dislocation and femoral acetabular impingement are associated with developing hip OA. Ligamentous or meniscal damage in the knee and surgical meniscectomy both increase the risk of knee OA. In parallel, quadriceps muscle weakness is linked to tibiofemoral and patellofemoral knee OA.

Malalignment and Physical Abnormalities

Joint malalignment may also increase the risk of developing OA. Varus alignment increases the risk of knee OA development and progression. This increased risk is most prominent in overweight and obese persons. Similarly, congenital hip dysplasia increases the risk of hip OA. Specific physical attributes, such as leg length inequality, having a higher knee height, and having an index finger shorter than the ring finger, have all been associated with increased risk of developing radiographic knee OA.

Genetics

Through the development of genome-wide linkage scan, the associations between 12 chromosomes (1, 2, 4, 6, 7, 9, 11–13, 16, 19, and X) and OA have been detected. Candidate genes that may be related with the osteoarthritic process have been identified. Genes that code for structural proteins of the extracellular matrix of the cartilage seem to have a significant role, especially those that code for collagen type II (COL2A1). Genes that code for different interleukins (eg, IL-1A, IL-1B, IL-1RN, IL-4R, IL-17A, IL-17F, and IL-6) may also affect genetic susceptibility to OA. Other genes that have also been implicated in the development of OA include the estrogen receptor α gene, vitamin D receptor gene, frizzled related protein gene, asporin, and others that code for structural proteins and proteins related to cartilage loss.

CLASSIFICATION AND PATHOPHYSIOLOGY

Classification

OA has traditionally been classified as either primary (idiopathic) or secondary to known causes (**Table 117-1**). Primary OA most commonly affects the joints of the hands, knees, hips, and spine. Nodal generalized OA is characterized by polyarticular finger involvement (distal interphalangeal [DIP], proximal interphalangeal [PIP], first carpometacarpal [CMC] joints) and a predisposition to OA of the knee, hip, and spine. It commonly affects middle-aged women with a strong family history of OA. Inflammation is being increasingly recognized as having a role in the pathophysiology of OA. However, only a minority of OA patients have inflammatory symptoms, such as swelling and

redness of the joints. And often, these symptoms are mild and intermittent. Erosive OA is a variant that occurs when there is an additional erosive/inflammatory component, often involving the DIP and PIP joints of the hands. Other individuals may have a phenotype that indicates a larger role for mechanical factors in the pathophysiology.

TABLE 117-1 SECONDARY CAUSES OF OSTEOARTHRITIS

Anatomical abnormalities	Bone dysplasia, congenital hip dislocation
Metabolic/endocrine	Diabetes mellitus, hemochromatosis, acromegaly, hyperparathyroidism, ochronosis
Crystal deposition disease	Gout, pseudogout
Inflammatory arthritis	Rheumatoid arthritis, systemic lupus erythematosus, seronegative spondyloarthropathy, juvenile idiopathic arthritis
Trauma	Fracture, surgery, infection
Others	Avascular necrosis, neuropathic charcot joints

Secondary OA occurs when OA is caused by another disease or condition. Conditions that can lead to secondary OA include trauma; inflammatory arthritis (eg, septic arthritis, rheumatoid arthritis [RA], seronegative spondyloarthropathy, gout); metabolic/endocrine disorders (eg, hemochromatosis, hyperparathyroidism); neuropathic disorders; and anatomical abnormalities. The American College of Rheumatology had also created specific criteria to standardize the definition of OA of the knee, hip, and hands. The criteria are based on patient age, clinical symptoms, physical examination, laboratory findings, and imaging test results. These criteria, though, are based on only patients with symptomatic disease, excludes patients with secondary OA and are intended to classify and not diagnose OA.

Pathophysiology

OA can be thought of as a failed repair of joint damage due to abnormal intra- and extra-articular processes involving a combination of biomechanical, biochemical, and genetic factors. A single or a variety of insults to the joints, including biomechanical trauma, chronic inflammation, and genetic and metabolic factors, can trigger or contribute to the cascade of events that lead to OA. In the earliest stage of OA, fibrillation of the superficial layer of the articular cartilage may be observed. Eventually, the fibrillation extends to the subchondral bone, the cartilage fragments into the joint, the matrix degrades, and the cartilage is completely lost, leaving a denuded bone.

Chondrocytes in the articular cartilage react to insults in the joint that lead to changes in cellular function and matrix elements. Chondrocytes and synovial cells release matrix metalloproteinase (MMP) enzymes, such as collagenases, stromelysins and gelatinases, which are responsible for cartilage degradation. While these MMPs may be susceptible to MMP inhibitors, synthesis of MMPs is enhanced and the inhibitors are overwhelmed in OA. Cytokines have been implicated in the regulation of this process. Interleukin-1 (IL-1), a catabolic cytokine, is known to suppress type 2 cartilage synthesis and to induce proteases. IL-1 level and cell sensitivity are increased in OA. Anabolic cytokines, such as insulin-like growth factor-1 and transforming growth factor β, on the other hand, are found in decreased levels in the serum and synovial fluid of OA patients. Besides cartilage degradation, subchondral bone may also increase in density, potentially reflective of a healing response to microfractures that have occurred. In addition, cyst-like bone cavities may form. Osteophytes, or bony projections that form along joint margins, are often considered a hallmark of OA.

Several other factors have also been implicated in the development of OA. Crystals, including calcium pyrophosphate dihydrate and basic calcium phosphate crystals, have been identified in the synovial fluid of OA joints. Besides their ability to induce inflammation, their role in the pathogenesis of OA remains unclear. The complement system may also stimulate inflammatory mediators and enzymes that can contribute to the pathogenesis of inflammatory OA. Nitric oxide, known to activate MMPs in articular cartilage, may also mediate the osteoarthritic development process. Supported by epidemiologic studies, sex-related hormones have also been considered to play a role in the development of OA, especially in women.

PRESENTATION

Symptoms

Patients with OA most commonly present with pain in the joint. Pain tends to worsen with increased activity or weight-bearing and to improve with rest. Early in the disease, patients may complain of pain that is sharp, intermittent, and unpredictable. These features may often lead patients to limit their activity to avoid the occurrence of this type pain. As the disease progress, the pain becomes more constant and aching in nature. Late in the disease, pain may be noted with progressively less activity, possibly occurring even at rest and at night. Patients may also complain of morning stiffness that typically resolves within 30 minutes or less. Joint stiffness may also occur after periods of prolonged inactivity, also known as the "gelling" phenomenon. Others may report of joint locking or joint instability. Joint stiffness lasting more than an hour, joint pain that improve with activity and persistent joint swelling all suggest an inflammatory type of arthritis, such as rheumatoid arthritis.

Knee OA patients may complain of localized or diffuse knee pain. They may have difficulty climbing the stairs or walking for even short periods of time. Hip OA patients may complain of pain in the anterior hip or inguinal area. Less commonly, their pain may also be felt laterally (ie, in the trochanter) or referred to the knee. They may have difficulty crossing their legs or putting on a pair of shoes.

Hand OA patients may report of pain involving the DIP, PIP and first CMC joints. Gripping, pinching, holding, or lifting objects may be particularly challenging in patients with symptomatic hand OA. OA of the cervical spine can cause neck pain, upper extremity radicular pain and occipital headaches. OA of the lumbar spine can cause lower back pain that may radiate into the posterior thigh and worsen with bending ipsilateral to the involved joint.

Physical Examination

OA patients may have a completely normal physical examination. Typically, they have joint-line tenderness, crepitus (ie, creaking on movement), and bony enlargement. There may be joint effusion or swelling that tends to be intermittent without warmth. With disease progression, the joint's range of motion may decrease. Joint deformity and/or laxity may also develop later in the disease.

In knee OA, there is often crepitus on active knee motion and bony tenderness. There may also be effusion (without warmth) and a limited range of motion. The joint fluid may migrate into the semimembranosus bursa posteriorly, causing swelling along the posterior knee known as the popliteal or "Baker's" cyst. Knee varus ("bow-legged") or valgus ("knock-kneed") deformities may be observed later in the disease. In hip OA, there may be reproducible pain with passive or active range of motion, particularly with extension and internal rotation. The range of motion in the hip joint may also be limited. Hip OA patients may also develop an antalgic gait in which the stance phase of the gait is abnormally shortened on the affected hip joint.

In hand OA, there is often tenderness of the first CMC joint. Enlargement of the joint can cause a squared appearance of the base of the thumb. Prominent bony enlargement due to osteophytes in the DIP and PIP joints of the fingers are known as Heberden nodes and Bouchard nodes, respectively.

EVALUATION

Diagnostic Imaging

X-rays Osteoarthritis can be clinically diagnosed primarily based on history and physical examination. Conventional radiography may be used to confirm the diagnosis, but it is often not necessary. Before making a clinical diagnosis of OA, however, other diseases should be excluded. At the very least, OA should be distinguished from referred pain, inflammatory arthritis conditions (eg, rheumatoid arthritis, gout, pseudogout), and periarticular bursitis (eg, trochanteric bursitis of the hip, pes anserine bursitis of the knee). Radiographic findings suggestive of OA are very common in older adults, yet many of these patients have minimal OA-related symptoms. Radiographic features of OA include joint space narrowing, osteophytes, subchondral sclerosis, subchondral cysts, and altered bone contours. X-rays may also show calcification of cartilage or other structures and soft-tissue swelling.

Radiographic findings in knee OA patients include medial tibiofemoral and/or patellofemoral joint space narrowing, along with osteophyte formation. Lateral joint space narrowing may also be seen but is less common (**Figure 117-1**). Osteophytes may be seen anteriorly and medially at the distal femur and proximal tibia, and posteriorly at the patella and tibia. Radiographic changes seen in hip OA include joint space narrowing (superior, axial, or medial), osteophyte (femoral or acetabular) formation and subchondral sclerosis.



FIGURE 117-1. Knee x-ray anteroposterior view showing severe joint space narrowing within the lateral compartment, genu valgus, and joint effusion.

With hand OA, the first CMC, the DIP, and the PIP joints are most commonly involved. Joint space loss is typically nonuniform and asymmetric. Hand x-rays of those with erosive OA will reveal erosions and the "gull-wing" deformity (**Figure 117-2**). X-rays of patients with lumbar or cervical OA will reveal intervertebral disc narrowing and osteophytes arising from the vertebral body margins (**Figure 117-3**). Sclerosis and cyst formation may also be seen. Neural foraminal narrowing may result from osteophyte formation, but this is best seen using a computed tomographic (CT) scan.



FIGURE 117-2. Hand x-ray showing joint space narrowing of the index, middle, ring, and small finger DIP joints, and middle finger PIP joint. There are possible central erosions of the index and ring finger DIP joints, suggestive of erosive osteoarthropathy.

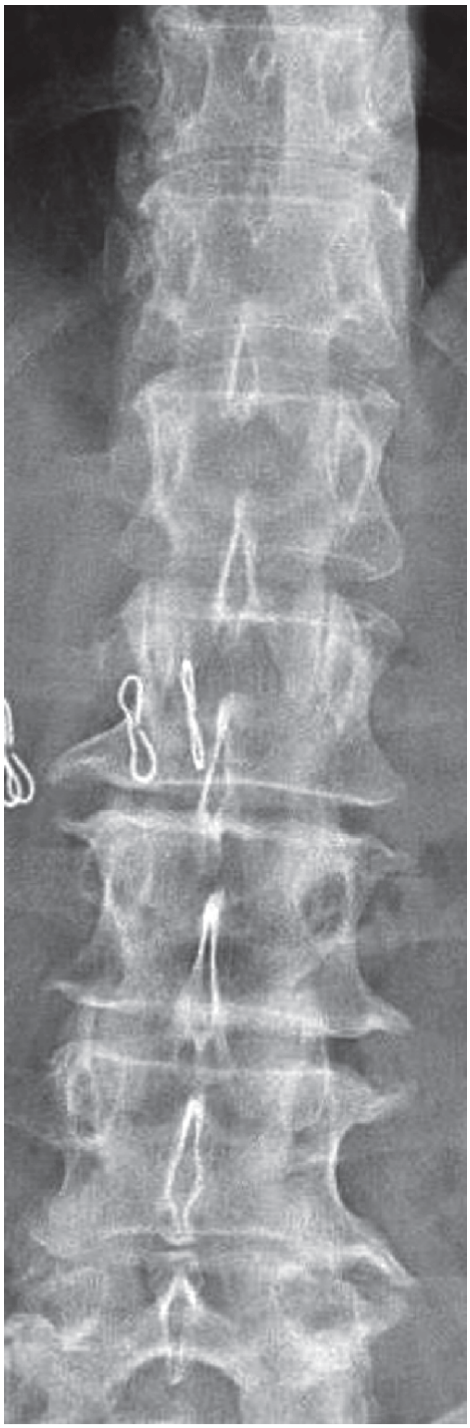


FIGURE 117-3. Lumbar spine x-ray showing extensive osteophyte formation.

Scoring systems, such as the Kellgren-Lawrence grading system, have been developed to assess OA disease severity using joint radiographs. However, these scoring systems are primarily used in research. Conventional radiographs also have limited resolution and cannot detect early disease. They also only provide images of bony structure and are simply two-dimensional projections of three-dimensional joints. Multiple views are necessary to properly visualize the joint and detect possible OA involvement.

Magnetic resonance imaging Magnetic resonance imaging (MRI) has allowed the detection of preradiographic OA. It has demonstrated that bone marrow lesions, meniscal damage and synovitis are important features of OA. It offers greater resolution than an x-ray, provides depiction in three dimensions, and allows visualization of bone and soft tissue structures. MRI allows visualization of subchondral cyst-like lesions, subchondral bone attrition, joint effusion, synovitis (with or without contrast enhancement), and meniscal damage. Integrity of ligaments, periarticular cysts and bursae, and osteophytes may also be assessed through MRI. In the process, MRI has contributed to the understanding of the relevance of these structures in explaining pain and structural progression in OA. MRI is not necessary to

diagnose OA. However, it should be considered to evaluate mechanical symptoms of locking or sudden weakness in the knees, instability of the hip and impingement symptoms of the shoulder.

Laboratory Studies

Laboratory tests are unhelpful in diagnosing OA but are helpful in excluding other causes of arthritis such as RA, gout, or infectious arthritis. Inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein level, and immunologic tests, such as antinuclear antibodies and rheumatoid factor, should not be routinely ordered unless there are signs or symptoms suggestive of inflammatory arthritis or autoimmune disease. Uric acid level may be ordered if gout is suspected.

Performing an arthrocentesis may be valuable in evaluating patients with presumptive OA. Synovial fluid findings in OA often show a white blood cell count that is less than 2000 cells/mm^3. Counts that are more than 2000 cells/mm^3 suggest an inflammatory arthritis etiology. Under polarized microscopy, there should be no visible crystals. The presence of gout or pseudogout crystals suggests crystalline arthritis as the underlying cause of joint pain.

A variety of OA-related biomarkers have been identified and validated for several OA outcomes. They are products of cartilage and bone turn over (eg, urine/serum carboxy-telopeptide of type II collagen, serum hyaluronan). However, their utility in diagnosing OA, determining the risk of disease progression and assessing the response to OA therapies are unclear and currently under investigation.

MANAGEMENT

The American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), the Osteoarthritis Research Society International (OARSI), and the American Academy of Orthopaedic Surgeons (AAOS) have all published recommendations for management of OA. The main goals of management are to minimize OA-related pain, improve physical functioning and optimize the quality of life of patients with OA. There are nonpharmacologic, pharmacologic, and surgical treatment options. OA management should be tailored to the individual patient, and optimal management likely includes a combination of these treatment modalities. Evidence suggests, for instance, that patient education, exercise programs, weight reduction, and wedge insoles all offer additional benefit in combination with an analgesic or nonsteroidal anti-inflammatory drug (NSAID).

Patient Education

OA patients should be taught about the goals of OA treatment, and the importance of changes in lifestyle, exercise, pacing of activities, weight loss, and various ways to minimize joint loading. The educational focus should be on initiating self-help and patient-driven treatments rather than simply accepting therapies delivered by providers. Thereafter, the emphasis should be on maintaining adherence to nonpharmacologic and pharmacologic therapies. Such information may be taught through group courses, individual consultations, and regular telephone calls. Participants of these programs report reduction in pain, improvement in function, and weight loss. The programs may also increase patient self-efficacy and physical activities, and decrease the number of OA-related physician visits.

Nonpharmacologic Interventions

Weight loss Weight loss in overweight and obese individuals with OA of the lower limb is recommended by all existing guidelines for knee and hip OA management. In many patients, a structured weight management program may be necessary. An effective program focuses on developing healthy eating and physical activity habits. It should include a plan for the individual to lose weight slowly and steadily and to maintain the weight-loss over the long run. A realistic goal is weight loss of more than 5% to be achieved within a 20-week period. The program may include ongoing feedback, monitoring and support. Weight reduction has been shown to improve knee OA-related pain, stiffness, and disability. Studies also suggest similar benefits in patients with hip OA, but the evidence is not as strong as for knee OA.

Exercise Aerobic exercise and muscle strengthening can significantly improve the physical health and symptoms of patients with OA. Regular aerobic activities that the older adults can engage in include walking, bicycling, or swimming. Quadriceps muscle strengthening can be particularly helpful for patient with knee OA. In general, there is no significant difference in reducing arthritis-related symptoms and disability in knee and hip OA patients between

aerobic and resistance training.

For patients with advanced OA, mobilization exercises (ie, stretching and flexibility training) and isometric strengthening exercise can initially be prescribed. Mobilization exercises increase length and elasticity in muscles and periarticular tissues. During isometric exercises, muscle length does not noticeably change and the affected joint does not move. Beneficial isometric exercises for the older adult include chair leg extensions, wall sits, and hip extensions. The exercise regimen may then progress toward isotonic strengthening and aerobic exercises. During isotonic exercise, muscle tension remains unchanged but muscle length changes. Beneficial isotonic exercises include squats, wall slides and leg presses. Finally, water-based exercise is a low-impact activity that takes the pressure off joints, muscles, and bones. It is particularly invaluable for those with severe OA and marked deconditioning.

Physical therapists may be helpful in providing instructions in appropriate exercises. They are essential in providing individualized treatment and a progressive home exercise program. Physical therapy evaluation may also result in provision of assistive devices, such as canes and walkers.

In summary, exercise can be a joint-specific range of motion and/or strengthening program, or a general aerobic conditioning regimen. It may be supervised on land or water, or it may be a home based, self-directed program. Regardless of the type of exercise regimen, extra attention is needed for older patients to enhance safety and compliance with the program, taking into account potential comorbidities. Those with knee or hip OA should also cautiously engage in moderately or severely strenuous exercises (eg, stair climbing, heavy weight lifting, and running).

Manual therapy Manual therapy entails passive physiologic and accessory joint movements, manual muscle stretching and soft-tissue mobilization. Therapy is often administered by a physical therapist in multiple sessions. Specific joints can be targeted. In combination with exercise, manual therapy can be highly beneficial in patients with knee and hip OA.

Braces, splints, and taping A knee brace can reduce pain, improve stability and diminish the risk of falling for knee OA patients with varus or valgus instability. Separately, a brace and a neoprene sleeve have additional beneficial effect for knee OA compared with medical treatment alone. A brace tends to be more effective than a neoprene sleeve, however. Splints can be helpful for patients with trapezio-metacarpal joint OA of the hand. Medially directed patellar taping may benefit patients with knee OA.

Orthoses All patients with knee or hip OA should receive advice regarding appropriate footwear. Among patients with knee OA, insoles can reduce pain and improve ambulation. Laterally wedged insoles can provide symptomatic benefit and decrease lateral thrust in the knee of patients with medial compartment OA. They can also potentially reduce NSAID usage. In parallel, medially wedged insoles can be beneficial for patients with lateral compartment knee OA. Comfort, fit, and adherence are all reasons that the use and benefit from orthotics have been limited.

Heat and cold therapy Thermal modalities may be effective for relieving OA symptoms, but benefits may also be temporary. All patients with hand, knee and hip OA should be instructed in the use of thermal agents. Heat can be administered by various techniques including the application of heat packs or immersion in warm water or paraffin baths. There are also store-bought heat patches, belts, packs, and wraps. Patients should be instructed that use of heat therapies should be limited to 20-minute intervals to reduce the risk of burns. Cold (or cryotherapy) can be administered by application of ice packs or massage with ice. It can decrease inflammation, minimize muscle spasms and reduce pain. Patients should be instructed to also limit the use of ice or cold packs to 20 minutes. Use of heat or cold is often based on patient preference.

Assistive devices Walking aids can reduce OA-related pain in patients with knee and hip OA. A cane can significantly reduce joint loading and symptoms. It should be properly fitted to approximately the level of the greater trochanter of the hip. Patients should be instructed to use the cane with the hand opposite the affected knee or hip. The final bend to the elbow when walking with the cane should be approximately 15 to 20 degrees. When disability is more severe or when OA is bilateral, then a walker may be a better option. Assistive devices, such as zipper pulls, built-up handles on pencils/pens, cushioned carrying tools, and meal preparation devices, can be very beneficial for patients with hand OA. Occupational therapists are likely to be helpful in recommending lifestyle modification changes and giving ideas for assistive devices to patients with arthritis symptoms.

Tai chi and acupuncture Tai chi, a practice which originated in China, is referred to as “moving meditation.” Practitioners move their bodies slowly, gently, and with awareness. It may be beneficial in treating lower extremity OA but the evidence is sparse.

In contrast, there is relatively good evidence that acupuncture relieves pain in patients with knee OA. Pain relief

from this treatment diminishes with time, however. It is also unclear if it actually improves daily function. The addition of acupuncture to patient education and exercises may also provide no additional benefit. Nevertheless, acupuncture is recommended in the guidelines for the management of knee/hip OA by the ACR, EULAR, and OARSI in patients with moderate to severe knee/hip OA-related pain, especially those who are unable or unwilling to undergo joint replacement surgery.

Transcutaneous electrical nerve stimulation (TENS) Such OA patients may also benefit from receiving TENS. It is a therapy that uses low-voltage electrical current for pain relief. Dose-dependent inhibition of nociceptive nerve transmission may provide a physiological rationale for the efficacy of TENS. No serious adverse events have been reported in its use. It can provide short-term pain relief in patients with knee or hip OA.

Topical Agents

Capsaicin and rubefacients Topical capsaicin creams contain a lipophilic alkaloid extracted from chili peppers which activates and sensitizes peripheral c-nociceptors. It is known to be effective in treating hand OA and may be used as an adjunct treatment for knee OA. Both 0.025% and 0.075% topical capsaicin have been shown to reduce pain in hand and knee OA. A dose of 0.025% topical capsaicin is better tolerated than 0.075%, however. Patients should be instructed to avoid inadvertent application of capsaicin in the eyes and mucous membranes. Rubefacients containing salicylates (eg, trolamine salicylate, hydroxyethyl salicylate, diethylamine salicylate) may also be used as adjunctive agents, despite scant supportive data. Skin burning, stinging, and erythema are potential side effects.

Topical NSAIDs Topical NSAIDs, such as diclofenac sodium gel, can be effective alternatives and adjunct agents to oral analgesic agents. They can be particularly helpful in treating hand and knee OA. They have a high margin of safety and are not associated with acute renal failure or gastrointestinal (GI) adverse events. Thus, they may be particularly useful in patients with cardiac, renal or GI comorbidities. However, they may also be less efficacious than oral NSAIDs.

Oral Pharmacologic Therapies

Acetaminophen Because it is inexpensive, safe and effective, acetaminophen may be a first-line agent in treating mild-moderate knee or hip OA. Many have tried using acetaminophen to relieve OA, but few have actually used the maximum daily dose of 4 g/day that was demonstrated to be efficacious in randomized controlled clinical trials. It is important to note that the Food and Drug Administration has reduced the maximum daily dose of acetaminophen to 3 g/day. It may relieve pain, but its effect may be relatively small. Hepatotoxicity is a potential side effect, but this is primarily seen only in patients with concurrent alcohol abuse or when used with other hepatotoxic drugs.

Oral NSAIDs NSAIDs inhibit the activity of cyclooxygenase (COX) -1 and -2 enzymes, providing analgesic and anti-inflammatory effects. They can be very helpful for OA patients who minimally respond to acetaminophen alone and with moderate-to-severe levels of pain. In fact, because of their efficacy, OA patients often prefer using NSAIDs over acetaminophen. There is no strong evidence that a particular NSAID is more effective than other NSAIDs. Patients also vary in regard to how much relief they receive and the side effects they may encounter from taking one NSAID over another. Others may prefer particular NSAIDs (eg, meloxicam, naproxen) based on convenience, as some NSAIDs only need to be taken one to two times a day.

Patients may be started on a low-cost NSAID with a short half-life, such as ibuprofen or naproxen. If they have minimal response after a few weeks, then the medication dosage may be maximized. Switching to a different NSAID is another OA treatment management option.

While efficacious, NSAIDs should be prescribed with caution. GI complications such as peptic ulcer and bleeding are potential side effects. This risk increases with older age, concurrent use of other medications (eg, glucocorticoids), and longer therapy duration. Using either a COX-2 selective inhibitor or a nonselective NSAID in combination with a proton-pump inhibitor reduces this risk. Nephrotoxicity is another potential side effect. Patients with chronic kidney disease (CKD) stage IV or V (estimated glomerular filtration rate less than 30 cc/min) should avoid NSAIDs. Nonacetylated salicylates, sulindac and nabumetone appear to be less nephrotoxic than other NSAIDs, however.

Patients with cardiovascular disease are also at increased risk for cardiovascular adverse events (eg, myocardial infarct or stroke) associated with NSAIDs. Patients should be made aware of such risks. Finally, concomitant use of low-dose aspirin and short-acting NSAIDs (eg, ibuprofen) may also render aspirin less effective when used for cardioprotection and stroke prevention. Other types of NSAIDs should be considered in OA patients taking low-dose

aspirin.

COX-2 selective inhibitors A COX-2 inhibitor (ie, celecoxib) or a COX-2 selective NSAID (eg, meloxicam) can be a better treatment option for a subset of OA patients. They can effectively relieve painful OA symptoms. The risk of GI side effects is also significantly lower with the use of these medicines than with the use of nonselective NSAIDs. Prescribing these medications to patients with cardiovascular risk factors should be done with caution, however. Taking COX-2 inhibitors may increase the risk of myocardial infarct, stroke, and other related conditions.

Narcotic analgesics Tramadol is a weak μ-opioid receptor inhibitor and inhibits the reuptake of serotonin and norepinephrine. It can significantly relieve pain in patients with hand, knee or hip OA. Patients may be started on 25 mg daily, and the dosage may be increased, thereafter. Just like other narcotic agents, it can also cause nausea, dizziness, somnolence, and vomiting. Long-term use may also lead to physical dependence. However, respiratory depression and constipation are considered less of a problem with tramadol.

Stronger narcotic medicines, such as oxycodone, hydrocodone, or morphine sulfate, may be considered in some OA patients after failure of other treatments. Patients who continue to have severe OA-related pain and disability despite trying other pharmacologic and nonpharmacologic OA treatments may be good candidates. Those who are unwilling or unable to undergo joint replacement surgery due to comorbid conditions (eg, significant cardiac or pulmonary disease) may also be reasonable candidates.

Narcotic agents, however, are poorly tolerated in older adults due to sensitivity to certain side effects, including constipation, urinary retention, confusion and sedation. The risk of falls may also be increased in this population who is already vulnerable to falls due to joint disease and other risk factors. If narcotic medicines are to be started in older adults, then the lowest dosages should be prescribed. Adjuvant therapies with nonnarcotic pain relievers should also be considered.

Nutraceuticals Glucosamine and chondroitin sulfate are naturally occurring constituents of cartilage proteoglycans. They are popular “nutritional supplements” used by many OA patients, but their use is highly controversial. Although several clinical trials had shown their efficacy in improving pain and function, these trials were all industry sponsored and utilized a pharmaceutical grade of glucosamine sulfate which is not available in the United States. Several other studies had demonstrated that they were no more effective than placebo. The ACR and OARSI conditionally recommend not using either supplement for the treatment of knee and hip OA. EULAR reports that glucosamine and chondroitin sulfate may provide symptomatic relief for knee OA. Therapy should be discontinued if patients do not respond after 6 months of therapy.

Other nutraceuticals previously used for arthritis include S-adenosylmethionine, pomegranate, green tea, turmeric, ginger, cat’s claw, devil’s claw, collagen hydrolysates, and avocado-soybean unsaponifiables. Evidence of efficacy of each of these treatments is highly limited.

Other options Use of serotonin and norepinephrine reuptake inhibitors, such as duloxetine, is promising in the treatment of OA. They can reduce pain and functional impairment in central and neuropathic pain conditions. Evidence of their efficacy in OA has been demonstrated in clinical trials, however, there have only been a limited number of these trials.

Disease-modifying osteoarthritis drugs (DMOADs) can potentially inhibit the structural disease progression of OA and ideally improve OA-related symptoms. At present, there are no DMOAD therapies available in the market. However, several research studies are being conducted to determine their efficacy and safety. Many studies have focused primarily on preventing hyaline cartilage loss. Because the pathogenesis of OA involves multiple tissues, more recent studies are also targeting other tissues including the subchondral bone. Most DMOADs that are under investigation have an anticatabolic effect on cartilage and may also structurally modify subchondral bone. These include calcitonin, bisphosphonates, inducible nitric oxide synthase inhibitors, interleukin-1β antagonists, matrix metalloproteinase inhibitors, aggrecanase inhibitors, and doxycycline. Others, such as strontium ranelate, BMP-7 and FGF-18, have an anabolic effect on cartilage. Most of these experimental therapies are given systemically, but some are administered intra-articularly.

Intra-articular Therapies

Glucocorticoid agents Intra-articular glucocorticoid (eg, methylprednisolone, triamcinolone) injections can significantly relieve pain due to OA. They can be most beneficial to OA patients who have one or a few joints that continue to be bothersome despite oral pharmacologic therapies. They are particularly efficacious in patients with knee

or hip OA. Knee joint injection can be administered in an ambulatory care setting. Hip joint injection, though, is often done with ultrasonographic or fluoroscopic guidance. When proper technique is used, complications from intra-articular injections such as heavy bleeding and infection are rare. Benefits may be short-lived, though, and repeated treatments at frequent intervals may be necessary to maintain efficacy. More than three injections in a 6-month period is not recommended.

Viscosupplementation Viscosupplementation, the intra-articular injection of hyaluronic acid, is commonly used for symptomatic knee OA. Hyaluronic acid is a large molecular weight glycosaminoglycan which is a constituent of synovial fluid. Hyaluronic acid in OA joints is often of low molecular weight, losing its biomechanical and anti-inflammatory property. Viscosupplementation can lead to significant reduction in pain, improvement in physical function, and reduction in stiffness. It may even be more effective than oral pharmacologic agents in relieving OA-related pain and longer-lasting than intra-articular glucocorticoid injections. However, the product usually needs to be administered at weekly intervals for 3 to 5 weeks. There is a small risk of postinjection reactive inflammatory synovitis and a slight risk of joint infection. Although the AAOS and OARSI OA management guidelines do not recommend the use of viscosupplementation based on multiple meta-analyses, there may be patients that would benefit after failure of other more conservative options. Its cost-effectiveness is also controversial.

Surgical Interventions

Surgical interventions should be considered in OA patients who continue to have significant pain and disability despite maximal use of nonpharmacologic and pharmacologic therapies. Patients must also be healthy enough to withstand surgery.

Arthroscopic debridement and joint lavage Arthroscopic debridement is the removal of loose bodies, debris, mobile fragments of articular cartilage, unstable torn menisci, and impinging osteophytes. The procedure variably includes joint lavage. While it is a relatively common procedure, its practice is highly controversial. While a few uncontrolled studies have demonstrated short-term efficacy, most studies have shown that it is no better than placebo in providing symptomatic benefit for knee OA. These procedures are not recommended as treatment options in the AAOS and OARSI OA management guidelines.

Osteotomy Osteotomy is a surgical procedure in which bone is cut to shorten, lengthen, or change bone alignment. High tibial osteotomy is a potential surgical treatment for knee OA. It is appropriate for unilateral knee OA with varus malalignment. Realignment of the varus deformity would reduce stress on the medial compartment of the knee by redistributing the weight of the body from the arthritic medial compartment to the healthier lateral compartment. The procedure can reduce pain, improve function, and delay the need for joint replacement. Overall failure rate at 10 years is approximately 25%.

Intertrochanteric varus or valgus osteotomy has been used for hip OA treatment for nearly a century. Pelvic or femoral osteotomies have also been used to correct the biomechanics and joint congruency in young patients with hip dysplasias to prevent the development of hip OA. Evidence in the efficacy of these procedures, however, is limited.

Arthroplasty Uncompartmental knee arthroplasty involves replacement of a part or section of the knee that is arthritic. It may be considered in patients with discrete knee pain and disease that is localized to the medial compartment. Compared to total knee arthroplasty, it may also improve knee pain and function but requires a smaller surgical incision. Consequently, there is less postoperative pain, and hospital stay is shorter. The rehabilitation process also tends to be more rapid. Postsurgical complications, such as deep vein thrombosis and infection, are also fewer with unicompartmental than with total knee replacement surgery. The concern about unicompartmental knee arthroplasty, though, is that it may make subsequent total knee replacement surgery more complex.

Total joint replacement surgery is an irreversible procedure used in those with severe OA who have failed conservative treatment modalities. It is usually selected for those with OA of the hip, knee or shoulder. Patients who undergo surgery often attain substantial improvements in pain and physical functioning. Maximal improvements are usually observed in the first 3 to 6 months with long-term benefit plateauing after 9 to 12 months. Quality of life indicators following joint replacement also improve approximately a year after surgery. With current advances, the implant typically lasts 15 years or more. Arthroplasty revision may be required due to aseptic loosening or infection. Risk of revision is also higher in patients with OA younger than 65 years than in those aged 65 years or older.

Joint fusion Joint fusion surgery, also known as arthrodesis, may be selected in patients with severe OA of the wrist, ankle, or first MTP joint. It may also be used as a salvage procedure when knee joint replacement has failed. During

the procedure, two bones on each end of a joint are fused, eliminating the joint itself. While a fused joint loses flexibility, it can bear weight better and may be completely pain free.

Hand surgeries Surgery is considered when nonsurgical options have not significantly helped patients with OA of the thumb base (ie, carpometacarpal or trapeziometacarpal joint OA). Surgical options include trapeziectomy, trapeziectomy with ligament reconstruction, joint replacement and joint fusion. The type of surgery chosen will likely depend on the patient anatomy, the joint involved, and the patient's occupation and recreational activities.

PREVENTION

There are currently no therapies known to prevent the progression of joint damage due to OA. This is largely due to the fact that current definitions of the disease are primarily based on radiographic changes which are insensitive to detecting changes early in the disease course (ie, preclinical OA). However, current research efforts are trying to identify preclinical biochemical and imaging biomarkers that will provide opportunities to diagnose and treat OA earlier. Hence, we may eventually prevent the development and further progression of the disease.

There are also known potential theoretical targets for primary and secondary prevention of OA. These include addressing weight gain/obesity, joint injuries/trauma related to recreational and/or occupational activities, as well as structurally abnormal joints. Patients need to be educated on the benefits of weight loss, including the reduction of knee and hip joint loads. They may also be educated on joint protection techniques (eg, using good body mechanics) to reduce joint injury while working or playing sports. Finally, nonsurgical and surgical strategies may be considered to correct anatomical abnormalities that may contribute to the development of early OA.

CONCLUSION

OA is a highly prevalent disease among older adults. Older age, obesity, structural abnormalities, and previous injury are among the known risk factors for disease development. Patients often present with chronic pain, stiffness, and functional disabilities. Diagnosis is based on history, physical examination, and characteristic radiographic findings. Management of OA should be tailored to the individual patient. Treatment may include a combination of nonpharmacologic, pharmacologic, and surgical approaches with different approaches used over the natural history of the disease.

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Chapter 118

Osteoporosis

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Learning Objectives

- To understand the features of osteoporosis in older persons.
- To identify fracture risk in older persons.
- To learn fracture prevention strategies in older persons.

Key Clinical Points

1. **Both older men and women are at risk of osteoporotic fractures.**
2. **Fracture risk assessment, including clinical factors, should be performed in every person older than 65.**
3. **Calcium and vitamin D should be an essential component of any osteoporosis treatment.**
4. **Antiresorptives (bisphosphonates and denosumab) and anabolics (teriparatide) are effective and safe treatments for osteoporosis in older persons.**

DEFINITION OF OSTEOPOROSIS

The term osteoporosis was first introduced in the nineteenth century based on histologic diagnosis ("porous bone"). Osteoporosis is a "disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture incidence." Osteoporosis may also be defined either by the presence of a fragility fracture or by bone mineral density (BMD) measurement. In defining BMD criteria for osteoporosis, the World Health Organization (WHO) used as the standard the BMD of young adult women who were at the age of peak bone mass. For each standard deviation below peak bone mass (or 1 unit decrease in T-score), a woman's risk of fracture approximately doubles. As seen in **Table 118-1**, a T-score less than −2.5 defines osteoporosis; osteopenia (low bone mass) and normal bone mass are also defined.

TABLE 118-1 WORLD HEALTH ORGANIZATION CRITERIA FOR OSTEOPOROSIS

WHO CLASSIFICATION	BMD T-SCORE
Normal	> −1
Osteopenia	≤ 1 but > −2.5
Osteoporosis	≤ −2.5
Severe osteoporosis	≤ −2.5 + fragility fracture

BMD, bone mineral density.

A BMD measurement may permit early diagnosis of osteoporosis and intervention prior to fracture in older adults. In addition, subjects with osteopenia could be still at risk of fractures and therefore should be followed carefully for

further bone loss. Although the original standards for definitions of osteoporosis were determined in white women, the standards for men and Hispanic women are similar to those of white and African-American women. However, defining osteoporosis solely by T-score does not effectively capture all patients at risk of a fracture. Greater than 50% of all hip fractures occur in those with T-scores that are better than −2.5. Failure to evaluate and treat such patients adds to the individual and societal cost and consequences of osteoporosis. Therefore, we are still faced with the challenge of improving the identification of the individual patient at risk of fracture and subsequently optimizing both prevention and treatment for older adults.

Primary or idiopathic osteoporosis has been historically classified as postmenopausal or senile osteoporosis. Postmenopausal osteoporosis, formerly known as type I, occurs in women between 51 and 75 years of age and is related to estrogen deficiency seen with the menopausal transition. In contrast, senile osteoporosis typically occurs in persons older than 60 years of age. It affects both men and women and has a different pathophysiology, which in some cases involves reduced levels of bone turnover owing to a reduction in the numbers of bone-forming cells. Increasing evidence points to a progressive age-related alteration in stem cell physiology that favors adipogenesis and thereby reduces osteoblastogenesis and bone formation. Nevertheless, estrogen probably plays a role in the pathophysiology of senile osteoporosis as well. Secondary osteoporosis is the result of an underlying disease or medications that adversely affect bone. In this chapter, we will focus on the typical characteristics of senile osteoporosis from its pathophysiology to therapeutic approaches.

EPIDEMIOLOGY

In the United States alone, 10 million people have osteoporosis, and 18 million more are at risk of developing the disease. In addition, women have more than 250,000 and 500,000 hip and spine fractures per year, respectively. Men account for an additional 250,000 fractures per year of which 75,000 are hip fractures.

By using BMD, osteopenia is estimated to be present in 8 to 13 million men (28%–47%) and in 13 to 17 million women (37%–50%); osteoporosis is estimated to be present in 1 to 2 million men (3%–6%) and in 4 to 6 million women (13%–18%). On reaching the age of 90 years, one-third of women and one-sixth of men will suffer a hip fracture. Both women and men have a similar lifetime vertebral fracture risk of 12%. The consequences of osteoporotic fracture include diminished quality of life, decreased functional independence, and increased morbidity and mortality. Pain and kyphosis, height loss, and other changes in body habitus resulting from vertebral compression fractures diminish quality of life in women and men. These changes lead to declines in functional status such as the inability to bathe, to dress, or to ambulate independently and may result in decrease pulmonary and gastrointestinal function. Approximately 50% of women do not fully recover prior function after hip fracture; older adults have 20% to 25% mortality in the year following hip fracture. Men are at a higher risk of dying after a hip fracture than women. Finally, the estimated annual cost of osteoporotic fractures in the United States is more than $22 billion, which is higher than the money spent treating cardiovascular disease. Therefore, prevention and early diagnosis and treatment of osteoporosis are vital to improving the health of older adults.

PATHOPHYSIOLOGY

New advances in the understanding of bone physiology have elucidated an active interaction among bone cells, growth factors, and hormones responsible for the maintenance of calcium levels, skeletal structure, and resistance to trauma. Bone is not simply a mineralized structure but a complex system of cell-cell, cell-matrix, and cell-hormone interactions influenced by genetic background, lifestyle, and diet.

Bone is composed of inorganic (calcium phosphate crystals) and organic compounds (90% collagen and 10% noncollagenous proteins). Noncollagenous proteins include albumin, osteopontin, osteocalcin, α2-HS-glycoprotein, and growth factors, constituting the so-called bone matrix. The bone matrix is produced by osteoblasts and is the environment in which bone and external factors interact in a well-coordinated manner. There are two types of bone: cortical and trabecular. Cortical bone predominates in the long bones of the extremities, while trabecular bone predominates in the vertebrae and pelvis and makes up 80% of skeletal mass. While both types of bone have an active remodeling process, trabecular bone is metabolically more active than cortical bone and more acutely responsive to alterations in sex steroid hormone status.

During childhood and adolescence, skeletal growth takes place at growth plates, areas in which cartilage

proliferates and gradually undergoes calcification, resulting in new bone formation. However, bone remodeling is a lifelong process that maintains bone in order to harbor bone marrow, support the body, and protect vital organs and to provide a source of minerals. The process of remodeling replaces older, frailer bone with newer, more resilient bone in an organized manner. The end product of remodeling is the maintenance of skeletal homeostasis and the preservation of anatomical integrity. With aging or with menopausal transition, the once-coordinated mechanism of bone remodeling with balanced formation and resorption becomes uncoupled, leading to bone loss and increased risk of fracture.

BONE CELLS

The cells involved in bone turnover are osteoclasts, osteoblasts, and osteocytes. Osteoclasts are macrophage-like cells that secrete proteolytic enzymes and hydrogen ions that are required for removal of the deposited bone matrix. The remodeling cycle begins when osteoclast precursors interact with other marrow cells and are activated, becoming multinucleated osteoclasts, which initiates resorption (**Figure 118-1**). Bone resorption occurs within the resorption lacuna, a tightly sealed zone beneath the ruffled border of the osteoclast where it has attached to the bone surface. Resorption depends on acidification of this extracellular compartment leading to demineralization, and, subsequently, the organic matrix is degraded by cysteine proteases, chief of which is cathepsin K. Osteoclasts consequently create a functional extracellular lysosome, containing both an acidic environment and typical lysosomal enzymes.

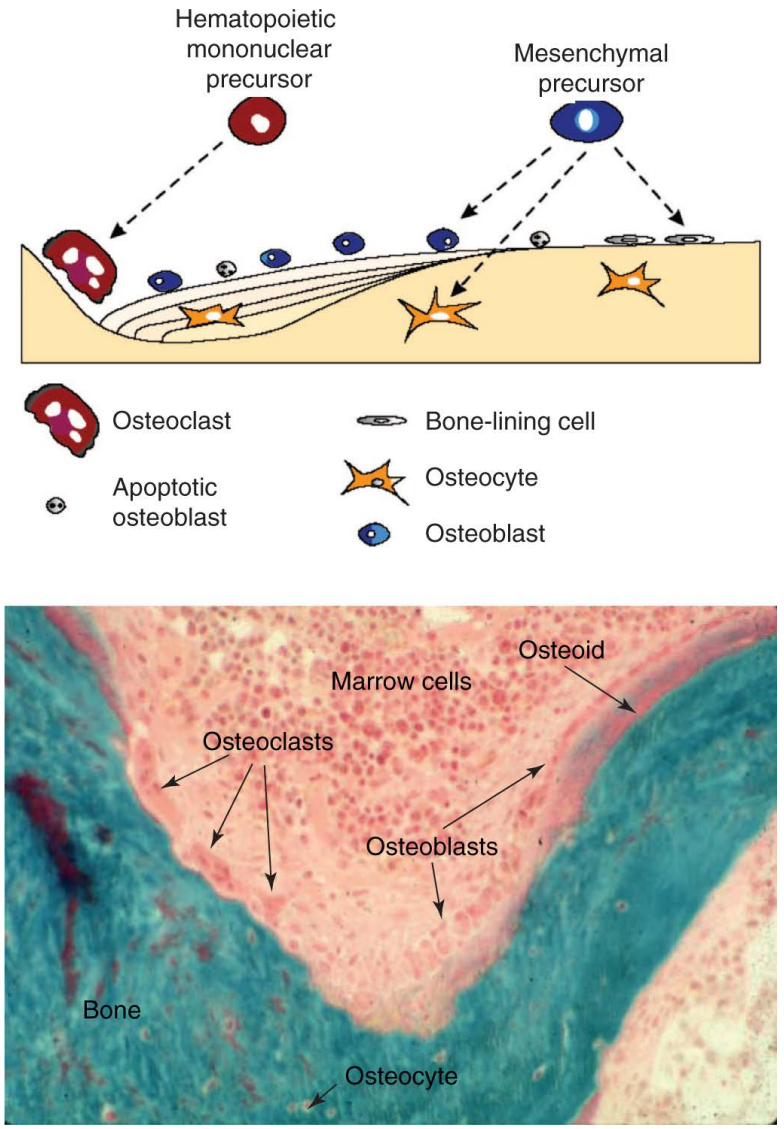


FIGURE 118-1. The cellular components of bone turnover. (**A**) Bone cell formation: After the expression of specific transcription factors, mesenchymal precursors differentiate into osteoblasts. In contrast osteoclasts differentiate from mononuclear precursors and will act as bone

resorbing cells in the bone multicellular unit (BMU). After the completion of bone resorption, osteoclasts die by apoptosis and are replaced by active osteoblasts, which are responsible for the formation of new bone. Osteoblasts finally end as either lining cells, as osteocytes embedded into the osteoid, or die by apoptosis. (Adapted from Chan DK, Duque G. *Gerontology.* 2002;48:62–71.) (**B**) Basic multicellular unit (BMU—also known as bone metabolic unit): Large multinucleated osteoclasts resorb bone on the left. Osteoblasts cascade into the resorption pit, laying down osteoid (unmineralized bone). The turquoise stain reflects mineralized bone. (From Dr. Susan M. Ott < http://courses.washington.edu/bonephys/>.)

In cortical bone, the resorption period lasts approximately 30 days; the final result is a resorption tunnel that will later be filled in by osteoblasts in a haversian manner, in which plates of bone are laid down in plate-like concentric rings around a central channel. The apposition of these haversian canals takes the shape of a "cut onion," which gives the cortical bone its typical morphology. In trabecular bone, the erosion period lasts approximately 43 days, resulting in a trench between the trabeculae. The life span of osteoclasts is approximately 2 weeks; once these cells complete their role as bone-resorbing cells, they undergo apoptosis or programmed cell death.

Osteoblasts are fibroblast-like cells derived from pluripotent mesenchymal cells and localized on periosteal surfaces. Such pluripotent stromal cells can be induced to differentiate along the osteoblastic, adipocytic, fibroblastic, or chondrocytic lineages when required. When bone integrity has to be conserved, mesenchymal stromal cells are committed toward the osteoblastic lineage. Many factors are involved in the process of osteoblastogenesis, including the bone morphogenic protein family; bone morphogenic proteins 2, 4, and 7 are potent inducers of osteoblast differentiation (**Table 118-2**). A transcription factor called Runx2/Cbfa1 plays a key role in osteoblast differentiation; mice lacking Runx2/Cbfa1 do not form bone. A mature osteoblast is a cuboidal cell with a large nucleus and enlarged Golgi highly enriched in alkaline phosphatase. It produces type I collagen and specialized bone-matrix proteins as osteoid, the basic protein for further bone formation and mineralization. Osteoblasts produce alkaline phosphatase, the specific function of which has yet to be determined. Nevertheless, it is used as a marker of osteoblast differentiation and activity, and indirectly as a marker of subsequent osteoclast resorption. Mice lacking functional alkaline phosphatase suffer from hypophosphatasia characterized by impaired mineralization of cartilage and bone matrix. After osteoblasts complete their bone-forming function, they face one of three fates: (1) they become embedded in the newly formed matrix, becoming osteocytes; (2) they remain on the surface of the newly formed bone and become lining cells; or (3) they undergo apoptosis (see **Figure 118-1**). Hormonal changes, the presence or absence of growth factors, and the aging process in bone determine the ultimate fate of the osteoblast.

TABLE 118-2 LOCAL FACTORS REGULATING BONE CELL INTERACTION AND ACTIVITY

Stimulators of bone resorption	**Stimulators of bone formation**
RANK ligand	Vitamin D
Interleukins −1, −6, −8, −11	Estrogen
Macrophage colony-stimulating factor	Androgen
Vitamin D	Insulin-like growth factors
Glucocorticoids	Transforming growth factor
Parathyroid hormone	Mechanical force
Tumor necrosis factor	Fibroblast growth factors
Reduced mechanical force/ low gravity	Platelet-derived growth factor
Epidermal growth factor	Bone morphogenetic proteins
Platelet-derived growth factor	
Fibroblast growth factors	
Leukemia inhibitory factor	
Prostaglandins	
Thyroid hormone	
Inhibitors of bone resorption	**Inhibitors of bone formation**
Estrogen	Sclerostin
Androgen	Dickkopf
Osteoprotegerin	
Interferon-γ	

Interleukin-4 Calcitonin	

In contrast, osteoclasts belong to the macrophage lineage and express multiple very potent degradative enzymes. Osteoclast differentiation, formation, and, to a lesser degree, activation absolutely depend upon the proximity and products of the osteoblast. Without exception, the fate of the osteoclasts is to die by apoptosis.

Finally, osteocytes constitute the third group of bone cells that are involved in bone metabolism. These cells are the most abundant cell type in bone and are the focus of intense research. Osteocytes are postmitotic terminally differentiated osteoblasts that are entrapped within the new bone matrix. These cells, once considered inert bystanders are now recognized to be key regulators of skeletal metabolism, mineral homeostasis, and hematopoiesis. Osteocytes are not only the key responders to mechanical forces but are also orchestrators of bone remodeling and mineral homeostasis (**Figure 118-2**). Although osteocytes are entombed within their hosting lacunae, they are not actually isolated and instead maintain close communication with other cells and micro environments through a complex network of channels (canaliculi) in which osteocyte projections (cilia) are in close contact with blood vessels. Several functions attributed to osteocytes include the synthesis of matrix molecules such as osteocalcin and an important role in direct communication with surface osteoblasts through molecules known as connexins. Two of those connexins, sclerostin and DKK1, are strong inhibitors of osteoblast differentiation and function and play an important role in the activation and regulation of bone in response to physiologic and mechanical stimuli. These modulate the response of bone during functional adaptation of the skeleton to mechanical forces and the need for repair of micro-damage. Any mechanical force applied on the bone (ie, exercise) will have an inhibitory effect on sclerostin and DKK1 thus facilitating osteoblast differentiation, formation, and function. Osteocytes are very long-lived cells with a half-life of 25 years after which most undergo apoptosis.

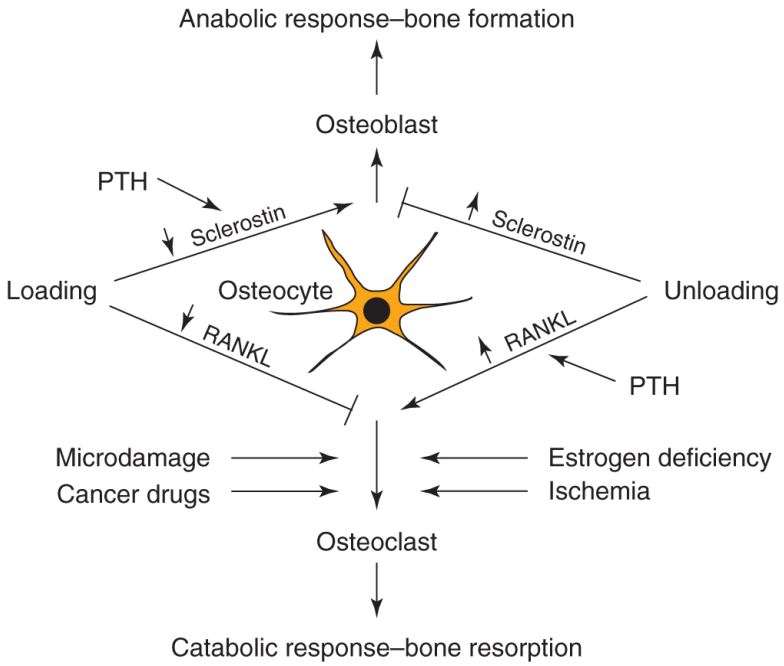


FIGURE 118-2. The central role of the osteocyte in both bone anabolism and catabolism. Mechanical stresses (loading) decrease osteocyte production of both sclerostin and RANKL leading to increased bone formation and decreased bone resorption, respectively. Conversely, lack of mechanical forces (unloading) induces increased production of sclerostin and RANKL leading to decreased bone formation and increased bone resorption, respectively. Interestingly, PTH facilitates both bone formation by inhibiting sclerostin expression and bone resorption by stimulating RANKL expression. This permits very fine regulation of bone remodeling. (Adapted from Atkins GJ, Findlay DM. *Osteoporos Int.* 2012;23(8):2067–2079.)

BONE TURNOVER

Bone homeostasis depends on the intimate coupling of bone formation and bone resorption. After bone is resorbed by osteoclasts, preosteoblasts differentiate into osteoblasts and migrate to the area of excavated bone and begin to deposit

osteoid, which is eventually mineralized into new bone. Osteoclasts and osteoblasts belong to a temporary structure known as basic multicellular unit (see **Figure 118-1**). The coordinated process of bone resorption and formation by the basic multicellular unit lasts 6 to 9 months and results in newly mineralized bone. Osteoblasts are not only active as bone-forming cells, but these also play an important role in the regulation of osteoclast activity. The interaction between osteoblasts and osteoclasts requires a complex system of factors and is facilitated by integrins and cadherins. Briefly, the major osteoclast/osteoblast interaction depends on the expression by osteoclast precursors and mature osteoclasts of a membrane receptor known as receptor activator of nuclear factor-κ B (RANK), which belongs to the family of tumor necrosis factor (TNF) receptors. Osteoclast differentiation, maturation, and survival depend on the activation of RANK by its cognate ligand (RANK ligand—RANKL), which is produced by osteocytes, osteoblasts and osteoblast precursors after exposure to different stimuli such as hormones and cytokines (**Figure 118-3**). Multiple other factors also act to either enhance or suppress osteoclast formation and activation and subsequent bone resorption (see **Table 118-2**).

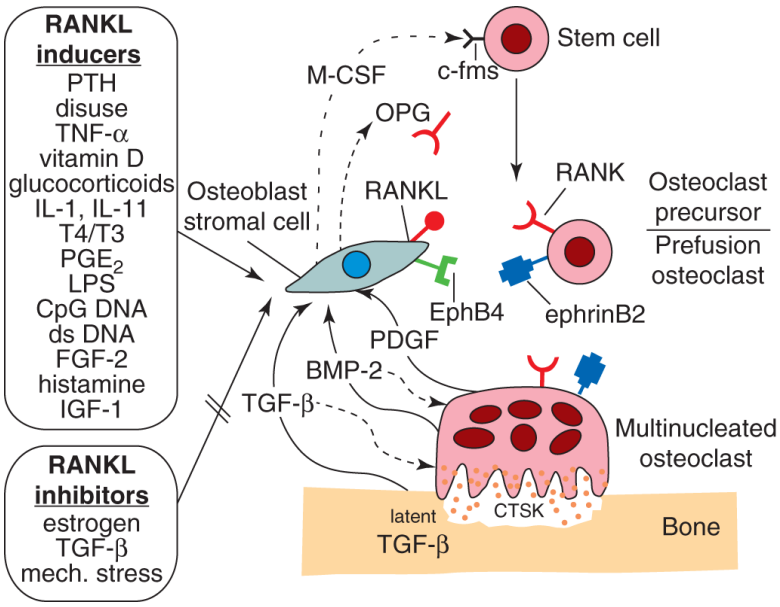


FIGURE 118-3. Osteoblast-osteoclast coupling and the regulation of RANK ligand expression. Osteoblast production of M-CSF and RANKL play critical roles in the differentiation and activation of osteoclasts. M-CSF acts to maintain monocytic stem cell survival, and subsequently RANKL acts to commit the cell toward osteoclast differentiation, fusion, polarization, and activation. EphB4 and ephrinB2 interact both to limit osteoclast activity and stimulate osteoblast differentiation. TGF-β acts only upon release from the extracellular matrix after osteoclastic resorption, which is mediated in large part by the excretion of CTSK. BMP-2, bone morphogenetic protein-2; CTSK, cathepsin K; M-CSF, macrophage colony stimulating factor; PDGF, platelet derived growth factor; RANKL, RANK ligand; TGF-β, transforming growth factor-β.

RANKL is mainly a cytoplasmic membrane-bound molecule; to a lesser extent it is secreted. Mature osteoblasts and osteocytes also produce a decoy receptor for RANKL called osteoprotegerin (OPG). OPG binds to RANKL in a competitive manner and prevents the interaction between RANK and RANKL, thus decreasing osteoclastogenesis and osteoclastic bone resorption and increasing osteoclast apoptosis. More recently a group of molecules known as ephrins has been identified as key players in the regulation of osteoblast/osteoclast interaction. This cellular communication is bidirectional and involves a transmembrane ligand known as ephrinB2, which is expressed by osteoclasts, and its receptor EphB4 expressed by osteoblasts (see **Figure 118-3**). This signaling seems to limit osteoclast activity while enhancing osteoblast differentiation. Consequently, osteoblastogenesis and osteoclastogenesis, along with corresponding bone formation and resorption, are tightly and ineluctably coupled. The differentiation and activation of both osteoblasts and osteoclasts depend critically on each other; however, recent evidence indicates that osteocytes also play an essential role in bone turnover by regulating osteoblast function and survival as well as osteocyte function, all regulated by hormones, growth factors, and mechanical forces.

GENETICS

Genetics plays a role in determination of peak bone mass. Racial differences in the incidence of osteoporosis have

been reported, including a lower relative risk of fractures and higher peak bone mass in African-American women as compared with white women. No single gene, gene product, or polymorphism has yet been credibly identified to account for the variance seen in BMD in specific geographic areas. Several environmental factors, such as diet, topography, and yearly sunlight exposure, almost certainly interact with genetic predisposition to explain variance seen in periosteal expansion before puberty and in trabecular number and thickness and periosteal-endosteal remodeling during aging. Several recently described candidate genes for determination of peak bone mass are the vitamin D receptor, vitamin D binding protein, the peroxisome proliferator activator gamma, the Jagged 1 gene, and the low-density lipoprotein receptor-related protein 5. All these polymorphisms have been associated with different levels of peak of bone mass and predisposition to fractures in the adulthood. However multiple studies have shown that BMD and fracture predisposition are complex traits controlled by multiple genetic loci. More generally, there does appear to be a familial predisposition to osteoporotic fracture. Therefore, the risk of fracture is increased if an immediate family member (most typically a mother or sister) has experienced an osteoporotic fracture.

MECHANICAL FACTORS

Approximately 95% of peak adult bone mass is gained by the end of puberty. The level of peak bone mass attained and the subsequent rate of bone loss are the primary factors that determine an individual's bone mass in early and late adulthood. Initial bone formation does not require a mechanical stimulus, but further appositional and endochondral growth is dependent on the mechanical forces generated by the muscles. The magnitude of this loading is directly related to body mass and physical activity. There is some evidence that after mechanical load, micro-fractures may occur in bone, with subsequent activation of interleukins (ILs) and growth factors, thereby regulating bone turnover and formation. In addition, osteocytes play an important role in the response to mechanical stress by stimulating bone turnover and facilitating bone formation through the release of RANKL and the inhibition of sclerostin and DKK1.

LOCAL FACTORS

Local factors are important in the regulation of bone turnover and in the interaction between bone matrix and systemic factors and hormones (see **Table 118-2** and **Figures 118-2** to **118-5**). The skeleton responds to mechanical forces by several regulatory mechanisms including release of cytokines, such as macrophage colony-stimulating factor (M-CSF) and granulocyte colony- stimulating factor, which regulate cell differentiation. Mediators and regulators of cell-cell interaction include insulin-like growth factor (IGF)-1 and IGF-2, parathyroid hormone (PTH)-related peptide, IL-1 and IL-6, and TNF-α. TNF-α, IL-6, IL-1, and prostaglandins largely mediate the response to sex-steroid hormones. Although high levels of these factors are necessary for osteoblast-osteoclast regulation and pathogenesis of osteoporosis, their usually stable systemic levels suggest that alterations in local secretion and concentration are critical to bone physiology. These local factors largely determine the activation or inhibition of bone cells, cell recruitment, cell differentiation, and life span.

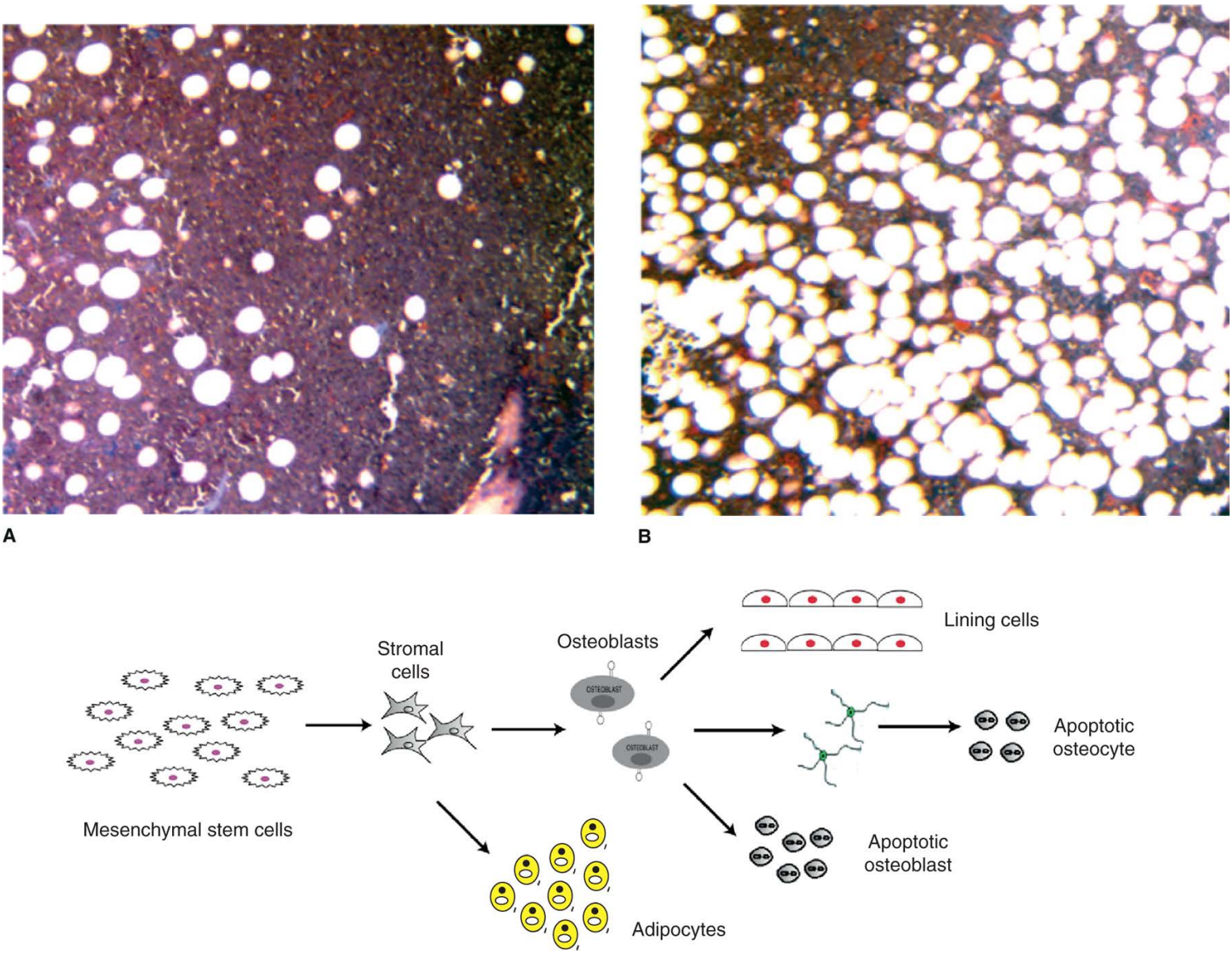


FIGURE 118-4. Cellular changes in senile osteoporosis. (**A** and **B**) The panel on the right shows the much higher levels of bone marrow fat in the iliac crest of a 85-year-old subject compared with a 38-year-old one in the panel on the left. There is also a marked reduction in the amount of hematopoietic tissue. (**C**) Changes in the confluence of mesenchymal stem cells (MSC) accompanied by a reduction in osteoblastogenesis result in the formation of fewer active osteoblasts in the bone multicellular unit. In addition, increasing levels of adipogenic differentiation leads to smaller numbers of differentiated osteoblasts. Finally, increasing osteoblast apoptosis reduces the number of active osteoblasts in the bone multicellular units.

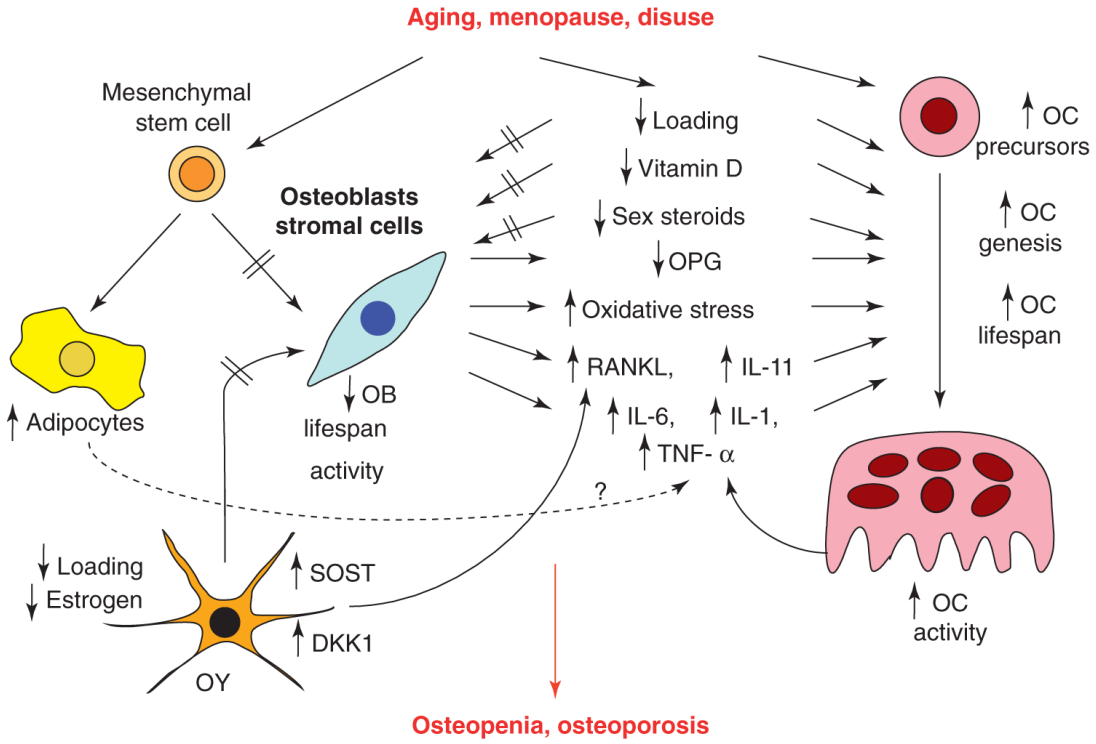


FIGURE 118-5. Changes in osteoblast-osteoclast interactions with aging. Aging predisposes to more adipogenesis and less osteoblastogenesis. In addition, trans-differentiation from osteoblasts to adipocytes may occur. Reduced physical activity/mechanical loading and decreased levels of bio-available estradiol and testosterone exert diminished effects upon osteoblasts (depicted by the arrows with the hatches) resulting in decreased osteoblast secretion of OPG and increased expression and secretion of RANKL, IL-1, IL-6, IL-11, and TNF-α. In turn, these compounds directly stimulate greater osteoclast formation and activity. The reduced OPG also permits greater binding of RANKL to RANK, which further facilitates increased osteoclastogenesis and resorption. Osteocytes (OY) respond to decreased mechanical stresses and diminished bio-available estrogen by increasing expression of sclerostin (SOST) of dickkopf (DKK1), which are antianabolic and by increasing RANKL expression, which is catabolic. (Adapted from Troen BR. *Exp Gerontol.* 2003;38(6):605–614.)

SYSTEMIC HORMONES

A number of systemic hormones affect bone metabolism, including vitamin D, PTH, calcitonin, and sex-steroid hormones (estrogens and androgens) (see **Table 118-2**). The major effect of vitamin D is to maintain calcium homeostasis by increasing the efficiency of the small intestine in absorbing dietary calcium. Vitamin D also plays a role in both bone resorption by inducing RANKL expression by osteoblasts, thereby inducing osteoclast differentiation and activation, and bone formation by stimulating osteoblastogenesis and inhibiting apoptosis of mature osteoblasts. Hypovitaminosis D, which is widespread in older adults, is associated with lower BMD, greater falls, and more osteoporotic fractures.

PTH is secreted by the parathyroid glands through a calcium sensor mechanism. When calcium levels decrease, PTH is released and exerts its function on two major target tissues: kidney and bone. In the kidney, PTH acts on the proximal tubule to reduce PO_4 resorption and to increase the activity of 1-α-hydroxylase, the enzyme that converts 25(OH)-vitamin D to 1,25(OH)2-vitamin D_3, the active form of vitamin D. In bone, PTH increases osteoclast-induced bone resorption by inducing RANKL expression and subsequent signaling via RANK. Hypovitaminosis D is often, but not always, accompanied by elevated PTH—secondary hyperparathyroidism. Acute and cyclical exposure to PTH in bone has an antiapoptotic as well as anabolic effect on osteoblasts. This is the basis for using PTH to treat severe osteoporosis (see further). Calcitonin is a hormone secreted by thyroidal C cells in mammals. Its main biologic effect is the inhibition of osteoclastic bone resorption. In vitro and in vivo studies in animals demonstrate that calcitonin causes the osteoclast to shrink and retract from the bone surface, which decreases its bone-resorbing activity and enhances bone formation by osteoblasts.

Sex-steroid hormones play a variety of roles in bone turnover. Although some aspects of its effects remain unclear, estrogen increases the level of OPG, inhibiting osteoclastogenesis. Estrogen also induces osteoclast apoptosis and regulates the action of IL-1, interleukin-1 receptor antagonist (IL-1Ra), IL-6, and TNF-α, and their binding proteins

and receptors. Declining estrogen levels lead to increased expression of IL-1, IL-6, and TNF-α, all of which enhance bone resorption. In response to diminished estrogen, osteoblasts produce more RANKL and less OPG, which induces RANKL–RANK interaction and signaling, further stimulating osteoclast differentiation and activation. Since estrogen increases osteoblast differentiation and decreases osteoblast apoptosis, bone formation declines at the time of menopause. Overall, there is a high turnover state with predominant bone resorption, which results in bone loss and susceptibility to fractures. Androgens play an important role in the formation of adolescent bone by regulating cytokines in the bone matrix. The effect of progesterone on bone seems to be indirect and limited, through its regulation of calcitonin secretion and thus bone resorption.

Women are at higher risk of osteoporosis because women have lower peak bone mass than men and experience accelerated bone loss during menopause, as described above. Histomorphometric data on the skeletal changes associated with postmenopausal bone loss show an increase in bone turnover in both cancellous and cortical bones. Biochemical markers also support high bone resorption after menopause. These markers return to normal with estrogen replacement. Trabecular bone is affected earlier in menopause than cortical bone because it is more metabolically active. Thus, rapid bone loss is seen primarily in the spine (3% per year) for approximately 5 years after menopause. Subsequently, there is a slower rate of bone loss that is more generalized (0.5% per year at many sites). A consistent finding in untreated postmenopausal women is a reduction in wall width of bone, indicating reduction in osteoblast activity. Although this could be related to the loss of the antiapoptotic effect of estrogen on osteoblasts, studies are inconclusive.

AGE-RELATED BONE LOSS

Age-related bone loss is a complex phenomenon, with many factors involved in its pathogenesis (see **Figures 118-4** and **118-5**). As an individual ages, distinct changes take place in trabecular bone, cortical bone, and bone marrow. The onset and triggers of age-related bone loss are not well defined, but densitometric studies show a slow and progressive decline in BMD after the third decade of approximately 0.5% per year, even though serum levels of estrogens are still within the normal range. With aging, osteoblastogenesis decreases, resulting in lower numbers of osteoblast precursors and increasing bone marrow adiposity (see **Figure 118-4**). The bone marrow of a young individual is virtually devoid of adipocytes. In older adults, however, adipose deposits may occupy up to 90% of the bone marrow cavity.

It has been postulated that pluripotent mesenchymal cells within the bone marrow stroma are, by default, programmed to differentiate into adipocytes, but the presence of specific osteogenic factors in the bone marrow induces osteoblastic differentiation. If this hypothesis is proven true, then it could offer the potential for novel therapeutic approaches to osteoporosis in older adults. In addition, osteoblast and osteocyte apoptosis increase with aging. Histomorphometric data demonstrate that 50% to 70% of the osteoblasts present at the remodeling site cannot be accounted for after enumeration of lining cells and osteocytes. The discrepancy in osteoblast numbers is believed to be a consequence of osteoblast apoptosis. This phenomenon may account for the significant reduction in bone formation that is associated with aging, which could also be due to high levels of marrow adipogenesis.

In addition, increasing levels of marrow fat play a direct negative role in bone metabolism by regulating function and survival of bone cells. By secreting fatty acids and adipokines, marrow adipocytes inhibit osteoblast differentiation, function, and survival. This effect has been described as lipotoxicity, which is defined as the accumulation of lipid and lipid products in nonadipose tissues leading to cellular dysfunction, cell death (lipoapoptosis) and disease. Additionally to lipoapoptosis, marrow adipocytes induce autophagy, which is defined as the conserved process whereby aggregated proteins, intracellular pathogens, and damaged organelles are degraded and recycled. Autophagy appears to play a significant role in skeletal maintenance after recent reports reveal that suppression of autophagy in osteocytes mimics skeletal ageing. The role of marrow fat in the pathogenesis of autophagy in osteoblasts and osteocytes is a subject of intense research. Furthermore, marrow adipocytes induce osteoclastic activity by facilitating the release of RANKL into the bone marrow milieu thus stimulating bone resorption in addition to decreasing bone formation.

In men and women, the early changes associated with age-related bone loss are similar, as described above. However, women also experience accelerated bone loss of approximately 3% to 5% per year during menopause. In men, the decline in bone mass is gradual until very late in life, when the risk for fractures increases rapidly. Concomitant with the changes in osteoblast and adipocyte formation, multiple factors enhance osteoclastogenesis and bone resorption (see **Figure 118-5**). In particular, the interactions between osteoblasts, osteocytes, and osteoclasts, which are crucial to the dynamic equilibrium that maintains healthy bone, are altered. Consequently, the combination

of decreased bone formation and increased bone resorption leads to diminished BMD, poorer bone structure and quality, and, ultimately, enhanced fragility and fractures.

In addition to cellular changes, there are two major changes in calciotropic hormones that have an impact on aging bone. Vitamin D levels decrease with age and reduce calcium absorption. Changes in the aging skin reduce the amount of 7-dehydrocholesterol, the precursor of cholecalciferol (vitamin D_3), as well as its rate of conversion. Furthermore, declining renal function leads to reduction in the production and activity of 1-α-hydroxylase, the enzyme responsible for the activation of vitamin D_3. Consequently, a negative calcium balance ensues, which activates the calcium sensor receptor in parathyroid glands. PTH is secreted as a physiologic response, stimulating osteoclast activity, which maintains normal serum calcium levels at the expense of bone mineralization. This theory of secondary hyperparathyroidism was once the classic explanation for age-related bone loss. However, not all individuals with hypovitaminosis D exhibit secondary hyperparathyroidism. Therefore, it is just one of the elements of a syndrome that results in osteoporosis in older adults. However, this mechanism has been recently associated with additional important risk factors for fractures, which are sarcopenia and falls. Vitamin D and PTH appear to modulate neuromuscular function, particularly in the frail older adults. Serum levels of 25(OH)-vitamin D lower than 35 nmol/L increase the risk of falls by 30%, which highly predisposes to fractures. Patients with serum levels between 35 and 80 nmol/L, which were considered normal in the past, are still at risk of falls, suggesting that the therapeutic goal should be to obtain serum levels higher than 75 nmol/L.

In summary, age-related bone loss results from changes at the cellular level, including decreased osteoblastogenesis, shortened osteoblast and osteocyte life span, increased adipogenesis and lipotoxicity as well as from hormonal changes, including decreased levels and activity of sex-steroid hormones and vitamin D and increased levels and activity of PTH. These mechanisms have been demonstrated both in vitro and in vivo, mostly in murine models. New histomorphometric data in humans support these findings, although more studies are required to completely explain the pathophysiology and to offer specific therapeutic approaches.

OSTEOPOROSIS IN MEN

Although the pathophysiology of osteoporosis in men has been a subject of active research in recent years, the relative contribution of hormones and aging, per se, remains to be elucidated. It is well established that androgen levels decrease with aging. Testosterone levels decrease by approximately 1.2% per year and the binding protein levels increase with aging, resulting in lower bioavailable testosterone. There is evidence that androgens exert their effect on bone through the action of IGF-1. IGF-1 levels are increased during puberty and are closely related to sex-steroid levels.

With aging, lower levels of sex-steroid hormones result in decreased levels of IGF-1, with a reduction in bone formation and bone mass. Dehydroepiandrosterone, another androgen, declines slightly at the sixth decade without major changes thereafter. Contradictory evidence is available about the importance of this decline in dehydroepiandrosterone and of its administration in the treatment of male osteoporosis. Thus, osteoporosis in men appears to result from cellular and hormonal changes, which include lower levels of testosterone, dehydroepiandrosterone, and IGF-1 with subsequent lower osteoblast activity and higher osteoblast apoptosis. However, further study is necessary to delineate the specific roles of these factors in the decline of BMD and high rate of fractures in men after the seventh decade of life.

Case reports of low bone mass and increased bone turnover in men with estrogen deficiency—either from an estrogen receptor abnormality or from an absence of aromatase, the enzyme responsible for the conversion of testosterone to estrogen—suggest that estrogen is required for normal bone homeostasis in men. Serum estrogen levels better predict BMD in men than do serum testosterone levels. In older men in whom both gonadotropin secretion and aromatase conversion are suppressed, estrogen acts as the principal sex-steroid-regulating bone resorption. Blocking the conversion of testosterone to estrogen with the use of an aromatase inhibitor has been shown to increase bone resorption in a short-term study conducted in healthy older men, further supporting a role for estrogen in bone metabolism. Some of the effects of testosterone on bone may be mediated through aromatization of testosterone to estrogen, a possibility that warrants further study. Ongoing studies will provide further information on the role of estrogen in the pathogenesis of osteoporosis in older men.

PRESENTATION

Osteoporosis is frequently underdiagnosed and undertreated by medical professionals. Osteoporosis is a silent disease, and symptoms may not appear until an incident fracture. Men and women can have osteoporosis prior to a fracture, which is why it is so important to consider clinical risk factors, use risk identification tools (see further), and perform BMD measurement in those at risk of osteoporosis. Osteoporosis may be detected on plain x-rays (usually a chest x-ray) either by the presence of vertebral fractures or by "osteopenia" in the x-ray report. As many as a third or more of those with "osteopenia" on an x-ray may have T-scores worse than −2.5, and as many as half will have T-scores in the −2.5 to −1.0 range. Therefore, persons who are diagnosed with "osteopenia" by plain x-ray should have BMD measurement. Osteoporosis may also present as an acute fracture. Most fractures that occur in old age are caused, at least in part, by osteoporosis, and it is important to initiate a therapeutic regimen in these adults. Even after a fracture, the diagnosis is often not considered. Three-quarters of postmenopausal women with a distal radius fracture were either undiagnosed or not treated in one study. As many as 50% of women with a hip fracture leave the hospital without treatment. The overall risk of repeat fracture within the first year is 20%. Fractures that are likely related to osteoporosis and thus should trigger treatment with an approved agent include wrist, vertebral, and hip fractures. Those with such fractures do not require BMD testing. Frequently, these fractures are classified as fragility fractures, because there is often little or no trauma associated with the event.

SECONDARY CAUSES OF OSTEOPOROSIS

The diagnosis of idiopathic or primary osteoporosis is made by BMD measurement prior to fracture or by incident fracture. Secondary osteoporosis is the consequence of diseases or drugs that affect bone either directly (involving changes in bone cells or bone matrix composition) or indirectly (by increasing endogenous or ectopic hormonal production). It is important to exclude diseases that may present as fracture or with low bone mass in the evaluation of women and men with osteoporosis. **Table 118-3** lists the major secondary causes of osteoporosis along with laboratory tests used to exclude each disease. These laboratory tests should be considered in persons who present with acute compression fracture or who present with a diagnosis of osteoporosis by BMD measurement. Men are more likely to have a secondary cause of osteoporosis than are women. The most commonly reported secondary causes of osteoporosis in men include hypogonadism and malabsorption syndromes. An additional secondary cause of osteoporosis in men relates to the use of luteinizing hormone-releasing hormone agonists in prostate cancer. Luteinizing hormone-releasing hormone agonists suppress the pituitary gland, decrease testosterone and estrogen to castrate levels, and render men. Several retrospective studies have found increased fracture rates in this population of men. A number of studies demonstrate rates of bone loss that are up to three- to fourfold higher in men treated with luteinizing hormone, releasing hormone agonists, as compared with annual rates of bone loss in normal aging men.

TABLE 118-3 RECOMMENDATIONS FOR EVALUATION OF SECONDARY CAUSES OF OSTEOPOROSIS

DISEASE	EVALUATION
Endocrine abnormalities	
Primary hyperparathyroidism	Ionized calcium, PTH
Paget disease	Alkaline phosphatase
Osteomalacia	Serum + urine Ca, PO_4, alkaline phosphatase, 25(OH)D
Hyperthyroidism	T_4, thyroid-stimulating hormone
Hypogonadism (men only)	Bioavailable testosterone, prolactin
Cushing syndrome	Urinary free cortisol
Neoplastic conditions	
Multiple myeloma	Complete blood count, serum and urine protein electrophoresis
Bone metastases	Serum calcium, bone scan
Other conditions	
Alcoholism	Medical history
Malabsorption syndromes	Medical history, antigliadin and antiendomysial antibodies

Medications	
Glucocorticoids	Medical history
Anticonvulsants	25(OH)D, alkaline phosphatase
Heparin (long term)	Medical history
Excess thyroid hormone replacement	Thyroid-stimulating hormone

Medications also may have a detrimental effect on bone. Consideration should be given to dose adjustment, discontinuation of the medications, or preventive treatment. Medications that adversely affect BMD include glucocorticoids, excess thyroid supplementation, anticonvulsants, methotrexate, cyclosporine, and heparin. In older adults, glucocorticoids and thyroid hormone are used quite commonly; accordingly, clinicians should consider the effects these medications may have on the already increased risk of fracture, when prescribing these to older adults.

The prevalence of osteoporosis in adults taking glucocorticoids is approximately 30%. Bone loss typically occurs in the first 6 months of therapy and increases with increasing glucocorticoid dose. Glucocorticoids both suppress bone formation through direct effects on osteoblasts and increase resorption through indirect effects on osteoclasts. Glucocorticoid-induced osteoporosis is preventable if treatment is considered when treatment with corticosteroids is initiated. Replacement of gonadal hormones and treatment with bisphosphonates or intermittent PTH has been shown to prevent bone loss in patients taking glucocorticoids. Other measures for prevention of bone loss are calcium and vitamin D supplementation and reduction of glucocorticoid dose to the lowest effective dose for the underlying disease.

In most cases, secondary osteoporosis can be either prevented or treated if suspected by the clinician. Immobilization predisposes to bone mineral loss; thus, a program of early mobilization of hospitalized older patients is important. Mild-to-moderate vitamin D deficiency may give rise to osteoporosis rather than to osteomalacia; oral replacement may prevent its occurrence. Finally, a comprehensive medication review could also identify those medications placing the patient at risk of osteoporosis thus adjusting their doses or reevaluating their indications constitute the most appropriate approach.

EVALUATION

Risk Identification

While approaches to the patient with osteoporosis have often based treatment on T-scores, assessment of clinical risk factors can improve identification of individual patients who are more likely to suffer from vertebral and nonvertebral fractures. This is particularly important, since the majority of fractures occur in postmenopausal women with T-scores that are *better* than −2.5. The age of the patient is the single most important contributor to fracture risk. Additional important factors include a previous fracture history as an adult, history of fracture risk in a first-degree relative, body weight less than 127 lb, current history of smoking, and corticosteroid use for more than 3 months **(Table 118-4**). Impaired vision, early estrogen deficiency, dementia, frailty, recent falls, low calcium and vitamin D intake, low physical activity, and alcohol consumption of more than two drinks per day are additional clinical risk factors. Prior recent fracture is a very strong predictor of future fracture. The increased risk is similar in both men and women and is the same as the risk of a first fracture in a woman who is 10 years older. Half of patients will refracture within 10 years, and half of those will occur within 2 years of the first fracture. Therefore, most older patients with a prior fracture are candidates for treatment. If additional clinical risk factors are present in such patients, BMD testing is not needed before initiating therapy. Conversely, in those patients without a history of fracture, clinical risk factors are useful in identifying women who should have BMD testing (**Figure 118-6**).

TABLE 118-4 ■ RISK FACTORS FOR OSTEOPOROTIC FRACTURE

POTENTIALLY MODIFIABLE	NONMODIFIABLE
Current cigarette smoking	Personal history of fracture
Low body weight (< 127 lb)	History of fracture in first degree relative
Estrogen deficiency	Advanced age

Early menopause (< 45 years of age)	
Prolonged premenopausal amenorrhea (> 1 year)	Female sex
	White or Asian race
Low calcium intake (lifelong)	Dementia
Alcoholism	
Taking sedative medication	History of corticosteroid medication
Impaired eyesight	Taking seizure medication
Recurrent falls	
Inadequate physical activity	Poor health/frailty
Arms usually required to stand	
Poor health/frailty	

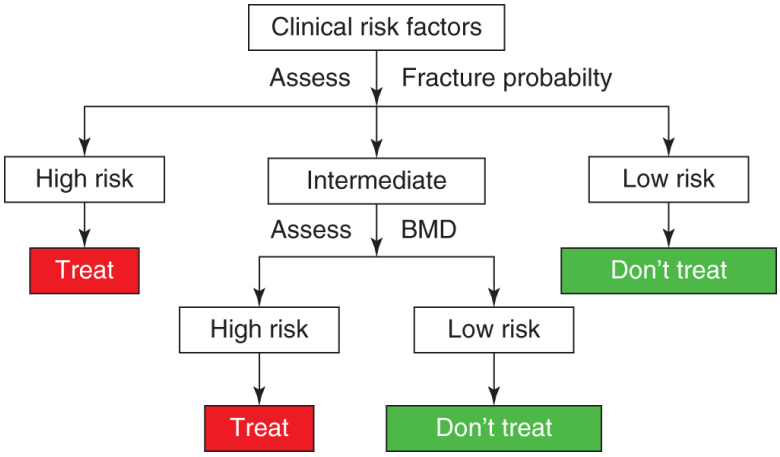


FIGURE 118-6. Approach to the osteoporosis patient. (*From Kanis J. Annual meeting of the ASBMR. Philadelphia, PA 2006.*) Clinical factors such as described in the text and in Table 18-4 help to assess contributions to fracture risk. The absence of these factors in younger women place them at low risk, and they do not require treatment. The presence of several factors in patients aged 70 years or more, particularly prior history of fracture and a fall history suggests that treatment should be initiated without the need for densitometry. The greatest challenge lies in those patients who may have one or two clinical factors such as postmenopausal with poor calcium intake and low physical activity. Assessment of BMD can help stratify fracture risk and guide the decision to treat. The combination of clinical factors plus the BMD can be utilized in fracture risk calculators (e.g., see http://courses.washington.edu/bonephys/FxRiskCalculator.html) to determine the cost-effectiveness of treatment.

Identifying patients at risk of osteoporosis and osteoporotic fractures should be routine practice in geriatric medicine. The presence of risk factors (see **Table 118-4**) has a very high predictive value for osteoporotic fractures, especially in older persons. However, with the exception of age, which has the highest predictive value, these risk factors have a different weight in terms of predicting the absolute risk of future fractures. Therefore, to help the clinician to accurately calculate their patient's absolute risk of suffering a fracture within 5 or 10 years, two online assessment tools have been recently validated.

The FRAX index (http://www.shef.ac.uk/FRAX) estimates the absolute risk of suffering a fracture in 10 years. This calculator has been demonstrated to be extremely useful since it includes specific data obtained from major cohorts worldwide. However, a major limitation of this tool is that falls are not included in the algorithm. Taking into consideration that falls are an important risk factor for fractures, the FRAX tool could be underestimating the level of risk in frequent fallers, particularly in the frail older adults.

In contrast to the FRAX tool, the Garvan tool (http://www.garvan.org.au/bone-fracture-risk) includes history of previous falls in its algorithm. Although it has been recently tested in non-Australian populations, this tool was originally developed and validated using the Dubbo Osteoporosis Study database. Another major advantage of this tool is that it calculates the risk of fracture in 5 and 10 years, providing valuable information that could be easily shared with the patient.

Since many osteoporotic fractures result from falls, it is essential to assess patients for fall risk and to institute preventive measures where appropriate. The causes of falls are often multifactorial and include medications, poor

vision, impaired cognition, maladaptive devices, alcohol, orthostatic hypotension, impaired balance and gait, environmental hazards, and lower extremity weakness. Recent studies suggest that specific performance measures can help to identify those at greater risk of falling. Individuals who are unable to maintain a semitandem stand for 10 seconds with their eyes open are at increased risk. A normal gait velocity of less than 0.8 m/s also predicts a greater propensity to fall. Additional office-based screening tests that identify potential fallers include the inability to complete the timed up and go test in 14 seconds, the inability to maintain a one-leg stand for at least 5 seconds, and a score of less than 19 on the performance-oriented mobility assessment.

Bone Density Measurement

Bone mineral density (BMD) measurement has historically been considered the gold standard for the diagnosis of osteoporosis in the clinical setting. BMD of the hip, spine, wrist, or calcaneus may be measured by a variety of techniques. The preferred method of BMD measurement is dual-energy x-ray absorptiometry. BMD of the hip, anteroposterior spine, lateral spine, calcaneus, and wrist can be measured using this technology. Quantitative computerized tomography is also used to measure BMD of the spine. Specific software can adapt computerized tomography scanners for BMD measurement. The advantages of dual-energy x-ray absorptiometry over quantitative computerized tomography include lower cost, lower radiation exposure, and better reproducibility over time. Peripheral dual-energy x-ray absorptiometry (measures wrist BMD) or ultrasonography of the calcaneus may be useful for general osteoporosis screening, and these have the advantage of reduced cost and portability. Peripheral bone densitometry (performed at the heel, finger, or forearm) is highly predictive of hip, spine, wrist, rib, and forearm fractures for the subsequent 12 months.

Assessment of BMD should be considered for (1) postmenopausal women younger than 65 years with one or more additional risk factors (other than menopause); (2) all women older than 65 years, regardless of additional risk factors; and (3) women considering therapy for osteoporosis, if BMD testing would facilitate the decision. A study of more than 200,000 postmenopausal women from more than 4000 primary care practices in 34 states reported that approximately 50% of this population had low BMD that was previously undetected, including 7% of women with osteoporosis. An additional study found that screening postmenopausal women with BMD reduced the incidence of hip fracture by 36%. These studies suggest that efforts should be made to increase BMD measurements in postmenopausal women. However, further investigation is required to determine if BMD screening is truly cost effective and to assess the usefulness of various clinical decision rules in medical practice. Postmenopausal women who present with a minimal trauma fracture do *not* require BMD to confirm a diagnosis of osteoporosis or to determine severity. In addition, postmenopausal women with a significant kyphosis and clinical risk factors also do not require BMD testing. Instead, both of these subsets of patients deserve treatment for osteoporosis. In a cohort of over 8000 women participating in the Study of Osteoporotic Fractures, of the 243 that suffered a hip fracture, 54% had a total hip BMD T-score *better* than −2.5 at the start of the study. Similarly, in a study of 257 men aged 70 and over, although those with lower T-scores had a higher rate of fracture, the majority of fractures occurred in men with T-scores *better* than −2.5. These studies emphasize that BMD is not the entire determinant of fracture risk; the micro-architecture and quality of bone is also important, and that is not directly assessed with densitometry. As noted above, clinical risk factors need to be assessed. Furthermore, it is very important to recognize that age is a much more significant factor than BMD in determining fracture risk. The 10-year probability of a fracture in an 80-year-old is more than twice as great as the probability of fracture in a 50-year-old with the same BMD T-score (**Figure 118-7**).

Age (years)	T-score 0	T-score -0.5	T-score -1.0	T-score -1.5	T-score -2.0	T-score -2.5	T-score -3.0
50	3.8	4.7	5.9	7.4	9.2	11.3	14.1
55	4.1	5.3	6.7	8.5	10.7	13.4	16.8
60	5.1	6.5	8.2	10.4	13.0	16.2	20.2
65	6.3	8.0	10.0	12.6	15.6	19.3	23.9
70	7.1	9.0	11.5	14.6	18.3	22.8	28.4
75	7.0	9.1	11.8	15.2	19.4	24.5	30.8
80	7.7	9.9	12.7	16.2	20.5	25.6	31.8

FIGURE 118-7. Ten-year probability of fracture in women by age and T-score. (From Kanis JA, et al. *Osteoporos Int.* 2001;12:989–995.)

Finally, BMD may also be used to establish the diagnosis and severity of osteoporosis in men and should be considered in men with low-trauma fracture, radiographic changes consistent with low bone mass, or diseases known to place an individual at risk of osteoporosis. Data relating BMD to fracture risk were originally derived from studies completed in women, but recent data suggest that similar associations may be valid in men as well. Assessment of BMD should also be strongly considered in both perimenopausal women and older men who are about to undergo long-term treatment with corticosteroids. Bone densitometry less frequently can be used to assess response to therapy. However, usually 2 years between tests are necessary to obtain accurate and useful information. Biochemical markers of bone turnover yield much quicker information about compliance and success of therapy (see further).

Biochemical Markers of Bone Turnover

Serum and urine biochemical markers that reflect collagen breakdown (or bone resorption) and bone formation are useful to monitor treatment of osteoporosis. Higher levels of resorption markers have been associated with increased hip fracture risk, decreased bone density, and increased bone loss in older adults in some studies. However, biochemical markers in many patients with osteoporosis will lie within the normal range. In addition, there is often substantial overlap of marker values in women with high and low bone density or rate of bone loss. Therefore, at this time, markers are not recommended for screening or diagnosis of osteoporosis. In addition, few studies have compared the response of a particular marker (or combination of markers) and bone density to therapy in order to determine the magnitude of decrease of a biochemical marker necessary to prevent bone loss or, more importantly, fracture. Markers are most useful in assessing the response of an individual patient to treatment. Markers of bone resorption and formation decrease in response to antiresorptive treatment and increase in response to PTH, a treatment with anabolic properties. The advantage of the serum versus urinary markers is that the intrapatient variability tends to be lower with serum markers, thus reducing error. It is important to assess a marker before initiating treatment. Many of the osteoclast-specific markers can then be rechecked as early as 6 weeks after beginning therapy. Bone markers yield quicker information, cost less, and incur no radiation when compared to repeating bone densitometry to assess response to therapy. The total alkaline phosphatase that is commonly obtained in routine serum chemistries, while not specific, is also useful to determine response to antiresorptives. However, it should be rechecked 12 weeks after beginning therapy. Successful antiresorptive therapy, which also means compliance, will result in a reduction of serum levels of markers of both resorption and formation, since these processes are tightly coupled. However, changes in bone formation markers, such as alkaline phosphatase, will lag several months behind changes in bone resorption markers.

Osteosarcopenia

Recently, it has been proposed that there is a subgroup of older persons presenting with the concurrent clinical criteria for both sarcopenia and osteopenia/osteoporosis. Clinical and densitometric criteria for osteosarcopenia combine those for osteopenia (BMD < T-score −1) plus those for sarcopenia (gait velocity < 0.8 m/s + grip strength < 20 kg in women and < 30 kg in men + lean mass < 7.26 kg/m^2 in men and < 5.45 kg/m^2 in women). These patients could be at a higher risk for poor outcomes such as falls, fractures, hospitalization, frailty, and death. Although the clinical and

biological characteristics of these patients remain unknown, there is enough evidence to suggest that patients presenting with both entities would have a combination of risk factors, pathophysiology and clinical outcomes that predispose them significantly more frequently to falls and fractures. In addition to age, there are risk factors associated with both sarcopenia and osteoporosis, including fat infiltration of muscle and bone, which was demonstrated in an animal model of sarco-osteopenia. Other risk factors include low levels of vitamin D associated with high levels of PTH, decreased physical activity and disuse, low levels of anabolic hormones in men and menopause in women, use of corticosteroids, malnutrition, and frailty. In addition, from the biological point of view, both entities are associated with high levels of circulating inflammatory cytokines, which are most likely secreted by both marrow and body fat thus inducing lipotoxicity. Whether patients start their decline as sarcopenic and then become osteoporotic or vice versa still remains unknown. In addition, since it is expected that poor outcomes are more frequent in this subgroup, appropriate identification of clinical outcomes and development of reliable and robust biomarkers are highly needed in this particular population.

MANAGEMENT

Osteoporosis develops in older adults when the normal processes of bone formation and resorption become uncoupled or unbalanced, resulting in bone loss. Osteoporosis prevention and treatment programs, then, should focus on strategies that minimize bone resorption and maximize bone formation, as well as strategies that reduce falls. A number of nonpharmacologic and pharmacologic options are available to health care providers (see **Tables 118-5** and **118-6**). Modification of risk factors (see **Table 118-4**) is an important first step in preventing osteoporotic fractures in older adults.

TABLE 118-5 TREATMENT OF OSTEOPOROSIS IN OLDER ADULTS

Exercise	Walking, weight bearing three times a week
Physical therapy	Postural exercises, gait and/or balance training, muscle strengthening
Calcium (carbonate or citrate)	1200–1500 mg QD
Vitamin D (cholecalciferol)	Minimum 800 IU QD, likely need 2000–5000 IU QD
Bisphosphonate	
-Alendronate	70 mg PO once a week
-Risedronate	35 mg PO once a week
-Ibandronate	150 mg PO once a month, 3 mg IV push once every 3 months
-Zoledronic acid	5 mg IV infusion (15 min) once a year
Teriparatide	20 μg SC QD for no longer than 2 y
Denosumab	60 mg SC once every 6 mo
Strontium ranelate	2 g PO QHS

TABLE 118-6 PHARMACOLOGIC EFFECT OF OSTEOPOROSIS MEDICATIONS ON BONE CELLULARITY

COMPOUND	OSTEOBLAST	ADIPOCYTE	OSTEOCLAST
Bisphosphonates	↑ differentiation ↑ activity ↓ apoptosis		↓ differentiation ↓ activity ↑ apoptosis
Calcitonin			↓ activity ↑ apoptosis
Denosumab	↓ differentiation ↓ activity		↓ differentiation ↓ activity
PTH	↑ activity	↓ differentiation	↑ activity

	↑ survival ↑ differentiation		
SERMs			↓ differentiation ↓ activity
Strontium ranelate	↑ activity ↑ differentiation		↓ activity ↓ survival
Vitamin D	↑ activity ↑ differentiation ↓ apoptosis	↓ differentiation ↑ trans-differentiation to osteoblasts	↑ activity

PTH, parathyroid hormone; SERMs, selective estrogen receptor modulators.

Nonpharmacologic

Exercise Exercise is an important component of osteoporosis treatment and prevention programs. Data in older men and women suggest a positive association between current exercise and hip BMD. Among regular exercisers, those who reported strenuous or moderate exercise had higher BMD at the hip than did those who reported mild or less-than-mild exercise. Similar associations were seen for lifelong regular exercisers and hip BMD. In a randomized study of women at least 10 years past menopause, the group receiving calcium supplementation plus exercise had less bone loss at the hip than did those assigned to calcium alone. Furthermore, high-intensity strength training effectively maintains femoral neck BMD as well as improves muscle mass, strength, and balance in postmenopausal women compared to non-exercising controls, suggesting that resistance training would be useful to help maintain BMD and to reduce the risk of falls in older adults.

Marked decrease in physical activity or immobilization results in a decline in bone mass; accordingly, it is important to encourage older adults to be as active as possible. Weight-bearing exercise, such as walking, can be recommended for older adults who should be encouraged to start slowly and gradually increase both the number of days and the time walked each day. Physical therapy is an important part of osteoporosis treatment programs, especially after acute vertebral compression fracture. The physical therapist can provide postural exercises, alternative modalities for pain reduction, and can suggest changes in body mechanics that may help prevent future falls and fracture. Gait training or balance training along with muscle strengthening can help to prevent falls, even for relatively frail elders. A meta-analysis of randomized clinical trial interventions to reduce falls concluded that all types of exercises achieved similar benefits in balance, endurance, flexibility, and strength. The key message is to prescribe a program for those patients who are mobile and functional enough, in addition to cognitively capable, to participate.

Nutrition (calcium and vitamin D) Calcium and vitamin D are required for bone health at all ages. Elemental calcium, 1200 to 1500 mg/day, for postmenopausal women and men older than 65 years is needed to maintain a positive calcium balance. The amount of vitamin D required is at least 800 IU/day, although recent evidence suggests that as much as 2000 IU of cholecalciferol per day and more are required to achieve serum levels (25[OH] vitamin D ≥ 80 nmol/L) that are optimally effective for fall and fracture prevention. Calcium plus vitamin D can increase or maintain bone density in pre- and postmenopausal women and prevent hip and other nonvertebral fractures in older adults. A Cochrane meta-analysis showed that vitamin D in combination with calcium was associated with an overall significant reduction in hip fracture (46,658 participants, RR = 0.84, CI: 0.73–0.96), but not nonvertebral fracture. In a follow-up subgroup analysis, a significant reduction was observed in both hip and nonvertebral fractures in institutionalized patients.

Boonen and colleagues in their meta-analysis demonstrated an 18% reduction in hip fracture risk associated with coadministered vitamin D and calcium (RR = 0.82, CI: 0.71–0.94). Pooled results for vitamin D alone did not reach significance. A dose-dependent effect was noted; however, a significant reduction in hip and nonvertebral fracture risk was only apparent at doses of vitamin D above 400 IU (nonvertebral fracture, *n* = 33,265, RR = 0.80, CI: 0.72–0.89; hip fracture, *n* = 31,872, RR¼ = 0.82, CI: 0.69–0.97). Subgroup analysis among the “higher dose” trials showed that a significant risk reduction in nonvertebral fracture was maintained in the more than 75 years group (*n* = 9879, RR¼ = 0.83, CI: 0.74–0.92). When the form of vitamin D was considered, subgroup analysis revealed that cholecalciferol resulted in a more substantial risk reduction than ergocalciferol. However, low numbers limited the strength of the pooled data for ergocalciferol.

Serum levels of 25(OH) vitamin D up to 120 nmol/L are correlated with greater BMD. Furthermore, women with acute hip fracture have lower 25(OH) vitamin D levels and higher PTH levels than do women admitted for elective hip replacement with or without osteoporosis as measured by BMD, supporting a direct role for vitamin D deficiency and secondary hyperparathyroidism in hip fracture. Thus adequate calcium and vitamin D should be recommended for all older adults, regardless of BMD, in order to maximize bone health. Furthermore, supplementation with vitamin D enhances the BMD response to bisphosphonates, and it is also worth noting that all pivotal trials of antiosteoporotic agents (antiresorptive, anabolic, or dual-action agents) have included supplementation with calcium and vitamin D.

Recently concerns have been raised with regard to calcium supplementation and a possible rise in rates of myocardial infarction (MI). A meta-analysis by Bolland and colleagues, reported an almost 30% increase in relative risk (RR = 1.27, CI: 1.01–1.59). However, the meta-analysis excluded trials that coadministered calcium and vitamin D, a linear relationship between calcium intake and MI risk was not observed, and the rise in myocardial infarction was only seen in those patients exceeding the recommended daily intake of calcium (supplements in addition to dietary intake). Thus the same authors updated the meta-analysis by examining calcium supplements with and without vitamin D and incorporating the Women's Health Initiative Calcium/Vitamin D Supplementation Study dataset (a seven year, randomized, placebo controlled trial of calcium and vitamin D (1 g calcium and 400 IU vitamin D daily) in 36,282 community dwelling postmenopausal women). The reanalysis suggested that calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction. Calcium and vitamin D increased the risk of myocardial infarction (RR = 1.21, CI: 1.01–1.44, P = .04), stroke (RR = 1.20, CI: 1.00–1.43, P = .05), and the composite risk of myocardial infarction or stroke (RR = 1.16, CI: 1.02–1.32, P = .02). Calcium or calcium plus vitamin D increased the risk of myocardial infarction (RR = 1.24, CI: 1.07–1.45, P = .004) and the composite risk of myocardial infarction or stroke (RR = 1.15, CI: 1.03–1.27, P = .009). These findings, however, have not been universally accepted. Other authors have noted that conclusions based on hazard ratios differ when examining the absolute incidence of cardiovascular events per 1000 patient years. In both experimental and placebo groups, those with the highest personal intake of calcium (> 1000 mg/day) have the lowest incidence of cardiovascular events. Conversely, the highest rates of adverse events are associated with the groups with the lowest personal intake (0 or 1–499 mg/day). A similar phenomenon is evident where the incidence of adverse events in the groups with personal use of calcium predominantly tends to be lower than that in the groups with no personal use. In no case was the incidence higher for those with personal supplementation. The incidence of death from all causes is lowest in the group with personal supplementation plus calcium and vitamin D (5.4/1000) and highest in the group that received no calcium at all (6.4/1000).

Further contrasting with the conclusions of Bolland and colleagues, the WHI trial group data considered specific cardiovascular endpoints but did not demonstrate an increase in MI risk with coadministered calcium and vitamin D. Similarly in the 5-year randomized double-blinded placebo-controlled trial (Calcium Intake Fracture Outcome Study [CAIFOS]) the intervention group that received calcium supplementation did not have a higher risk of death or first-time hospitalization from atherosclerotic vascular disease in either the 5-year RCT (multivariate-adjusted HR = 0.938, 95% confidence interval [CI] 0.690–1.275) or during the 9.5 years of observational study (multivariate-adjusted HR = 0.919, 95% CI: 0.737–1.146). Additional analysis suggested that calcium supplementation may actually reduce the risk of hospitalization and mortality in patients with preexisting atherosclerotic cardiovascular disease.

Nutrition—additional factors Two recent prospective studies examined the effect of additional nutritional factors on bone loss and fracture risk in older adults. The Framingham Osteoporosis study found that higher baseline magnesium, potassium, and fruit and vegetable intakes were associated with higher baseline BMD. In men, increased potassium and magnesium intakes were associated with lower bone loss at the femoral neck. Additionally, this study showed a correlation of hip fractures with higher serum levels of homocysteine. Although homocysteine levels are associated with vitamin B_{12}, serum levels of this vitamin have not been associated with lower BMD, suggesting that the role homocysteine plays in bone biology remains to be elucidated. However, other studies have not found a clear association of homocysteine levels and fracture. Lower baseline protein intake or percent of total energy from animal protein, however, has been associated with greater bone loss at the femoral neck and lumbar spine. In another prospective cohort study, the Study of Osteoporotic Fractures, BMD was not associated with the ratio of animal to vegetable protein intake, but a higher ratio of animal to vegetable protein intake was associated with greater femoral neck bone loss and increased risk of hip fracture. These studies suggest that nutritional factors other than calcium and vitamin D are important for bone health in older adults. Prospective randomized studies are indicated to further elucidate the role of nutrition in prevention and treatment of osteoporosis in older adults.

Pharmacologic

Pharmacologic agents for the treatment of osteoporosis consist of antiresorptives and anabolic agents. The main antiresorptive medications are bisphosphonates, selective estrogen receptor modulators and denosumab. Currently only one anabolic agent (teriparatide) is approved for osteoporosis treatment.

Estrogen replacement therapy Multiple studies demonstrate that postmenopausal estrogen use will prevent bone loss at the hip and spine when initiated within 10 years of menopause. However, there have been few prospective studies of ERT (estrogen replacement therapy) and fracture prevention. One small study demonstrated a reduction in vertebral fractures in postmenopausal women with transdermal estradiol, compared to placebo. The Women's Health Initiative study demonstrated a 24% reduction in all fractures and a 33% reduction in hip fractures in women taking estrogen plus progestin. However, the Women's Health Initiative study also concluded that the overall risks of estrogen plus progestin outweighed the benefits, including those associated with reduction of fractures.

Few studies have evaluated the use of estrogen in women in older than 70 years. Observational data, however, from the Study of Osteoporotic Fractures support a protective effect of current estrogen use against hip fracture, even in the oldest women. Furthermore, small short-term studies suggest that older women are responsive to estrogen treatment, and a recent study demonstrated that ERT increased BMD of the spine and hip in frail older women with just 9 months of treatment. Other studies suggest that low-dose estrogen, in combination with calcium and vitamin D, has an additive effect on bone turnover in women older than 70 years of age.

Lower doses of estrogen are also effective in reducing bone resorption and bone loss in older women; the lower doses also result in fewer side effects than the usual replacement doses typically used by clinicians. In a randomized placebo-controlled study, 0.25 mg/day was as effective as 0.5 and 1.0 mg/day of 17β-estradiol in reducing biochemical markers of bone turnover in 75-year-old women compared to placebo. The side-effect profile of 0.25 mg/day was similar to placebo and significantly different from the two higher doses. In a longer-term study, 0.3 mg/day of conjugated equine estrogen plus 2.5 mg/day of medroxyprogesterone acetate increased bone density of the hip and spine in older women who were vitamin D replete. While a recent report from the Women's Health Initiative study demonstrates cardiovascular benefit in women aged 50 to 59 years who took estrogen, at this time better alternatives to treatment of osteoporosis in older patients exist. Therefore, in older patients, particularly those at least 5 to 10 years postmenopausal, estrogen is not recommended.

Bisphosphonates Bisphosphonates have gained wide acceptance as the primary antiresorptive treatment for osteoporosis. Bisphosphonates act on the osteoclast, inhibiting differentiation, formation, and activation and also inducing apoptosis. Additionally there is recent evidence showing that bisphosphonates can enhance bone formation through the inhibition of bone marrow adipogenesis and induction of osteoblastogenesis.

Most of the bisphosphonates have well-established antifracture efficacy. Alendronate reduces vertebral fracture in postmenopausal women, in men, and in glucocorticoid-induced osteoporosis. Alendronate also reduces nonvertebral fracture including those at the hip. Similarly risedronate reduces vertebral fractures, nonvertebral fractures, hip fractures in osteoporotic older women, and fracture secondary to glucocorticoid-induced osteoporosis. Ibandronate has demonstrated efficacy against vertebral fractures in postmenopausal women and against nonvertebral fractures in higher-risk subgroups with femoral neck BMD T-scores less than −3.0. The intravenous bisphosphonate zoledronate also significantly lowers fracture incidence in the spine, hip, and in other nonvertebral fractures in both men and women and in glucocorticoid-induced osteoporosis.

Although bisphosphonates have demonstrated their effectiveness in fracture prevention and gain in bone mass, their effectiveness in the very old (75 years and older) remains unclear because of the limited number of subjects included in the major trials. The only study using alendronate in older adults (> 75 years) is a subpopulation of the Fracture Intervention Trial. Although the initial intention-to-treat study demonstrated benefit for vertebral and nonvertebral fractures, the older subgroup only exhibited evidence for reduction of vertebral fracture at three years (RRR 38%; $p < .05$). No published data are available for nonvertebral or hip fracture in the older population. Increase in spine and hip BMD have been reported in older women receiving alendronate but there were no fracture end points. The efficacy of risedronate in reducing vertebral fracture risk in women aged 80 and older with osteoporosis was examined in a pooled analysis of three randomized double-blind controlled 3-year-fracture-end point trials (Hip Intervention Program [HIP], Vertebral Efficacy with Risedronate Therapy-Multinational [VERT-MN], and VERT-North America [NA]). Significant reductions in vertebral fracture relative risk were observed at one year (RRR 81%; $p < .001$) and 3 years (RRR 44%; $p = .003$). The number needed to treat (NNT) to prevent one new vertebral fracture at 1 year was 12. However no significant reduction was seen in osteoporosis related nonvertebral fractures.

The HIP study investigated the efficacy of risedronate on the risk of hip fracture. Two groups of women were recruited, those aged between 70 and 79 years with osteoporosis and those aged 80 years or over who were selected primarily on the basis of nonskeletal risk factors. There was a significant 40% reduced risk of hip fracture in the younger treatment group (n = 5445, RR = 0.60, CI: 0.40–0.90). In the older treatment group, no significant reduction in hip fractures was seen (n = 3886, RR = 0.8, CI: 0.60–1.20). However in the combined intention-to-treat population (age 70–100 years) a significant 30% hip fracture risk reduction was seen (n = 9331, RR = 0.70, CI: 0.60–0.90). A post hoc analysis of the HIP and VERT studies showed that, compared with placebo, risedronate reduced the risk of hip fracture by 46% (RR = 0.54, CI: 0.32–0.91) in women aged 70–100 years with established osteoporosis.

In the MOBILE (Monthly Oral iBandronate In LadiEs) study, monthly administration of ibandronate has shown efficacy on BMD, similar to that observed for the weekly administration of either alendronate or risedronate. Ibandronate has been approved for intravenous administration every 3 months to treat postmenopausal osteoporosis. However, its effectiveness in very old populations has not been studied.

In the pivotal Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Trial (HORIZON-PFT) intravenous zoledronic acid, at a dose of 5 mg once yearly over 3-year period, significantly reduced the risk of vertebral and hip fractures by 70% (n = 5675, RR = 0.30, CI: 0.24–0.38) and 41% (RR = 0.59, CI: 0.42–0.83), respectively. Nonvertebral fractures were similarly significantly reduced in the zoledronic acid group by 25% (RR = 0.75, CI: 0.64–0.87). Thirty-nine percent of the patients recruited in this study were aged 75 years or over (age range 65–89 years). A subsequent study, the HORIZON-Recurrent Fracture Trial, looked at the efficacy and safety of zoledronic acid administered once yearly for the prevention of new clinical fractures in women and men who had undergone recent surgical repair of a hip fracture. More than half of those recruited were over the age of 75 years (age range 50–85 years). The risk of any new clinical fracture was reduced by 35% (n = 2127, RR = 0.65, CI: 0.50–0.84) and a 28% risk reduction in death from any cause in the zoledronic acid group was also observed (RR = 0.72, CI: 0.56–0.93). A post hoc subgroup analysis of pooled data from the HORIZON Pivotal Fracture Trial and the HORIZON Recurrent Fracture Trial was performed on postmenopausal subjects aged 75 years or more with documented osteoporosis (T-score $\leq$ 2.5 at femoral neck or $\geq$ 1 prevalent vertebral or hip fracture) or a recent hip fracture. At 3 years, incidence of any clinical, clinical vertebral, and nonvertebral fractures was significantly lower in the zoledronic acid group than in the placebo group (hazard ratio (HR) = 0.65, CI: 0.54–0.78, P < .001; HR = 0.34, CI: 0.21–0.55, P < .001; and HR = 0.73, CI: 0.60–0.90, P = .002, respectively). Although patients younger than 75 years significantly benefited in hip fracture risk reduction at 3 years (p < .001), this was not observed in the older subgroup and the treatment-by-age interaction was statistically significant between the two groups (p = .04). A recent trial of frail women 65 and older residing in nursing homes or assisted living facilities demonstrated that a single 5 mg dose of zoledronic acid improved BMD over a period of 2 years. Subjects included those with multiple comorbidities, cognitive impairment, and decreased mobility. Furthermore, additional studies have revealed that zoledronic acid improved the quality of life in hip fracture patients and over a 3-year span reduced the number of days of back pain, limited activity owing to back pain, and limited activity and bed rest secondary to subsequent fracture.

One of the major advantages of bisphosphonates is the dosing, since these can be given at different intervals from weekly to annually, depending on the medication used. Bisphosphonates are generally safe, but administration can cause a rash or transient hypocalcemia. Bisphosphonates are contraindicated in patients with marked renal insufficiency (creatinine clearance < 35 mL/min). It is important to stress that frail older patients with mild to moderate renal insufficiency can be safely and successfully treated with bisphosphonates. Oral bisphosphonates can cause esophageal irritation and ulceration, hence, patients need to take oral bisphosphonates with 8 oz of water and remain upright for at least 30 minutes. Intravenous bisphosphonates can acutely cause fever, myalgia, transient leukopenia, acute-phase reaction, arthralgia, headache, bone pain, and atrial fibrillation. However, the flu-like symptoms can be successfully ameliorated with acetaminophen. In addition, the symptoms are less prevalent with subsequent administration. Transient increases in serum creatinine can be observed after infusion of ibandronate or zoledronic acid, but no long-term impairments in renal function have been reported.

Osteonecrosis of the jaw and atypical femoral fractures Longer-term administration of bisphosphonates has been associated with two major complications: osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFFs). ONJ is defined as the presence of exposed and necrotic bone in the maxillofacial region that does not heal within 8 weeks. The risk of ONJ may be increased in those undergoing invasive dental procedures such as tooth extractions. It is important to stress that the great majority of cases of osteonecrosis of the jaw occur in patients with underlying neoplastic disease who have received high doses of intravenous pamidronate or zoledronate. The risk of osteonecrosis of the jaw in patients with postmenopausal osteoporosis taking oral bisphosphonates is proportional to the duration and

cumulative dose of antiresorptive agents and is exceedingly low. A recent meta-analysis showed this complication to be extremely rare with an estimated incidence of 0.02% to 0.06%. Therefore, in general, the very small risk of ONJ associated with bisphosphonate use appears to be significantly outweighed by the potential benefit of fracture risk reduction and the reduction in subsequent morbidity due to fractures.

AFFs are stress or insufficiency fractures located in the subtrochanteric region and diaphysis of the femur. Radiographically AFFs are located in the lateral cortex and with transverse short oblique configuration, and are associated with cortical thickening (periosteal stress reaction). They have been reported in patients taking BPs and in patients on denosumab, but they also occur in patients with no exposure to these drugs. The absolute risk of AFFs in patients on BPs is low, ranging from 3.2 to 50 cases per 100,000 person-years. However, long-term use may be associated with higher risk (100 per 100,000 person-years). Although there seems to be an association between bisphosphonates and AFFs, causality has not been proven, and more importantly, the number of fragility fractures prevented by bisphosphonate therapy far outweighs the number of AFFs that occur. To enable early detection, intervention, and prevention of atypical femoral fractures clinicians should be vigilant and obtain imaging studies when patients taking a bisphosphonate present with thigh pain, as this may be an early sign of an AFF.

Bisphosphonate drug holiday Clinical studies in postmenopausal women with osteoporosis showed that long-term use of bisphosphonates resulted in persistent antifracture effects and maintenance of bone mineral density (BMD) beyond 3 years of treatment.

Ten years of continuous alendronate treatment (n = 662; mean age, 72.7–72.9 years) compared with cessation of therapy (n = 437; mean age, 73.7 years) after 5 years of initial treatment was associated with a significantly lower risk of clinical vertebral fracture (2.4% vs 5.3%; relative risk, 0.45; 95% confidence interval [CI], 0.24–0.85) and net gains in BMD relative to baseline at the femoral neck, lumbar spine and total body (0.46%–5.26%). Net loss of BMD at the total hip, trochanter and forearm during the FLEX study was reported in both groups, but the losses in the continuation group were significantly smaller than in the group that discontinued treatment for 5 years. For both groups, the BMD values at the femoral neck, lumbar spine, trochanter, and total body at year 10 remained above the FIT baseline.

However, discontinuation did not appear to increase the risk of nonvertebral or morphometric vertebral fractures during the 5 years of the extension study. A post hoc analysis to identify specific subgroups of patients who may benefit from continued alendronate treatment found that among women with no vertebral fractures but with femoral neck BMD T-score less than or equal to −2.5, continued alendronate treatment significantly reduced the risk of nonvertebral fractures (relative risk, 0.50; 95% CI, 0.26–0.96). For women with a baseline vertebral fracture, however, no significant interactions between baseline femoral neck BMD and the effect of continued alendronate treatment were observed on any fracture outcomes. This analysis was based on a small number of fractures and may have limited statistical power.

Risedronate has also been examined in long-term studies of up to 7 years. In the first extension study of the 3-year Vertebral Efficacy with Risedronate Therapy Multinational (VERT-MN) trial, compared with placebo, risedronate was associated with a 59% reduction in the relative risk of radiographic vertebral fracture (95% CI, 19%–79%) between years 4 and 5 of treatment (p = .01); the magnitude of this reduction was consistent with that observed in the first 3years of risedronate treatment in VERT-MN (relative risk reduction, 49%; 95% CI, 27%–64%), suggesting a persistent effect over time. The VERT-MN extension study was continued for a further 2 years in which 81 and 83 patients who had received placebo and risedronate for 5 years, respectively, received risedronate in an open-label fashion. This second extension trial reported a decrease in the incidence of radiographic vertebral fracture in the placebo/risedronate group in years 6 to 7 (6.2%) compared with years 0 to 5 (7.6%–12.3%). However the numbers of patients in these extension studies were small and the patients included may not be representative of the VERT-MN core study population. Lumbar spine BMD, continued to increase in the first extension study with BMD at all hip sites remaining stable. Lumbar spine BMD was maintained among those who had received risedronate for 7 years in the second extension of VERT-MN.

In the 3-year extension of the Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture Trial (HORIZON PFT), zoledronic acid treatment for 6 years was associated with significantly lower risk of morphometric vertebral fractures (odds ratio, 0.51; 95% CI, 0.26–0.95; p = .035) than treatment discontinuation after 3 years. No statistically significant between-group differences were seen with all clinical, clinical vertebral, nonvertebral or hip fractures, but the incidence of morphometric vertebral, nonvertebral and hip fractures in the treatment discontinuation group remained below that in placebo group in the HORIZON PFT. Relative to baseline, continuation of zoledronic acid treatment for an additional 3 years was associated with a net 0.24% increase in femoral neck BMD, and 3.20% increase in lumbar spine BMD compared with a net loss of 0.80% and a net gain of 1.18%, respectively, in

the discontinuation group. Decreases in total hip BMD from the extension study baseline were seen in both groups but was significantly less with the continuation group.

In long-term studies of ibandronate, fractures were not analyzed as a study endpoint but were reported as adverse events. The 3-year double-blind Monthly Oral IBandronate in LadiEs (MOBILE) study was extended an additional 2-years [ibandronate 100 mg (n = 348) and 150 mg (n = 350), mean age of the extension study population, 67.6 years] and similarly, the 3-year, open-label Dosing IntraVenous Administration (DIVA) study [ibandronate 2 mg bimonthly (n = 381; mean age, 66.1 years) and 3 mg quarterly (n = 400; mean age, 65.9 years)]. The fracture rates in both the MOBILE long-term extension and DIVA long-term extension study appeared to be higher than in the MOBILE and DIVA core studies. However, limited conclusions can be drawn from these results due to the difference in study populations between the core and extension studies and the absence of placebo arms in the studies.

In light of the above data and the US Food and Drug Administration (FDA) findings from pooled analyses of three long-term extension trials involving bisphosphonates, FLEX (alendronate), HORIZON-PFT (zoledronic acid) extension, and the VERT-VFERT-MN (risedronate) trial extension, that patients who received 6 years or more of bisphosphonates had fracture rates of 9.3% to 10.6%, whereas the fracture rate for patients switched to placebo was 8.0% to 8.8%, raise the question of "whether continued bisphosphonate therapy imparts additional fracture-prevention benefit, relative to cessation of therapy after 5 years." Thus it is recommended that when considering patients who may benefit from a drug holiday, evaluation of fracture risk after treatment is important. A drug holiday may be considered after 3 to 5 years of bisphosphonate therapy in patients with moderate or low risk of fracture because stopping bisphosphonates for a short period of time poses minimal risk to the patient. In high-risk patients, careful consideration for the timing and/or duration of a bisphosphonate holiday is needed, as these patients may derive benefit from treatment beyond 5 years.

Calcitonin Calcitonin is a peptide hormone that is used to treat osteoporosis. It is available as a subcutaneous injection and a nasal spray. The advantages of a nasal spray over injectable calcitonin are fewer reported side effects and greater patient acceptance. Calcitonin has been shown to increase bone density in the spine and to reduce vertebral fractures. In epidemiologic studies, calcitonin reduces hip fractures, although in clinical trials hip bone density does not increase. In the Prevent Recurrence of Osteoporotic Fractures (PROOF) study in postmenopausal women with osteoporosis (mean age 69 years), 200 IU salmon calcitonin nasal spray per day decreased the risk of new vertebral fractures by 33% to 36% at the end of 5 years. Other doses, 400 and 100 IU, did not have any significant effect on ver tebral fracture rate. Bone density at any site and markers of bone turnover did not change, compared to placebo. Furthermore, the discontinuation rate at the end of the study was 59%. Nasal spray calcitonin does not appear to be as effective in preventing fractures as other approved agents; therefore, its use should be limited to those women who are unable to tolerate other treatments. The only current indication for the use of calcitonin is for analgesic treatment in acute compression fractures, in the Paget disease of bone and in bone pain because of metastatic disease.

Selective Estrogen Receptor Agonists

The selective estrogen receptor modulators (SERMs) are agents that act as estrogen agonists in bone and heart but act as estrogen antagonists in breast and uterine tissue. These medications have the potential to prevent osteoporosis or heart disease without the increased risk of breast or uterine cancer. Tamoxifen, an agent used in breast cancer treatment, has been shown to have beneficial effects on bone in several studies but has stimulatory effects on the uterus; it is not approved for treatment or prevention of osteoporosis. Raloxifene, a nonsteroidal benzothiophene, is a newer selective estrogen receptor modulator that has been approved for prevention and treatment of osteoporosis in postmenopausal women. In one study of postmenopausal osteoporotic women, raloxifene resulted in decreased bone turnover and increased BMD of the hip, spine, and total body bone density, as compared to placebo. Furthermore, raloxifene did not increase endometrial thickness for more than 2 years and had positive effects on the lipid profile.

In the large 3-year randomized Multiple Outcomes of Raloxifene Evaluation (MORE) trial (n = 7705 postmenopausal women with osteoporosis, mean age 67) the effect of 60 or 120 mg/day raloxifene on fractures was examined. After 1 year, raloxifene significantly reduced the risk of new clinical vertebral fracture by 68% in the overall study population (absolute risk reduction, 1.3 per 1000) despite only modest gains in BMD. After 3 years, raloxifene reduced the relative risk of vertebral fracture by 55% in women at high risk with BMD T-score of −2.5 or below (120 mg group), and by 30% in women with low T-scores and an existing vertebral fracture (60 mg group). There was no difference in hip fracture or nonvertebral fracture incidence in the raloxifene-treated groups, as compared to placebo. Although, in a post hoc analysis, a decrease in new vertebral and nonvertebral fracture risk was seen in the subgroup of women with the most severe vertebral fractures at baseline.

BMD of the lumbar spine and femoral neck increased in both raloxifene-treated groups compared to placebo (in the femoral neck by 2.1% [60 mg] and 2.4% [120 mg] and in the spine by 2.6% [60 mg] and 2.7% [120 mg]). Despite the modest BMD increases in this study, the reduction in vertebral fracture risk was clinically significant, suggesting that antiresorptive agents have effects on bone that are not reflected in BMD measurement. In fact, a meta-analysis of seven head to head randomized controlled trials comparing efficacy of raloxifene with ALN concluded that, despite ALN being more effective at increasing BMD, the efficacy of the drugs in preventing fractures; vertebral ($p = 0.45$) and non vertebral ($p = 0.87$) did not differ significantly at the end of the 2-year follow-up period.

The major serious adverse effect of raloxifene was an increase in stroke in postmenopausal women at risk of coronary heart disease and venous thromboembolic events, including deep vein thrombophlebitis and pulmonary embolism events (RR 3.1 [1.5–6.2]). However, raloxifene-treated women in this study had a reduced risk of breast cancer incidence (RR 0.3 [0.2–0.6]). In a 6-month study, raloxifene had effects on bone histomorphometry and bone turnover that were similar in direction to conjugated equine estrogen but were lower in magnitude. Although older women have been included in some studies, the numbers are small and there are no published data for fracture outcomes in older cohorts or subgroups. However, a study examining the effect of raloxifene in older women living in long-term care facilities did show that raloxifene reduces bone turnover in these women to a level comparable to what is seen in younger postmenopausal women.

Denosumab Since identified as a key molecule in mediating osteoclast development, activity, and survival, the inhibition of receptor activator of nuclear factor kappa-B ligand (RANKL) activity has been tested as a therapeutic target for osteoporosis. Recently, a fully human monoclonal antibody to RANKL called denosumab was developed and tested. Denosumab blocks RANKL binding to RANK thus inhibiting the development and activity of osteoclasts. Denosumab administered every 6 months to postmenopausal women with low BMD over 12 months resulted in an increase in bone mineral density at the lumbar spine of 3.0% to 6.7%, at the total hip of 1.9% to 3.6%, and at the distal third of the radius of 0.4% to 1.3%. Near-maximal reductions in mean levels of serum CTX, a bone resorption marker, from baseline were evident 3 days after the administration of denosumab.

In the FREEDOM trial involving 7868 women with osteoporosis (60–90 years; 32% of women were ≥ 75 years), denosumab administered subcutaneously every 6 months for 36 months significantly reduced vertebral fractures (RR 0.32; 95% CI 0.26–0.41), hip fractures (RR 0.60; 95% CI 0.37–0.97), and nonvertebral fractures (RR 0.80; 95% CI 0.67–0.95). There was no increase in the risk of cancer and infection compared to placebo, however the major concern about the long-term use of denosumab relates to its possible effects on the immune system, since RANKL is expressed not just on bone cells but also on immune cells. Most phase II and phase III trials of denosumab have not shown an increased risk of infection, and there have not been reports of opportunistic infections. When studied in patients with RA, denosumab also was not associated with an increased incidence of infection. The data on concurrent use of denosumab and other biologics are limited. Combination regimens of denosumab with either biologic or nonbiologic disease-modifying antirheumatic drugs (DMARDs) did not appear to have a significant increased risk of infections in small case series. Nevertheless denosumab has several advantages: (1) convenient biannual subcutaneous administration that could improve adherence; (2) lack of gastrointestinal side effects; (3) reversibility, because it targets RANKL and is not incorporated into the bone mineral; and (4) useful for impaired renal function because of nonelimination by the kidneys.

Denosumab may be more potent than oral alendronate as supported by findings from a phase III, double blind trial in which 1189 postmenopausal women (with a T-score of ≤ −2.0 at the total hip or lumbar spine) were randomized to receive either denosumab (60 mg/6 months) or oral alendronate (70 mg/week) over a 1-year period. There was a significantly larger increase in BMD at all skeletal sites at 12 months with denosumab compared to ALN, particularly at the total hip (3.5% vs 2.6%, $p < .0001$). Bone turnover markers were more markedly reduced with denosumab compared to alendronate, although bone quality, an important determinant of fracture risk, was not assessed.

Parathyroid hormone PTH, when administered daily subcutaneously, markedly increases bone mass and BMD. PTH increases osteocalcin, a marker of bone formation, more rapidly than deoxypyridinoline cross-links, a marker of bone resorption, suggesting early uncoupling of the bone remodeling cycle and providing a potential mechanism for the anabolic effect on bone. Multiple studies demonstrate significant reductions in vertebral and nonvertebral fracture risk. The PTH analog teriparatide effectively increases spinal BMD in osteoporotic men and women and reduces both vertebral and nonvertebral fractures in postmenopausal women. PTH also enhances BMD in glucocorticoid-dependent osteoporosis. Efficacy in the older population is however limited. A subgroup analysis of the Fracture Prevention Trial showed that teriparatide treatment (teriparatide 20 mg vs placebo) was associated with a significant reduction in the risk of new vertebral fracture (RRR 65%, $p < .05$) in postmenopausal women aged 75 years and older but no

significant reduction in nonvertebral fractures at 1 year.

The recommended dose is 20 μg SQ/day. Indications for PTH include a T-score worse than −3.5 or prevalent fractures in the setting of a T-score worse than −2.5. In addition, patients who continue to fracture or lose BMD after 2 years of bisphosphonate treatment are also candidates for PTH. The side effects that occurred more frequently in the PTH-treated groups were headache, nausea, dizziness, and hypercalcemia. The major limitations to the use of PTH in older adults are its significant cost and the mode of administration, since subcutaneous dosages require an appropriate cognitive status, a high degree of motivation, and a significant level of functional independence. At present, studies suggest that PTH should not be combined with bisphosphonate therapy, since concurrent bisphosphonate treatment appears to blunt the BMD response to PTH. PTH therapy should continue no longer than 2 years. It is very important, however, to treat with an antiresorptive after discontinuation of PTH, in order to maintain gains in BMD.

Strontium ranelate This agent appears to acts as both an anabolic and an antiresorptive medication for osteoporosis. Its fracture efficacy data result from two major phase III studies: the SOTI study (Spinal Osteoporosis Therapeutic Intervention, n = 1649, mean age 70 years, range 50–96) and the TROPOS study (Treatment of Postmenopausal Osteoporosis, n = 5091, mean age 77 years, range 70–100). Treatment with strontium ranelate reduces new vertebral fractures by 49% at 1 year (RR = 0.51, CI: 0.36–0.74) and 41% over 3 years (RR = 0.59, CI: 0.48–0.73). The TROPOS study showed a reduction in the relative risk for all nonvertebral fractures of 16% and a reduction of 19% for all major nonvertebral fractures (hip, wrist, pelvis, sacrum, ribs, sternum, clavicle, and humerus) after 3 years of treatment at a dose of 2 g/day. There was a trend towards a reduction in hip fracture in the intention-to-treat population of 15%, but this did not reach statistical significance.

However in a subgroup analysis of high-risk women (age > 74 years, femoral neck BMD T-score < −3.0), strontium ranelate reduced hip fractures by 36% (RR = 0.64, CI: 0.41–0.99). In a preplanned pooled analysis of SOTI plus TROPOS in women aged 80 years or more (n = 1488), strontium ranelate reduced the risk of vertebral fracture in the first year by 59% (RR = 0.41, CI: 0.22–0.75) and nonvertebral fractures by 41% (RR = 0.59, CI: 0.37–0.95). At 3 years, the risk reductions were 32% (RR = 0.68, CI: 0.50–0.92) and 31% (RR = 0.69, CI: 0.52–0.92), respectively. In a follow-up pooled analysis at 5 years in this age group, the relative risk reductions were maintained: 31% for vertebral fractures (RR = 0.69, CI: 0.52–0.92) and 27% for nonvertebral fractures (RR = 0.73, CI: 0.57–0.95). The fact that this agent is given as a soluble powder favors its acceptance and tolerance except for mild gastrointestinal adverse effects (nausea and diarrhea), which usually resolved by 3 months of treatment.

Recently strontium is restricted to treatment of severe osteoporosis, in postmenopausal women and in adult men, at high risk of Fx for whom treatment with other medicinal products approved for the treatment of OP is not possible due to, for example, contraindications or intolerance. This resulted from a number of adverse findings from ongoing safety evaluations and post marketing data. Pooled data from the SOTI and TROPOS trials showed an increased risk of VTE in the Strontium group (0.6% vs 0.9% per year). A study published by the UK General Practice Research Database (GPRD) also showed increased age-adjusted rate ratios for VTE, gastrointestinal disturbance, minor skin complaint, and memory loss were 1.1 (95% CI 0.2–5.0), 3.0 (95% CI 2.3–3.8), 2.0 (95% CI 1.3–3.1), and 1.8 (95% CI 0.2–14.1), respectively. A small but significant increase in nonfatal myocardial infarctions was also recently observed when pooling all studies assessing the effect of SR in OP and osteoarthritis. However this was refuted by findings from the analysis in the UK Clinical Practice Research Datalink (CPRD) and the Danish National Prescription Database analysis which did not show an increased risk of MI. Nevertheless the European Medicines Agency (EMA) warned that SR should be avoided in patients with ischemic heart disease (IHD), peripheral vascular disease (PVD), or cerebrovascular disease (CVD), and in patients with uncontrolled hypertension.

Sequential/combination therapies The scenario of sequential or combination therapy arises when a patient continues to fracture and/or lose BMD despite being on antiresorptive therapy or else exhibits drug intolerance and is therefore switched to another antiresorptive or an anabolic agent. The STAND trial explored the effect of denosumab on BMD in post menopausal women 55 years of age and older with a BMD T-score of −2.0 or less and −4.0 or more who had been receiving alendronate therapy for at least 6 months. In subjects transitioning to denosumab, total hip BMD increased by 1.90% at month 12 compared with a 1.05% increase in subjects continuing on alendronate (p < .0001). Significantly greater BMD gains with denosumab compared with alendronate also were achieved at 12 months at the lumbar spine, femoral neck, and 1/3 radius (all p < .0125). Median serum CTX levels remained near baseline in the alendronate group and were significantly decreased versus alendronate (p < .0001) at all time points with denosumab. Adverse events and serious adverse events were balanced between groups.

In contrast, long-term therapy with a bisphosphonate prior to initiating teriparatide blunts the effectiveness of PTH.

In one study it was found that the increase in lumbar spine BMD after 18 months of teriparatide (20 μg/day) was only 4.1% in postmenopausal women who had been previously treated with alendronate for 18 to 36 months. In comparison, patients pretreated with raloxifene, also an antiresorptive agent, resulted in an incremental increase of 10.2% (ALN vs raloxifene, $p < .05$). The reverse scenario, antiresorptive therapy after PTH, has also been examined. In one follow-up study, treatment with bisphosphonates for at least 24 months during a 30-month postteriparatide treatment phase demonstrated additional increases in BMD (4.3% increase in total hip BMD from baseline in the 20 μg group and 6.8% increase in the 40 μg group). In contrast, those who did not receive any antiresorptive therapy during this time period experienced a reduction in BMD that was similar to placebo ($p < .05$). A comparable improvement in BMD occurred when teriparatide was followed by raloxifene.

Few studies have examined combination therapies. Two randomized controlled trials have looked at the effects of combining teriparatide with alendronate. One study conducted in postmenopausal women treated with intact PTH (100 μg/day) and the other in men treated with teriparatide (40 μg/day). Neither study found additive effects on BMD gains when intact PTH and ALN were combined, and ALN in fact reduce BMD gains when compared to teriparatide alone. In contrast, combined treatment with teriparatide and denosumab led to a greater increase in spinal, femoral neck, and hip BMD (9.1%, 4.2%, 4.9%, respectively) compared to teriparatide (6.2%, $p = 0.014$, 0.8%, $p = 0.007$, 0.7%, $p = 0.001$) or denosumab alone (5.5%, $p = 0.0005$, 2.1%, $p = 0.0238$, 2.5%, $p = 0.001$). Interestingly, neither oestrogen nor SERMs (such as raloxifene) appear to blunt the effects of PTH, despite being antiresorptive in nature. One study showed PTH + HRT increased bone mass by 13.4 ± 1.4% in the spine, 4.4 ± 1.0% in the total hip, and 3.7 ± 1.4% in the total body. The combination also reduced the percent of women who had vertebral fractures from 37.5% to 8.3% (using a 15% height reduction criterion) and from 25% to 0% (using a 20% height reduction criterion) compared with women receiving HRT alone. It must be noted that none of these studies have been powered to assess differences in fracture incidence between combination therapy and monotherapy.

Thus in patients on bisphosphonates who suffer hip fractures or who have very low hip BMD, strong consideration should be given to starting teriparatide and continuing a bisphosphonate (possibly switching to zoledronic acid or even denosumab) to maximize hip BMD and strength. Furthermore, in treatment-naive individuals with very severe osteoporosis, such as those with spine and hip fractures, combination therapy with PTH and denosumab or PTH followed by combination treatment with a potent bisphosphonate or denosumab should be considered to maximize early increases in BMD.

Antiosteoporosis Agents on the Horizon

Sclerostin antibody The osteocytes play an integral role in the bone remodeling process by secreting a number of molecules involved in the activation and inhibition of bone formation. Sclerostin (SOST) is a glycoprotein secreted almost exclusively by the osteocytes and is a crucial regulator of osteoblast activity. It inhibits osteoblast differentiation and function by antagonizing the Wnt signaling pathway. The activation of the Wnt canonical pathway prevents the degradation of β-catenin, which therefore accumulates in the cytoplasm and translocates to the cell nucleus where it binds to specific transcription factors that promote osteoblast differentiation, maturation, and proliferation. Therefore, antibodies against sclerostin represent a strategy to target bone formation specifically.

Two human monoclonal antisclerostin antibodies have been investigated in preclinical studies, romosozumab and blosozumab. In one phase I, randomized, double-blind, placebo-controlled, single-dose study, 72 healthy subjects received romosozumab (AMG-785) (subcutaneously 0.1, 0.3, 1, 3, 5 or 10 mg/kg, or intravenously 1 or 5 mg/kg) or placebo. The antibody injections were well tolerated and were associated with increases in bone formation markers, reductions in bone resorption markers, and dose-dependent increases in BMD at the lumbar spine and total hip after 3 months. The efficacy and safety of romosozumab were recently confirmed in a phase II multicenter international randomized placebo-controlled parallel-eight-group study over a 12-month period in 419 postmenopausal women, 55 to 85 years of age, who had low bone mineral density (a T-score of −2.0 or less at the lumbar spine, total hip, or femoral neck and −3.5 or more at each of the three sites). Subcutaneous doses of romosozumab monthly (at a dose of 70, 140, or 210 mg) or every 3 months (140 or 210 mg) were compared with subcutaneous placebo, or an open-label active comparator—oral alendronate (70 mg weekly) or subcutaneous teriparatide (20 μg daily). At month 12, romosozumab induced significant increase in bone mineral density at the lumbar spine, total hip as well as femoral neck regardless of dose frequency (monthly or every 3 months) and dose level (140 or 210 mg) compared with placebo. The largest gains were observed with the 210-mg monthly dose of romosozumab, with mean increases from baseline to 12 months of 11.3% at the lumbar spine, 4.1% at the total hip, and 3.7% at the femoral neck. These increases were significantly greater than those observed in the alendronate and teriparatide groups. There were

transitory increases in bone-formation markers and sustained decreases in bone-resorption markers. Except for mild, generally nonrecurring injection-site reactions with romosozumab, adverse events and serious adverse events were comparable with placebo, and no apparent relationship between dose and adverse events was observed. Phase III studies examining the effect of romosozumab on fracture risk are currently ongoing.

Another human monoclonal antibody against sclerostin, blosozumab, has also been trialed in phase I and II studies. In a phase I study healthy postmenopausal women receiving intravenous or subcutaneous single or multiple escalating doses of blosozumab exhibited dose-dependent decreases in bone resorption markers and increases in bone formation markers and BMD at the lumbar spine (up to 3.4% and 7.7% from baseline at day 85 after single and multiple administrations of blosozumab, respectively). Blosozumab was generally well tolerated and demonstrated an overall favorable safety profile.

A phase II study examining postmenopausal women with low BMD showed that subcutaneous blosozumab treatment (180 mg every 4 weeks, 180 mg every 2 weeks or 270 mg every 2 weeks) resulted in statistically significant dose-related increases in BMD at both the lumbar spine and the hip (17.7% and 6.2%, respectively after 12 months in the highest dose group). Bone formation markers increased rapidly during blosozumab treatment and trended toward pretreatment levels by study end. However, bone specific alkaline phosphatase remained higher than placebo in the highest-dose group. Markers of bone resorption decreased early in blosozumab treatment to a concentration less than that of the placebo group by 2 weeks and remained reduced throughout blosozumab treatment. In a follow up study, at doses of 270 and 180 mg every 2 weeks, lumbar spine BMD remained significantly greater than placebo 1 year after discontinuing treatment (6.9% and 3.6% above baseline, respectively). Total hip BMD also declined following discontinuation of treatment, but at 1 year after treatment remained significantly greater than placebo (3.9% and 2.6% above baseline, respectively). During follow-up, median serum P1NP, a bone formation marker, was not consistently different between the prior blosozumab groups and placebo. A similar pattern was apparent for median serum CTX levels with more variability. Mean serum total sclerostin concentration increased with blosozumab, indicating target engagement and declined to baseline following discontinuation. There were no adverse events related to prior treatment with blosozumab. Antidrug antibodies generally declined in patients who had detectable levels during prior treatment.

Cathepsin K inhibitors Cathepsin K is an enzyme secreted by osteoclasts while resorbing bone. Bone resorption begins when osteoclasts bind firmly to bone surfaces forming resorption pits. An acid medium is produced within these pits resulting in the dissolution of the osseous mineral component exposing the organic matrix. The matrix is then degraded by the enzymes metalloproteinases and cathepsin K. Drugs that inhibit cathepsin K are suggested to have less effect on osteoclast-osteoblast interaction because they do not result in osteoclast apoptosis as do bisphosphonates. Several cathepsin K inhibitors have been evaluated, but so far only odanacatib and ONO-5334 have showed adequate efficacy and safety.

Odanacatib (ODN) is a selective cathepsin K inhibitor characterized by long half-life and oral availability. It concentrates in the resorption lacunae where it prevents the binding of cathepsin K to its substrates and, unlike bisphosphonates, it does not affect osteoclast formation and survival. Preclinical studies of ovariectomized animals treated with ODN showed a reduction in bone turnover, increased bone mass at lumbar spine and hip, and improved cortical thickness by preserving endocortical bone formation and stimulating periosteal bone formation. Phase I and II studies of postmenopausal women treated with ODN (10, 25, or 50 mg once weekly) demonstrated efficacy and good safety profile. Twenty-four months of treatment produced progressive dose-related increases in BMD. With the 50-mg dose of ODN, lumbar spine and total-hip BMD increased 5.5% and 3.2%, respectively, whereas BMD at these sites was essentially unchanged with placebo (−0.2% and −0.9%). Continued treatment with 50 mg of ODN for 3 years produced significant increases from baseline and from year 2 in BMD at the spine (7.9% and 2.3%) and total hip (5.8% and 2.4%). Urine cross-linked N-telopeptide of type I collagen (NTx) remained suppressed at year 3 (−50.5%), but bone-specific alkaline phosphatase was relatively unchanged from baseline. Treatment discontinuation resulted in bone loss at all sites, but BMD remained at or above baseline. After ODN discontinuation at month 24, bone turnover markers increased transiently above baseline, but resolved by month 36. Extending treatment to 5 years by switching treatment combinations of ODN (10, 25, or 50 mg once weekly for the first 2 years) to 50 mg once weekly for the following 3 years resulted in almost linear percentage increases in spine and hip BMD from 9.5% to 11.9% depending on the measured site compared to baseline, and showed larger reductions of bone resorption than bone formation markers. In the group of women switched from ODN to placebo for 3 years, bone turnover markers returned near baseline, demonstrating the reversibility of ODN effect.

In another phase III study, ODN 50 mg weekly for 2 years increased trabecular volumetric BMD and strength at

the spine and integral and trabecular volumetric BMD and estimated strength at the hip. Odanacatib improved integral, trabecular, and cortical BMD and total bone mineral content at all femur regions relative to placebo. Cortical volume and thickness increased significantly in all regions except the femoral neck. However data on fracture risk reduction is not yet available. As of 2015 a multinational, randomized, double-blind, event-driven placebo-controlled trial of approximately 5 years duration and involving over 16,000 osteoporotic postmenopausal women investigating the efficacy of ODN in preventing fractures of the hip, spine, and of nonvertebral sites is ongoing. Although with several limitations, two recent meta-analyses evaluated available clinical trials on ODN that reported fractures as adverse events, and both suggested beneficial effect of ODN 50 mg once weekly on fracture prevention.

ONO-5334 is an oral synthetic low molecular weight inhibitor of cathepsin K. A phase II trial with ONO-5334 at different dosing regimens (50 mg twice daily, 100 mg once daily, or 300 mg once daily) demonstrated significant increases in BMD at lumbar spine, total hip (except 100 mg once daily), and femoral neck, as compared with placebo. The effect on BMD and bone resorption markers of ONO-5334 was comparable to that of alendronate 70 mg once weekly. However, compared to bisphosphonates, ONO-5334 induced minimal or no suppression of bone formation markers. When extended to 2 years, statistically significant improvements at all BMD sites and at all doses of ONO-5334 were observed at 24 months as compared with placebo. The effect of ONO-5334 on biochemical markers rapidly reversed upon treatment cessation, and there were no clinically relevant safety concerns. Furthermore statistically significant and persistent increases of integral, trabecular and, to a smaller degree, cortical BMD at the lumbar spine and the hip versus placebo were demonstrated. Sustained-release formulations of ONO-5334 (50, 100, or 300 mg) showed clear dose–response suppression of bone resorption markers and greater efficacy dose for dose versus the immediate-release tablets while being equally well tolerated.

Similar to sclerostin, as noted above, DKK1 is another modulator of the Wnt signaling pathway leading to suppression and decreased bone formation. Monoclonal antibodies against DKK1 have been shown to accelerate bone formation and increase BMD in animal models. In humans pharmacologic DKK1 inhibition has been examined in patients with relapsed or refractory multiple myeloma.

Src tyrosine kinase is an enzyme with multiple regulatory functions and is expressed at high levels in osteoclasts. It contributes to their survival and seems to be essential for osteoclastic bone resorption since it plays an important role in the development of the ruffled border on the resorption surface. Saracatinib (AZD0530) is an orally available ATP-competitive inhibitor of Src kinase and in vitro has shown significant antiresorptive effects. In a randomized, double-blind, placebo-controlled, multiple ascending dose phase I trial, 72 healthy men received saracatinib (a single dose of 60, 125, 185, or 250 mg followed 7–10 days later with daily doses for further 10–14 days) or placebo. Dose-dependent decreases in bone resorption markers were observed with no significant effect on bone formation markers and without serious adverse events.

OSTEOPOROSIS IN NURSING HOMES

There is increasing concern about the underdiagnosis and undertreatment of patients with osteoporosis in special settings, such as long-term care institutions. Institutionalized patients, whether mobile or immobile, are at high risk of osteoporosis. Residents should be assessed upon admission and multifactorial prevention measures implemented. All should be treated with a combination of vitamin D (minimal dose of 800 IU/day) plus calcium (1500 mg/day). Because the frail older adults may be markedly vitamin D insufficient or exhibit an unpredictable response to supplementation, the serum level of 25(OH) vitamin D should be obtained before beginning supplementation. Between 1500 and as much 5000 IU/day may be needed. If the 25(OH) vitamin D level is less than or equal to 50 nmol/L, patients should be started on 2000 IU/day of cholecalciferol. For those who are frankly deficient with a 25(OH) vitamin D less than 20 nmol/L, 50,000 units of either cholecalciferol or ergocalciferol weekly for 8 to 12 weeks should be administered, and then the 25(OH) vitamin level again assessed. Additionally, the presence of risk factors and/or previous fractures strongly supports the use of pharmacologic treatment with either antiresorptives or anabolic agents. The clinician should consider the patient's level of functionality, quality of life and life expectancy before starting pharmacologic treatment for osteoporosis in a long-term care setting. However, since hip fractures lead to a decline in the quality of life and life expectancy, and fracture risk reduction can be achieved as quickly as 6 months of treatment, pharmacologic approaches are justified in institutionalized patients who are at risk. Bisphosphonates are the first-line choice, and intravenous administration is likely to achieve better adherence. Denosumab appears to offer equal protection and because of its administration subcutaneously may also enhance adherence. Teriparatide not a first line agent and should only be used in those with severe osteoporosis and repeated fractures in the setting of antiresorptive

treatment.

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Chapter 119

Hip Fractures

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Learning Objectives

- To be able to describe the medical issues commonly experienced by older hip fracture patients.
- To be able to describe the physiological and functional trajectories experienced by older hip fracture patients during the year after the fracture event.
- To be able to describe the psychosocial issues commonly experienced by older hip fracture patients and their families and/or caregivers.
- To be able to describe the medical and psychosocial management strategies for older hip fracture patients in the acute care and rehabilitation settings.
- To understand the role of the geriatrician in providing care to older hip fracture patients during the perioperative and recovery periods.

Key Clinical Points

1. **Hip fracture in older adults is associated with significant morbidity and mortality.**
2. **Complications of hip fracture can be prevented or mitigated, through careful perioperative screening and intervention strategies initiated during the acute hospitalization, period of formal rehabilitation services, and over the course of the year after the fracture event.**
3. **Geriatricians can play a critical role in coordinating care for hip fracture patients, initiating appropriate state-of-the-art interventions, and optimizing communication between the patient, family members, and the health care team.**

INTRODUCTION

Hip fracture is a major public health problem with significant consequences for older patients, their families, and the health care system. In 2010, there were approximately 260,000 adults aged 65 years and older hospitalized for a hip fracture in the United States and this number is expected to increase to 289,000 by 2030 due to the aging of the population and people living longer. Recent worldwide estimates are in the order of 1.7 million hip fractures annually, and are expected to surpass 6 million by the middle of this century. As seen in **Figure 119-1**, hip fracture incidence increases exponentially in both men and women with advancing age. The average age of a patient with hip fracture is 82 years. Among those who reach age 85, approximately 19% of women and 12% of men will experience a hip fracture and, of those who reach 90 years of age, 30% of women and 20% of men will sustain a hip fracture. Although the majority of hip fractures occur in older white women, 25% to 30% of hip fractures occur in men and, in the United States, 8% occur in nonwhites. Prominent risk factors for hip fracture are osteoporosis and propensity to fall. Underlying these essential conditions for having a hip fracture are the reduced bone strength and quality that are characteristic of osteoporosis and the multiplicity of medical, psychosocial, and environmental factors that lead to falls.

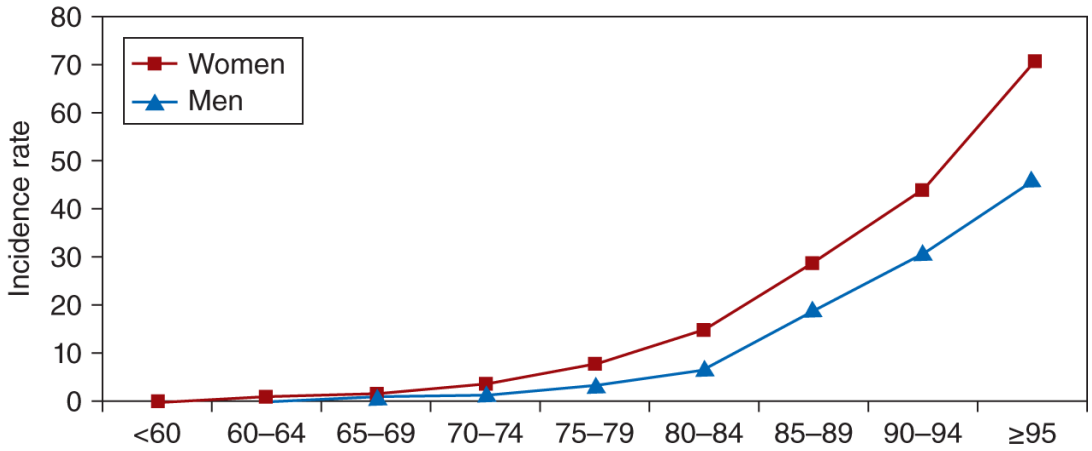


FIGURE 119-1. Age-specific incidence rates of hip fracture (per 1000 person-years): the Framingham study. (Samelson EJ, et al. *Am J Public Health*. 2002;92(5):858–862.)

The direct medical and indirect nonreimbursed costs (eg, unpaid caregiving services and lost wages of patients and caregivers) of hip fracture have been estimated to be as high as $20 billion annually in the United States. Among those who have experienced a hip fracture, approximately 18% of women and 36% of men are expected to die within the first year of their fracture. The highest mortality rates occur within the first few months after a fracture among those who are in the poorest health. In addition, comparison of survival rates of female hip fracture patients to similarly impaired women without fractures indicates that the fracture itself is responsible for nine extra deaths per 100 patients during the first 4 years following the fracture. Epidemiological data from studies of women indicate that even in those with the lowest number of medical comorbidities and best functioning at the time of fracture, the mortality attributable to hip fracture continues to increase well beyond the first year postfracture. Causes of death in women and men are similar and approximately four times greater than their nonfracture counterparts for heart disease, three times greater for cerebrovascular disease, and three times greater for chronic obstructive pulmonary disease. Interestingly, one study showed that men are far more likely than their nonfracture counterparts to die from infectious causes such as septicemia and pneumonia, in the first 2 years following hip fracture.

The intent of this chapter is to provide information about the medical and psychosocial status of the older patient who presents with a hip fracture and to discuss strategies for care and the role of the geriatrician in providing care during the acute hospital stay and the subsequent year or more of follow-up care.

WHAT TO EXPECT WHEN SEEING PATIENTS IN HOSPITAL

The cumulative effect of environmental exposures, lifestyle, and genetic factors result in a remarkably heterogeneous geriatric population. Aging impacts most organ systems, although the degree to which organs are impaired from aging varies from individual to individual. In addition, several chronic medical conditions may also exist in a given individual. Medical care of the patient with hip fracture must, therefore, be adapted to the individual patient's needs. This requirement for a tailored approach to care is the source of both the challenge and the satisfaction of geriatric medicine.

The changes that occur with aging physiology result in decreased resilience to stress, or the so-called "homeostenosis" in most organs. For example, older individuals have stiffening of their rib cages and decreased mucociliary clearance of their lungs, resulting in an increased propensity for postoperative atelectasis and pneumonia and poorer tolerance of these complications when they occur. Because of this decreased physiological reserve, older individuals are at particular risk for a wider range of iatrogenic complications and do not recover as well when complications and adverse events do occur. For example, by mechanisms that are not yet understood, older individuals can more easily become delirious during the pre- and postoperative period. This complication not only increases the patient's risk of dying in the subsequent year, but also can impair an individual's ability to participate in rehabilitation. Thus, all interventions must be monitored very closely to quickly determine their impact on the patient.

Medical Presentation and Fracture Characteristics

Classically, a patient with a hip fracture presents with a painful, shortened, and externally rotated lower extremity after

a fall and landing on the affected hip. Usually, but not always, such patients are unable to bear weight on the extremity. There are many exceptions to this description, however. While a small percentage of hip fractures occur without trauma preceding the fracture event, nearly a third of patients do not recall or cannot give a clear history of the precipitating fall. When a nondisplaced femoral neck fracture occurs, the extremity may be neither shortened nor externally rotated, and patients with stable impacted fractures or nondisplaced "hairline" fractures may be able to bear weight and ambulate. Occasionally, patients like this are sent home without fracture management but soon return for care, due to continued pain and discomfort when ambulating. Thus, a better guiding principle is that all older patients with hip pain after trauma should be considered to have a hip fracture until proven otherwise. Similarly, patients having pain with gentle rolling of the lower extremity must be ruled out for hip fracture, irrespective of recollection of trauma.

Approximately half of all hip fractures occur in the area of the femoral neck (or "intracapsular fractures"), and the other half occur in the area between the greater and lesser trochanters ("intertrochanteric fractures" or "extracapsular fractures"). Far less common are fractures that occur within 5 cm below the lesser trochanter; these are called "subtrochanteric fractures." Patients with intertrochanteric fractures tend to be older than those with femoral neck fractures and are more likely to have multiple medical comorbidities prefracture. A schematic of the hip anatomy is shown in **Figure 119-2**, which also indicates the anatomy of the vascular supply to the hip region. This schematic is useful to understand the various surgical approaches to hip fracture care and the potential for blood loss at each site. As demonstrated in the schematic, the regions of the femoral neck and the femoral head derive their main blood supply from fine retinacular arteries that stem from the medial circumflex femoral artery. These delicate vessels are closely apposed to the femoral neck in this region. Therefore, a fracture in this region of the hip, particularly if any displacement occurs, is more likely to disrupt the vascular supply to the femoral neck and head, which can result in longer-term nonunion and osteonecrosis. Thus, fractures in the femoral neck region, particularly displaced fractures, are usually managed with surgical replacement rather than internal fixation. In contrast, the blood supply to the intertrochanteric area is plentiful and redundant, such that nonunion and osteonecrosis are less common in this region, and fractures can heal well after internal fixation procedures.

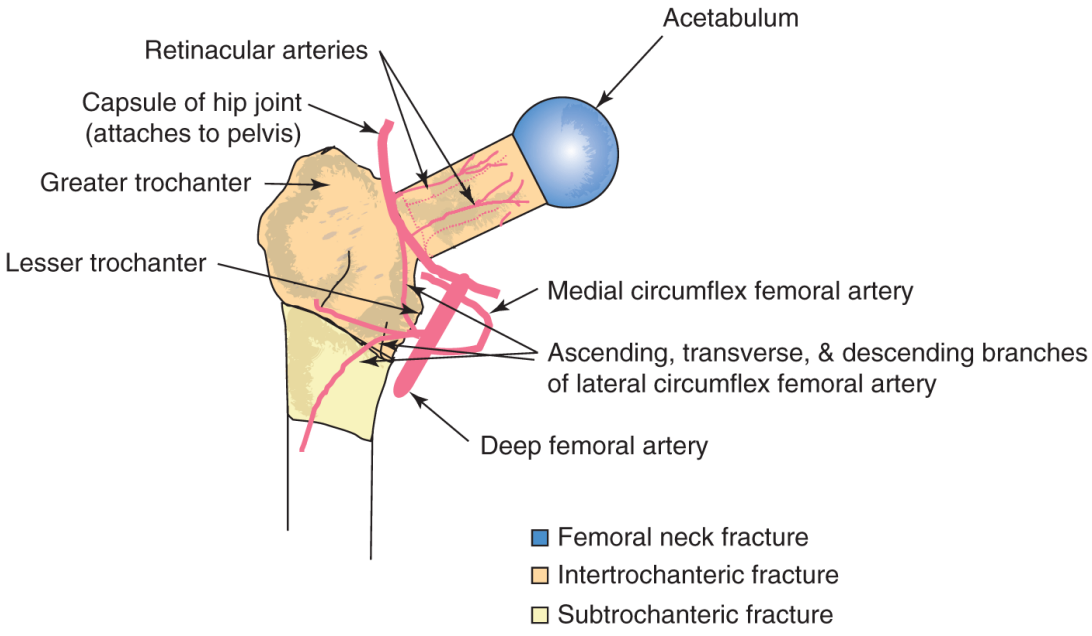


FIGURE 119-2. A schematic diagram of the anatomy of the hip.

Cognitive Status

Dementia is a prominent risk factor for falls and fractures and, not surprisingly, a significant number of patients with hip fracture have underlying cognitive impairment. Delirium is also a very common occurrence both at time of presentation to the emergency department and especially postoperatively, where up to 60% may develop confusion after hip fracture repair, with underlying dementia again being a powerful risk factor for the development of delirium. The presence of delirium and cognitive impairment portend a worse functional recovery for patients with hip fracture. Identification of underlying dementia and risk factors for delirium is important for both prognostication, and so that

some of the modifiable delirium risk factors may be avoided or minimized, in hopes of reducing the occurrence and severity of delirium. Given the high risk of delirium in this patient population, it is particularly important to prepare the patient and family emotionally for this potential complication, especially in those with identified risk factors, because the manifestations of delirium can be quite frightening to unprepared family members.

Risk factors for delirium in hospitalized patients have been well described. Some of the most consistently reported risk factors include advanced age, chronic cognitive impairment or dementia, sensory impairment, male sex, presence of comorbid psychiatric disease, use of psychoactive drugs, infection, polypharmacy, use of restraints, sleep deprivation, and undertreatment of pain. Allowing people to sleep at night and remain alert during the day, minimizing sensory impairment, promptly removing unneeded tethers such as Foley catheters and IVs, providing daily orientation, and careful attention to pain and polypharmacy may be useful in reducing the incidence of delirium in patients with hip fracture, as has been demonstrated in geriatric general medical in-patients. Undertreatment of pain, particularly in cognitively intact individuals, appears to be a stronger predictor of delirium than use of narcotics. Studies of proactive geriatric consultation with targeted recommendations such as oxygen delivery, fluid balance, analgesia, elimination of unnecessary medications, regulation of bowel and bladder function, nutritional intake, mobilization, prevention of postoperative complications, assessment of environmental stimuli, and treatment of agitated delirium have shown reductions in the incidence of delirium overall by a third, and in one study, a reduction in the incidence of severe delirium by half.

The Geriatrician's Role in Caring for Hip Fracture Patients Upon Admission to Acute Care

The geriatrician can serve a central role in caring for patients upon entry to the acute care hospital by evaluating the medical and perioperative issues, ensuring maximal medical stabilization prior to surgery, and providing vigilance and early detection of postoperative medical complications.

Studies indicate that a multidisciplinary approach to acute care for hip fracture can improve clinical outcomes. Several models of orthogeriatrics comanagement have been developed. Models vary from geriatric consultation or liaison services, management on a geriatric ward with orthopedic consultation, and integrated inpatient orthogeriatric units. A recent systematic review and meta-analysis of 18 studies found that orthogeriatric collaboration was associated with reduced in-hospital mortality, reduced long-term mortality, and reduced length of stay. A recent randomized trial of orthogeriatric care provided on a geriatrics ward (vs an orthopedic ward without geriatrics consultation) did not reduce the rate of in-hospital delirium, but did improve mobility at four months after surgery.

Because surgical approaches usually offer more benefits than nonsurgical approaches, surgical repair is usually presented as the only option, despite the fact that nonsurgical approaches may be equally or more appropriate for some selected patients. The clearest benefit of surgery over the nonsurgical approach of bed rest, pain management, bowel regimen, and prophylaxis against pressure ulcers and deep venous thrombosis, is that surgery results in better anatomic alignment and better likelihood of ambulation. Nonsurgical approaches may be considered in patients who are unable to ambulate prior to the fracture and who are not likely to ambulate despite surgery, for those in whom surgical risks are very high or life expectancy is very short. The geriatrician can first help by providing a "big picture" view of whether or not the patient will benefit from pursuing surgery to repair the hip. The determination of what may be most appropriate for a patient requires an understanding of that patient's prior goals, values, and priorities, as well as the patient's functional and cognitive status, medical conditions and psychosocial milieu, to determine how the patient can best achieve his or her goals.

The majority of patients with a hip fracture will undergo surgical repair. The types of surgical approach and anesthesia employed are largely the purview of the surgeon and the anesthesiologist and often depend on local trends and physician training. The use of regional anesthesia via epidural, regional, or peripheral nerve blockage has been advocated to reduce risks of postoperative complications after hip fracture repair, especially in older, frailer patients who have not been taking anticoagulants. A recent study found that compared to general anesthesia, regional anesthesia was associated with modestly reduced length of hospital stay (0.6-day reduction), but there was no difference in 30-day mortality. A 2004 Cochrane review found that regional anesthesia was associated with a 50% reduction in the rate of postoperative delirium.

As with any surgery, in preparing a patient for hip fracture surgery, the attending physician should determine the risks of cardiovascular, pulmonary, and other complications and strive to reduce those risks. (Refer to Chapter 31 for more details on the use of preoperative testing for risk stratification, preoperative pulmonary treatments, and the use of β-blockers and other medications to reduce the risk of perioperative adverse cardiac events in high risk patients.) The geriatrician is well positioned to discuss with the patient and family the anticipated hospital and postacute care

procedures and transitions, thereby reducing uncertainty and alleviating anxiety at this unanticipated and challenging time. Discussion of options for those not considered good candidates for surgery, including palliative and hospice care, also can be initiated and led by the geriatrician.

Finally, while soliciting the preoperative history, the geriatrician should use this opportunity to determine the patient's risk for subsequent falls and fractures. A thorough falls history should be obtained, including a complete description of the fall that led to the fracture as well as any previous falls, with particular attention to remediable risk factors to be addressed prior to discharge back to home (see Chapter 48).

POSTOPERATIVE CARE IN HOSPITAL

The Geriatrician's Role in Postoperative Care

In the United States, a patient will usually remain in the acute hospital for 2 to 5 days after surgery for hip fracture. Depending on the surgical approach used and the adequacy of the anatomic repair, most patients will resume a normal diet, have bladder catheters removed, and begin getting out of bed with physical therapy on postoperative day number 1. Early mobilization has been shown to be safe and effective for minimizing deconditioning, reducing the risk of complications such as delirium, constipation, pneumonia, thromboembolism, and pressure ulcer formation. Adequate treatment of postoperative pain is important for maximizing participation in physical therapy and increasing mobility. The optimal pain medication regimen has not been determined. A 2003 study of 541 hip fracture patients showed that severe pain increased the risk of delirium, and patients on very low doses of opioid narcotics were more likely to develop delirium than those on higher doses (> 30 mg/day morphine equivalents). Care should be taken to prescribe a customized regimen that provides sustained pain relief early in the postoperative period, minimizes sedation, and also anticipates episodic increases in pain associated with activities such as therapy sessions.

The geriatrician must monitor the patient very closely for development of postoperative complications and is in a key position to detect subtle delirium that could be a harbinger of an ominous underlying complication, such as pulmonary embolus, urinary tract infection, and pneumonia. Postoperative pulmonary complications are among the most lethal complications in this population, so the geriatrician should be particularly wary of these and emphasize the use of deep breathing exercises with or without an incentive spirometer, early mobility, and use of physical and/or pharmacological approaches to reduce the risk of deep venous thrombosis. Other important postoperative medical considerations the geriatrician may be particularly adept at managing are reducing polypharmacy, pressure ulcer detection and management, maximizing sensory input, explaining the treatments and progression of care to patients and family, and communicating across the transitions of care to reduce errors during this vulnerable time.

POSTFRACTURE CHANGES IN PHYSICAL AND PSYCHOSOCIAL FUNCTION AND IMPLICATIONS FOR CARE

Physical Function

Hip fractures have significant effects on functioning and body composition. **Figure 119-3** shows the proportion of patients with hip fracture who, prior to their fracture, were able to perform routine tasks involving lower extremities but were not able to perform them a year later. Twenty percent of those who could put on their own pants without assistance prior to their fracture required assistance to do so one year later. More striking is the proportion of patients who needed assistance from another person or required the use of equipment to walk across a small room (40%), use the toilet (66%), or climb five stairs (90%). Instrumental tasks also are affected, with 62%, 53%, and 42% who could do their own housecleaning, get to places out of walking distance independently, and shop without assistance, respectively, prior to their fracture, requiring assistance to perform these tasks a year later. Other functional consequences of hip fracture include increases in cognitive impairment and depressive symptoms, as well as increases in problems with gait and balance. Despite advances in surgical procedures, postoperative care, and long-term rehabilitation, hip fractures rank in the top 10 of all impairments worldwide in terms of causing disability and functional decline.

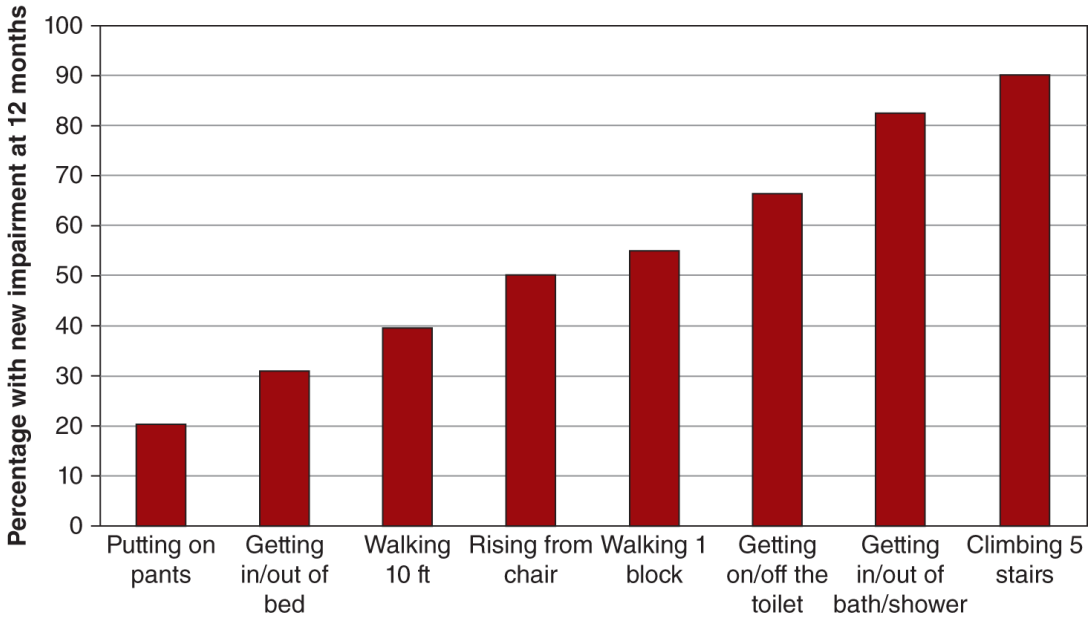


FIGURE 119-3. Lower extremity activities of daily living—percentage of those unimpaired before fracture with impairment at 12 months after fracture. (Magaziner J, et al. *J Gerontol Med Sci*. 2000;55A(9):M498–M507.)

Psychological Status

The diagnosis of hip fracture conveys to patients and families a significant degree of psychological stress. Most lay persons are quite aware of the poor recovery of function for many hip fracture patients, the high rate of nursing home use and long-term placement and, for those who do return home, the high rates of dependency on others for care. Although not the case for most patients, many patients and families believe that having a hip fracture signifies the "beginning of the end." These psychological stressors may contribute to the high rates of postoperative depression that have been described. Patients may endorse depressive symptoms during their hospital stay and for up to 6 months after fracture; those who report symptoms of depression even transiently tend to recover less well than those who do not endorse depressive symptoms at all.

Physiologic Changes Post-hip Fracture

Changes in body composition also are notable after a hip fracture. The average woman who fractures a hip can expect to lose 3% to 6% of her muscle mass within 2 months of the hip fracture and to have an increase in fat mass of 3% to 4% during the postfracture year. Losses of bone mineral density also are profound in this already osteoporotic group of older women. Older women lose nearly 3% of their total hip bone mineral density and more than 4.5% of their bone mineral density in the contralateral femoral neck during the year following a hip fracture. This is 12.5 times more than the loss of 0.5% that would have been expected in a group of women of the same age, comorbid disease status, and starting level of bone mineral density (**Figure 119-4**). Analogous data are not available for male hip fracture patients, although ongoing studies are collecting such data presently.

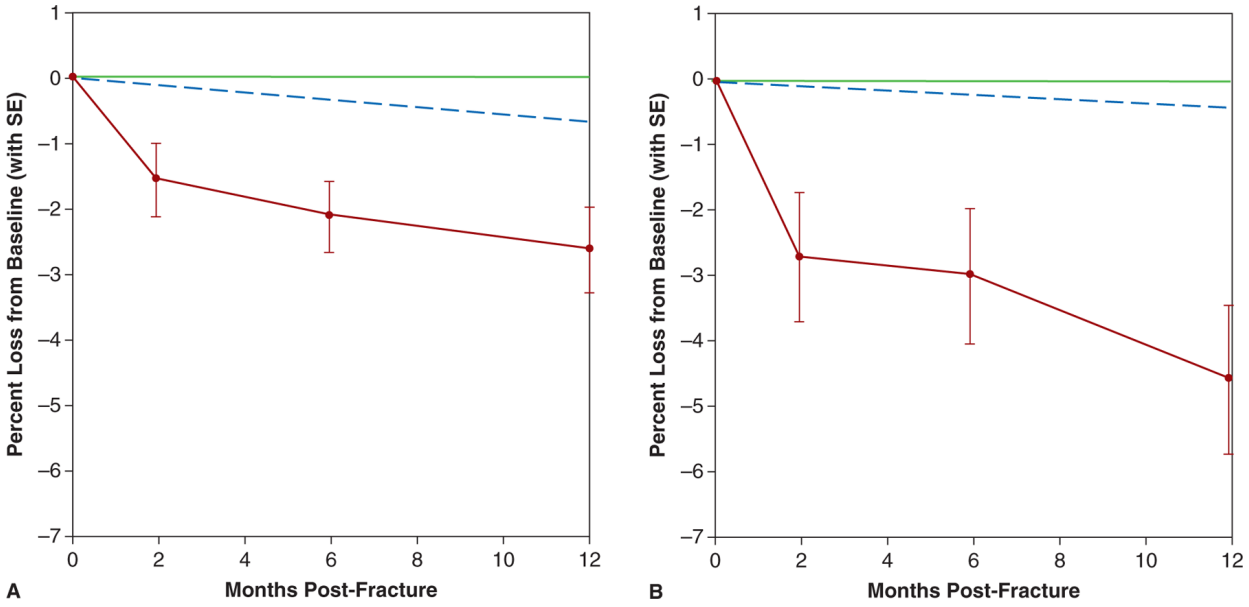


FIGURE 119-4. Expected and observed change in total hip bone mineral density **(A)** and femoral neck bone mineral density **(B)** during the 12 months following fracture. Legend for both panels: solid line, hip fracture (observed mean and standard error); broken line, Study of Osteoporotic Fractures (SOF; expected mean based on interpolated data obtained for a 42.3-month period). (Magaziner J, et al. *Osteoporos Int*. 2006;17:971–977.)

In addition, the prevalence of vitamin D deficiency among hip fracture patients is very high, and contributes to the observed losses in bone density and muscle strength, and fall and fracture risk. The geriatrician should discuss with the patient, family, and other providers the issue of osteoporosis treatment, to reduce the risk of subsequent fractures (see Chapter 118). If antiresorptive therapy is being considered for treatment of osteoporosis, the vitamin D level should be repleted prior to starting a bisphosphonate. Therefore, if not performed recently, a serum vitamin D level should be checked during the acute hospital admission.

FUNCTIONAL RECOVERY POST-HIP FRACTURE

Recovery in function following a hip fracture can be anticipated in most patients, although many will fail to reach their prefracture functional levels. This recovery appears to follow a sequence that may be instructive for management during the initial year after the fracture. Depression, upper extremity activities of daily living, and cognitive function reach their peak level of recovery by approximately 4 months postfracture, while tasks associated with mobility, such as balance and gait, reach a plateau at approximately 9 months postfracture. Interestingly, the more complex tasks that are indicative of disability, such as performing lower extremity activities and instrumental tasks, recover by approximately a year (**Figure 119-5**).

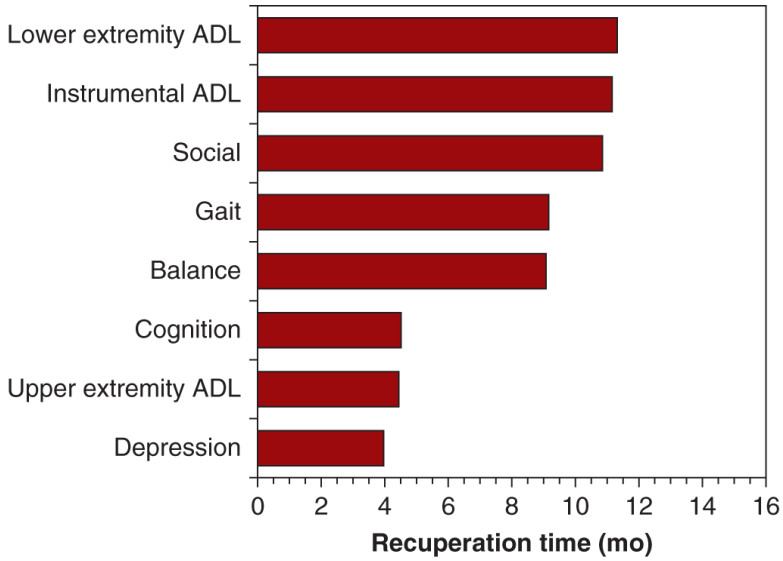


FIGURE 119-5. Time to recuperation following hip fracture in eight areas of function. ADL, activities of daily living. (Magaziner J, et al. *J Gerontol Med Sci*. 2000;55A(9):M498–M507.)

Patients who recover more slowly than anticipated should have an assessment of factors that may be contributing, such as persistent delirium, depression, polypharmacy, vitamin D and other nutritional deficiencies, and social isolation, so that a targeted multidisciplinary plan can be developed to address the issues of concern.

POSTFRACTURE REHABILITATION

Discharge Planning

Prior to discharge from the in-patient setting, a multidisciplinary assessment involving the geriatrician, the orthopedic surgeon, nursing, social work, physical therapy, and occupational therapy should be performed. The goal of this assessment is to decide on discharge plans and rehabilitation needs and goals. The following considerations should be taken into account: the patient's current level of mobility, the patient's postoperative medical and skilled nursing needs, the home environment, social support and economic resources available, self-care skills, and requirements for activities of daily living. The geriatrician plays a key role in coordinating the patient's care and communicating with patients and families as they transition through the health-care system. A critical role for the geriatrician is to ensure continuity of care. Recent studies have shown that, with each transition to a different site of care, there is the potential for an adverse effect on the care of patients with hip fracture, and physicians must, therefore, be vigilant to ensure adequate communication and good continuity of care to minimize this risk.

While a patient's medical diagnoses and baseline functional status are important considerations for maximal functional recovery, his or her social support network and home environment are equally important. Social support will often dictate how long a patient needs to stay in in-patient rehabilitation before safe to discharge to home or the appropriate level of care. For example, if a patient had been previously living independently in a multistory home where the bathroom and bedroom are on the second floor and the kitchen on the first floor, one of three things would need to occur prior to discharge home: (1) the patient would need to be able to negotiate a full flight of stairs independently and safely; (2) the patient would need to rearrange the home to live on the ground floor and be able to transfer and ambulate short distances on a level surface independently and safely; or (3) the patient would need a responsible caregiver to assist with daily tasks. Not all patients have access to, or resources for, assistance in their homes, but some have families or friends who are able to provide this support, usually un-reimbursed. This can also be a major stressor when the caregiver has to take time off from work and/or travel long distances to provide assistance. In collaboration with the interdisciplinary team, the geriatrician can assist family members and caregivers to anticipate and prepare for the patient's upcoming needs. An assessment of the home environment by an occupational and/or physical therapist provides essential information for home discharge planning.

Rehabilitation Services

The majority of patients with hip fracture will undergo a period of rehabilitation therapy after the fracture repair.

Rehabilitation services are provided only if both of the following requirements are fulfilled: (1) the patient has a functional loss and (2) is able to participate in rehabilitation efforts. Individuals with severe cognitive impairment or those with unresolved delirium that interferes with participation in standard rehabilitation, those with severe prefracture disability (eg, bed-bound), and those with terminal illness, may not qualify for standard rehabilitation services. Alternative approaches may be required. The geriatrician can judge potential benefits and work with the multidisciplinary rehabilitation team to recommend the most appropriate rehabilitative care.

Rehabilitation services can be provided in one or more of the following settings: an inpatient acute rehabilitation unit, a subacute rehabilitation unit in a skilled nursing facility (SNF), or on an outpatient basis, either at home or in a clinic. The location of post discharge rehabilitation is determined by a number of factors, including the patient's functional impairments, comorbidities, ability to participate in skilled therapy sessions, social support, and personal preferences. In the United States, rehabilitation is typically limited by Medicare reimbursement and rarely goes beyond 30 days. In one study, approximately 50% of hip fracture patients were discharged to a SNF subacute unit, 20% to an acute inpatient rehabilitation unit, 15% were discharged to home, and 14% were discharged directly to a long-term care facility.

Inpatient acute rehabilitation units are usually located in specialized units of an acute care hospital, or in a dedicated rehabilitation hospital. Patients with complex medical or rehabilitation needs and with good endurance may receive their rehabilitation in the acute setting. The requirements for acute rehabilitation are that the individual must be able to participate in therapy for at least 3 hours/day, and at least two rehabilitation therapeutic disciplines be involved (eg, physical therapy and occupational therapy).

Patients with less complex medical or rehabilitation needs, who are not be able to participate in 3 hours/day of rehabilitation but who otherwise have a functional decline that would benefit from rehabilitation and are unable to be discharged to home, can receive rehabilitation in the subacute SNF setting. These patients typically receive interventions from a licensed professional 5 days a week, however, on a less intense basis than in the acute rehabilitation setting.

Patients with more mild functional and mobility impairments or with good support at home may receive their rehabilitation on an outpatient basis, either at home or at an outpatient facility. In order to qualify for home rehabilitation, patients must have a functional decline that would benefit from rehabilitation, have sufficient caregiver support to enable them to be cared for at home, and be homebound and therefore unable to attend rehabilitation at an outpatient clinic. Since rehabilitation will be delivered by homecare professionals in the patient's home, heavy equipment must not be required.

For individuals with less complex rehabilitation needs, services may be delivered in an outpatient clinic. Outpatient rehabilitation may also continue after acute, subacute, and homecare services, to facilitate attainment of rehabilitation goals.

The Role of the Geriatrician in the Rehabilitation Setting

The geriatrician can also play a key role in medical management at rehabilitation settings, especially at SNFs. Regardless of the rehabilitation setting, medical care should focus on the following principles: treatment of chronic medical conditions, continued postoperative hip fracture care, prevention of complications from the associated functional decline and immobility, and prevention of future falls and fractures.

Despite ongoing therapy by rehabilitation professionals, increased risk for complications related to immobility, such as DVT, pressure ulcers, and constipation, persist at the rehabilitation setting. Thus, continued vigilance to their prevention and detection must be exercised. Based on current recommendations, DVT prophylaxis should be continued for 21 to 31 days after hip fracture surgery. Pressure ulcers are common after hip fracture surgery, with reports of an incidence rate of stage II or greater ulcers within 21 days of fracture of approximately 35%. Given the decreased mobility and frequency of use of narcotic analgesics for postoperative pain, constipation is a common occurrence and efforts should be made to prevent this with an adequate bowel regimen.

Many patients with hip fracture in the acute and subacute rehabilitation settings receive their medical care from a physician who was not their primary care provider prefracture and may not be familiar with their history or support system. Care for these patients represents a challenge for the attending physician, as these patients are typically older and with significant and complicated comorbid disease. More than 75% of patients with hip fracture have at least four comorbid medical conditions prior to their fracture. In addition to supervising the care of the hip fracture and any sequelae, the attending physician must ensure that these chronic medical conditions continue to be addressed.

What to Tell the Patient and Family to Expect With Regard to Function

Because hip fracture may result in persistent functional limitations and disability, patients with hip fracture may anticipate significant changes in their lifestyle. The geriatrician needs to provide support and encouragement during the initial recovery period following hip fracture surgery when pain and disability are greatest. Patients and their families can be reassured that significant improvements in lower extremity function during the first few months postfracture are likely to occur, while at the same time cautioned that lower extremity limitations can be prolonged. Up to 50% of elders who had previously been independent may be dependent on mobility aids, such as a cane or a walker, for ambulation at 1 year postfracture. These limitations and fear of recurrent falls may result in self-limitation of daily activities.

These declines in function may result in loss of independence in the older patient, and, as a result, the older patient with hip fracture may be facing the prospect of moving from their independent residence to a higher level of care for the first time. Individuals who have an injury as a result of a fall, such as a hip fracture, are 10 times more likely to be admitted to a skilled nursing facility. This may be one of the most frightening aspects of the post-fracture recovery period, and helping patients to understand that this is an expected reaction to having a hip fracture may enable them to overcome this fear and resume their activities more quickly.

Older patients and those with multiple health conditions may need to be told that their recovery may be slower than for others. Compared to younger patients, those who are older than 85 years have been found to require longer rehabilitation stays, have worse recovery of lower extremity function, are more likely to be discharged to long-term care, and are more likely to have persistent pain, which may be accompanied by activities of daily living (ADL) limitations and reduced quality of life. Depression and cognitive limitations should also be discussed with patients and families. It is important for them to understand that depressive symptoms and cognitive limitations are common after a hip fracture. They should also be informed that these changes are not always persistent, as depressive symptoms and cognitive limitations will frequently resolve with limited intervention within 2 months, and that treatment for mild depression is often useful to avoid any lingering anxiety or depression that accompanies the hip fracture.

The Geriatrician’s Role After Formal Rehabilitation for the Hip Fracture

After the patient has returned home, the focus of follow-up care should be to monitor whether the patient is making expected gains in recovery, evaluate barriers if expected gains are not achieved, and prevent subsequent falls and injury. Most hip fracture patients plateau in their functional level by 6 months after fracture event. The occurrence of complications may alter that course and many will continue to realize gains with longer amounts of time. Geriatricians are well trained to identify barriers to recovery after a hip fracture and initiate interventions that can further enhance recovery and reduce fall risk. Optimally, the patient should be reevaluated at the time of discharge from the acute rehabilitation setting, and again upon discharge from home physical therapy, to assess the patient’s recovery level, physical impairments, and need for outpatient services. Community-based multidisciplinary fall risk assessment (eg, home environment assessment, medication review, vision testing, postural blood pressure measurement, gait and balance testing, and targeted neurological, musculoskeletal, and cardiac examinations) followed by interventions directed at these risks has been shown to reduce fall risk and to be cost effective in older adults at risk of recurrent falls.

A 2004 study of intensive exercise delivered in the outpatient setting showed improved recovery at approximately 12 months postfracture, compared with low-intensity home-based exercise (**Figure 119-6**). However, another study published in 2014 of a home-based exercise program for hip fracture patients showed modest improvement in physical function, compared to a nutrition education program. The physician should discuss with patients their options for continued outpatient therapy and/or exercise, determine their preferences, and provide appropriate referrals and prescriptions.

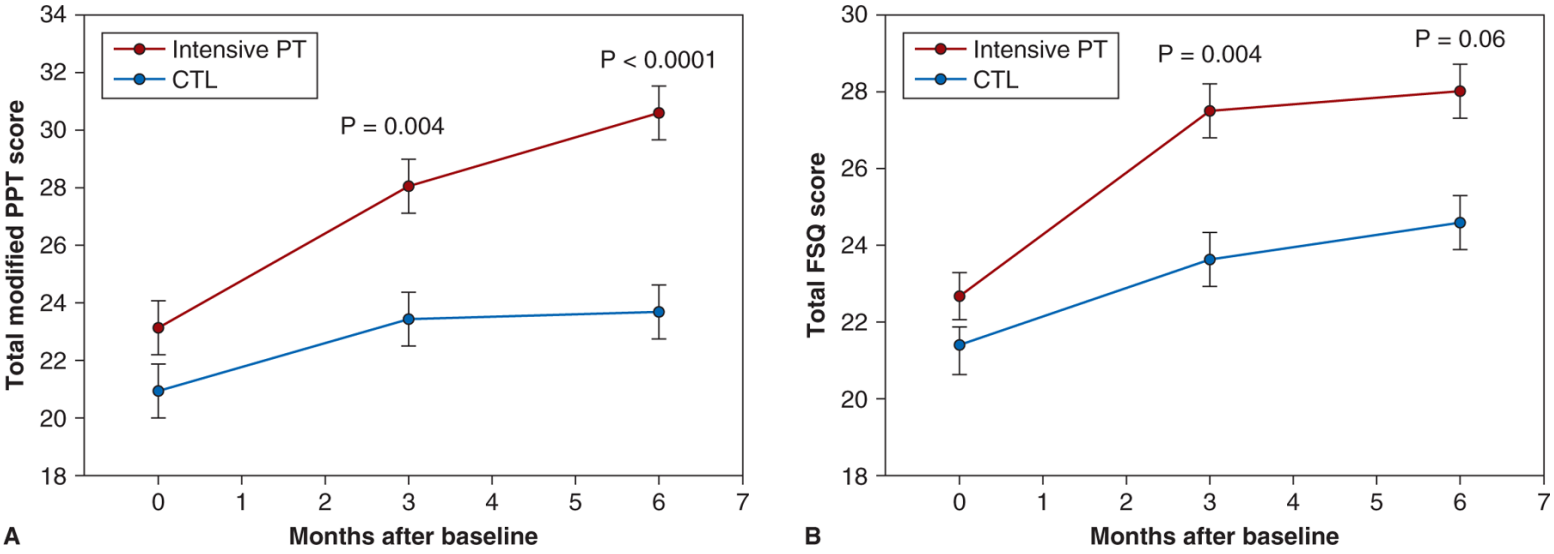


FIGURE 119-6. Changes in total modified Physical Performance Test (mPPT) score and total Functional Status Questionnaire (FSQ) score from baseline to end of study (6 months). (Binder EF, et al. *JAMA*. 2004;292:837–846.)

Despite the fact that almost all older adults who have a hip fracture have preexisting osteoporosis, only a minority receive treatment for osteoporosis prior to, or after the fracture event. The occurrence of a minimal trauma fracture, such as hip fracture, should provide a compelling opportunity to address issues related to bone health. A hip fracture is associated with an increased risk of subsequent fracture, including a second hip fracture. Although there is only one published randomized study on the secondary prevention of fractures in elders post hip fracture that demonstrated a benefit of a bisphosphonate therapy (ie, zoledronic acid), interventions such as vitamin D and calcium supplementation, weight-bearing exercise, and pharmacological treatment with other antiresorptive agents such as bisphosphonates or the anabolic agent teriparatide, are also believed to be of benefit and should be considered.

Although hip protectors have recently received significant attention for their potential to reduce hip fractures, many older adults and their care providers may prefer their use to taking additional medication. The evidence for the efficacy of hip protectors in prevention of hip fracture is conflicting. Meta-analyses suggest that these offer little or no benefit for patients in randomized studies. As a result, these devices should not be considered as alternatives to the other fall reduction and bone-strengthening interventions listed above.

CONCLUSION

Care for older patients with hip fracture represents one of the greatest challenges for the geriatrician because of the multiplicity of medical and psychosocial factors involved in postfracture care. A summary of some of the key issues a geriatrician should focus on at various stages of hip fracture care appears in **Table 119-1**. Answering these questions requires vigilant attention preoperatively, postoperatively, in the rehabilitation setting, and after rehabilitation efforts have terminated. Although a hip fracture event has significant consequences for patients and their families, through this attention and communication with patients, families, and the other clinicians involved in the care of patients as they transition through the various sites of care, it is the goal of the geriatrician to minimize long-term adverse effects and to ensure that the overall well-being of the patient is maximized.

TABLE 119-1 FOCUS OF THE GERIATRICIAN AT VARIOUS STAGES OF CARE FOR PATIENTS WITH HIP FRACTURE

SETTING OF CARE	WHAT THE GERIATRICIAN IS FOCUSED ON
Acute hospital—preoperative	1. Do surgery or nonoperative approaches best meet this patient's goals? 2. What are the preoperative cardiac, pulmonary, cognitive, and other risks for this patient and what can be done to reduce these? 3. What must be done to prevent postoperative complications, especially pressure ulcers, delirium, anemia, and pneumonia?

	4. Why did this person fall and how can this information be used to ensure that medical status is optimized for surgery or nonoperative management?
Acute hospital—postoperative	1. What can be done to prevent postoperative complications, such as pressure ulcers, delirium, anemia, and pneumonia? 2. Is pain adequately treated? 3. Is there delirium and how can it be addressed? 4. What is the next appropriate level of care and when is the patient ready to go there? 5. Who will next provide medical care and how can continuity of care be ensured?
Subacute setting—rehab	1. Is pain adequately treated? 2. Are there any complications requiring treatment, such as constipation, delirium, pneumonia, venous thrombosis, deconditioning, and pressure ulcers? 3. Are there signs of active depression limiting participation in rehabilitation and what can be done to address this during rehabilitation and after discharge? 4. Why did this person fall and what can be done to reduce the chances of future fractures? 5. Is this person on appropriate osteoporosis therapy? 6. What does this person need to do to be able to go home safely? 7. Who will next provide medical care and how can continuity of care be ensured?
Outpatient setting—primary care	1. Is this person receiving appropriate interventions to prevent falls and fractures and increase activity level and reengagement into community life? 2. Is this person safe in the current living arrangement? 3. Is recovery occurring in the expected sequence and in the expected time frame? 4. Is pain resolved?

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Chapter 120

Myopathies, Polymyalgia Rheumatica, and Giant Cell Arteritis

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Learning Objectives

- Be able to characterize common muscle disorders of aging.
- Contrast the clinical presentation and management of polymyalgia rheumatica and giant cell arteritis.

Key Clinical Points

1. **Sarcopenia, a condition of reduced muscle mass and strength with functional consequences, is emerging as a common clinical problem in older adults.**
2. **Most myopathies tend to present with shoulder and hip girdle weakness.**
3. **Inclusion body myositis, a gradual and insidious loss of muscle mass and strength associated with a characteristic histology and normal to mildly elevated muscle enzyme levels, is the most common form of inflammatory myositis in older adults.**
4. **Older adults are at risk for multiple drug–induced myopathies including those related to corticosteroids, heavy ethanol use, and lipid-lowering agents.**

The contributions made by healthy muscle to maintaining basic metabolic processes and functional status cannot be underestimated. Muscle disease symptoms and myopathies are not uncommon in older adults, and when present magnify the effects of age-related decline in muscle structure, mass, and function. This chapter surveys the more common myopathies seen in older people, highlighting the differences in presentation and/or therapy between older and younger adults. The discussion of these inflammatory and noninflammatory conditions will be based on an overview of the changes that occur in muscle with aging, and how these age-related changes can alter the results of the standard assessments of muscle disease symptoms.

SARCOPENIA AND MUSCULAR DEBILITY WITH AGE

Sarcopenia is a geriatric syndrome, associated with findings common to other such conditions; multiple etiologic factors work through multiple pathogenic pathways, leading to a unified clinical phenotype. The word sarcopenia, from the Greek for loss of flesh, was first coined in 1988 to refer to the intrinsic age-related loss of lean body (muscle) mass. Population estimates of sarcopenia, previously based solely on the measure of relative muscle mass (derived from either anthropometric data or imaging modalities, and defined as appendicular muscle mass in kg/height in m^2), calculated its prevalence to be up to 30% of those over 60 years of age and more than 50% in those over 80, with moderate to severe sarcopenia in 45% of older adults.

The definition of sarcopenia continues to evolve, expanding beyond an early characterization based solely on a threshold for low muscle mass—less than 2 standard deviations below that of a healthy young adult—to one that should incorporate the physiologic and functional consequences (loss of strength and/or performance) associated with aging muscle. Loss of muscle strength ("dynapenia") with age ("presbydynami") better predicts adverse outcomes and

functional loss than does loss of muscle mass. Loss of strength has been linked to impaired functional status, falls, disability, and increased mortality. Impaired strength may lead to immobility, a shared risk factor for multiple common geriatric syndromes which themselves predispose to frailty. Sarcopenia is thus currently defined as the loss of muscle mass and function with age, with function further specified as a reduction in strength and/or performance. Reduced muscle strength is commonly measured clinically in terms of gender-specific grip strength (< 26–30 kg for men, < 16–20 kg for women), while reduced performance is assessed by the measurement of gait speed (≤ 0.8 m/s). Sarcopenia can be further categorized as primary (due to the effects of aging alone) or secondary (either activity-related [bed rest, sedentary lifestyle, deconditioning], disease-related [advanced organ failure, inflammatory disease, malignancy, endocrine disease], or nutrition-related [inadequate dietary intake from malabsorption, gastrointestinal disorders, or medications that induce anorexia]).

Peak isometric strength is reached by the late twenties, and correlates with the time of maximal cross-sectional fiber size. By age 65, approximately one-third of isometric strength is lost, with more rapid decline occurring at more advanced ages. Strength declines more rapidly than muscle mass, the latter demonstrated by loss of muscle cross sectional area, detectable histomorphologically as well as radiologically. Muscle aging is associated with a net loss of muscle fibers as well as a decrease in muscle fiber size, both changes preferentially affecting type II (fast twitch, glycolytic fibers) more than type I fibers. These losses not only contribute to declining muscle strength but also to a decrease in muscle power—the measure of work performed over time. Animal models have demonstrated that with age comes a decline in muscle force-producing capacity, maximum velocity of shortening, and generalized slowing of contraction and relaxation. With a loss of strength and power there is a decreased ability to develop rapid joint torques, necessary for rapid-onset muscular activities requiring moderate strength such as to recover balance and avoid falling when avoiding obstacles. Type II fibers, which experience the greatest functional and volume loss with age, are the first to be recruited in this situation. Similar disproportional type II fiber loss with age is evident in the age-related decline in other activities requiring rapid-onset muscular activities (eg, shivering to generate body heat).

A combination of age-related neurologic, muscular, and behavioral alterations is thought to contribute to the development of sarcopenia. *Neurologically*, the age-related change with the largest morphologic impact is the decrease in the number and/or size of large, anterior horn motor neurons with age, innervating primarily type II fibers, mostly seen after the age of 60. Affected fibers undergo denervation, followed by reinnervation by axonal sprouting from intramuscular neurons. This process leads to a net loss of functioning motor units affecting type II more than type I fibers, fiber type grouping, and fiber remodeling as fibers assume the histochemical status of the innervating neuron. Alone, however, the relatively low percentage of motor neuron loss with advanced age (10%–15%) is not sufficient to explain the structural and functional declines in muscle with age. Cellular markers of regeneration have been documented in both aging motor neurons and muscle suggesting that cellular responsiveness to muscle fiber atrophy and loss is present but insufficient to overcome progressive loss of muscle mass and function. *Muscular* alterations with age include both changes in vascular and cellular density and microstructure, as well as decreased myocellular anabolic and restorative capacity in response to age-related alterations in the systemic and intramuscular levels of hormones, receptors and cytokines. The major *behavioral* alteration is the age-related decline in physical activity, “kinesiophobia,” contributing to muscle atrophy. Only 20% to 25% of older adults meet CDC criteria for sufficient levels of physical activity, and only 5% to 6% of older males and 1% to 3% of older females perform activities that increase muscle strength. Disuse deconditioning, as a consequence of enforced immobility through limb casting or prolonged bed rest, can have devastating effects on muscle strength in older people, who may enter such a period with little muscle mass reserve. Strict bed rest may lead to a decline in strength of 1% to 1.5% per day. Antigravity muscle groups and large muscles of the lower limbs lose strength twice as fast as small muscle groups. Resistance exercise training, particularly of back extensors, quadriceps and hip extensors, and ankle plantar flexors can within several weeks regain losses induced by bed rest. As strength losses are recovered sooner than immobility-induced loss of bone mass, there is a risk of bone fracture with reambulation, especially in those with baseline low bone mass.

The results of clinical studies that investigate potential intrinsic causes of muscle aging should be interpreted with caution in light of coexistent constitutional states and acquired medical disorders in older people that may affect muscle. Intrinsic muscle aging should be distinguished from protein and energy-store wasting from starvation (correctible with refeeding), and wasting in the presence of hypermetabolic states or inflammatory diseases. Severe wasting from cytokine-driven inflammatory or malignant conditions is referred to as cachexia. Both cachexia and sarcopenia may lead to decreased muscle mass, impaired muscle protein synthesis, increased muscle apoptosis and muscle mitochondrial dysfunction. However, in contrast to sarcopenia, patients with cachexia have decreased fat mass, weight loss, and increased resting energy expenditure.

Not all older persons decline functionally despite intrinsic changes in muscle structure and function. The muscular

system is the largest reservoir of protein in the body, accounting for up to 45% of body weight. Individuals vary in their muscle mass and functional reserve, and only when the effects of sarcopenia cross an arbitrary threshold individualized to the patient do functional and physical consequences occur. This threshold is analogous to when individuals assume a higher risk for osteoporotic fracture when their bone density falls below a threshold level. A simple, validated screening tool, the SARC-F (Strength–Assistance in walking–Rise from a chair–Climb stairs–Falls) questionnaire, which assigns points for functional tasks, may be used as a means to screen patients for sarcopenia.

Exercise is the most effective treatment to reverse the effects of sarcopenia, and can increase muscle mass and strength even in the oldest old, although the magnitude of the reported effect varies based on the study's exercise method, duration, intensity, and the population evaluated. Increase in muscle mass is predominately produced through hypertrophy. Increased physical activity is associated with reduced markers of inflammation, and both aerobic and resistance exercise training will stimulate an increase in muscle protein synthesis, muscle satellite cell activation, and muscle fiber area. The most important variable is exercise intensity, and the most dramatic effects are seen with high-intensity resistance (strength) training. Whereas aerobic exercise improves metabolic functions with benefits seen more in type I fibers, resistance exercise improves neuromuscular integration, muscle strength and muscle hypertrophy to a greater extent. Regimens demonstrate that strength can increase 50% to 200% despite an increase in muscle mass of only 10% to 20%, supporting a role played by factors other than just muscle hypertrophy. Strength training has been shown in older adults to reduce fall risk by 10% to 49%. There is no agreed upon single guideline for resistance training for the treatment of sarcopenia. Components of an exercise prescription for the older individual entering strength training may include some form of a baseline cardiovascular stress test, instructions on proper warm-up activities and postexercise cool-down stretching, review of breathing techniques during lifting, and a plan of exercise prioritizing muscle groups of the spine and lower extremities. Resistance exercise variables include number of sets and repetitions, repetition velocity, rest intervals, intensity, frequency, and duration. It generally takes twice as much time to recover muscle strength as it did to lose it, and strength decreases rapidly when resistance training programs stop.

Obtaining and maintaining gains from exercise requires increased protein intake. The anabolic effect of dietary protein, particularly essential amino acids such as leucine, is mediated through its ability to increase circulating levels of IGF-1, and by increasing protein synthesis through activation of the mTOR signaling pathway. The recommended adult daily allowance for protein intake of 0.8 g/kg body weight is inadequate to maintain a positive nitrogen balance in older people, and certainly insufficient to support the metabolic needs of the exercising elder. Dietary protein intake of 1.0 to 1.2 g/kg, with at least 20 to 25 g of high-quality protein with each main meal, is suggested to maintain protein requirements without risking renal insult. Strategies recommended to maximize protein absorption and anabolic effect include protein consumption immediately after the time of resistance exercise, meal content high in protein, meal protein mixture high in branched chain amino acids (eg, leucine) and quickly digested and absorbed proteins, and "pulsing" the majority of daily protein intake during one meal per day.

Other than vitamin D supplementation, the use of medication and hormonal therapies to improve muscle mass and strength in older people have led to less than encouraging results. Studies involving inhibitors of angiotensin-converting enzyme (ACE) and of HMG-CoA reductase (statins) have demonstrated promising effects on muscular outcomes, but not to the clinical effect, or depth of study, to recommend as part of routine treatment for sarcopenia. Despite the known decline in the levels of various anabolic stimuli with age, hormonal and substrate replacement therapies are currently not routinely recommended due to their lack of efficacy, side effect profile, and/or lack of sufficient data on their ability to improve disability and physical performance. Tested therapies have included creatine, growth hormone, testosterone, estrogens, tibolone (a synthetic steroid with estrogenic, androgenic, and progestogenic activity), and IGF-1. Therapies in development or postulated based on preclinical data include myostatin inhibitors, cytokine inhibitors, and those directed at reversing the age-related decline in satellite cell capacity for activation and proliferation.

CLINICAL EVALUATION OF MUSCLE DISEASE SYMPTOMS IN OLDER PEOPLE

The age-unrestricted list of conditions that can cause muscle disease symptoms is extensive. Candidate conditions are typically categorized as either acquired (autoimmune, endocrine disorder-related, toxin or drug associated, amyloid, infectious, cancer-related, and others) or inherited (muscular dystrophies, metabolic myopathies, muscle channelopathies). The approach to the individual with myopathic symptoms is not age-specific, but the results must account for age-related variations within each component of the evaluation.

History

As most extremity muscle bulk is proximal, symptoms of myopathic weakness tend to be associated with shoulder and hip girdle motions. Patients may report the inability to perform a specific task due to weakness, or poor stamina in performing tasks once readily accomplished. Independence with ADLs, maintenance of balance and gait, and freedom from falling should be addressed as all are sustained in part by maintenance of muscle strength. Muscle pain is an uncommon symptom of a primary myopathy, and in older people should suggest polymyalgia rheumatica, or a regional or generalized musculoskeletal disorder, such a rotator cuff tendinopathy or fibromyalgia syndrome.

Examination

Documenting the severity of initial and serial assessments of muscle strength should be based on the MRC grading scale of 0 to 5. The healthy older person should be able to sustain muscle contraction against full resistance for 2 to 4 seconds normally allotted to test individual muscles. More physiologically complex yet standard functional assessments, such as arising from a chair without the use of the arms, measuring the time necessary to perform this maneuver 5 to 10 times, or squatting from the standing position then arising without assistance, should be accomplished without difficulty by normal younger adults but may be difficult even for the healthy older person. The distribution of weakness may provide clues as to broad categorical etiologies: symmetric proximal extremity weakness with a normal neurologic exam suggests a myopathy, whereas distal weakness, distal and proximal weakness, or asymmetric weakness, suggests an underlying neuropathic problem or inclusion body myositis. Compared with objective muscle weakness, muscle tenderness is a less common finding in most primary myopathies. Muscle tenderness in older people, without demonstrated significant weakness, may be seen with fibromyalgia (diffuse muscle tender points), regional musculoskeletal disorders (focal findings), as well as in some patients with polymyalgia rheumatica (symmetric proximal extremities).

Laboratory Markers

Routine laboratory measurements of electrolytes (sodium, potassium, calcium, magnesium, and phosphorous) and muscle enzymes (primarily CK and aldolase, and secondarily AST, ALT, and LDH) is an essential component of muscle disease evaluation. Older people have an age-related decrease in CK and aldolase specific activity per unit DNA in muscle. Despite this fall in mean CK levels with age, the diagnostic accuracy of an elevated CK level in patients over 65 years of age with histologically proven myopathy is equal to that in patients aged less than 65 in two retrospective studies.

Electromyography

Electromyogram (EMG) assessment of voluntary motor unit action potentials (MUAP) and spontaneous muscle electrical activity can categorize muscle symptoms as arising primarily from either muscle or nerve, and provide information on the distribution, severity, and if done serially, the progression of myopathic changes. MUAP duration best distinguishes between a myopathy and neuropathy: total duration increases in neuropathies but decreases in myopathies. Other myopathic findings include MUAPs of small amplitude, and polyphasic composition. Increased needle insertional activity (increased in damaged muscles, decreased in muscles replaced by fat or scarring), and spontaneous activity (fibrillation potentials [a degenerating muscle fiber with an unstable membrane fires spontaneously at a regular rate] and positive sharp waves [needle touching damaged, degenerating fibers]) are features of an inflammatory myopathy. Older people have a slight tendency toward prolonged MUAP duration above the age of 55, and a small increase in the proportion of polyphasic potentials. These changes are due to the process of denervation followed by intramuscular axonal spouting from neighboring axons and reinnervation as described above. This process occurs slowly, and thus the typical features of active degeneration—fibrillations and positive sharp waves—are not seen with aging alone. EMG assessment of a cool limb will also produce a higher percentage of increased duration, polyphasic potentials, as well as reduced spontaneous activity. This must be taken into account during EMG testing in older people, who are at increased risk for cool limbs from circulatory insufficiency and reduced insulation (subcutaneous fat).

Muscle Biopsy

Clinical features—history, exam, laboratories, and EMG—infrequently provide a diagnosis of a specific muscular disorder. Muscle biopsy is then necessary to make or confirm a diagnosis and to provide a basis for therapy. In most

clinical circumstances, satisfactory muscle samples for evaluation can be provided by either open or percutaneous techniques. A combination of complementary tissue stains is chosen to evaluate general muscle morphology and fiber typing and distribution, and screening tests are chosen for evaluating enzyme deficiencies and storage diseases. Based on autopsy and muscle biopsy studies, muscle biopsy specimens from older people show an increased frequency of type II muscle fiber atrophy, type II fiber-specific decline in muscle satellite cell content, neurogenic changes (including fiber type grouping, angular atrophic fibers, target or "targetoid" fibers), and changes indicating mitochondrial dysfunction (ragged red fibers, and fibers staining negative for cytochrome c oxidase [COX] with concomitant increase in succinate dehydrogenase [SDH] activity). Findings of necrosis, cytoplasmic bodies, ring-fibers, and fibers with increased central nuclei have been noted in muscle specimens from those over the age of 70. Clinically, the diagnostic accuracy of muscle biopsy findings for inflammatory myopathy in patients aged 65 and older approximates that of younger adults.

MYOPATHIES IN OLDER PEOPLE

Table 120-1 provides a more specific list of conditions that should be considered in the older patient suspected of having a myopathy. These diseases, both primary muscular diseases and diseases or drug-related syndromes with symptomatology in the muscular system, represent a more focused list of inflammatory and noninflammatory conditions and assumes a comprehensive evaluation has excluded electrolyte disturbances and organ failure syndromes as causes of weakness. These disorders can also be separated into those causing primarily proximal muscle weakness or spinal weakness. The discussion to follow will survey these diseases, highlighting clinical findings of presentation or therapy that are more distinctive in older patients.

TABLE 120-1 MYOPATHIES MORE SPECIFIC FOR THE OLDER PERSON

Acquired Myopathies
Idiopathic inflammatory myopathies
Sporadic inclusion body myositis
Polymyositis
Dermatomyositis
Endocrine/metabolic diseases
Thyroid disease
Osteomalacia
Amyloid myopathy
Drug-induced myopathies
Corticosteroids
Alcohol
Colchicine
Lipid-lowering agents
Inherited Myopathies
Late-onset muscular dystrophies
Facioscapulohumeral dystrophy
Oculopharyngeal dystrophy
Late-onset limb girdle dystrophy
Late-onset mitochondrial myopathy
Paraspinal myopathies
Bent spine syndrome (camptocormia)
Dropped head syndrome

Idiopathic Inflammatory Myopathies

As a group, the idiopathic inflammatory myopathies (IIM) are the most common cause of primary myopathy in older people. These conditions—polymyositis (PM), dermatomyositis (DM), and sporadic inclusion body myositis—share, to varying degrees, findings of slowly progressive muscle weakness which is usually symmetric and proximal, elevated serum levels of muscle enzymes, characteristic changes of an inflammatory myopathy on EMG, and abnormal muscle pathology, with degenerating and regenerating myocytes, and inflammatory cells in and around muscle cells and sometimes around vessels. Extramuscular manifestations in common include constitutional symptoms and dysphagia; polyarthralgias/polyarthritis and cardiopulmonary involvement are more likely to occur in PM and DM. Other unique features that serve to define the clinical subsets of IIM include certain demographic characteristics, skin manifestations, myositis-specific antibodies, and pathologic criteria.

Sporadic inclusion body myositis and the hereditary inclusion body myopathies The term inclusion body myositis (IBM) was first used in 1971 to describe patients with IIM whose muscle biopsies displayed degenerating muscle fibers with rimmed vacuoles and unique, tubulofilamentous nuclear and cytoplasmic inclusions. Patients with IBM are now separated into two distinct sets based on patterns of inheritance, clinical findings, muscle biopsy changes at the light- and electron-microscopic levels, and immunoreactivities demonstrated in the filaments: sporadic IBM (s-IBM) and the hereditary inclusion body myopathies (h-IBM). These two patient subsets share similar features on muscle biopsy, but unlike in s-IBM, there is an absence of inflammatory change in muscle biopsy specimens from patients with h-IBM, hence the term inclusion body “myopathy” not “myositis.”

S-IBM is the most common inflammatory myopathy in patients over the age of 50, although it has been reported in younger ages. Older age of onset has been associated with faster progression of weakness. As contrasted against PM and DM, s-IBM affects males two to three times more frequently than females, and is more common in Caucasians than other races. The course of painless, proximal muscle weakness and atrophy develops insidiously, commonly over years, but distal limb muscle involvement is seen in 50%, occurs early, and may predominate in up to a third of patients. A characteristic pattern of (often asymmetric) finger and wrist flexor, knee extensor, and ankle dorsiflexor weakness has been described and may be specific enough to make the diagnosis even when rimmed vacuoles and other characteristic histologic muscle biopsy findings are absent. Although interosseous muscles of the hand are generally spared, characteristic involvement of the flexor digitorum profundus and the flexor pollicis longus impairs the ability to oppose the thumb and index finger and perform fine motor movements, leading to significant disability. The prominent involvement of the quadriceps muscles may be severe enough in some patients that patellar reflexes are diminished, simulating an underlying neuropathy. Quadriceps weakness and knee giving-way may lead to an increased frequency of falling. Pharyngeal muscles are often part of the initial clinical presentation. Muscle enzymes are normal in approximately 20% and elevated no more than 12 times normal in most patients. A recently described autoantibody against cytosolic 5′-nucleotidase 1A (cN1A) has been recognized in patients with s-IBM. While not a diagnostic test, early studies have described good sensitivity (72%) and high specificity (92%). EMG findings are atypical in 30%, including the absence of inflammatory changes or the presence of a prominent neuropathic component. A small percentage of patients may have an associated autoimmune, infectious (most commonly viral), or other systemic inflammatory disease. There are at least 12 published criteria sets for s-IBM, which encompass at least 24 diagnostic categories. Categories include age threshold, symptom duration and progression, strength assessment, CK level, EMG findings, and histologic and immunoreactivity assessments on muscle pathology. A data-driven assessment of these patient variables demonstrated that the combination of (1) finger flexion or quadriceps weakness, (2) endomysial inflammation on biopsy, and (3) either invasion of nonnecrotic muscle fibers or rimmed vacuoles had 90% sensitivity and 96% specificity as diagnostic criteria.

Rehabilitation strategies, more so than medical treatments, play key roles in disease management. A physical therapy program of strength training should be prescribed for all patients with s-IBM, and will not elevate serum CK levels. The presence of foot drop or knee instability requires splinting or bracing, respectively, to prevent contractures and aid in ambulation. Dysphagia should prompt evaluation to assess the need for intravenous immunoglobulin (IVIg), esophageal dilation, injections of botulinum toxin, or cricopharyngeal myotomy. Standard medical therapy for IIM—corticosteroids with or without immunosuppressive agents—does not stop disease progression. This lack of improvement with medical therapy has been described as a clinical hallmark of the disease. Furthermore, corticosteroids decrease CK levels if even the underlying pathophysiology is not autoimmune, and CK level changes do not always correlate with changes in strength. A recent study demonstrated that in comparison to untreated patients, those treated with immunosuppressive medication developed difficulty walking faster.

The mechanisms that underlie the pathogenesis of s-IBM are not well understood. It should no longer be

considered solely a myodegenerative disorder, and often cited reports of intramuscular accumulation of β-amyloid and tau proteins have been refuted. Current evidence suggests a more complicated pathophysiologic process that involves a genetic contribution (strong association with the HLA-B8-DR3-DR52-DQ2 haplotype), immunologic activity (autoantibody to cN1A, T and B cells surrounding and displacing myofibers, B cell maturation and differentiation within muscle in the absence follicles, active myeloid dendritic cells), and other abnormalities of unclear relationship to the immune system (nuclear degeneration, sarcoplasmic accumulation of normally nuclear nucleic acid binding proteins, and loss of fast-twitch sarcomeric proteins).

Polymyositis and dermatomyositis The clinical and laboratory findings which lead to a diagnosis of either PM or DM are not age specific, and are based on criteria initially set forth by Bohan and Peter: symmetric limb-girdle and anterior neck flexor muscle weakness, skin rash (in patients with DM), elevation of skeletal muscle enzymes, EMG evidence of an inflammatory myopathy, and muscle biopsy evidence of an inflammatory infiltrate, cellular necrosis, and regeneration. These criteria describe a heterogeneous group of disorders that lead to chronic muscle inflammation. While muscle biopsy specimens from patients with an IIM will stain positive for MHC class I molecules (diffuse staining in PM, perifascicular staining in DM)—differentiating these conditions from dystrophies and certain metabolic myopathies causing mononuclear cell infiltrates; dermatomyositis has distinct pathologic features: perimysial (more so than perifascicular) myofiber injury/atrophy, endothelial cell damage and tubuloreticular inclusions, and higher intramuscular expression of type I interferon-inducible genes. Advances in autoantibody detection have identified clinical subgroups of patients with either PM, DM, or myositis associated with malignancy. These myositis-specific autoantibodies define more homogeneous populations within the spectrum of the IIM, each with distinct clinical findings and immunogenetic associations (**Table 120-2**). The syndromes marked by these autoantibodies are more commonly seen in younger adults, with mean age at diagnosis between 36 and 46, but can be seen in older people.

TABLE 120-2 ■ ASSOCIATIONS OF MYOSITIS-SPECIFIC AUTOANTIBODIES IN INFLAMMATORY MYOPATHIES

AUTOANTIBODY	TARGET AUTOANTIGEN AND FUNCTION	FREQUENCY IN IDIOPATHIC INFLAMMATORY MYOPATHIES, %	CLINICAL PHENOTYPE
Anti-ARS	ARS—intracytoplasmic protein synthesis		Antisynthetase syndrome myositis, mechanic's hand, Gottron papules, arthritis, fever, high frequency of interstitial pneumonitis; sometimes clinically amyopathic
Anti-Jo-1	Histidyl	15–20	
Anti-PL-7	Threonyl	5–10	
Anti-PL-12	Alanyl	< 5	
Anti-EJ	Glycyl	5–10	
Anti-OJ	Isoleucyl	< 5	
Anti-KS	Asparaginyl	< 5	
Anti-Ha	Tyrosyl	< 1	
Anti-Zo	Phenylalanyl	< 1	
Anti-200/100	HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase)	40% of necrotizing myopathy	Immune-mediated necrotizing myopathy, frequently associated with prior statin use
Anti-SRP	SRP—intracytoplasmic protein translocation (six polypeptides and RNP 7SLRNA)	5–10	Acute-onset necrotizing myopathy (severe weakness, high CK, frequent myocardial involvement); may be refractory to treatment
Anti-Mi-2	Helicase protein—nuclear transcription (forms the NuRD complex)	5–30	Adult DM and JDM (classical DM, often sudden onset, generally without ILD or malignancy, milder muscle disease with good response to treatment)

Anti-p155/140	TIF1-γ (p155)—nuclear transcription + cellular differentiation	15%–25% adult DM 40%–75% cancer-associated DM 30% juvenile DM	CAM in adult DM; severe cutaneous disease in adult DM and JDM
Anti-MJ	NXP-2—nuclear transcription + RNA metabolism	< 5; 25% juvenile DM	JDM with calcinosis
Anti-SAE	SAE—post-translational modification (targets include transcription factors)	5	Adult DM; may present with CADM first
Anti-CADM-140	Intracytoplasmic MDA5—innate immune	50% of CADM	CADM; rapidly progressive interstitial pneumonia
Anti-PMS1	Subunit of a DNA-binding protein complex	7.5	Rare DM and PM

ARS, aminoacyl-tRNA synthetase; CADM, cancer-associated dermatomyositis; CAM, cancer-associated myositis; ILD, interstitial lung disease; JDM, juvenile dermatomyositis; MDA5, melanoma-differentiation associated gene 5; NA, not applicable; NuRD, nucleosome remodeling histone deacetylase; NXP-2, nuclear matrix protein NXP-2; SAE, small-ubiquitin-like modifier activating enzyme; SRP, signal recognition particle; TIF1-γ, ranscriptional intermediary factor 1-gamma.

Adapted from Lazarou IN, Guerne PA. Classification, diagnosis, and management of idiopathic inflammatory myopathies. J Rheumatol. 2013;40:550–564, with permission.

Incidence rates of PM-DM are bimodal, peaking in childhood and then again in adults of mean age 45 to 64. The mean age is higher (60 years) for those with malignancy-associated myositis, and conversely older people with PM-DM have a higher incidence of malignancy. Three retrospective studies of patients identified clinically with either PM or DM, two by hospital records and one study of both outpatients and inpatients, have specifically addressed the frequency of age more than or equal to 65 at diagnosis. Of the 380 patients represented in these reports, 76 (20%) were 65 or older (range 6.5%–29%). The gender distribution in these 76 patients was 47 females and 29 males, for a ratio of 1.6:1, slightly less women than the range of 2 to 2.5:1 in younger adults with PM-DM.

Few studies address the differences in clinical manifestations, response to therapy and prognosis between older and younger adults with PM-DM. In a comprehensive review of an older cohort, Marie and colleagues retrospectively analyzed 79 consecutive patients with PM-DM presenting to a university's clinic or hospital over a 14-year period. Twenty-three (29%) of the patients were 65 years of age or older (9 men and 14 women, median age 69), 11 who had dermatomyositis and 12 with polymyositis. Comparing older with younger patients, there were no differences in the duration of symptoms prior to diagnosis, or in frequencies of myositis diagnoses, Raynaud phenomenon, dysphonia, cardiac impairment, interstitial lung disease, and peripheral neuropathy. There was a statistically higher frequency ($p < 0.05$) in the older cohort of esophageal dysfunction (35% vs 16%) and bacterial pneumonia (21% vs 5%), as well as a trend ($p = 0.12$) toward ventilatory insufficiency. Aspiration from esophageal dysfunction, combined with ventilatory insufficiency, were postulated factors leading to the higher frequency of pneumonia. The diagnostic accuracy of an elevated CK or aldolase, myopathic EMG findings, and characteristic inflammatory changes on muscle biopsy were similar to that in younger patients, but older patients had a statistically higher frequency of elevated acute phase reactants and lower levels of hemoglobin, total protein, and albumin. These latter findings may be owing to concurrent malignancy.

The frequency of malignancy in patients with PM-DM increases with age and is supported by the study of Marie: 11 of the 23 older patients (49%) had a malignancy at the time of presentation versus only 9% of younger patients. There were no differences in cancer occurrence by gender. Fifty percent of the malignancies were colon cancer, and 10 of the 11 older patients with DM had a malignancy. The literature supports an association, based mainly on case control and cohort studies, of DM with malignancy: up to 15% of patients with DM will have or develop an internal malignancy. The risk for malignancy in PM is greater than for those in the general population but to a lower extent than in patients with DM. Thus, in older people with PM-DM, heightened awareness for the possibility of an underlying malignancy must be maintained. Although an intensive clinical evaluation to exclude an occult malignancy is not without patient risk and is not cost-effective in all patients, patients should complete gender-specific health care maintenance evaluations and investigations directed to determine the source of any abnormal sign or symptom uncovered through a comprehensive review of systems and physical examination.

The response to therapy and outcome of older patients with PM-DM is poorer than in younger adults. Despite a similar distribution of most therapeutic modalities (steroids, azathioprine, intravenous immunoglobulin, methotrexate)

between younger and older adults in the study of Marie, only 13.6% of older patients achieved complete remission of PM-DM versus 41% of younger patients. This trend is supported in previous reports. The age specific mortality rate is also higher in older patients with PM-DM. Older age is but one of many described poor prognostic factors in PM-DM including presence of malignancy, gender, disease severity, dysphagia, bacterial pneumonia, delays in initiating therapy, and resistance to therapy. It is therefore not surprising that older patients reported by Marie, who overall had a higher frequency of malignancy, dysphagia, bacterial pneumonia, and inability to induce remission with therapy versus younger patients, had a higher mortality rate as well: 48% versus 7%. Malignancies were directly responsible for 6 of the 11 deaths (54%) in older patients, and bacterial pneumonia for four (36%). As the development of aspiration and ventilatory insufficiency are associated with bacterial pneumonia, an early assessment of esophageal and lung involvement in patients presenting with PM-DM can lead to detection of subclinical muscle involvement, early intervention for which may reduce subsequent morbidity and mortality.

Endocrine/Metabolic Diseases

Thyroid disease Thyroid disease is prevalent in the older population. Though hypothyroidism is more prevalent than hyperthyroidism (approximately 7% vs 2%, respectively), both conditions are more common in women than men, and either condition can lead to myopathic symptoms.

The diagnosis of hypothyroidism in older people can be difficult, as they present with fewer signs and symptoms, and a diminished frequency of the classical signs of chilliness, paraesthesias, weight gain and cramps compared to younger patients. Weakness is a common sign and symptom in older people with hypothyroidism, occurring in 53% of patients over the age of 70 in one prospective study. Myopathic symptoms may be the sole presenting feature of hypothyroidism. The spectrum of muscle involvement in hypothyroidism is broad. The serum CK may be elevated (usually to < 10 times the upper limit of normal) without either clinical hypothyroidism or muscle symptoms. Symptomatic patients may present with myalgias without CK elevation, muscle hypertrophy with stiffness, with weakness and cramps, a myopathy that may simulate polymyositis with CK elevation, and rarely rhabdomyolysis. Pain and stiffness when predominant may suggest polymyalgia rheumatica or fibromyalgia. A delay in muscle relaxation after hand grip or muscle percussion—pseudomyotonia—may be seen. The severity of the myopathy parallels the degree and duration of the hormone deficiency. Creatine kinase levels are usually elevated, and electromyography may either be normal or show myopathic features. Muscle biopsy may be normal, may show focal necrosis and mild inflammatory infiltrates, or demonstrate nonspecific morphologic changes including fiber size variation, type I fiber predominance and type II fiber atrophy. Thyroid hormone replacement therapy leads to rapid improvement of myopathic signs and symptoms, with complete recovery over several weeks or months, although weakness may take longer to improve than chemical and EMG abnormalities. Most patients have recovered by 6 months, but up to 10% have weakness on examination 1 year after initiation of treatment.

Hyperthyroidism may also cause a proximal myopathy. The reported prevalence of hyperthyroidism in older people is up to 4%, but those over the age of 60 account for 10% to 17% of all hyperthyroid patients and 35% of all patients with thyrotoxicosis. Similar to patients with hypothyroidism, one prospective cohort study of hyperthyroid patients greater than age 70 demonstrated a paucity of clinical signs as compared with a younger adult population, emphasizing the difficulty in making a diagnosis. Clinically, the proximal myopathy of hyperthyroidism develops insidiously and progresses slowly, but may lead to marked weakness. Weakness is not uncommonly greater than the degree muscle atrophy. Paradoxically, serum CK levels are usually normal or minimally elevated. EMG and muscle biopsy features may show a myopathic process. As with hypothyroid patients, therapy is directed at correcting the underlying thyroid dysfunction.

Osteomalacia Osteomalacia is a metabolic bone disease of undermineralized collagen matrix in which unmineralized matrix (osteoid) accumulates at bone surfaces. This disease most often affects older people in whom the most common etiology is vitamin D deficiency, superimposed on age-related decrease in muscle vitamin D receptor number and or function. In this way, presentation may mimic that of osteoporosis. Nonspecific bone pain and tenderness with or without fractures are the dominant symptoms, but muscle weakness is not uncommon. Patients with severe weakness may mimic the presentation of PM. The myopathy is characteristically proximal in distribution, and in the lower limbs may produce a waddling gait. CK levels are typically normal, and a myopathic pattern may be seen on EMG. Minimal inflammatory infiltrates may be found with other myopathic features on muscle biopsy. The myopathy usually responds to administration of vitamin D, with or without supplemental calcium or phosphate, depending on the etiology of osteomalacia.

Amyloid Myopathy

Muscle involvement in patients with amyloidosis is a common finding in this rare disorder. Typical manifestations in skeletal muscle include pseudohypertrophy, palpable nodular masses within muscle, and a "wooden consistency" firmness of muscles. These abnormalities may be severe enough to lead to weakness, pain, and immobility. Amyloid myopathy may present without these more typical features, but rather with progressive proximal muscle weakness and dysphagia, elevated serum CK levels, and EMG changes of an inflammatory myopathy. Muscle biopsies may reveal extracellular amyloid deposits around muscle fibers and some small vessels. This proximal myopathy from amyloid is rare, but should be considered in the older patient with a proximal myopathy without pseudohypertrophy.

Drug-Induced Myopathies

Although the exact percentage is not known, the prevalence of drug-induced myopathy in older people is not trivial. Older people are at risk for drug-induced myopathies as the medications commonly causing myopathic symptoms are given for diseases which themselves have an increased incidence with age, and such drugs usually require a cofactor (eg, renal insufficiency), some of which are age related. A drug-induced myopathy may present as a necrotizing myopathy (eg, autoimmune necrotizing myopathy from statins), inflammatory myopathy (eg, procainamide), mitochondrial myopathy, anti-microtubular myopathy (eg, colchicine), lysosomal storage myopathy (eg, amiodarone), myofibrillar myopathy, or as type II muscle fiber atrophy (eg, corticosteroids). The scope of this chapter does not allow for an in depth discussion of all possible toxic myopathies, and the reader is referred to recent reviews. Summary comments below are limited to selected drugs with risk for toxic myopathy in older people.

Corticosteroids Myopathy is a well-known side effect of corticosteroids. The myopathy is more prevalent in women than men, and is generally seen with larger doses, longer duration, and more frequent dosing. The likelihood is also higher with the use of fluorinated steroids. Proximal hip girdle muscles are mainly affected, but shoulder girdle and diffuse muscle involvement may be seen. Respiratory muscles can be affected, even when limb muscles remain strong. Typical findings include normal serum CK levels, a myopathic EMG without inflammatory changes, and muscle biopsy findings of excessive type II (IIb) muscle fiber atrophy or normal changes for age. Steroids induce a decrease in muscle protein synthesis and an increase in protein degradation. Antianabolic effects include inhibition of amino acid transport into muscle, inhibition of the ability of insulin, insulin-like growth factor I (IGF-I) and certain amino acids to stimulate the initiation of mRNA translation, and downregulation of myogenin and the degradation of MyoD, transcription factors required for differentiation of satellite cells into muscle fibers. Catabolic effects of steroids are mediated by stimulating proteolysis of muscle contractile proteins through ubiquitin proteasome, lysosomal (cathepsins), and calcium-dependent (calpains) systems. Muscle wasting leads to increased urinary creatine excretion, detected as an increase in % creatinuria; urine creatine divided by the sum of urine creatine plus creatinine in a 24-hour specimen should be less than 6%, but is elevated in a steroid myopathy. This test is useful when trying to distinguish steroid myopathy from myalgias without myopathy in the setting of a normal CK level. Therapy for steroid myopathy involves steroid taper and reconditioning exercises, with exercise additionally beneficial for its ability to reduce glucocorticoid receptors in muscle.

Alcohol Older people are not immune to alcohol-related health problems. Nearly 10% of older people self-report unhealthy drinking. Alcoholic myopathy may present in three forms. A subclinical form is manifested solely by elevation of muscle enzymes that return to normal during abstinence. Acute alcoholic myopathy is associated with acute intoxication. There may be profound weakness, myalgias, and rhabdomyolysis, with marked elevation of CK and myoglobinuria. Findings of an inflammatory myopathy are seen on EMG, and biopsy shows necrosis with varying degrees of inflammation. With conservative care, the CK may rapidly drop over days to a week. This observation is important to keep in mind so that the patient may be kept from the inappropriate early use of corticosteroids, as the syndrome may mimic severe polymyositis at onset. Alcohol more commonly causes a chronic proximal myopathy. Chronic alcohol use may lead to muscle atrophy, more in the legs than arms, with evaluation showing normal CK levels, noninflammatory myopathic EMG, and type II fiber atrophy on muscle biopsy.

Colchicine Colchicine is an uncommon cause of drug-induced myopathy. Patients present with proximal muscle weakness, elevated CK, and a nonspecific vacuolar myopathy on biopsy. Renal insufficiency is a major risk factor, making even low daily prophylactic doses (eg, in the treatment of gout) in this situation prone to causing neuromyotoxicity. Colchicine dose should always be adjusted for the degree of renal function.

Lipid-lowering agents All lipid-lowering agents, except for bile acid sequestrants (resins) and plant sterols, may

cause either myalgias and/or myopathy. Nicotinic acid uncommonly may cause myalgias and elevated CK levels. Ezetimibe (an inhibitor of the intestinal intraluminal sterol transporter) has been documented in case reports to cause tendinopathy and myopathy, either alone or when given with statins. Fibric acid derivatives can cause muscle cramps, an acute or subacute painful myopathy, and elevated CK levels with or without signs of myoglobinuria. Myopathy from fibrates is more likely to occur in a patient with renal insufficiency. Among the lipid-lowering therapies, fibrates appear to have a higher relative risk for myopathy than do statins.

Statin drugs have been associated with myalgias (cramping, aching or stiffness, transient or persistent, with normal CK level) in 5% to 10%, myositis (elevated CK) in approximately 1%, and rhabdomyolysis in approximately 0.1% of treated patients. Statins have also been reported to cause tendon-associated pain, and it is estimated that up to 25% of statin users may develop exercise-induced muscle pain, cramping or fatigue. Older people are at higher risk for the development of statin-induced myopathy. Other risk factors include patient characteristics (female sex, renal insufficiency, hepatic dysfunction, hypothyroidism, biliary tract obstruction, underlying muscle disease, grapefruit juice intake) and properties of the statin (higher dose, lipophilicity, and potential for drug-drug interactions with other medications metabolized by cytochrome P450 [especially CYP3A4] pathways, eg, amiodarone, fibrates, cyclosporine, HIV protease inhibitors and numerous antibiotics including erythromycin, clarithromycin, rifampin). The median duration of statin therapy prior to symptom onset is 6 months, but may be as long as 4 years. The myopathy is self-limited, with a median duration of myalgias and resolution of CK elevation following cessation of statin therapy of 2 to 3 months. Persistent symptoms and/or elevated CK level despite statin discontinuation may indicate an underlying other myopathy or the development of a statin-induced necrotizing myopathy (see further). There is no agreed-upon case definition for statin-induced myopathy, contributing to the inconsistent recommendations from national organizations (ACC/AHA/NHLBI, FDA, National Lipid Association) on how to screen for statin-related toxicity and manage symptoms. There is agreement that the statin be discontinued if the CK is more than 10-fold the upper limit of normal, but differing recommendations as to when to measure CK (at baseline +/− at regular follow-up intervals, or just with symptoms) and how to manage statin therapy at lower levels of CK elevation. Treatment strategies include reducing the statin dose, changing to nondaily statin dosing, changing to a statin metabolized by a route other than by the CYP3A4 pathway, changing to a nonstatin lipid lowering agent, and adding supplemental coenzyme Q10. The precise mechanisms of statin-induced myopathy are incompletely understood, but may include induction of apoptosis, induction of atrogin-1 (a ubiquitin ligase active in proteolysis), instability of myocyte membranes from decreased cholesterol content, depletion of isoprenoids (isoprenylation being responsible for the posttranslational modification of up to 2% of cellular proteins) or coenzyme Q10, mitochondrial dysfunction, and increased hepatic uptake of statins in individuals heterozygous (odds ratio for myopathy of 4.4) or homozygous (odds ratio 17.4) for the C-allele variant of the *SLCO1B1* gene.

As mentioned above, persistent myopathic symptoms and/or hyperCKemia following discontinuation of statin therapy may indicate the development of a medication-triggered immune-mediated necrotizing myopathy. Statins not only inhibit HMG-CoA reductase (HMGCR), but lead to a compensatory increase in HMGCR levels. Detection of an autoantibody (anti-200/100) against HMGCR is found in those patients with a progressive myopathy despite discontinuation of statin therapy, but this antibody may also be detected in patients without prior statin exposure who presumably have sustained muscle damage (eg, from a toxin, or infectious agent) leading to increased HMGCR expression from regenerating muscle cells. In statin exposed patients this autoimmune myopathy shows no gender bias, but the risk for developing anti-HMGCR antibodies is strongly associated with the HLA-DRβ1*11:01 gene allele. A number of statins have been associated with this syndrome. The duration of statin therapy before onset of the myopathy is 31 months but may be as long as 7 years. Muscle biopsy shows a necrotizing myopathy without significant inflammation, similar to that in seen in patients with anti-SRP antibodies. In contrast to those with no prior statin exposure, statin-exposed patients with this immune mediated necrotizing myopathy respond to immunosuppressant therapy, but aggressive therapy may be required and the course of treatment may be prolonged.

Late-Onset Muscular Dystrophies

Muscular dystrophies are genetically determined, degenerative myopathies that usually present before adulthood. These diverse groups of inherited muscle protein disorders are characterized by their patterns of inheritance and penetrance, age of onset, progression, severity, and muscles involved. Weakness proceeds slowly, and arrest of progression has been described. Depending on the particular disease, some patients may proceed into older adulthood with minimal or undetectable symptoms before the cumulative effects of muscle degeneration lead to functional decline. Three late-onset muscular dystrophies are described, each causing proximal limb weakness: facioscapulohumeral dystrophy,

oculopharyngeal dystrophy, and late-onset limb girdle dystrophy. These dystrophies are associated with normal or mild elevations of serum CK and a nonspecific myopathic pattern on EMG. Muscle biopsy findings are nondiagnostic, and can show loss of muscle fibers, variation in fiber size, and degrees of muscle fiber necrosis. Therapy is limited to patient and family education, palliative measures to prevent aspiration, and empiric physical therapy.

Facioscapulohumeral dystrophy is an autosomal dominant disease that typically begins with facial muscle weakness (eg, inability to tightly close eyes or whistle), sparing the extraocular and pharyngeal muscles. Weakness tends to proceed caudally, involving muscles of the shoulder (scapular winging) then pelvic girdles, although early tibialis anterior involvement is characteristic. Extramuscular features include sensorineural hearing loss and retinal vasculopathy. Diagnosis can be made by molecular genetic testing of blood.

Oculopharyngeal dystrophy is also inherited through an autosomal dominant pattern with complete penetrance, and is the only dystrophy that presents more commonly in older people. It is classified as a polyalanine disorder, with the mutation in poly (A) binding protein 1 (PABPN1). Symptoms begin in the fifth or sixth decade of life. Proximal upper and lower extremity weakness is a late finding, following onset of symptoms with ptosis (bilateral, but can be asymmetric) and dysphagia. Supportive care includes surgery to correct ptosis and cricopharyngeal myotomy for severe dysphagia. The pathologic hallmark is unique, filamentous intranuclear inclusions which have been shown to contain aggregations of mutated PABPN1. Diagnosis is made through molecular genetic testing.

Limb girdle dystrophy represents a group of disorders with heterogeneous phenotypes, but with predominant scapular and pelvic girdle involvement (legs earlier and more severely than the arms). The presence of dysrhythmia or contractures suggests a laminopathy. Mutations in at least 19 genes have been described, encoding proteins for calpain 3, caveolin, dysferlin, lamin, sarcoglycans, and telethonin. Autosomal dominant (with incomplete penetrance) and recessive inheritance patterns are observed, thus the clinical phenotype does not allow for accurate prediction of the genotype. A specific diagnosis is based on the combination of results from DNA mutation testing and muscle protein analysis.

Late-Onset Mitochondrial Myopathy

Ragged red fibers are the histologic hallmark of mitochondrial dysfunction, and represent the end result from a diverse set of conditions including normal aging, sporadic inclusion body myositis and other neuromuscular diseases, and myopathies from drugs that cause mitochondrial damage. The mitochondrial myopathies/encephalomyopathies are a heterogeneous group of disorders displaying specific clinical manifestations, maternal inheritance, excessive ragged red fibers on muscle biopsy, altered energy state of resting muscle, mutations in mitochondrial DNA (mtDNA), and deficiencies in the activities of oxidative phosphorylation enzymes. Most patients present symptomatically within the first three decades of life. A syndrome of late-onset mitochondrial myopathy has been described. Patients have progressive proximal muscle weakness of insidious onset, and limb muscle fatigability, mainly in the lower limbs. Serum levels of CK are mildly elevated and myopathic changes can be seen on EMG. Excessive ragged red fibers are noted on muscle biopsy. This condition is thought to represent an exaggerated form of the accumulation of mtDNA mutations that occurs with aging, which manifests clinically as a proximal myopathy.

Paraspinal Myopathies of Older People

Severe weakness isolated to paraspinal muscles is uncommon and usually a manifestation of another underlying neurologic disease, muscular dystrophy, or myopathy. Weakness is evident when in the erect position and the postural abnormality resolves when supine or with passive extension. Conditions reported to be associated with this finding include inflammatory and noninflamatory myopathies (including polymyositis, inclusion body myositis, and certain endocrine/metabolic myopathies), facioscapulohumeral and limb girdle dystrophies, neurologic diseases of the motor neuron (ALS, postpolio syndrome) and peripheral nerves (chronic inflammatory polyneuropathy), Parkinson disease, and as a paraneoplastic phenomena. Involvement of the cervical spine is termed dropped head syndrome, while the phenotype of thoracolumbar spinal weakness is referred to as bent spine syndrome.

Although kyphosis is a frequent finding in older people, it is usually limited to the thoracic spine and rarely involves the lumbar spine. Bent spine syndrome, or camptocormia (from the Greek for active forward trunk bending), is the consequence of chronically progressive lumbar and thoracic kyphosis in the absence of an architectural abnormality of the vertebral column to account for the postural change. The majority of cases of muscular origin are due to an idiopathic, late-onset, axial myopathy. Those affected are predominately older women, and a positive family history of similar symptoms is reported in up to three-fourths of patients. CK levels are normal or mildly elevated. EMG testing can reveal myopathic and/or neuropathic changes in paravertebral muscles, and mild myopathic changes

(some with inflammatory infiltrates) with marked increase in connective tissue and fatty infiltration is seen in muscle biopsy specimens from affected patients. Radiographic, computerized tomographic and magnetic resonance scanning analyses show diffuse muscle atrophy limited to the spinal muscles, without evidence of significant bony changes, in a pattern of muscle involvement distinct from that caused by spinal stenosis. Treatment for this primary axial myopathy is largely supportive, including exercise therapy, orthoses, and use of assistive devices for ambulation. Patients with secondary forms or with myositis on biopsy may respond to corticosteroids.

A more limited form of spinal weakness of the neck extensors causes dropped head syndrome. Weakness leads to the inability of keeping the head from dropping on the chest. CK is usually normal but may be elevated, and EMG testing of affected muscles shows myopathic changes. Muscle biopsy may reveal inflammatory infiltrates as well as nonspecific mild myopathic abnormalities. Dropped head syndrome from isolated myositis may respond to steroid therapy.

POLYMYALGIA RHEUMATICA AND GIANT CELL ARTERITIS

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are discussed together as they share similar epidemiologic, clinical, laboratory, and treatment findings. Each is a systemic inflammatory disease that probably forms the ends of a spectrum of illness. Individual patients may be affected by one disease or both conditions simultaneously. The reported frequency of GCA occurring in patients with PMR ranges from 0% to 80%, and varies according to how aggressive an approach to temporal artery biopsy is undertaken. A more realistic estimate is that GCA occurs in 15% to 20% of PMR patients. Conversely, PMR occurs in 40% to 60% of patients with GCA and is the presenting symptom in 25%. Apart from the approach taken as to the clinical timing and size of temporal artery biopsy, differences in these prevalence data likely reflect selection bias of the populations studied, and use of differing diagnostic criteria.

Polymyalgia Rheumatica

PMR is a clinical syndrome of neck and limb girdle aching of older adults. Patients have laboratory evidence of a systemic inflammatory response, an excellent response to low dose corticosteroids, and no evidence to support other causes of a systemic illness such as malignancy or another connective tissue disease.

Epidemiology and pathogenesis PMR is seen in patients aged 50 and older, 90% in those older than 60. The female-to-male ratio is 2:1, and Caucasians are the most commonly affected subgroup. The condition is especially prevalent among those from northern European ancestry. The incidence rate is 50 cases per 100,000 persons over the age of 50 per year, rises with increasing age, and is two- to threefold higher than the rate for GCA. The corresponding prevalence rate for PMR is 600 per 100,000.

The etiology of PMR is unknown, and the source of pain symptoms is not clearly defined. At the phenotypic level, evidence from studies of the shoulder, hip, and surrounding tissues using radioisotopes, ultrasound and fat-suppressed magnetic resonance imaging with gadolinium enhancement have demonstrated the presence of combinations of nonerosive synovitis, bursitis, tenosynovitis, and muscle edema in patients with active PMR. The diffuse distribution of these findings—particularly the presence of abnormalities outside synovial compartments—may explain the generalized pain felt by patients, and reflects a pattern of inflammatory changes distinct from that seen in rheumatoid arthritis. Microscopically, arthroscopic biopsy studies have documented the presence of synovitis. In the synovial lesion, vascular proliferation is accompanied by an inflammatory infiltrate composed primarily of macrophages, CD4+ T-cells, and scarce neutrophils. A relative absence of B cells and γδ T cells serve to differentiate the synovitis of PMR from that seen in rheumatoid arthritis. The cellular milieu parallels that seen in the temporal arteries of patients with GCA (see further). This finding, and the presence of GCA histology, as well as proinflammatory cytokines without typical histologic changes in temporal artery biopsy specimens of PMR patients without GCA symptoms, further strengthens the association between the two diseases. At the genetic level, there is a reported association of PMR with the markers HLA-DRB1*0401 and HLA-DRB1*0404. Cases occurring in family members support a possible genetic component to the disease. The event that triggers disease in the setting of potential genetic risk is unknown. Seasonal outbreaks of cases have suggested an infectious etiology, but to date no specific, causal pathogen has been identified. PMR, unlike certain of the idiopathic inflammatory myopathies, is not associated with malignancy.

Clinical features and diagnostic criteria Acute or slowly progressive, symmetric pain (of at least 1 month) and stiffness develop in the neck and proximal limb girdle areas. Symptoms may be difficult to localize, and can be severe

enough to limit activity analogous to that from a proximal myopathy or impingement syndrome. Shoulder pain (75%–90%) is more common than hip pain (50%–70%). Constitutional symptoms to include fever, malaise, night sweats, and weight loss occur in a third of patients, but high fever is uncommon. Other associated symptoms include prolonged morning stiffness upon awakening of affected areas, daytime gelling with inactivity, and arthralgias. Symptoms of GCA (see below) are noted in 15% to 20% of patients. A thorough history including an extensive review of systems, and general physical exam, is essential to exclude conditions which may present with similar complaints, including sources of myopathy (see section Myopathies in Older People), occult malignancy, other connective tissue diseases, chronic infections, and spinal and regional musculoskeletal disorders.

Physical examination is usually unrevealing. Palpable muscular tenderness, when present, is not dramatic. Shoulder and hip motion may be limited by pain, but true weakness is usually not present. A mild, symmetric, nonerosive polyarthritis of the hands, wrists, and knees may be seen in a third of patients, and be difficult to distinguish from the presentation of late-onset rheumatoid arthritis. Synovitis of the glenohumeral joint and tenosynovitis of the long head of the biceps tendon can be present in more than half of patients. Synovitis of small foot joints is less common than in older patients with rheumatoid arthritis. Steroid-responsive, dorsal hand pitting edema, occurring with hand and wrist synovitis and similar to that seen in RS3PE syndrome (remitting seronegative symmetric synovitis with pitting edema), is seen in up to 8%.

An elevated acute phase reactant is present in at least 80% to 90% of cases at presentation. The Westergren ESR is greater than 40 mm/h and not uncommonly as high as 100 mm/h. C-reactive protein is also elevated, but no specific cutoff is universally used to support the clinical diagnosis. Using the height of serum IL-6 level elevation as a marker for adjusting initial corticosteroid therapy and monitoring response to treatment has been investigated, but continues to undergo evaluation. Similarly, some have suggested that the height of ESR at presentation correlates with severity and prognosis. A normochromic, normocytic anemia during active disease may be seen in two-thirds of patients, and abnormal liver function tests in up to a third. Rheumatoid factor and antinuclear antibody testing are negative. CK levels are normal, but EMG testing on rare occasions may show changes of an inflammatory myopathy.

PMR is a clinical diagnosis, based on a combination of clinical and laboratory findings, as no single manifestation is pathognomonic for the disease. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) have proposed provisional classification criteria for PMR (**Table 120-3**).

TABLE 120-3 PROVISIONAL CLASSIFICATION CRITERIA FOR POLYMYALGIA RHEUMATICA

REQUIRED FINDINGS: AGE ≥ 50, BILATERAL SHOULDER ACHING, ABNORMAL CRP AND/OR ESR

VARIABLE FINDINGS (ODDS RATIO [95% CI])	POINTS WITHOUT ULTRASOUND (0–6)	POINTS WITH ULTRASOUND (0–8)
Morning stiffness duration > 45 min (5.0 [2.8, 9.1])	2	2
Hip pain or limited range of motion (1.4 [0.8, 2.6])	1	1
Absence of rheumatoid factor or anticitrullinated peptide antibody (eg, CCP) (5.2 [2.1, 12.6])	2	2
Absence of other joint involvement (2.2 [1.3, 4.0])	1	1
At least: *1 shoulder*: subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis AND *1 hip*: synovitis and/or trochanteric bursitis (2.6 [1.3, 5.3])	Not applicable	1
Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis	Not applicable	1

(2.1 [1.2, 3.7])		
Score to be categorized as PMR	**≥ 4**	**≥ 5**
Sensitivity of criteria	68%	66%
Specificity of criteria	78%	81%

Adapted with permission from Dasgupta B, Cimmino MA, Kremers HM, et al. 2012 Provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Arthritis Rheum. 2012;64:943–954.

Treatment The mainstay therapy for PMR is systemic corticosteroids. An initial dose of 15 to 20 mg of prednisone per day usually leads to prompt improvement, if not complete remission, of subjective symptoms within hours to days. Lack of initial response should prompt an evaluation for an alternate diagnosis. Despite rapid clinical improvement, further tapering of the dose is done slowly in order to prevent relapse. Once the ESR normalizes and symptoms resolve, but usually after 4 to 8 weeks, the dose is reduced in small decrements: by 2.5 mg every 2 to 4 weeks until 10 mg QD is reached, then by 1 mg every 4 weeks. The lowest dose that controls symptoms should always be used. If exacerbations occur during taper (approximately 25% of patients), the dose can be increased (although not necessarily to the starting level) and the tapering recommenced. Patient symptoms rather than the ESR level alone are the main parameter to follow. Alternate-day dosing of steroids is less effective than a daily schedule. A course of steroids under these guidelines may take a minimum of 12 to 18 months to complete. Three quarters of patients are off steroid therapy by 2 years. Persistent elevation of the ESR, rise of the ESR after initial fall and symptom improvement during therapy, or failure to improve with low dose corticosteroids, may indicate the presence of GCA and the consideration for temporal artery biopsy, or an alternate diagnosis. Patients should be evaluated for signs and symptoms of GCA at every visit, and if present, referred for temporal artery biopsy even while on corticosteroid therapy. All patients receiving corticosteroids should be started on measures to prevent osteoporosis, and be closely monitored for other metabolic side effects.

A percentage of patients, ranging from 10% to 30% depending on the reported series, may require longer courses of corticosteroids or chronic daily doses (eg, prednisone at 5 mg or less per day) to maintain symptom control. The benefits of such prolonged therapy should be weighed against the serious risk of steroid-induced side effects in older people. Alternative therapies are not well supported by conclusive clinical trials. Methotrexate may be marginally effective as a steroid sparing agent, while hydroxychloroquine, azathioprine, and other cytotoxics have been used albeit with only limited success. Analgesics may be added to improve pain symptoms. An NSAID or COX-2 inhibitor may be used as initial therapy in very mildly affected patients, but should be changed over to corticosteroids if marked improvement is not seen in 2 to 4 weeks. NSAIDs do not alter ESR levels, nor suppress subclinical GCA if present. More frequently these agents are used as a means of providing adjunctive anti-inflammatory therapy to ongoing steroid therapy. Their use must be balanced against the risk of eliciting renal, cardiovascular, gastrointestinal, and hematologic side effects.

Giant Cell Arteritis

GCA is a systemic, granulomatous, segmental, and focal panarteritis usually focused along the internal elastic lamina of medium- and large-sized extracranial arteries. The aorta and branch vessels from the aortic arch are most frequently involved. Disease manifestations are generally the result of tissue-organ ischemia or necrosis downstream from the site of vascular occlusion. Certain disease manifestations are steroid-responsive but require higher doses at the initiation of therapy as contrasted against treatment for PMR.

Epidemiology and pathogenesis As in PMR, GCA is seen in patients older than 50 years, most commonly in Caucasians, women, and in those from northern Scandinavian ancestry, with an incidence rate of approximately 17 to 27 cases per 100,000 persons over the age of 50, and prevalence rate of about 200 per 100,000. The disease is rare in the US in those of African and Asian descent, with an associated incidence rate of approximately 1 case per 100,000 persons.

The cause of GCA is unknown, but histologic and biochemical evaluations of affected arteries suggest that it is an antigen-driven disease with a cell-mediated immune response. Association with an *HLA-DRB1* gene polymorphism parallels that seen in the immunogenetics of patients with PMR, and the cellular infiltrate throughout the vessel wall mirrors that seen in the synovium of patients with active PMR. Destruction of the arterial wall is centered on the elastic fibers of the internal elastic lamina. The process is thought to begin in the adventitia, where activated dendritic cells recruit CD4+ T-cells co-expressing CD161 into the vessel wall. Based on the cytokine milieu secreted by

dendritic cells, these ultimate T-effector cells (a) following exposure to IL-1β, IL-6 and IL-23, differentiate into IL-17 producing Th17 cells, or (b) following exposure to IL-12 and IL-18, differentiate into interferon-gamma (IFN-γ) producing T-helper-1 (Th1) cells. Research implicates these two independent inflammatory cytokine pathways in driving disease pathogenesis: the IL-17 axis thru activation of endothelial cells, vascular smooth muscle cells, and fibroblasts and associated with IL-6-mediated systemic/constitutional symptoms, and the IFN-γ axis activating macrophages, endothelial cells and cytotoxic cells and associated with vascular occlusion and ischemic complications. The IL-17 mediated pathway is very steroid-sensitive, whereas the IFN-γ pathway is steroid resistant, and is the predominant cell type in intramural infiltrates. Early disease is characterized by activity of both pathways, but chronic disease is characterized by persistent Th1-inducing signals, independent of IL-17-mediated inflammation. In combination with proteolytic enzymes and growth factors, a granulomatous reaction develops in the vessel wall, while secondary smooth muscle and matrix proliferation contributes to vascular occlusion.

Clinical features and diagnostic criteria Most patients have clinical findings attributable to involved arteries at some time during the illness. The most prevalent symptoms include headache (65%) in the distribution of either the temporal or occipital arteries, visual disturbance (30%), permanent visual loss (15%), jaw claudication symptoms (eg, from chewing or talking; 45%), dysphagia or swallowing claudication (8%), tongue claudication (6%), limb (usually arm) claudication (4%), and persistent cough or sore throat (4%). Rare manifestations include tinnitus and ischemia of the scalp or tongue. Headaches may be severe, acute, and associated with scalp sensitivity in temporal and or occipital artery distributions. Typical PMR is seen in 40% to 60%, and may be the presenting finding in 25%. In approximately 25% of patients a nonerosive arthritis may be present, typically involving the metacarpophalangeal joints, wrists, and knees. Constitutional symptoms are common, and may exist as the sole manifestation of disease. These include weight loss or anorexia (50%), fever (which may be prolonged and meet the criteria for fever of unknown etiol ogy; 45%), fatigue (40%), and depression symptoms. Overall, the nonspecific nature of many of the aforementioned symptoms contributes to the delay, which on average can be weeks, before diagnosis is made. **Table 120-4** lists the test characteristics of individual symptoms and their combinations as expressed by likelihood ratios.

TABLE 120-4 LIKELIHOOD RATIOS FOR SINGLE SYMPTOMS AND IN COMBINATION FOR GIANT CELL ARTERITIS

	LIKELIHOOD RATIO (LR)	
	LR+ (95% CI)	LR− (95% CI)
Single Symptoms		
Jaw claudication	6.9 (5.0–9.5)	0.64 (0.59–0.70)
Diplopia	3.7 (1.5–9.2)	0.97 (0.95–0.99)
Scalp tenderness	3.1 (2.4–4.0)	0.75 (0.70–0.81)
Myalgia/arthralgia	2.2 (1.6–3.1)	0.90 (0.86–0.95)
New headache	1.7 (1.5–1.9)	0.54 (0.46–0.63)
Decreased vision	1.5 (1.0–2.1)	0.95 (0.91–0.99)
Weight loss	1.3 (1.0–1.6)	0.93 (0.87–0.99)
Combinations of Symptoms		
Jaw claudication + decreased vision	44 (5.9–322)	0.98 (0.97–0.99)
Jaw claudication + diplopia	30 (1.7–519)	0.98 (0.97–0.99)
New headache + jaw claudication + scalp tenderness	19 (8.1–42)	0.86 (0.82–0.90)
Jaw claudication + scalp tenderness	18 (8.3–39)	0.84 (0.80–0.88)
New headache + jaw claudication	8.7 (5.8–13)	0.71 (0.66–0.76)
New headache + decreased vision	6.2 (2.7–14)	0.95 (0.93–0.98)
New headache + scalp tenderness	3.9 (2.9–5.3)	0.77 (0.72–0.82)

CI, confidence interval; LR+, positive likelihood ratio; LR–, negative likelihood ratio.

Data from Simel DL, Rennie D: The Rational Clinical Examination: Evidence-Based Clinical Diagnosis. Chicago: American Medical Association; 2009.

Examination reveals signs related to affected arteries in up to two-thirds of patients. Scalp artery tenderness (27%) is a less frequent finding than a decreased temporal pulse (46%) in one study. Care should be taken to differentiate temporal artery findings from the signs of radiating pain from an ipsilateral C2 radiculopathy (tenderness in the paraspinal area of the ipsilateral upper cervical spine, pain exacerbated by head position or motion), or scalp pain radiating from a myofascial pain emanating from the suboccipital muscles at the base of the skull (focal muscular tenderness, which may "trigger" radiating pain into the temporal scalp). A swollen, nodular or erythematous scalp artery is detected with equal frequency as a large artery bruit (20%). Large vessel vasculitis occurs in 25% of patients. Involvement of the thoracic or abdominal aorta may lead to aneurysmal dilation and possibly rupture, usually occurring years after the onset of disease during a time when most patients are not otherwise thought to have active disease. Hypertension from renovascular involvement is rare. Involvement of the ophthalmic, central retinal, and posterior ciliary arteries to the eye can cause optic nerve ischemic lesions (either anterior or posterior ischemic optic neuropathy, the former the commonest lesion and associated with partial or complete visual loss) or retinal ischemic lesions (either central retinal or cilioretinal artery occlusions which may also lead to severe visual loss). Fundoscopic exam revealing a chalky white edematous optic disc suggests infarction of the optic nerve head, whereas optic disc cupping is a late finding. Visual loss occurs in 10% to 15% of patients, may be sudden and without warning, with risk for permanent loss increased in patients with prior transient loss. Warning signs include symptoms of amaurosis fugax, visual disturbance with postural change, or diplopia. Vision loss for more than a few hours only very rarely returns. Less common findings in patients with GCA include peripheral neuropathy, scalp necrosis, cerebral infarction, and lesions that may mimic CNS vasculitis, tinnitus, and deafness.

The ESR is usually markedly elevated, not uncommonly to 80 to 100 mm/h or higher. A normo to hypochromic anemia may be seen, and can be accompanied by reactive thrombocytosis. Other acute phase reactants such as C-reactive protein, haptoglobin and alpha-2 globulin can be elevated; however, these measures, including an elevated ESR, should not be the only indication to begin immunosuppressive medication. A mild hepatic transaminitis and or an elevated alkaline phosphatase can occur. The presence of anticardiolipin antibodies at presentation may be a poor prognostic marker for the subsequent development of vascular complications.

Radiographic investigations can help define the extent of disease, but alone are rarely sufficient to make the diagnosis of GCA. The combination of positron emission tomography (PET) with computed tomography (CT) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) can detect hypermetabolic activity in vascular walls, but cannot reliably distinguish between vasculitis and atherosclerotic changes. Magnetic resonance (MR) or CT angiography of the aorta and its proximal major branches can demonstrate the vascular occlusion or dissection responsible for limb claudication, or clinically suspected aortic involvement, but wall thickening or delayed enhancement of the arterial wall may not change with treatment, and is not a reliable measure of disease status. Doppler ultrasonography (US) of the temporal arteries may show hypoechoic changes representing edema of the vessel wall ("halo sign") and decreased blood flow and velocity as noninvasive diagnostic signs of active inflammation. However, Doppler US is neither sufficiently sensitive nor specific to routinely replace diagnostic arterial biopsy.

As clinical features are not specific, temporal artery biopsy remains the gold standard diagnostic test. The yield is increased when the artery to be biopsied is palpably or visibly abnormal. As the pathologic changes in an involved artery tend to occur as skip lesions along its length, a biopsy specimen of a minimum 1 cm, and preferably greater than 2 cm, is preferred. The artery should be sectioned at 3- to 5-mm intervals prior to microscopic examination. The need for biopsy should not delay steroid therapy, but biopsy performance should preferably occur within the first few days of steroid use. Prior or ongoing therapy with steroids (eg, in a patient with PMR) should not prevent a decision to confirm the diagnosis by biopsy if the patient has active signs and symptoms of GCA. The temporal artery is the preferred site for biopsy, although a diagnosis can be confirmed by biopsy from a symptomatic occipital artery. A positive biopsy demonstrates evidence of vasculitis centered at the intima-media junction with predominance of mononuclear cell infiltrates or granulomatous inflammation, usually with multinucleated giant cells. However, multinucleated giant cells are found in only 50% of specimens. Rarely is the inflammation restricted to the vasa vasorum or periadventitial small vessels. Histologic changes of GCA need to be distinguished from the normal changes that occur in aging vessels, although distinguishing between "healed arteritis" and senescent changes may be difficult at best due to a significant overlap in the microscopic findings. Normal senescent changes in the temporal artery include progressive and relatively regular intimal thickening, medial degeneration and thinning with occasional calcium deposition, focal internal elastic fiber fracture, and fibrosis.

An initial negative biopsy occurs in up to one-third of patients, and should first lead to careful reevaluation of the specimen. Biopsy of the contralateral artery only infrequently provides pathologic confirmation when the initial biopsy is negative, but may be pursued in a patient for whom the diagnosis remains in doubt, especially if systemic symptoms

predominate and there is a very high clinical suspicion for GCA. The diagnostic sensitivity of a temporal artery biopsy remains high even if steroid therapy was begun preoperatively, but biopsy is ideally not delayed for more than 1 week. A negative biopsy does not preclude a diagnosis of GCA if sufficient other clinical findings are present, and is a situation more commonly seen in patients who have predominately subclavian artery involvement.

The 1990 American College of Rheumatology classification criteria for GCA have become de facto diagnostic criteria in clinical practice (**Table 120-5**). These criteria provide structure to making the diagnosis if artery biopsy is either not available or temporal artery abnormality is not present. In the original derivation, the criteria had a sensitivity of 94% and a specificity of 91%.

TABLE 120-5 CLASSIFICATION CRITERIA FOR GIANT CELL ARTERITIS

CRITERION	DEFINITION
1. Age at onset ≥ 50 years	Development of symptoms or findings beginning at age 50 older
2. New headache	New onset of or new type of localized pain in the head
3. Temporal artery abnormality	Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries
4. Elevated ESR	Erythrocyte sedimentation rate (ESR) ≥ 50 mm/h by the Westergren method
5. Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

For purposes of classification, a patient shall be said to have GCA if at least 3 of the 5 criteria are present.

From Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33:1122, reprinted with permission.

Treatment The risk of acute visual loss mandates that corticosteroid therapy should be initiated in anyone suspected of having GCA. Initial doses of 1 mg/kg (eg, 40–60 mg) of prednisone per day in a single morning dose, higher than starting doses for PMR, are standard. Even higher doses of 15 mg/kg (eg, 1000 mg given intravenously) per day are suggested for patients with active visual symptoms. The initial dose is maintained for 4 to 8 weeks to suppress clinical symptoms and normalize the ESR and/or CRP, then slowly tapered over months. Most patients require an average of 2 years of therapy to control symptoms. One suggested schedule for tapering is to reduce the initial dose by 10 mg every 2 to 4 weeks until 40 mg daily is reached, then by 5 mg every 2 to 4 weeks until 20 mg daily, followed by a reduction of 2.5 mg every 2 to 4 weeks until 10 mg/day. Thereafter, the dose is tapered following the pattern for patients with PMR, by 1 mg every 2 to 4 weeks. Disease exacerbations during tapering of steroids or after completion of therapy occur in up to two-thirds of patients, are more commonly manifested as PMR than ischemic complications, and require a transient increase or resumption in dose followed by further attempts at weaning. There are no clinical predictors for those at risk for relapse. The ESR is an imperfect indicator of disease activity, and must be used in combination with clinical symptoms for assessment of disease and adjustment of therapy. Persistent elevation of ESR despite absence of clinical disease activity may indicate silent large vessel disease (eg, aortitis), or be associated with another condition such as an unrecognized infection masked by steroid use. The utility of steroid-sparing agents remains debatable. There may be a modest benefit from methotrexate as a steroid-sparing agent to lower relapse rates and total cumulative steroid dose, but steroid-associated side effects are not reduced. Infliximab was not effective as a steroid-sparing agent, and only anecdotal reports of utility for this purpose are described for trials of dapsone, adalimumab, leflunomide, hydroxychloroquine, and azathioprine. A clinical trial using the IL-6 receptor blocker tocilizumab is in progress. Low-dose aspirin has been demonstrated to reduce the incidence of cranial ischemic events (particularly anterior ischemic optic neuropathy), and aspirin is known to reduce IFN-γ levels. All patients beginning steroids should be started on bone-protective therapy, and prophylaxis against infection from *Pneumocystis jirovecii* should be considered for those on a daily prednisone dose of 20 mg or higher. As aortic aneurysms occur more frequently in patients with GCA within 10 years of diagnosis, a yearly chest radiograph should be performed, with more sensitive studies such as chest CT reserved for patients with equivocal plain radiographic findings.

Although the life expectancy of patients with GCA is similar to that of the age-matched general population unless severe aortitis is present, morbidity from the disease itself and its therapy may be substantial. Twenty to 50% of patients develop toxicities from corticosteroids. The impact from disease manifestations and the side effects of therapy

cannot be underestimated in older people.

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Chapter 121

Rheumatoid Arthritis and Other Autoimmune Diseases

Raymond Yung

Learning Objectives

- To relate the consequence of aging to the clinical manifestations of rheumatoid arthritis (RA) and other autoimmune diseases.
- To understand the effects of age-associated physiologic changes and comorbidities on the use of common anti-rheumatic disease drugs.
- To identify the use and limitations of current rheumatic disease classification and treatment guidelines in older patients with autoimmune diseases.

Key Clinical Points

1. **Patients with various autoimmune diseases exhibit evidence of accelerated aging.**
2. **Recent rheumatoid arthritis classification criteria focus on early disease diagnosis; their usefulness is untested in older patients with the disease.**
3. **Injectable and oral biologic therapies targeting multiple immune system pathways represent major advances in the treatment of autoimmune diseases, but these therapies are all associated with significant risk of side effects in older patients, particularly those with multiple comorbidities.**
4. **Functional and social assessments are important components in the management of autoimmune diseases in older adults.**
5. **It is important to exclude iatrogenic causes of rheumatic symptoms in older patients, as polypharmacy is a common issue in this age group.**
6. **Paraneoplastic rheumatic syndromes occur in many malignancies prevalent in older patients.**

The past decade has witnessed tremendous strides in our understanding of the pathogenesis and approach to treatment of autoimmune diseases. This is mirrored by a growing knowledge of the many immune system changes in aging, and clinicians' experience in administration of biological therapies in older adults with rheumatic diseases. While the field of rheumatology continues to focus on individual rheumatic illnesses, there is also a greater appreciation of the corresponding risks and side effects of these powerful agents on older patients with multiple comorbid illnesses. This chapter summarizes recent key advances, with specific references to the geriatric population.

RHEUMATOID ARTHRITIS

Definition

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that preferentially affects diarthrodial joints. The American College of Rheumatology (ACR), in collaboration with the European League Against Rheumatism

(EULAR), updated the classification criteria of RA in 2010 (**Table 121-1**). The impetus for updating the original 1987 criteria was the recognition of the importance of early diagnosis and treatment of this disease. The new classification criteria therefore no longer include late sequelae of RA such as rheumatoid nodules or radiographic evidence of bony erosions. The new set of criteria should allow the study and treatment of patients with earlier stages of the disease. It should be noted that the new classification criteria apply to patients with objective evidence of synovitis in at least one joint, and the synovitis is not better explained by another disease such as lupus, psoriatic arthritis, or crystal-associated arthritis. It is also important to understand that the mean age of patients in the nine arthritis cohorts used to develop the new classification criteria ranges from 46 to 58 years. While the criteria set is useful for diagnosing early and active disease in younger patients, its usefulness in detecting community elderly-onset (> 60 years old) rheumatoid arthritis (EORA) has not been established. This is important because the disease presentation in EORA may be distinct from that of young-onset RA (YORA).

TABLE 121-1 THE 2010 AMERICAN COLLEGE OF RHEUMATOLOGY/EUROPEAN LEAGUE AGAINST RHEUMATISM CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS [a]

Patients who (1) have at least 1 joint with definite clinical synovitis, (2) with the synovitis not better explained by another disease. A patient with a score of > 6 is classified as having definite disease.

	Score
A. Joint involvement	
1 large joint	0
1–3 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

[a] *Adapted with permission from Aletaha D, Neogi T, Silman AJ, et al: Arthritis Rheum. 2010;62:2569.*
2010 Rheumatoid Arthritis Classification Criteria: An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheum. 2010;62:2569.

One important change in the 2010 classification criteria for RA is the inclusion of blood circulating anticyclic citrullinated peptide (anti-CCP) antibodies as equal to rheumatoid factor (RF) in its scoring system. Citrullination is a posttranslational modification of protein-bound arginine into the nonstandard amino acid citrulline, and many citrullinated proteins have been found to be expressed in inflamed joints. Anti-CCP antibodies are as sensitive (70%–78%) as, and more specific (88%–96%) than IgM rheumatoid factor (RF) in early and fully established disease. Furthermore, the presence of these antibodies is a marker for erosive disease and may predict the eventual development of RA in patients presenting with undifferentiated arthritis. These antibodies may also be detected in healthy individuals, years before the onset of clinical RA. Anti-CCP antibodies may be helpful in assessing arthritis symptoms in high-risk groups, such as those with a strong family history of RA. Unlike classical RF, the incidence of anti-CCP antibodies does not appear to increase with normal aging, making it a particularly useful marker for this disease in older patient population.

In addition to classification criteria for the diagnosis of RA, the ACR has established criteria for functional status and for determining clinical remission in RA. The usefulness of these classification systems in older patients who often suffer functional disability from concomitant osteoarthritis, soft-tissue rheumatism, and cardiovascular or neurologic diseases is unclear.

Epidemiology

The overall incidence of RA has been declining for a few decades. Interestingly, a long-term study from Mayo Clinic suggests that this may no longer be true. The study examined medical records in Olmsted County, Minnesota between 1995 and 2007, and found a steady incidence of RA in men, and a small rise in the incidence of RA in women. The authors speculated that environmental factors such as increasing cigarette smoking in females, vitamin deficiency, and lower doses of synthetic estrogens in contraceptives are potential factors contributing to the increase in the diagnosis of RA in women.

The disease affects approximately 0.8% of the population in the United States and in many Western developed countries. Lower prevalence rates of 0.2% to 0.3% have been observed in China, Japan, some regions in Greece, and Africa. Southern Europeans may have a milder disease, with less extra-articular complications and less evidence of radiographic damage. Conversely, a much higher prevalence rate (up to 7%) and a more aggressive clinical course have been reported in several American-Indian and Alaska native populations. Gender and age are important factors in RA. Overall, women are affected by the disease two to three times more than men. However, this gender parity disappears in old age. The prevalence of RA increases with age and is commonest in the oldest group studied (often 65 years and older or 70 years and older). Approximately 5% of women older than the age of 55 years are affected by the disease. The incidence of RA also increases with age, with the peak incidence occurring in the sixth to eighth decades (**Figure 121-1**). The reason for the age-associated increase in disease susceptibility is currently unknown.

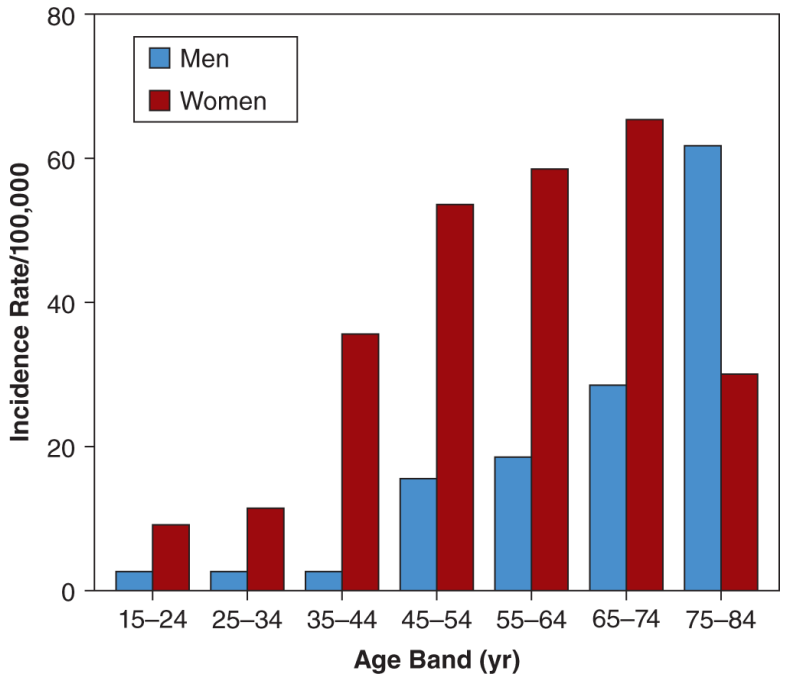


FIGURE 121-1. Age-related incidence of rheumatoid arthritis. (Adapted from Symmons DPM, et al. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis register. *Br J Rheumatol*. 1994;33:735.)

Pathophysiology

There has been marked progress in our understanding of the pathogenesis of RA. In the future, it is very possible that we will see subclassification of RA and other autoimmune diseases based on the individual's genetic and molecular signatures. This will in turn inform clinicians of the most appropriate treatment(s) in the brave new world of individualized medicine. RA begins as a disease of the synovium. Early on in the disease the synovium becomes markedly hyperplastic and edematous, accompanied by prominent new blood vessel proliferation. Left unchecked, this is followed by the activation and recruitment of T cells into the RA joint, which set into motion a complex cascade of

inflammatory responses (**Figure 121-2**). These responses result in further accumulation of inflammatory cells, panus formation, localized osteoporosis, bony erosions, and destruction of periarticular structures, which are characteristic of this disease. Rheumatoid synovitis is accompanied by the accumulation of inflammatory joint fluid with white cell count typically in the range of 2000 to 20,000 cells/mL. Soluble proteins that have been implicated in the inflammatory process include a number of proinflammatory cytokines (interleukin [IL]-1, IL-6, IL-13, IL-15, and tumor necrosis factor [TNF]), metalloproteinases (stromelysin, collagenases, and gelatinases), transforming growth factor-β, granulocyte colony-stimulating factor, and activated complement components.

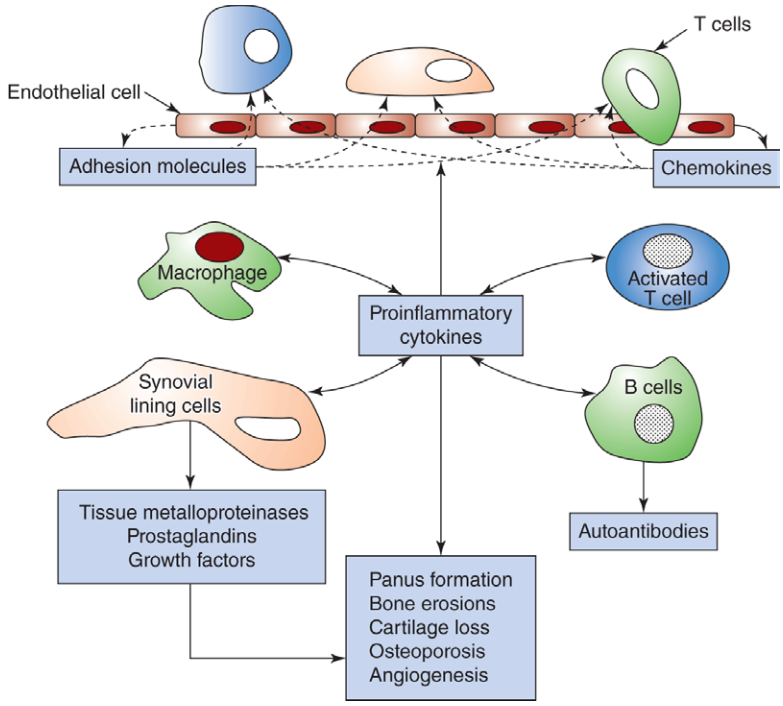


FIGURE 121-2. The inflammatory cascade in rheumatoid arthritis.

Genetic factors play an important role in RA susceptibility. The concordance rate for monozygotic twins is between 12% and 15%, approximately three times that of dizygotic pairs and much higher than the 1% background prevalence rate of the general population. The fact that most monozygotic twins are discordant for RA also highlights the importance of environmental factors. The association between RA and human leukocyte antigen (HLA) has been refined to alleles coding for a "shared" epitope (the sequences QRRAA or QKRAA) on the HLA-DRB1 genes. The presence of the DRB1*04 (DR4) allele is a marker for increased susceptibility and severe disease. Population differences in the prevalence of the "shared epitope" may help to explain in part the geographic variation in the prevalence of RA. Genome-wide association studies (GWAS) have identified over 35 genetic susceptibility loci, including the HLA-DRB1 allele. Interestingly, the GWAS association with DRB1 allele is only true for RA patient who are anti-CCP positive. Other genetic associations include genetic regions coding for peptidyl arginine deiminase, type IV (PADI4) which converts arginine to citrulline, protein tyrosine phosphatase (PTP) nonreceptor 22 (PTPN22) which inhibits T cell signaling via the Csk kinase pathway, interferon regulatory factor 5 (IRF-5), which regulates the transcription of genes for inflammatory cytokines, C-C chemokine receptor 6 (CCR6), and genes (CD40, TNFAIP3) that regulate the TNF signaling pathways. Findings in GWAS may also help explain racial and geographical differences in RA susceptibility. Importantly, GWAS have identified new and exciting pharmaceutical targets for this disease.

An infectious etiology for RA has been postulated for more than half a century. The onset of RA can be heralded by polyarthralgias, fever, and malaise that are indistinguishable from an acute infection. The joints are known targets for diverse microorganisms from gonococci to *Borrelia burgdorferi* and *Mycobacterium tuberculosis*. Acute and chronic "reactive" arthritis can follow specific gastrointestinal (GI) or genital urinary infection. A transient RA-like illness can be seen in viral infections including parvovirus B19, Epstein-Barr virus, and human T-lymphotropic virus type 1.

Tantalizing evidence of a potential pathogenic role for micro-organisms in RA includes the following: (1) Retroviral-like particles have been observed in RA synovial fluid. (2) Viral or bacterial superantigen can reawaken a

latent or subclinical disease in animal models of inflammatory arthritis. (3) Heat shock proteins (viral and cellular) can act as autoantigens. Both the DnaJ class of bacterial heat shock protein and the gp110 capsid protein of Epstein-Barr virus have the QKRAA "shared epitope" amino acid sequence. Accumulating evidence suggests that "dysbiosis" of the oral and intestinal microbiomes may be important in RA pathogenesis. For example, *Porphyromonas gingivalis*, which causes periodontal diseases and contains the citrullination enzyme peptidyl-arginine deiminase, has been linked to RA autoantibody formation and joint inflammation. A 2013 study examined the genome sequence of bacteria in stool of RA and control subjects, and found new-onset untreated RA to be strongly correlated with the presence of *Prevotella copri*. Gnotobiotic animals (germ-free mice colonized with defined microbiota) have been used to define the role of microorganisms in the development of inflammatory arthritis. It is anticipated that new research will improve our understanding of which microbiota is protective or, in some cases, arthritogenic.

It is possible that transient exposure of the joints to microorganism protein with homology to normal antigen could attract lymphocytes to the synovium. This, in turn, may set up an autoimmune response through a molecular mimicry mechanism without requiring the presence of the inciting organism (the "hit-and-run" theory). Some investigators have shown that RA synovial cells may have defective apoptosis and a transformed phenotype. This opens up the possibility that environmental agents, including viruses, may transform synovial or lymphoid cells to cause inflammation and tissue destruction without requiring the presence of the inciting agent.

Gender differences in reproductive hormones may explain the high female prevalence in RA. However, since the peak incidence of RA in women is in their 50s, high levels of female sex hormones may play a modifying, but not necessary, role in the pathogenesis of this disease.

The linkage of RA to specific major histocompatibility complex alleles, the abundance of specific T-cell subsets in synovial tissue and fluid, and other evidence from animal models of inflammatory arthritis all point to a central role of T lymphocytes in the immunopathogenesis of this disease. RA had been considered to be primarily a Th (T helper) 1-mediated disease based on the cytokine and chemokine receptor profile of T cells in synovial joints. However, the related Th 17 (IL-23/IL-17) pathway may be even more important in driving disease chronicity and joint destruction. Although it is tempting to postulate that RA-associated DRB1 epitope triggers disease by presenting an arthrogenic peptide to T cells, extensive search of unique peptides that are displayed selectively by RA-associated HLA molecules has so far been unsuccessful. Costimulatory molecules, including CD28 and CD60, may play a role in activating T cells in RA joints. Dysfunctional T and non-T cell immune signaling has been increasingly recognized to be important in RA pathogenesis. This has resulted in the successful development of tofacitinib, a janus kinase inhibitor, as a novel therapy for RA.

A central role of T cells in RA pathogenesis is well established, whereas the precise contribution of B cells is less well defined. The recent success of B cell depletion therapy has refocused attention on the role of these immune cells beyond autoantibody production, including plasma cells differentiation, and their immunomodulating effects on proinflammatory cytokines such as IL-6 and IL-17.

Aging effects The reason for the age-associated increase in RA susceptibility is unclear. The traditional view that aging is associated with a "decline" in immune response does not explain the high incidence and severe onset of this autoimmune disease that is commonly seen in older adults. Decline in sex hormone production also cannot account for the high incidence of RA in postmenopausal females. Age-related decline in thymic function has been suggested as a possible mechanism in autoimmunity in aging. While features of accelerated immune system aging are prevalent in RA patients, it is unclear if these represent primary or secondary events. Unlike in their younger counterparts, EORA occurs with equal frequency in males and females. Again, the rising incidence of RA in postmenopausal women suggests that reproductive hormones may influence the disease manifestation. However, they are unlikely to play a major pathogenic role in older adult population.

Animal studies suggest that aging is accompanied by a shift to a dominant Th2 cytokine profile. However, such changes cannot explain the high incidence of RA in older patients. Studies on the effect of age on the adenovirus vectors model of inflammatory arthritis have yielded conflicting results, with some strains showing more chronic and destructive arthritis in older female animals. The enhanced production of proinflammatory cytokines in aging, including IL-6, TNF-α and IL-1, may contribute to the clinical features of EORA. The recruitment and retention of T cells in the RA synovial joint are complex processes determined by the interaction of leukocyte adhesion molecules and chemokine receptors interacting with their respective ligands expressed by synovial and vascular endothelial cells. T cells from aged animals may express high levels of selective chemokine receptors that are important in the recruitment of T cells to RA joints. These lines of research may eventually provide the explanation for the increased susceptibility and severity of RA in older patients. Aging-associated obesity is an important source of chronic low-

grade inflammation in older patients, which in turn may play a role in age-related diseases such as coronary artery disease, metabolic syndrome, Alzheimer disease, and cancer.

Presentation

Whether EORA is a different disease from YORA is controversial. The clinical studies that address the issue were mostly descriptive or cross-sectional studies done in the 1950s and 1960s that have significant methodologic problems. The older definition of RA used in these studies also allowed terms such as "classical," "definite," and "probable" RA, which are no longer used today. As mentioned before, the most current RA classification criteria have not been validated in older patients.

Table 121-2 summarizes the features of EORA. In general, patients with EORA have a more equal gender distribution. The large joints, including the shoulder joint, are more often involved at presentation in EORA. Whether this is a result of concomitant rotator cuff disease that is prevalent in this age group is unclear. Symptoms in the proximal girdles have led to the belief that EORA may present with a polymyalgia rheumatica-like illness. Erythrocyte sedimentation rate (ESR) normally increases with age, especially in females. Elevated ESR is also more common in EORA. The prevalence of RF similarly increases after the age of 60 years, reaching 30% by the age of 90 years. Earlier reports suggest a lower frequency of RF in EORA than YORA. However, this has not been confirmed in more recent studies. As in younger patients, patients with EORA who are seropositive for RF have more severe clinical disease, more bony erosions on x-ray, worse functional outcome, and increased mortality. Whether patients with EORA who are seropositive have worse prognosis than do their younger counterparts is unclear. It is possible that the poor prognosis of EORA reported in some studies reflects the greater number of comorbid conditions that are present in older patients.

TABLE 121-2 CLINICAL FEATURES OF ELDERLY ONSET RHEUMATOID ARTHRITIS

Age of onset > 60 years
Male:female ~1:1
Acute presentation
Oligoarticular (2–6 joints) disease
Involvement of large and proximal joints
Systemic complaints, eg, weight loss
Absence of rheumatoid nodules
Sicca symptoms common
Laboratory: high erythrocyte sedimentation rate; often negative rheumatoid factor

"Benign polyarthritis of the elderly person" occurs in up to a third of patients with EORA. They have a more explosive disease onset associated with systemic features such as fever and night sweats. The clinical features have led some to describe the disease as "infectious like." The disease is called benign because its general prognosis is good, with most people going into remission within 1 year with or without treatment. Within this group can be included a peculiar syndrome unique to older patients called the RS_3PE (remitting, seronegative, and symmetric synovitis with pitting edema) syndrome. This typically affects older adult men (2–3:1 male:female ratio) and is characterized by acute onset of symmetric polyarthritis/tenosynovitis with pitting edema involving both upper and lower extremities. As the name implies, these patients generally have negative RF and antinuclear antibody (ANA). They often have high ESR and respond to low-dose prednisone. The association with HLA-B7 has been reported inconsistently. RS_3PE may occasionally be associated with other rheumatic diseases, including polymyalgia rheumatica, spondyloarthropathies, psoriatic arthritis, RA, and sarcoid, and, rarely, malignancies.

Evaluation

The assessment of RA in older adults is different from that of the younger age group. The nonspecific symptoms and signs of RA are prevalent in older patients. Rheumatic diseases that can mimic EORA, such as polymyalgia rheumatica, osteoarthritis, and crystal-induced arthritis, are prevalent in the older patient population. Anti-CCP antibody measurement may be useful in distinguishing EORA from polymyalgia rheumatica. In one small study, 65%

of patients with EORA were anti-CCP antibody positive, but none of the patients with PMR or aged healthy subjects had the antibodies. Arthritis associated with malignancy can be misdiagnosed as RA before the correct diagnosis is made months or years later. Other differential diagnoses of RA in older population include inflammatory (erosive) osteoarthritis, late-onset spondyloarthropathy, endocrinopathy (eg, hypothyroidism, hyperparathyroidism, and diabetic cheiroarthropathy), amyloidosis, and the edematous phase of scleroderma. Conditions such as sarcoidosis, adult Still disease, hemochromatosis, and glycogen storage diseases can mimic RA but are unlikely to present for the first time so late in life. In addition to the above considerations, the initial evaluation of an older patient with RA should include a careful assessment of the patient's living condition, social support, and cognitive and functional status. Many older patients have the misconception that there is no effective treatment for arthritis, and they should accept their physical suffering as part of normal aging. Older adults are often embarrassed about their arthritis pain. They may minimize their symptoms by using terms such as "aching" and "stiff" instead of pain. Unfortunately, many clinicians also do not take their symptoms seriously, resulting in the patients frequently feeling that their care resembles "a lick and a promise." Because pain is, by far, the commonest presenting symptom of RA, pain assessment should be an integral part of the patient's evaluation at presentation and in subsequent office visits. This can be difficult in olderly patient who has significant cognitive or verbal impairment. Information from caregivers, nonverbal pain behavior, physical evidence of active joint inflammation, and decline in function are important clues that more aggressive therapy may be necessary.

The ACR classification system for assessing the functional status of patients with RA is shown in **Table 121-3**. However, use of this classification for an older patient may be difficult because of functional disability from other coexisting diseases. This quick assessment tool is useful for describing the global functional status and allows patients to be grouped for studies. Patients with RA with the worst (class IV) functional status were reported to have extremely poor prognosis, with survival similar to patients with multiple vessel coronary artery disease and stage IV Hodgkin lymphoma. Many clinicians now feel that the prognosis for RA has improved with the advent of better therapeutic regimens for RA in the past two decades. Whether this translates into prolonged survival remains to be determined. Concomitant medical conditions affecting the patient's hearing, eyesight, continence, and balance need to be addressed to optimize functional ability and to prevent falls. Current and past medical histories are important elements of the initial evaluation. This information is needed for the selection of specific treatment (see "Management" section). In contrast, family history is not as helpful in assessing older patients with RA.

TABLE 121-3 AMERICAN COLLEGE OF RHEUMATOLOGY 1991 REVISED CRITERIA FOR THE CLASSIFICATION OF GLOBAL FUNCTIONAL STATUS IN RHEUMATOID ARTHRITIS

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

Adapted from Hochberg MC, Cahne RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum. 1992;25:498–502.

In addition to excluding diseases mentioned above, a new patient suspected of having RA should be tested for the presence of anemia, cytopenia, liver or renal dysfunction, RF, anti-CCP, and elevated ESR. The presence of extremely high RF should prompt the clinician to consider the possible diagnosis of cryoglobulinemia. Some patients have negative RF but positive ANA. These patients tend to have more severe disease, similar to the patients with positive RF. A workup for secondary Sjögren syndrome should be done in patients with concurrent sicca symptoms (dry eye and dry mouth). In general, ESR is a better indicator of disease activity than changes in the titer of RF. For some patients C-reactive protein level may more closely parallel their clinical course than ESR. Anti-CCP titer is not useful in following RA disease activity, although patients with reduced anti-CCP antibodies may have less joint damage in the long run. Antimutated citrullinated vimentin (MCV) antibodies have been touted as potentially new biomarkers for RA; early studies suggest the test could be a better predictor of aggressive disease and bone erosion than the anti-CCP test. Age does not appear to impact anti-MCV antibody titer, although this has not been demonstrated to be true in olderly RA population. A multi-biomarker blood test of 12 proteins, Vectra DA, for determining RA disease activity has been approved by the US FDA. The test has good correlation with traditional clinical assessment of RA disease activity. The test is intended to complement, and not replace, sound clinical judgment. The test could be a useful

objective tool in older RA patients who are unable to provide reliable feedback to the clinician because of impaired cognitive function or other comorbidities.

Radiographic joint examination is an integral part of the evaluation of patients with RA. Older patients with RA for more than 10 years are at particular risk of cervical spine disease and atlantoaxial joint instability. This is an important consideration before a patient is submitted to a surgical procedure, as overextension of the cervical spine during intubation may compromise the brainstem or spinal cord. Early x-ray changes include soft-tissue swelling and regional osteoporosis around the joint. Typical erosions in hands and feet involve the juxta-articular "bare areas" of bone not covered with cartilage (**Figure 121-3**). Isolated erosions in the first and second metacarpophalangeal joints may prompt the clinician to search for occult calcium pyrophosphate depositive disease, hyperparathyroidism, or hemochromatosis. Erosions are less common in the knee and hip joints. At these sites, RA typically causes cartilage loss and joint-space narrowing. Joint-space narrowing occurring predominantly in the lateral compartment of the knee and diffusely in the hip without bony proliferation is helpful for distinguishing RA from osteoarthritis. To assess joint-space narrowing of the knees, clinicians should request semiflexed weight-bearing films.

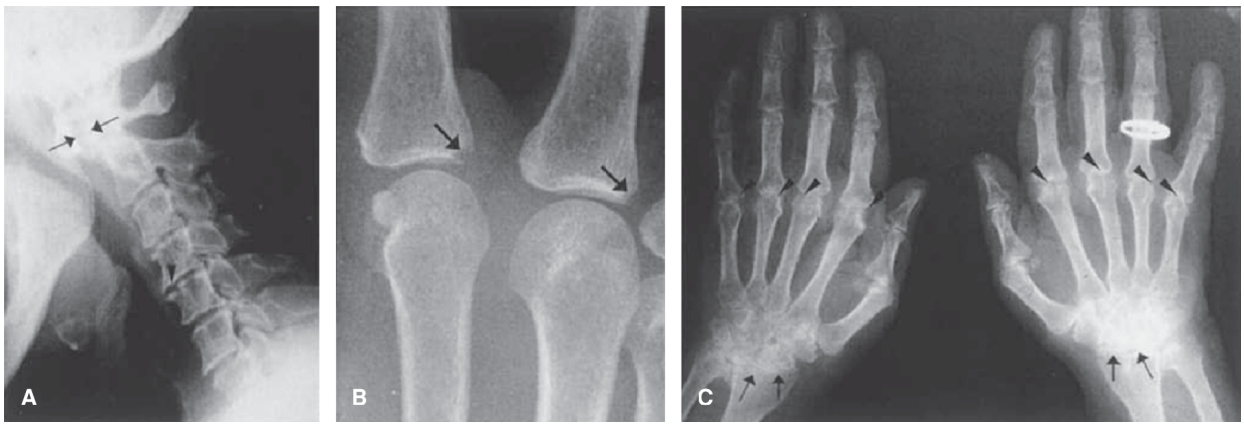


FIGURE 121-3. Radiographic changes of rheumatoid arthritis. **(A)** An x-ray of the cervical spine in the flexed position showing severe atlantoaxial joint subluxation in a patient with chronic rheumatoid arthritis, with *arrows* highlighting the abnormal distance between the posterior surface of the anterior arch of the atlas and the anterior surface of the odontoid process. *Arrowhead* points to the erosion on the surface of C5. **(B)** Early erosive changes in the metacarpal phalangeal joints affecting the "bare area" of the bone not protected by cartilage. **(C)** Bilateral hand x-ray with advanced rheumatoid arthritis. Some of the features include juxta-articular osteoporosis, collapse of the carpal bones, radial deviation of the radiocarpal joint of the wrist (*arrows*), and erosion and destruction of metacarpal phalangeal joints (*arrowheads*). Note also the symmetric nature of the disease. (Courtesy of Curtis Hayes, MD, University of Michigan.)

Because of the limitation of clinical examination in detecting subtle signs of inflammation, peripheral joint ultrasound and magnetic resonance imaging have been increasingly used for detecting early or mild synovitis. The majority of patients with treated disease and considered by their physicians to be in remission continue to have evidence of active synovitis in advanced imaging such as ultrasound and magnetic resonance imaging. The unanswered question is whether more aggressive treatments of patient with clinically inactive disease but imaging evidence of ongoing synovitis affect patient outcomes such as overtreatment (and drug side effects), and long-term disability.

Older patients with RA have additional facets that need to be taken into consideration, such as a more limited lifespan and greater infection risk with immunosuppression. Although embraced by many rheumatologists, the utility of these sensitive imaging modalities in clinical practice remains incompletely defined. The American College of Rheumatology "Choosing Wisely" recommends that MRI of the peripheral joints should not be used to routinely monitor inflammatory arthritis. The American College of Rheumatology Musculoskeletal Ultrasound Task Force 2010 report recognized a potentially important role of the imaging modality in rheumatology practice, but also acknowledged a lack of cost-effectiveness data.

There is no evidence that patients with EORA are more likely to develop extra-articular disease, as compared to those with YORA. However, older patients may be disproportionately affected because extra-articular manifestations are more common in chronic RA. High titer of RF is a risk factor for extra-articular RA, especially in male patients. Rheumatoid nodules are the most characteristic extra-articular manifestation of RA and are present in up to 40% of seropositive white patients. These are most commonly found in areas of pressure such as the elbows, heels, and sacrum. Their presence does not correlate with disease activity and may increase in number during methotrexate therapy when synovitis is improving. Rheumatoid vasculitis affects vessels of all sizes. This complication may present as cutaneous vasculitis, mononeuritis multiplex, nail fold infarcts, or deep "punched-out" ulcers at atypical sites that

fail to respond to conventional therapy. Pleuritis and pericarditis are found in 20% to 30% of patients with RA and do not usually cause any symptoms. Other respiratory complications of RA include pulmonary granuloma (often in the upper lobes), Caplan syndrome, fibrosing alveolitis, and bronchiolitis obliterans. Felty syndrome (RA with splenomegaly and neutropenia) typically occurs in white patients with long-standing, chronic erosive RA. These patients are at increased risk of developing lymphoproliferative malignancies. Thrombocytopenia may occur, in part, because of splenic sequestration. Mild-to-moderate normochromic, normocytic anemia is extremely common in patients with chronic RA. Iatrogenic causes (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] and methotrexate) of anemia need to be excluded in all patients with RA who have anemia.

Management

A number of treatment concepts and standards have emerged in RA clinical management. There is increasing recognition of the benefits of early and aggressive therapies in improving the long-term outcomes of this disease. Outdated treatment goals have focused on improving patient symptoms by 25% or 50%. The concept of "treat-to-target" has long been embraced by clinicians treating diseases such as hypertension, hyperlipidemia, and diabetes. A similar "treat-to-target" approach has gained wide acceptance in RA management, utilizing composite disease activity indexes that have traditionally been confined to research, such as the disease activity score in 28 joints (DAS28), or the clinical disease activity index (CDAI). The advent of biological therapies has allowed clinicians to aim for disease remission in many RA patients. Nevertheless, there are unanswered questions about this aggressive management approach. These include a lack of consensus as to what disease measurement tool should be used, and frequency of monitoring. Important issues which need to be addressed in future research include treatment burden (including cost and side effects), and benefits in remaining life (prognostication) in older patients with multi-comorbid diseases.

Nonpharmacologic therapies Successful management of RA involves patient participation in his/her care. In addition, family, social, and psychological supports are particularly critical in maintaining the older RA patient's independence. Older patients diagnosed with the disease may be particularly fearful of what it means to their independence or may become depressed. Establishing a good rapport, gaining the trust of the patient and the family, providing information about the nature of the disease, and setting realistic goals are all important elements of the initial management of RA. Many patients and their relatives also find it helpful to seek out support groups in their local area. Increasingly, older patients and their families are turning to the Internet, health magazines, and other nontraditional sources for information about treatment options, including over-the-counter complementary therapies. There is a need for health care professionals to become knowledgeable in web and social media medical resources. Unexpected side effects of over-the-counter medications are increasingly being recognized. The latest information is often not available in traditional textbooks. Directing the patients to reputable websites such as that offered by the National Institute on Aging, the National Center for Complementary and Integrative Health, the American College of Rheumatology, or the Arthritis Foundation can be useful for more up-to-date information.

Nonpharmacologic therapies are crucial components of the total care of the patient with RA, which should be emphasized throughout the treatment course. In addition to their inherent usefulness, participation in these treatment modalities often provides the patients and their families with a sense of control over their chronic illness. The interprofessional team approach that typifies geriatric medicine is eminently suitable for treating older patients with chronic arthritis. Physical and occupational therapy should be offered to every patient with RA, including those with mild and early disease. Education about rest/activity, use of cold/heat, massage, adaptive devices (to improve function and to prevent/correct joint deformity) are important. Performing exercises to strengthen muscles and ligaments for joint protection, gait training, and fall prevention can make a big difference in the life of patients with RA. Community-based exercise programs such as PACE (Patients with Arthritis Can Exercise, the Arthritis Foundation) are a good resource for those who are able to participate. Psychological counseling and support groups are often helpful, especially to those who are socially isolated because of their arthritis. Depression is increasingly recognized as a common problem in older patients and in those with chronic illness. Adequate treatment will help break the vicious cycle of pain, depression, and disability. Although nonpharmacologic therapies do not affect the progression of RA joint destruction, they can improve the patient's quality of life and help to reduce the requirement for pain medications that have significant potential for side effects in this vulnerable population.

Pharmacologic therapies There has been an exciting explosion of new drugs available for the treatment of RA. Pharmaceutical companies have increasingly included the geriatric population in pre- and postmarketing clinical trials. Additionally, there are an increasing number of rheumatology research consortia and registries that have provided "real

world" data on the benefits and side effects of new treatments on older RA patients. Knowing that these agents may be efficacious in older patients provides some reassurance to clinicians. However, it is important to remember that subjects participating in these studies rarely mirror the patients geriatricians see in their clinic who have multiple comorbidities and who already suffer from polypharmacy. The costs of the newer agents may be out of reach for patients who do not have prescription coverage. Because of the complexity of modern treatment regimens, coupled with the need to monitor many potentially serious side effects, drug therapy for RA should ideally be instituted in consultation with a rheumatologist. Involvement of physicians experienced in the use of immunosuppressive therapies (eg, hematologists and oncologists, or a gastroenterologist in the case of infliximab) will be helpful in patients living in isolated communities where there may not be a local rheumatologist.

The gradualism of the "pyramid approach" to RA treatment in the 1980s has been replaced with the widespread belief that rheumatoid inflammation should be suppressed as completely and as soon as possible once the diagnosis is confirmed. This change in philosophy is, in part, a result of the recognition that joint damage occurs much sooner than was previously believed. Results of well-designed clinical trials have persuaded many that this new standard is attainable with more aggressive drug regimens. In the 2012 ACR *Recommendations for the Use of Disease-Modifying Anti-rheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis,* it is suggested that the target should be to achieve remission or low disease activities. Newly diagnosed patients with low disease activity, or with moderate disease activities and without poor prognostic features (functional limitation, extra-articular disease, positive rheumatoid factor/anti-CCP antibodies, bony erosions), should be treated with disease-modifying antirheumatic drug (DMARD) monotherapy. RA patients with moderate disease activities with features of poor prognosis should immediately receive combination (double or triple) DMARD therapies. Patients with highly active disease but who lack poor prognostic features can be first treated with DMARD mono- or combination therapies. Patients with high disease activities and poor prognostic features could be treated with either combination DMARD therapies or anti-TNF therapy (with or without methotrexate). As new data emerge and new therapies become available, it is anticipated that updated treatment guidelines will be available much more frequently than in the past.

Although NSAIDs are useful adjunct therapies for RA, many geriatricians are reluctant to prescribe this class of medication because of concern that older patients are vulnerable to the potential serious toxicity that can occur in almost every major organ system in the body. NSAID use is associated with a 5- and 3.5-fold increased risk of serious upper GI tract disease in women and men, respectively. Age alone is a risk factor for upper GI bleeding (relative risk of 4.5 in 70–80 years age group, and 9.2 in those older than age 80 years). Because of the high background rate of upper GI events in older patients, the relative risk for GI bleeding only increases modestly in older patients on an NSAID. Not surprisingly, older patients with history of GI bleeding are at the greatest risk of serious GI complications when they are placed on an NSAID. The concurrent use of glucocorticoids further increases the risk of GI bleeding.

The use of selective cyclooxygenase-2 (COX-2) inhibitors decreased substantially when it was discovered that some of these agents are associated with an increased incidence of cardiac events in large population studies. In addition, COX-2 inhibitors share similar renal toxicity, including hypertension, peripheral edema, and rising serum creatinine as traditional NSAIDs. Chronic use of these agents should, therefore, be avoided when possible. NSAID-induced renal complications are more likely to occur in patients who are on concurrent diuretics or angiotensin-converting enzyme inhibitors. One study showed that prolonged dosing of ibuprofen blocked the platelet inhibition effects of aspirin. Although other NSAIDs tested so far do not appear to have the same problem, this raises the concern that the aspirin/ibuprofen combination may not be ideal for patients having RA with cardiovascular risk factors. Concurrent use of low-dose (≤ 325 mg/day) aspirin increases the already high risk for GI events in older patients taking traditional NSAIDs and may negate most of the GI-sparing effect of COX-2 inhibitors. At present, it appears that most at-risk older patients with RA requiring a traditional NSAID or a COX-2 selective agent plus aspirin should receive GI cytoprotection. To maximize cardioprotective effects of aspirin, patients should take their aspirin first thing in the morning, then wait at least 1 hour before using their NSAID.

Clinicians continue to debate the role of glucocorticoids in the management of RA. There is general consensus that high-dose chronic oral steroids should not be used in RA. Low-dose glucocorticoid is effective for short-term symptom control in patients with active RA. There are also intriguing data showing that prednisone in early disease may be "disease modifying." Unfortunately, older patients commonly develop significant side effects, but become functionally dependent on the drug. The lowest dose, and, if possible, alternate-day dosing should be prescribed. Assessment, prophylaxis, and treatment of osteoporosis, cardiovascular risk factors, diabetes, and GI complications are important. Judicious use of intra-articular steroid injections may provide local (and systemic) symptom relief and may be safer than oral glucocorticoids in older patients with poorly controlled diabetes, severe osteoporosis, and congestive heart failure. Older RA patients in Canada (mean age 74 years) taking as little as 5 mg prednisolone had a 30%, 46%,

or 100% increased risk of serious infection when used continuously for the prior 3 months, 6 months, or 3 years, respectively, compared to nonsteroid users. Overall, it is important to use the lowest dose of corticosteroids in this population, and to discontinue the drug when it is feasible. A time-release prednisone formulation has been approved by the US FDA, and the drug can be taken at night to improve morning symptoms in RA patients.

Antimalarials including hydroxychloroquine and chloroquine are useful in mild cases of RA and are most often prescribed as part of a combination regimen. Hydroxychloroquine is often preferred over chloroquine because it has a lower incidence of ocular complications. Approximately 50% of hydroxychloroquine is protein bound in the plasma, a property that is important in older patients with low serum albumin and who are taking other highly protein-bound drugs. The mechanism of drug action is uncertain but is postulated to include changes in intracellular pH, which, in turn, affect antigen presentation by immune cells. An added benefit in patients with RA who are at increased risk of coronary heart disease is the drug's favorable effect on serum cholesterol level. There are also intriguing data suggesting that patients with RA on hydroxychloroquine have up to 77% less risk of developing diabetes. The major side effect of hydroxychloroquine and chloroquine is retinal (macular) toxicity with the classical "bull's-eye" lesion, or "flying saucer" sign due to foveal thinning. The drug can also cause reversible corneal deposits. Older patients with macular degeneration or inoperable dense cataract are not candidates for this drug. A large study from Kaiser Permanente of North California has raised the concern that the risk of irreversible retinopathy is much greater than previously believed. By using spectral domain optical coherence tomography (OCT), the study identified retinal thinning and photoreceptor damage or visual field loss in 7.5% if patients on the drug. The risk is both dose and duration related, and reaches a prevalence of almost 20% in patients exposed to the medication for 20 years. While there is no "safe" daily dosage of the drug, less than 2% of patients taking a daily dose of 5.0 mg/kg (real body weight) of the drug can be expected to develop retinal toxicity in the first 10 years of treatment. Patients with stage 3 chronic kidney disease with an estimated glomerular filtration rate below 60 mL/min (a common scenario in older patients with comorbid diseases), have a four- to fivefold increase in the risk of developing hydroxycholorquine retinopathy. Many practitioners are now recommending OCT as the preferred method to monitor for early signs of hydroxycholoroquine eye toxicity.

Sulfasalazine is only occasionally used as monotherapy in the United States, although the drug may slow the progression of radiographic damage in RA. Its mechanism of immunosuppression is unclear but may include reducing immunoglobulin (Ig) levels, suppressed T- and B-cell proliferative response, and cytokine inhibition. Cytopenias (particularly leukopenia), GI symptoms (nausea and vomiting, and dyspepsia), and skin rashes are the commonest side effects. In addition to monitoring for hematologic toxicity, some experts recommend that liver enzyme levels should be tested regularly as well.

Methotrexate, an analog of folic acid, is the most commonly prescribed DMARD for RA in the United States. More than 50% of patients on methotrexate continue the drug beyond 3 years, longer than any other DMARD. The drug and its metabolites are potent inhibitors of dihydrofolic acid reductase and other distal enzymes in the folic acid metabolic pathway. The immunosuppressive effects may be partly a result of folate-dependent inhibition of lymphocyte proliferation. Methotrexate has also been reported to reduce the production of leukotriene B_4 and to directly alter phospholipase A_2 activity. Subcutaneous methotrexate is superior to oral therapy at a dosage above 15 to 20 mg/week. In many cases, split dose (over 24 hours) oral therapy can improve the drug's bioavailability.

Methotrexate can boost the therapeutic efficacy of selected biologics including anti-TNF therapies and rituximab. Common side effects include cytopenias (particularly anemia), liver toxicity (fibrosis and cirrhosis), hypersensitivity pneumonitis, infections, mucosal ulceration, and alopecia. Older patients are particularly susceptible to these side effects because methotrexate is excreted primarily by the kidneys and renal impairment is common in this group. Great caution and dose adjustment are, therefore, needed when using the drug to treat older patients with RA and those with a history of hepatitis. A 2014 study of older veterans (mean age 71 years) found a 6% incidence of moderate increase ($\geq$ 1.5 times upper limit of normal) in liver function after a mean follow-up of 7 months. Risk factors of drug-induced liver toxicity include obesity, premethotrexate transaminase elevations, use of biologic agents, and lack of folic acid supplementation. Folic acid (1–3 mg/day) or folinic acid (leucovorin, 2.5–5 mg given 24 hours after methotrexate) supplementation reduces the incidence of many methotrexate side effects and should be used routinely. In selected patients, measuring methotrexate polyglutamate levels may help the provider to adjust methotrexate dosage, but it should not be done for routine monitoring.

A number of other DMARDs are occasionally used as monotherapy for RA. Clinicians are often reluctant to use them because of their limited efficacy, high dropout rate, and potential serious side effects, especially in older patients. These include cyclosporine, azathioprine, gold (no longer available in the United States), and penicillamine. Staphylococcal protein A immunoabsorption column may be useful in a small subset of patients with RA who have

refractory disease. However, difficulty in administering treatment and high cost has prevented the treatment from being used widely.

Most combination therapies involve adding one or more DMARD to methotrexate. The triple therapy of methotrexate, hydroxychloroquine, and sulfasalazine is more efficacious than methotrexate alone. Interestingly, although methotrexate plus hydroxychloroquine is the commonest combination used in this country, its efficacy, as compared to methotrexate, has not been examined systematically. The main advantage of using combination therapy over the anticytokine treatments is cost. Many European countries and US insurance companies continue to require patients to have a trial of methotrexate before receiving biologic therapies. The argument that biologics may be cost effective because they reduce work disability may not apply to older, retired patients. However, whether older patients tolerate combination therapies as well as monotherapy is uncertain. As many as 60% of patients receiving both methotrexate and leflunomide develop elevated liver enzyme levels.

Biological Response Modifiers

The number of biological response modifiers available to clinicians has expanded considerably, and many more are in the late stages of clinical development. The success of these agents, which target soluble inflammatory proteins, T cells, and B cells, suggests that targeting the downstream mediators may be sufficient to modulate the disease. A critical issue is to determine which patient will best benefit from which class of biologic agent. While it is unlikely that primary-care providers will prescribe biologics for their patients with RA, understanding their use and potential side effects will be helpful in the day-to-day care of these patients. This portion of the chapter includes a general description of the currently available drugs and will emphasize the safety issues associated with these drugs, as these issues have great relevance to geriatrics health care providers.

An important advantage of these agents is rapid onset of action, with many patients experiencing improvement within a few weeks of treatment. The author has also found in his own practice that biologics are more efficacious in reducing specific symptoms such as fatigue in RA patients, compared to traditional DMARDs. These agents appear to be effective in patients with both seropositive and seronegative rheumatoid. The decision as to which biological modifier to use will depend on individual patient characteristics such as comorbidity, patient preferences such as administration schedule, physician experience, and insurance coverage owing to the high cost of these drugs.

Leflunomide is an inhibitor of pyrimidine synthesis and has been available for the treatment of RA in the United States since 1998. The oral medication is rapidly metabolized to an active metabolite that is partially excreted in the bile and reabsorbed by the enterohepatic circulation. The plasma half-life of leflunomide is approximately 14 days. However, the excretion can be accelerated by oral cholestyramine. In clinical studies, leflunomide has been shown to be equal to methotrexate in efficacy. It is also the first drug to receive an FDA-approved label indication to retard structural damage in RA as evidenced by x-ray erosions and joint-space narrowing. The most common side effects include diarrhea (20%), reversible alopecia (10%), and elevated liver function enzymes. The use of leflunomide has decreased over the years as more biologic agents have become available.

There are currently five TNF antagonists in clinical use. *Etanercept* is a recombinant soluble p75 TNF receptor fused to the Fc portion of human IgG_1. The drug is usually given by subcutaneous injection once or twice a week, with or without concomitant methotrexate. *Infliximab* is a chimeric (mouse-human) anti-TNF monoclonal antibody that is given to patients intravenously every 4 to 8 weeks, usually in combination with methotrexate. *Adalimumab*, a fully human anti-TNF antibody, is given subcutaneously every 2 weeks, usually with methotrexate. *Certolizumab pegol* is a monoclonal antibody with an extended half-life due to PEGylation, and is typically administered subcutaneously every 4 weeks during maintenance dosing. The drug can be administered alone, but is more efficacious if the patient is also taking methotrexate. *Golimumab*, an intravenous TNF inhibitor, is usually given every 8 weeks, and is used in combination with methotrexate. Around 40% of RA patients do not have an adequate response to an anti-TNF drug, and patients who have “failed” one anti-TNF agent may still benefit from a trial of a different anti-TNF drug.

Anakinra is a recombinant human form of IL-1 receptor antagonist (IL-1ra) that blocks the binding of IL-1α and β to the IL-1 receptor. The drug is administered daily by subcutaneous injection with or without methotrexate. Anakinra has not been as popular as the anti-TNF agents among rheumatologists in part because of the high incidence of local skin injection site reactions and the requirement of daily injection. Furthermore, many have found the drug to be less efficacious than the anti-TNF agents, although there is no randomized comparison trial to date. Because the plasma clearance of the drug is reduced by 16%, 50%, and 70% to 75% in patients with mild (creatinine clearance 50–80 mL/min), moderate (creatinine clearance 30–49 mL/min), and severe (creatinine clearance < 30 mL/min) renal insufficiency, respectively, it is usually necessary to adjust the dose when used in older adults because of the frequency

of reduced renal function in this population.

Rituximab is a chimeric anti-CD20 antibody, originally used for the treatment of a subset of patients with non-Hodgkin lymphoma. The drug works by depleting B cells with CD20 on their surface. The drug is approved in the United States for the treatment of patients with RA who have an inadequate response to anti-TNF agents. Since rituximab has nonhuman protein sequences, it should be used in conjunction with another immunosuppressive agent such as methotrexate. Patients are usually given one course of two infusions 2 weeks apart. It is possible to repeat the treatment every 6 months. Patients can receive repeated courses of two or three infusions if necessary.

Abetacept is a recombinant fusion protein combining the extracellular domain of human CTLA-4 and an Fc domain of human IgG1 that has been modified to avoid complement fixation. The drug competitively binds to the costimulatory molecules CD80/CD86 to prevent these molecules from engaging CD28 on T cells and thereby prevents full T-cell activation. This, in turn, suppresses T-cell proliferation and inhibits the production of TNF-α, interferon (IFN)-γ, and IL-2. Abetacept is dosed according to the patient's body weight and is generally given in combination with methotrexate.

Tocilizumab is a humanized monoclonal antibody drug targeting the interleukin-6 (IL-6) receptor. It is given either as a subcutaneous injection of intravenous infusion, and can be used with or without concomitant methotrexate. In the United States, the drug is approved for RA patients who have had an inadequate response to anti-TNF therapies.

Tofacitinib is an oral agent targeting the janus kinase (JAK) signaling pathway. The drug is approved in the United States for RA patients with inadequate response/intolerance to methotrexate. Of note, the drug may increase cholesterol levels, and may increase the risk of gastrointestinal perforation.

Besides side effects, cost is the main limitation of widespread use of these medications. The anticipated availability of "biosimilars" and increasing competition among the growing number of biologics will help drive down the cost. Additionally, lower doses (than FDA guidelines) and, in some cases, reducing dose frequencies or duration of biologic treatments may be acceptable in selected patients without adversely affecting outcomes.

Safety and other issues with biologics While there is little doubt about the potential efficacy of the biologics in RA, there remains significant concern about their side effects, especially in vulnerable populations such as older patients with RA having multiple comorbidities. In addition, the significant cost associated with these drugs is prohibitive to many older patients without prescription drug coverage. One useful acronym for the safe use of biologics is SAFETY, outlined in **Table 121-4**. TNF is involved in host defense against foreign pathogens and in tumor surveillance. The most important risk associated with anticytokine therapy for older patients with RA is the increased incidence of fungal infections, tuberculosis, and atypical mycobacterial infections. As tuberculosis is usually caused by reactivation of latent infection, tuberculosis skin testing and a chest x-ray should be done prior to starting these agents. Whether yearly skin test and chest x-ray to detect new exposure are necessary in countries with a low incidence of tuberculosis is unclear. Yearly screening is recommended for selected patients who are at risk, such as those who travel regularly to TB endemic areas and nursing home residents.

TABLE 121-4 CONSIDER THE FOLLOWING WHEN USING IMMUNOMODULATORY THERAPY IN OLDER ADULTS

Comorbidities: The patient's underlying conditions such as cancer, unhealing pressure ulcers, chronic lung diseases, frequent urinary tract infections, hypercholesterolemia, or diverticulitis can increase the risk of complications when using immunosuppressive medications. Cognitive issues may also result in noncompliance and increases the risk for side effects.

Opportunistic infections: The older and more frail patients are at an even greater risk of developing opportunistic infections when exposed to biologics, such as reactivation and new acquisition of tuberculosis, viral (eg, herpes zoster, cytomegalovirus, viral hepatitis), or fungal infections.

Novel presentation of side effects: Older adults often have novel or atypical presentation of infection complications. For example, the patient may present with altered mental status and be unable to mount a fever or adequate white cell count elevation.

Screening: The physician should ensure that the older rheumatic disease patient be appropriately screened for cancer, infection, dental health, and heart disease. There should be a low threshold for re-screening for health conditions and to initiate early treatment as necessary.

Immunization: If at all possible, older adults should receive vaccinations against infections before they are started on an immunomodulating agent.

Drug dosing and interactions: Older patients are more likely to suffer from polypharmacy. While there is a paucity of information regarding drug interactions with biologics, old age has an effect on pharmacokinetics of selected biologics. In addition, it may be prudent to select shorter acting biologics in the older adult population who are at risk for severe infection complications.

Evaluate: Physicians need to aggressively evaluate and monitor older patients for early sign of adverse events, including more frequent follow-up, than younger patients.

Remainng lifespan: The potential benefit of biologics should be considered in the context of a patient's life expectancy. Frail older patients with limited remaining lifespan are at high risk of side effects from biological therapies.

Rituximab dramatically lowers the peripheral blood B-cell count for months after the infusion, and these patients also have lower IgG and IgM levels. The use of rituximab has been associated with the reactivation of JC polyoma virus infection, resulting in the disease progressive multifocal leukoencephalopathy. This complication, although very rare, highlights the potential for the development of all B-cell-dependent viral diseases in patients receiving the drug. Interestingly, progressive multifocal leukoencephalopathy has also been reported in patients with multiple sclerosis receiving natalizumab, a chimeric anti-α4 integrin antibody. Patients on rituximab are at risk for hepatitis B reactivation, and should be screened for the virus before initiation of therapy. Interestingly, rituximab has been successfully used in hepatitis C virus (HCV)-associated cryoglobulinemia without worsening of HVC-associated liver disease.

Rare cases of demyelinating disorders, aplastic anemia, lupus-like illnesses, and depression have also been associated with anti-TNF therapies. The long-term consequences of anticytokine suppression are unknown. One meta-analysis reported a fourfold higher rate of malignancies in patients treated with TNF inhibitors.

In addition to the concern about infection risk, abetacept can be potentially problematic in older adults with multiple comorbidities. Patients with chronic obstructive pulmonary disease have a higher incidence of adverse drug reaction and respiratory complaints such as chronic obstructive pulmonary disease exacerbation, cough, and dyspnea. Diabetic patients should be alerted to the fact that the abetacept formulation contains maltose and can give falsely elevated glucose readings in some glucose monitors on the day of the infusion.

Are biologics "cost effective" in the treatment of older adults with rheumatic diseases? Cost effectiveness for young patients with RA is based on remaining in the work force, but there are no such data for the geriatric cohort of retirees, and it is hard to define the economic value of improved functional status or quality of life.

As in other populations, cardiovascular disease is the single largest cause of death in patients with autoimmune inflammatory disorders. However, after accounting for the known traditional risk factors for heart diseases, patients with RA and lupus are at greater risk of developing coronary artery disease and stroke than those without these conditions. The reason for the increased incidence of cardiovascular disease in patients with these disorders of autoimmunity is not clear. Furthermore, a patient with RA who has a myocardial infarction has a similar prognosis as that of a diabetic patient with a similar event. Conventional therapies, such as the use of lipid-lowering agents, may not reverse the cardiovascular risk associated with these inflammatory conditions. While not proven, it is hoped that use of more aggressive immunosuppressive regimens will help reduce the cardiovascular morbidity and mortality in these patients. However, the use of anti-TNF agents has been linked to an increased rate of congestive heart failure and cardiac mortality when these were used in heart failure clinical trials. Aging per se has been described by some as a state of chronic low-grade inflammation that has been termed "inflamm-aging," which may play a role in frailty and sarcopenia in both normal aging and chronic inflammatory conditions such as RA. Current data do not support an increased risk of major adverse cardiovascular events in tocilizumab-treated RA patients, despite the drug's propensity to increase lipid levels.

A disease-associated inflammatory state, chronic use of steroids, and the lack of exercise owing to arthritis-associated disability may all contribute to the high incidence of osteoporosis in older patients with rheumatic diseases. Since these are chronic conditions, aggressive treatment with antiresorptive agents, adequate calcium intake, and vitamin D to prevent and treat osteoporosis and fracture is critical.

Many RA therapies involve significant immunosuppression that may affect the patient's ability to mount an antibody response to immunization, worsening the already-impaired immune reaction as a result of immune senescence in older patients. It is, therefore, important that these patients are given their age-appropriate immunizations such as pneumococcal and flu vaccines preferably prior to receiving therapy with biologics. Patients already on biologics should avoid receiving any live vaccines.

Surgical interventions Surgery can be useful to restore function and in many cases reduce pain in end-stage RA joints. These procedures include small-joint arthroplasty, joint fusion, and resection of metatarsal heads. Improvements in surgical techniques, prosthetic materials, perioperative care, and rehabilitation have resulted in much better outcomes in patients undergoing surgical treatments. However, it should be noted that there are very little long-term data examining the outcome of small joint arthroplasty. A number of ongoing National Institute of Health-sponsored

studies will provide much needed data in the near future. Synovectomy and tendon repairs are important surgical procedures to prevent and treat tendon rupture that can have disastrous functional consequences in patients with RA. Careful planning and timing of various joint procedures in patients with RA are important. For example, it may be wise to first correct upper extremity deformities before lower-extremity surgery is performed to allow the use of the upper extremities to assist in transfers, rising from a chair, and stair climbing during rehabilitation.

Prevention

A major problem in attempting to prevent the disease is identifying those who are at risk of developing the disease in the first place. Although genetic studies provide some clues as to which segment of the population may be at risk, the available information is not precise enough to be of practical use. There is some evidence that oral contraceptive pill use and hormone replacement therapy may reduce the risk of developing RA. Conversely, epidemiologic data suggest that smoking is associated with a slightly increased risk for the disease, as well as more active and difficult to control disease. Despite promising animal data, T-cell receptor peptide vaccination has not progressed to human trials. One study suggests that the use of aggressive drug therapy in patients with inflammatory arthritis but who do not yet fulfill the criteria for full-blown RA may reduce the number developing the disease. Whether this applies to EORA is unknown. The detection of RA-associated autoantibodies such as anti-MCV antibodies before clinical disease may identify a preclinical patient cohort and holds promise for future personalized strategies in targeting high-risk patients for early intervention. Ongoing studies are examining the use of immunotherapy in patients with joint pain and laboratory markers of autoimmunity, but who do not fulfill the classification criteria for RA, to determine if such approaches will prevent development of the full-blown chronic disease.

Special Issues

Patient preference and comorbidity The choice of therapy should be made in conjunction with the patient and the caregivers. Although exercises are important to maintain joint and muscle functions in patients with RA, some older patients are unable to perform regular exercises because of their other medical conditions, or if they have lived an inactive lifestyle for many years and are reluctant to adopt any change. In these situations, emphasizing the positive aspects of exercise (physical, psychological, and social), setting realistic goals, and recommending exercise programs specially tailored for the older population are helpful. In this regard, finding a physical and occupational therapist accustomed to working with older adults is important. Too often the author has seen patients who refuse to return to their therapist because of unrealistic short-term exercise goals.

The importance of assessing a patient's risk of developing GI, renal, or cardiac complications, and osteoporosis prior to starting NSAIDs and corticosteroids has already been emphasized. Patient preference is important when deciding on a specific DMARD. Older patients with poor eyesight are often reluctant to begin antimalarials out of fear of potential ocular complications, however small the risk may be. These drugs are contraindicated in older patients who cannot be monitored for retinal toxicity, including individuals with macular degeneration or untreated cataract. Older adults who do not want to give up drinking alcohol may choose not to take methotrexate. Some older women have refused to take methotrexate because the drug was part of their breast cancer chemotherapy in the distant past. Intramuscular methotrexate can be used in older patients who experience dyspepsia or who have difficulty swallowing. Methotrexate and biological response modifiers must be used with extreme caution or not at all in patients with chronic or active infection. Whether older patients with chronic lung disease taking DMARDs should receive *Pneumocystis carinii* prophylaxis is unclear. Assessment of the patient's tuberculosis status should be done prior to beginning anticytokine therapy. The appropriate use of biologics has already been discussed extensively.

Older patients on biologic therapies are faced with several important questions about immunization. Older patients with RA should have their immunization history thoroughly reviewed, and ideally have received all the appropriate immunizations prior to receiving DMARDs and biologic therapies (particularly rituximab). Influenza and pneumococcal vaccines should be given as they are in the general population. Those who have not received the pneumococcal 13-valent vaccine (Prevnar 13) should receive the vaccination. The use of tetanus toxoid should be as per normal guidelines except for patients who have received rituximab within the previous 24 weeks, when passive immunization with tetanus immunoglobulin is recommended. The use of live vaccine in biologics-exposed patients remains controversial. Because of the lack of data, the current recommendation is against the use of live vaccines in patients on biologic therapies. However, two studies suggest that RA patients on biologics may be safely vaccinated with the attenuated live herpes zoster vaccine, particularly if their disease is under good control. High rheumatoid

disease activity, the use of biologics; prednisone or hydroxycholoroquine are all risk factors for zoster in RA patients.

One study examined the influence of comorbidities on clinical outcomes of over 1500 DAMRD/biologics-treated RA patients in the community-based Consortium of Rheumatology Researchers of North America (CORRONA) registry. As expected, older patients have more comorbidities than the younger cohort. Although disease activity measures at entry to the registry were similar across age categories, older patients have less improvement in their disease and functional measures over time, and were less likely to attain remission at follow-up. Importantly, the age difference can be largely accounted for by the number of comorbidities in the older patient population.

Care settings The physician's choice of therapy has to take into account the patient's overall state of health and mobility, and the care setting. In most cases, home laboratory monitoring for DMARD toxicity can be arranged for patients with significant mobility problems. Instead of DMARDs, the use of corticosteroids (oral, intra-articular, or parenteral; low- or high-dose "pulse" treatment) may be a good option in patients with RA with active disease in the end stages of their lives. Therapeutic goals may also be different in a patient near the end of life, when either long-term treatment outcome or side effects may not be important considerations. An example is a patient with RA who has end-stage dementia, when judicious use of corticosteroid rather than high-dose immunosuppression for active disease may be more appropriate. Biologic therapies achieve their therapeutic effect much sooner than DMARDs, such as methotrexate, and may therefore be a reasonable choice in DMARD-naïve patients whose disease is not controlled by corticosteroids and who are near the end of life.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease that predominantly affects the female population. The incidence of lupus has been increasing with an estimated quarter of a million patients now with the disease in the United States. Late-onset lupus (LOL) is defined as symptoms beginning after the age of 55 years, representing approximately 10% of all cases of lupus. However, the United Kingdom General Practice Research Database (a population database covering 5% of the United Kingdom) has surprising data that the peak incidence of lupus in females occurs at age 50 to 54 years and for males it is 70 to 74 years (**Figure 121-4**). Comparable data are not available for the United States, since previous lupus surveillance studies have been confined to relatively small geographic areas. An ongoing Centers for Disease Control and Prevention-sponsored study in Southeast Michigan will eventually provide a better estimate of the true age-specific incidence of this disease in the United States. Improved therapies and greater appreciation of the importance of treating comorbid conditions such as coronary artery disease have resulted in more patients with lupus surviving into old age.

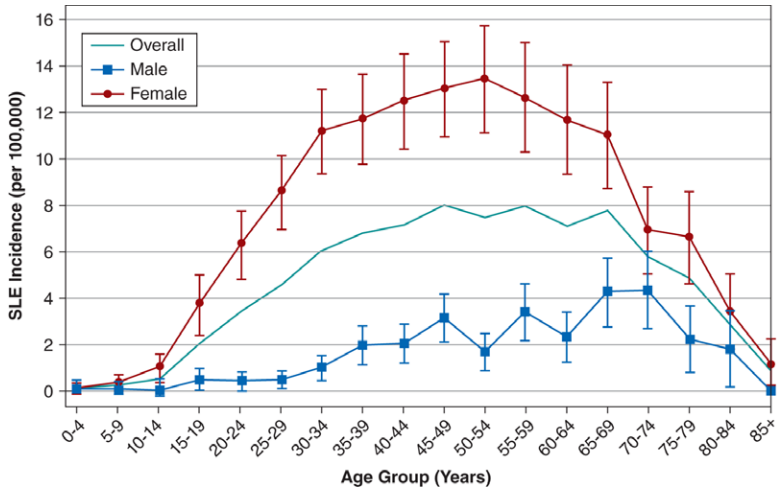


FIGURE 121-4. Incidence of systemic lupus erythematosus in the United Kingdom, 1990–1999. (Reproduced with permission from Somers EC, et al. *Arthritis Rheum.* 2007; 57(4):612.)

Diagnosis

The diagnosis of SLE is based on the presence of signs, symptoms, and laboratory features of autoimmunity. The 1982 ACR Classification Criteria for SLE were revised to include the presence of antiphospholipid antibodies (**Table 121-**

5). The United States criteria were designed for research purposes and have not been validated in LOL. Low-titer ANA may be present in up to one-third of older adults. Positive ANAs (titer ≥ 1:160) have high sensitivity but poor specificity for SLE when measured by indirect immunofluorescence using the standard Hep-2 substrate. In contrast, the presence of anti-dsDNA (double-stranded deoxyribonucleic acid) or anti-Sm (Smith) antibodies is highly specific for SLE. However, these antibodies are only detected in 31% to 86% and 0% to 24% of patients with LOL, respectively.

TABLE 121-5 REVISED CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Serositis	Pleuritis, pericarditis, or peritonitis
Oral or nasal ulceration	Oral ulcers are often painless and occur in unusual parts of the oral cavity
Arthritis	Nonerosive polyarthritis involving the small joints
Photosensitivity	Skin rash when exposed to sunlight
Blood dyscrasia	Hemolytic anemia, leukopenia/lymphopenia, or thrombocytopenia
Renal disease	Proteinuria (> 0.5 g/d), cellular casts, unexplained hematuria
ANA	≥ 1:160 titer in the absence of lupus-inducing drug
Immunologic abnormalities	Anti-dsDNA, anti-Sm, or antiphospholipid antibody
Neuropsychiatric illness	Seizures or psychosis
Malar rash	Tends to spare the nasolabial folds
Discoid rash	Often scarring

ANA, antinuclear antibody; dsDNA, double-stranded deoxyribonucleic acid; Sm, Smith (antigen).
Data from Berney SM. Systemic lupus erythematosus. Hospital Physician. 1998;1(3):2–12.

Pathogenesis

The cause of SLE is unknown. The concordance rate of SLE in monozygotic twins is between 25% and 50%, suggesting that genetic and environmental factors are both important. Human SLE is a polygenic disease. At least 50 susceptibility or resistance loci have been identified in human and murine lupus (eg, *sle*1, 2, 3). A defect or deficiency in gene product(s) regulating immune complex clearance, such as in some cases of inherited complement (C1, C4, and C2) deficiencies, is associated with a high likelihood of the development of SLE. Variability in the Fcγ receptor alleles is believed to play a role in determining the susceptibility to SLE in some racial and ethnic populations. Defective apoptosis as a consequence of mutations of the Fas or Fas-ligand gene is the central mechanism responsible for the lupus-like disease seen in MRL/*lpr* and MRL/*gld* mice. However, such defects are exceedingly rare in humans, and, when present, they cause a much more limited autoimmune disease (the Canale-Smith syndrome).

Hormonal factors are important in the pathogenesis of SLE. The disease often affects females of childbearing age. The decline in female sex hormones in postmenopausal years was believed to be an important reason for a lower incidence of SLE in this age group, but the United Kingdom General Practice Research Database study raises questions about the validity of this association. Furthermore, exogenous estrogens (hormone replacement therapy and oral contraceptive pills) may impose a small risk for developing lupus. The SELENA (Safety of Estrogens in Lupus Erythematosus National Assessment) trial showed that postmenopausal women receiving hormone replacement therapy have a slight increase in the number of mild-to-moderate lupus flares, but there was no increase in the number of severe flares. Similar to other autoimmune diseases, an inciting role for microbial organisms has been postulated but not proven.

In addition to changes in the adaptive arm of the immune system, there is a pathogenic role for aberrant innate immune responses in lupus. Immune cells such as dendritic cells, macrophages, and other myeloid cells all participate in both the adaptive and innate arms of immune responses. Interferon alpha, a key mediator of innate immunity, may also be important in lupus pathogenesis. A Toll-like receptor 7 (TLR7) signaling defect may be important in sustaining the inflammatory response in this disease.

An unanswered question is whether LOL is a different disease than the one that occurs at a younger age. Many older adults have a low level of circulating autoantibodies. Additionally, measures of various markers of immunosenescence suggest that patients with autoimmune diseases have accelerated aging of the immune system.

Given the apparent high incidence of lupus in middle-aged and late life, a better understanding of how immune senescence can affect the normally tightly regulated process that prevents the development of autoimmunity is needed. One hypothesis is that defective T-cell activation in aging may result in a suboptimal immune response to foreign antigen, which, in turn, may allow these cells to cross-react with self-antigens. Secondly, thymic involution and the accumulation of memory T cells in aging may "force" the proliferation of naïve T cells with high affinity for self-antigen. Thirdly, epigenetics, which refers to the regulation of gene expression through cellular processes including DNA methylation, histone modification, and RNA interference, is affected by aging. Both DNA methylation and histone acetylation are important mechanisms for the development of lupus and potentially other autoimmune diseases. Whether the age-dependent epigenetic changes also affect genes that are important in the development of autoimmunity in aging is unknown. Finally, it has been postulated that age-related DNA methylation changes may "reawaken" X-chromosome genes that have previously been inactivated in females. This, in turn, may help to explain the gender differences in lupus in the older adult population.

Presentation

Because of the lack of awareness of this disease in older people, the average time it takes from the onset of symptoms to the diagnosis of LOL is long, averaging between 2 and 3 years. The female:male ratio of LOL is approximately 4:1, much lower than the 9:1 ratio in the younger age group. The high prevalence of SLE in younger African-Americans is not so apparent in LOL. However, whether this merely reflects the demographics of the study locations is unclear.

The clinical features of patients with LOL are quite different from those of patients who develop lupus at a younger age (**Table 121-6**). The patients with LOL tend to have a milder disease and are less likely to develop alopecia, malar rash, photosensitivity, oral/nasal ulceration, glomerulonephritis, and lymphadenopathy. Patients with LOL may be more prone to develop cytopenias, serositis, and interstitial pneumonitis. Interestingly, the incidence of cancer, with the exception of non-Hodgkin lymphoma, may be lower in LOL than in younger patients with lupus. The cause of death in patients with LOL is usually related to complications of treatment such as infections, cardiovascular disease, and stroke.

TABLE 121-6 THE FREQUENCY OF SYMPTOMS AND SIGNS OF SLE IN OLDER ADULTS

SYMPTOMS/SIGNS	FREQUENCY (%)
Arthritis/arthralgia	60
Rash	47
Cytopenias	45
Interstitial pneumonitis	41
Serositis	32
Raynaud phenomenon	28
Neuropsychiatric	25
Peripheral neuropathy	25
Glomerulonephritis	24

Adapted from Kammer GM, Mishra N. Systemic lupus erythematosus in the elderly. Rheum Dis Clin North Am. *2000;266:475.*

Management

The choice of therapy is largely dictated by the specific disease manifestations. Antimalarials (see above) are useful for many lupus symptoms including arthritis, serositis, mucositis, and skin disease. Available evidence strongly supports the long-term use of antimalarials in patients with lupus. Quinacrine, available from many compounding pharmacists, does not cause retinal damage and may be used in older patients who cannot take potentially retinotoxic drugs. NSAIDs are used by the majority of patients with lupus for symptomatic relief of arthralgias, myalgias, serositis, fever, and headaches. Their use in older patients must be weighed against their potential side effects. This class of drugs is best avoided in patients with lupus having renal involvement.

Local corticosteroid treatments such as (short-term) topical or intradermal injections can be helpful in cutaneous lupus. Systemic steroids are often reserved for more severe disease such as lupus pneumonitis, carditis, hemolytic

anemia, or new-onset renal disease. Intravenous "pulse" methylprednisolone in doses of 1 g/day for up to 3 consecutive days can be lifesaving in rapidly progressive or fulminant disease.

The use of cytotoxic drugs such as cyclophosphamide has significantly reduced the morbidity and mortality associated with lupus nephritis. Monthly intravenous pulse cyclophosphamide is generally well tolerated and has fewer side effects than daily oral administration of the drug. Azathioprine, chlorambucil, or nitrogen mustard may be used in lupus patients with renal disease who are unable to tolerate high-dose corticosteroids or cyclophosphamide. Mycophenolate mofetil has gained acceptance in the treatment of many lupus manifestations and may be better tolerated than azathioprine. Cytotoxics should not be withheld from older patients with lupus who have major organ involvement. The use of alkylating agents is associated with an increased risk of future cancer development. However, this may be a more important consideration in younger patients with a longer life expectancy. Gonad toxicity is not a very important issue in the older adult population.

There has been an explosion of interest in clinical treatment trials of newer drugs in lupus. Promising preliminary data include drugs that target the interferon pathway. In 2011, belimumab, a human monoclonal antibody that inhibits soluble B-lymphocyte activating factor (BAFF), became the first lupus drug in its class to receive U.S. FDA approval. While the drug has been shown to help mild lupus, it is not intended for patients with serious complications such as lupus nephritis, and unfortunately has poor efficacy in African Americans, a population that is preferentially affected by this disease.

SJÖGREN SYNDROME

Definition

Sjögren syndrome is a chronic inflammatory autoimmune disease characterized by progressive lymphocytic and plasma cell infiltration of the exocrine glands, leading to dry mouth (xerostomia) and dry eye (keratoconjunctivitis sicca). The syndrome can occur in isolation (primary) or in association with other autoimmune diseases (secondary) such as RA, SLE, or polymyositis. In addition to the sicca symptoms (dry eyes and dry mouth) serologic evidence of autoimmunity and objective assessment of oral and ocular involvement need to be documented before the diagnosis of Sjögren syndrome is made. The Schirmer test, in which a strip of Whatman No. 41 filter paper is placed in the lower conjunctival sac, is considered positive if less than 5 mm of the paper is wet after 5 minutes. Ocular involvement can also be documented by staining the conjunctiva with 1% Rose Bengal stain and slit-lamp eye examination. Minor salivary gland biopsy is the most commonly performed test used in diagnosing salivary gland involvement in Sjögren syndrome. The test is considered positive when there is more than one focus (aggregate of ≥ 50 lymphocytes) per 4 mm^2 of biopsy specimen. Biopsy of the parotid, rather than of a minor salivary gland, should be done in patients complaining of parotid gland swelling. Saliva production is measured after overnight fasting without oral stimulation (brushing of teeth, smoking, etc). A normal person should produce at least 1.5 mL of saliva in 15 minutes. Parotid sialography and salivary gland scintigraphy are alternate procedures for documenting salivary gland involvement.

Epidemiology

Depending on the definition and the age of the population studied, the prevalence of Sjögren syndrome has been estimated to be between 0.04% and 4.8%, making it the second commonest autoimmune disease after RA. The disease is likely underdiagnosed as patients often fail to discuss their symptoms with their physicians or believe that the symptoms are part of the inevitable consequence of aging. One study on a geriatric population suggests that subclinical disease may occur in up to 3% of the nursing home population. Although the prevalence of sicca symptoms increases with age, the peak incidence of primary Sjögren syndrome occurs in the fourth and fifth decades of life, with a 9:1 female:male ratio.

Pathogenesis

Most cases of Sjögren syndrome occur sporadically, although there are examples of familial aggregation. An association with HLA antigens has been reported, including HLA-DR3, HLA-DR2, and HLADRw52 in white populations. In addition, HLA-DR3 and HLADQw2.1 are linked to the development of anti-Ro antibodies. Like most other autoimmune diseases, an environmental or viral trigger has been proposed for Sjögren syndrome. One theory suggests that autoimmune lymphocytes are "homed" to salivary and lacrimal glands. This is followed by clonal expansion of the autoreactive cells in the glands, upregulation of major histocompatibility complex and adhesion

molecules by epithelial cells, and secretion of proinflammatory cytokines by lymphocytes and epithelial cells. Defective apoptosis causing the failure to delete autoreactive cells has been proposed as a central mechanism explaining the lymphoid aggregates seen in the exocrine glands. α-Fodrin, a cytoskeletal protein, was recently identified as a candidate autoantigen in Sjögren syndrome. Interestingly, neonatal immunization with this antigen can prevent the development of the disease in an animal model of Sjögren syndrome.

Presentation and Clinical Features

Most patients with Sjögren syndrome have a slowly progressive and benign course. The onset of the disease is insidious, and it may take up to 10 years for the full-blown disease to develop. Older patients with Sjögren syndrome usually present with sicca symptoms. They may complain of difficulty chewing and swallowing dry foods, the frequent need to drink liquid especially at night, difficulty wearing dentures, abnormal taste, sore/burning sensation in the mouth, and intolerance to spicy foods. Xerostomia also predisposes these patients to dental decay and the development of oral candidiasis. Instead of the classical white candida plaque, patients with Sjögren syndrome may have erythematous oral candidiasis. In addition to the feeling of dryness in the eyes, patients with ocular involvement may complain of an itching or burning sensation, the feeling that there is a foreign body in the eye, and photosensitivity. Unilateral or bilateral parotid gland swelling occurs in one-third of all patients with primary Sjögren syndrome and is more commonly seen in the younger age group. The differential diagnosis of unilateral or bilateral parotid gland swelling includes viral (including HIV-1) and bacterial infections, sarcoidosis, salivary gland ductal obstruction, and neoplasm. Immunoglobulin G4-related disease (IgG4-RD) is increasingly being recognized to have clinical features that overlap with Sjögren syndrome. This heterogeneous collection of disorders shares features of tumor-like swelling of involved organs such as salivary and parotid glands, a lymphoplasmacytic infiltrate of IgG4-positive plasma cells, and elevated serum IgG4 levels in 60% to 70% of affected patients. This disease should be considered in patients with sicca symptoms but who have negative autoantibodies.

Approximately 60% of patients with Sjögren syndrome develop extraglandular disease (**Table 121-7**). Nonerosive arthritis/arthralgia is the commonest extraglandular manifestation and may precede sicca symptoms. Any part of the pulmonary tree from the trachea to the pleural lining may be involved, causing cough, hoarseness, and shortness of breath. Pseudolymphoma and lymphoma should be suspected when an unexplained pulmonary nodule or lymphadenopathy is seen on chest radiograph. Patients with Sjögren syndrome may experience dysphagia because of dryness of the oral pharynx or abnormal esophageal motility. Chronic atrophic gastritis, gastric lymphoma, vitamin B_{12} deficiency, and antibodies to parietal cells have all been described in this disease. Autoimmune thyroid disease is present in 13% to 45% of patients with Sjögren syndrome. Patients with Sjögren syndrome often have an elevated liver enzyme profile, especially if antimitochondrial antibodies are present. Interestingly, sicca symptoms are present in 50% of patients with primary biliary cirrhosis. Renal disease occurs in approximately 10% of patients with Sjögren syndrome. Lymphocytic infiltration and immune complex deposition, proximal renal tubular acidosis with Fanconi syndrome, renal stones, electrolyte imbalance, and cryoglobulinemia have all been reported.

TABLE 121-7 EXTRAGLANDULAR MANIFESTATIONS OF SJöGREN SYNDROME

Cutaneous	Xerosis (including dryness of nasal passage, skin, and vagina); Raynaud phenomenon; cutaneous vasculitis
Pulmonary	Desiccation of the tracheobronchial tree; lymphocytic infiltration (alveolitis, interstitial pneumonitis, pseudolymphoma, lymphoma); pleuritis/pleural effusion; vasculitis; pulmonary hypertension
Gastrointestinal	Dysphagia; atrophic gastritis; malabsorption; pancreatic dysfunction and pancreatitis; hepatomegaly and hepatitis; primary biliary cirrhosis
Renal	Interstitial nephritis; glomerulonephritis; distal renal tubular acidosis; kidney stones
Hematologic	Anemia; cryoglobulinemia
Neuromuscular	Sensory and trigeminal neuralgia; vasculitis; mononeuritis multiplex; neuropsychiatric disorders; seizures; encephalopathy; myelitis; aseptic meningitis; dementia; myopathy and myositis
Endocrine	Autoimmune thyroid disease

The association of RA and Sjögren syndrome was first described by Henrik Sjögren in 1933. Although it is

believed that RA is the commonest cause of secondary Sjögren syndrome, its true prevalence in RA is unknown. Patients with secondary Sjögren syndrome have milder disease with primarily sicca symptoms (dry eyes and dry mouth). Systemic complications such as salivary gland swelling, central nervous system disease, renal disease (interstitial nephritis or glomerulonephritis), and lymphoproliferative disease are uncommon.

Patients with Sjögren syndrome often have polyclonal hypergammaglobulinemia, as well as selective increased production of specific autoantibodies. ANA and RFs are present in more than 75% and 66% of patients with Sjögren syndrome, respectively. Anti-Ro and anti-La antibodies are detected in 70% and 40% of the affected patients. Interestingly, anti-La antibodies are less common in the secondary form of the disease.

Management

Simple lifestyle changes such as air humidification and avoidance of cigarette smoke are helpful. Nasal dryness can be treated with saline drops or gel. Vaginal dryness can be reduced using water-soluble lubricants and estrogen cream. Dry skin can be improved by using moisturizers and bath oil. Lipstick and lip balm can be used to reduce lip dryness. Meticulous oral hygiene and frequent dental visits are important to prevent dental decay and oral candidiasis. Frequent fluid replacement, topical fluoride treatment, the use of non-alcohol-based mouthwash, and sugarfree chewing gum can all be helpful. Unfortunately, artificial saliva substitutes that are currently available are not very helpful. Oral candidiasis can be treated with a prolonged course (1–4 months) of a noncariogenic antifungal drug (eg, nystatin vaginal tablets 100,000 units two to three times a day), with separate treatment of dentures.

The mainstay of treatment for dry eye remains artificial tears. Preparations now available can penetrate into the epithelial cell layer, extending duration of action. However, these may occasionally cause blurring and leave residue on eye lashes. Because patients with Sjögren syndrome generally require long-term tear replenishment, preservative-free artificial tears should be used. Topical low-dose cyclosporine can be used for Sjögren eye disease. Tear drainage can also be reduced by the placement of occlusive elements (eg, silicon implants) in the puncta or permanently by laser or thermal cautery. Soft contact lenses may be used to protect the cornea, especially in the presence of keratitis filamentosa. Because the contact lenses require wetting, the patient needs to be careful not to introduce infection to the eyes. Plastic wrap or swimming goggles can be used at night to reduce tear evaporation.

Whenever possible, drugs with significant cholinergic side effects should be discontinued. Muscarinic agonists (pilocarpine and cevimeline) may be helpful in alleviating dry mouth symptoms in patients with Sjögren syndrome. Systemic corticosteroid and immunosuppressive drugs (eg, cyclophosphamide) are sometimes used for severe extraglandular diseases such as interstitial pneumonitis, interstitial nephritis, and vasculitis. Musculoskeletal symptoms are often alleviated by the judicious use of NSAIDs, hydroxychloroquine, or sulfasalazine. IFN-α may improve salivary flow in a subset of patients with Sjögren syndrome. Unfortunately, while treatments are helpful for symptomatic relief, the destruction of exocrine gland continues despite best current effort.

DRUG-INDUCED RHEUMATIC SYNDROMES

Polypharmacy and iatrogenic diseases are important geriatric issues. Medications are also increasingly recognized as common causes of rheumatic syndromes. These can be broadly categorized into drug-induced lupus (DIL), drug-induced myopathy/myositis, and drug-induced vasculitis.

Drug-Induced Lupus

More than 100 drugs have now been implicated in DIL (**Table 121-8**), although a much smaller number have a strong association. The average age of onset is between 50 and 70 years. However, specific criteria for the diagnosis of DIL have not been established. Compared to the idiopathic disease, patients with "classical" DIL have a milder illness and a more restricted autoantibody profile. Antihistone antibodies are present in high frequencies in DIL associated with drugs such as procainamide or hydralazine but are not as frequently seen in patients with drugs such as minocycline or anti-TNF agents. The incidence of DIL has been estimated to be approximately 15,000 to 20,000 per year, with between 30,000 and 50,000 patients currently affected in the United States.

TABLE 121-8 DRUGS IMPLICATED IN DRUG-INDUCED LUPUS

Acebutolol	Interferon (α, γ)	Phenylacetylurea

Aminoglutethimide	lnterleukin-2	*Phenytoin*
Amiodarone	*Isoniazid*	Practolol
Amoproxan	Labetalol	Prazosin
Anthiomaline	Lamotrigine	Primidone
Atenolol	Leuprolide acetate	Prinolol
Benoxaprofen	Levodopa	*Procainamide*
Canavanine (L-)	Levomeprazone	Promethazine
Captopril	Lithium carbonate	Propylthiouracil
Carbamazepine	Lovastatin	Psoralen
Chlorpromazine	Mephenytoin	Pyrathiazine
Chlorprothixene	Mesalazine	Pyrithoxine
Cimetidine	Methimazole	*Quinidine*
Cinnarizine	*Methyldopa*	Quinine
Clonidine	Methysergide	Rifamycin
Clozapine	Methylthiouracil	*Sulfasalazine*
COL-3	Metrizamide	(5-Amino) salicylic acid
Danazol	*Minocycline*	Simvastatin
Diclofenac	Minoxidil	Spironolactone
1,2-Dimethyl-3-hydroxypyride-4-1 (Ll)	Nalidixic acid	Streptomycin
Disopyramide	Nitrofurantoin	Sulindac
Estrogens	Nomifensine	Sulfadimethoxine
Etanercept	Oral contraceptives	Sulfamethoxypyridazine
Ethosuximide	Olsalazine	Terbinafine
Flutamide	Oxyphenisatin	Tetracycline
Fluvastatin	Para-aminosalicylic acid	Tetrazine
Gold salts	*Penicillamine*	Thioamide
Griseofulvin	Penicillin	Thioridazine
Guanoxan	Perazine	Timolol eye drops
Hydralazine	Perphenazine	Tolazamide
Hydrazine	Phenelzine	Tolmetin
Ibuprofen	Phenopyrazone	Trimethadione
Infliximab	Phenylbutazone	Zafirlukast

Drugs with the strongest associations are in italic.
Adapted from Yung RL, Richardson BC. Drug-induced rheumatic syndromes. Bull Rheum Dis. *2002;51(4):1.*

Procainamide (procainamide-induced lupus, PIL) and hydralazine (hydralazine-induced lupus, HIL) are drugs historically associated with DIL and are well-defined DIL models. Patients with DIL are usually older and more likely to be men, reflecting the age and sex of the population receiving these drugs. One-third of patients receiving procainamide for more than a year will develop symptoms, and almost all will become ANA positive after 2 years. In contrast, fewer than 20% of hydralazine-treated patients will develop DIL. The risk for developing HIL is dose dependent and is highest in patients taking more than 200 mg/day and in those who have taken more than 100 g cumulative dose. Compared to patients with idiopathic lupus, patients with PIL and HIL have fewer renal, neuropsychiatric, and skin manifestations. Pleuropulmonary complaints are particularly common in PIL, while immune cytopenias are uncommon in DIL in general. By definition, all patients with DIL are ANA positive (mostly

homogenous pattern). More than 90% of patients with PIL and HIL have antihistone antibodies, and 20% to 40% are RF positive.

Up to 19% of patients treated with IFN-α develop some form of autoimmunity. Approximately 12% of patients receiving this drug develop positive ANA, and between 0.15% and 0.7% will develop a lupus-like illness. Anti-dsDNA antibodies occur in 8%, and almost all the patients with IFN-α-induced lupus have elevated anti-dsDNA antibodies. The development of autoimmunity appears to be dependent on the dose and duration of treatment. Other rheumatic syndromes associated with IFN-α include RA, polymyositis, psoriatic arthritis, Reiter syndrome, and sarcoidosis. Autoimmune thyroid diseases are common following IFN-α treatment. It is important to differentiate this from idiopathic hypothyroidism that is prevalent in the older adult population.

Patients receiving TNF antagonists often develop serologic evidence of autoimmunity. In one study, new ANA and anti-dsDNA antibodies were found in 33% and 9% of infliximab recipients, respectively. However, there is clear discordance between the development of autoantibodies and clinical autoimmunity, with only a handful of symptomatic patients reported, mostly with skin diseases. Approximately 13% of patients exposed to infliximab develop infliximab-specific antibodies. Patients receiving concurrent immunosuppressants such as methotrexate or azathioprine are less likely to develop these antibodies. The presence of antibodies to infliximab increases the likelihood of an infusion reaction but does not predict the development of autoantibodies or DIL.

Drug-Induced Myopathy/Myositis

Drug-induced muscle diseases include myopathy/myositis and rhabdomyolysis. In addition, drugs that impair consciousness (eg, sedatives and hypnotics) and those that cause seizures (eg, theophylline), hyperthermia (eg, halothane and cocaine), malignant neuroleptic syndrome (eg, haloperidol and phenothiazines), and dystonia (eg, butyrophenones) can also result in muscle necrosis and elevated creatine phosphokinase (CPK). Drug-induced myopathy typically appears within weeks to months after exposure, and resolves within a few weeks after the offending drug is discontinued.

Hydroxymethylglutaryl coenzyme A reductase inhibitors (the “statins”) are well known to cause different muscle complications varying from myalgias without elevated CPK, elevated CPK without any clinical symptom, to myopathy and rhabdomyolysis. The incidence of statin-induced myopathy (defined as a greater than 10-fold increased in CPK and muscle pain or weakness) is approximately 1 in 1000 patients taking the drug. The risk is greater when these drugs are used in conjunction with gemfibrozil, cyclosporin, niacin, erythromycin, itraconazole, and diltiazem. Other risk factors include renal insufficiency, hypothyroidism, advanced age, and serious infection. The mechanism of statin-induced myopathy is unclear, but appears to be genetically linked in some cases. In one study, a single-nucleotide polypeptide within the SLC01B1 gene was strongly associated with an increased risk of simvastatin-induced myopathy. These cholesterol lowering agents may interfere with mitochondrial metabolic pathways, and patients with underlying metabolic muscle disorders may be at greater risk of developing the complication. Myopathy associated with one statin does not predict the development of a similar problem with a different statin. However, there are rare reports of statin-induced rhabdomyolysis in patients with a previous history of statin-induced myopathy. Although statin myopathy is usually self-limiting, there have been reports of patients developing a persistent autoimmune necrotizing myopathy with autoantibodies recognizing 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the pharmacologic target of statins.

A number of drugs rheumatologists prescribe can cause significant muscle disease. Neuromyopathy occasionally develops in patients receiving colchicine. Older patients and those with renal impairment may develop this complication even if they are taking conventional doses of the drug. Patients receiving either chloroquine or hydroxychloroquine are at risk of developing a proximal myopathy and rarely cardiomyopathy. Steroid myopathy usually occurs when greater than 20 mg of prednisone is prescribed. The onset can be acute or insidious, involving the proximal muscle groups (especially the thighs and hip girdle). Serum creatinine kinase level is usually normal, but urine creatine may be elevated. Biopsy of the affected muscle classically shows type 2b fiber atrophy. Corticosteroid use is also associated with rhabdomyolysis when it is administered in the intensive care unit, often in the setting of concurrent paralytics or sedatives (“critical care myopathy”). Penicillamine used in the treatment of RA and Wilson disease may cause polymyositis, myasthenia gravis, and other autoimmune disorders, including lupus, pemphigus, and Sjögren syndrome.

Interest in over-the-counter “complementary” medicine has exploded in recent years. Several of these oral supplements have now been linked to the development of musculoskeletal syndromes. The best example is the eosinophilia-myalgia syndrome, believed to be caused by one or more contaminant(s) (the identity of which is still

unclear) introduced during the manufacturing process of L-tryptophan by a single manufacturer from Japan. Patients who consumed the product developed peripheral eosinophilia, incapacitating myalgias, and tight skin and/or fasciitis. DL-Carnitine is sold in health food stores and is being promoted as a supplement to increase muscle strength. Although L-carnitine may improve fatigue and muscle strength in some individuals, the DL-carnitine preparation may rarely cause muscle weakness and a myasthenia-like syndrome.

RHEUMATIC SYNDROMES AND CANCER

Clinicians are often concerned that a patient's rheumatic complaints may represent the early systemic presentation of an occult tumor. Patients with autoimmune diseases are also at higher risk of developing cancers. Many cancer therapies are complicated by rheumatologic side effects. Finally, immunosuppressive therapies used for treating autoimmune diseases may predispose the patients to malignancies.

Musculoskeletal Symptoms Associated With Cancer

Although the mechanisms for paraneoplastic rheumatologic complications are often poorly understood, many are believed to be endocrine or immune-mediated. An extensive search for an occult malignancy is not recommended in patients with most rheumatic syndromes unless there are specific symptoms or findings suggesting the possible presence of a tumor. Nevertheless, the possibility of metastatic disease should be considered in an older patient presenting with severe pain in or around a joint. Metastatic joint disease caused by lung or breast cancer is usually monoarticular or oligoarticular (two to five joints). Pain and synovitis are caused by synovial inflammation in response to tumor cells in and around the joint. Large joints (eg, knee and hip) are most commonly affected. However, asymmetric polyarthritis can occur at the late stages of cancer. The vertebral column is a common place for metastatic disease. A malignancy workup should be done if an older patient presents with intractable or nocturnal back pain that is increasing in severity and if the patient has constitutional symptoms such as fever or weight loss. Multiple myeloma frequently causes lytic lesions and pathologic fractures. Light-chain amyloidosis occurs in 15% of these patients and is associated with a symmetric small-joint arthropathy. In addition, amyloid infiltration in the shoulder joint produces the classical "shoulder pad sign." Hyperuricemia and gout may develop in patients with large tumor bulk, especially during chemotherapy. Raynaud phenomenon with or without panniculitis in older adults has been described in occult malignancy including as cutaneous manifestations of myeloma.

Hypertrophic osteoarthropathy is the most common rheumatic syndrome associated with malignancy and is almost always caused by metastatic lung cancer in the Western world. Ankles, wrists, knees, and fingers are the sites most frequently affected. The cause is unknown, but a neurally mediated mechanism is suggested by improvement with vagotomy and atropine. Carcinomatous polyarthritis can precede or follow the diagnosis of the underlying cancer, most commonly breast in women and lung in men. The classical description is an acute-onset asymmetric seronegative polyarthritis in an older patient that resembles EORA. The arthritis often improves with cancer therapy and may relapse with tumor recurrence. A polymyalgia rheumatica-like disease has been linked to metastatic cancer. This is suggested by a younger age of onset, prominent constitutional symptoms, asymmetric involvement of proximal muscle groups, a relatively low sedimentation rate, and an incomplete response to prednisone. The Lambert-Eaton syndrome is characterized by an antibody-mediated defect in acetylcholine release at the neuromuscular junction. It is most commonly associated with small cell carcinoma of the lung. Ptosis, distal muscle involvement, and characteristic electromyogram findings distinguish the disease from common inflammatory myopathies. Bilateral palmar fasciitis with or without polyarthritis is associated with gynecologic tumors, in particular, ovarian carcinoma. This is usually associated with late metastatic disease and carries a poor prognosis. Panniculitis with synovitis and serositis is a well-known accompaniment of pancreatic cancer. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-[monoclonal] protein, and skin abnormalities) is associated with plasma cell dyscrasias, including multiple myeloma. Finally, there are sporadic reports of steroid-resistant eosinophilic fasciitis associated with hematologic malignancies.

Rheumatic Diseases and Cancer

Patients with autoimmune diseases are at an increased risk of the development of a variety of malignancies. This tendency may be exacerbated by the use of specific immunosuppressive drugs. Patients with RA have a two- to fivefold increased risk of developing hematologic malignancies, including Hodgkin and non-Hodgkin lymphomas. The risk is even higher if secondary Sjögren syndrome or a serum paraprotein is present. An increased risk for oral-

pharyngeal cancers has been described in geographic locations where these tumors are prevalent. Interestingly, patients with RA may be at a lower risk of developing colorectal cancer. Whether the lower risk is related to the regular use of NSAIDs in this population is unknown. Patients with Sjögren syndrome are 44 times more likely to develop lymphoma than are age-, sex-, and race-matched normal subjects. The risk may be higher if the patient is anti-Ro or anti-La positive. In some of these patients, there appears to be a progression from benign exocrinopathy to pseudolymphoma to lymphoma. These tumors are almost exclusively B-cell lymphomas with a high frequency of a t(14;18) chromosomal translocation. The malignant transformation is likely the result of chronic B-cell stimulation. The presence of a monoclonal IgM spike on serum protein electrophoresis may herald the transformation to malignant lymphoma. Hypogammaglobulinemia and loss of autoantibodies may eventually occur when the lymphoma cells replace the normal antibody-producing plasma cells.

Patients with polymyositis have a twofold increased risk of developing cancer, particularly in the 1 to 5 years following the diagnosis of the muscle disease. The risk of cancer in patients with dermatomyositis is much higher (four to five times), and the cancer may be discovered years before or after the muscle disease is diagnosed. Older age, the presence of digital vasculitis, and normal serum creatinine kinase levels have all been cited as possible risk factors for cancer development in patients with inflammatory myositis. Patients with overlap syndromes and those with myositis-specific antibodies do not appear to have a higher incidence of cancer than other patients with polymyositis or dermatomyositis. The cancers associated with inflammatory myositis are those that are commonly seen, including breast, lung, gynecologic, and GI malignancies. Interestingly, nasopharyngeal carcinomas are the dominant cancers associated with myositis in countries that have a high prevalence of these malignancies.

It is controversial whether patients with other autoimmune diseases are more likely to develop cancer. Some reports have described an increased risk of lymphoma (particularly non-Hodgkin lymphoma) and possibly lung, breast, and cervical cancers in patients with SLE. Patients with scleroderma may be predisposed to skin cancer, and patients with systemic sclerosis who have pulmonary fibrosis are at risk of developing lung cancer.

Risk of Cancer With Immunosuppression

Patients with RA treated with methotrexate may be at increased risk of developing cancer and lymphoma. The actual risk is unclear, however, because the relative risk has been compared to that of the general population. Nevertheless, there are a large number of case reports or case series linking the occurrence of lymphoma (mostly diffuse large-cell non-Hodgkin lymphomas) in patients with RA receiving low-dose weekly methotrexate. In most cases, cessation of therapy is associated with complete regression of the lymphoid cancer, suggesting a causative relationship. DNA analysis shows that approximately 50% of these lymphomas harbored the Epstein-Barr virus genome. It is, therefore, possible that the drug regimen may promote the malignant transformation of normal lymphoid tissue by the oncogenic virus. Patients with RA on azathioprine and cyclosporin A have a twofold increased risk of lymphoma relative to control patients with RA. A real association between the use of immunosuppressive therapy and the development of lymphoproliferative disorders also occurs with organ transplantation. The incidence of non-Hodgkin lymphoma is 50-fold greater in patients with renal transplant, especially if they receive cyclosporin A as part of their immunosuppressive regimen.

The issue of cancer risk in patients on anti-TNF agents has already been discussed. Cyclophosphamide is commonly used to treat severe lupus manifestations, including nephritis and cerebritis. Patients with lupus on cyclophosphamide are more likely to develop bladder cancer, lymphoma (primarily non-Hodgkin lymphoma), and possibly skin cancer. A small increased cancer risk has also been reported in patients with RA treated with the drug.

Chemotherapy-Associated Rheumatologic Complications

As many as half of women receiving aromatase inhibitors for breast cancer experience subjective joint achiness or pain, but these symptoms rarely translate to frank arthritis. Taxanes (eg, paclitaxel and docetaxel) are used for many breast and gynecologic cancers, as well as for HIV-related Kaposi sarcoma. These drugs may cause myalgias and arthralgias, as well as skin rashes with histologic features of subacute cutaneous lupus. Rapid cell turnover from chemotherapy, particularly in cases of lympho- and myelo-proliferative malignancies, can result in an acute gout attack if the patients are not given adequate prophylactic treatment. Bisphosphonates are increasingly used as part of chemotherapeutic regimens in metastatic bone disease, and their use is associated with a number of musculoskeletal complications including complications of hypocalcemia, osteonecrosis of the jaw, and atypical femur fractures. Bleomycin use has been linked to Raynaud phenomenon and scleroderma-like skin diseases.

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Chapter 122

Back Pain and Spinal Stenosis

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Learning Objectives

- Review the epidemiology of back pain in older adults, including associated psychosocial factors.
- Understand how back pain is classified and its clinical course.
- Recognize the broad differential of back pain etiology in older adults.
- Understand the value of history, physical examination, and observation when evaluating an older adult with back pain and the indications for imaging in this population.
- Select management of back pain in older adults that combines pharmacologic and nonpharmacologic (including behavioral, activity-based) modalities.

Key Clinical Points

1. **Back pain is one of the most common pain complaints among older adults leading to considerable morbidity and cost.**
2. **Diagnostic and therapeutic costs have increased; however, outcomes have not improved.**
3. **Back pain must be assessed in the context of comorbid conditions (including mental health conditions and potentially other sites of pain) as multimorbidity impacts management.**
4. **Psychosocial factors (such as depression and pain related fear avoidance and/or pain catastrophizing) play an important role in the experience of back pain and potentially mediate the relationship with subsequent outcomes (such as disability).**
5. **Infection, malignancy, and compression fractures must be ruled out prior to characterizing nonspecific mechanical back pain.**
6. **Imaging of the spine often demonstrates anatomic abnormalities in asymptomatic older adults and should only be ordered in presence of red flags.**
7. **A combination of pharmacologic, nonpharmacologic, and rehabilitative approaches (including physical therapy, occupational therapy, and/or spinal manipulation) in addition to a strong therapeutic alliance between the patient and physician is essential in setting, adjusting, and achieving realistic goals of therapy.**
8. **Multimodal management programs for back pain can be tailored to the older adult's preferences and abilities.**

EPIDEMIOLOGY

Low back pain in older adults is a major public health problem with significant consequences. Prevalence estimates range from 6% to 84% depending on the population evaluated, the study design, and the definition of back pain used. One study conducted in Israel found that 44% of 70-year-olds and 58% of 77-year-olds reported back pain. In the Framingham Heart Study cohort (ages 68–100), 22% of participants reported back pain on most days. As the second

most common reason for visiting a physician, annual costs related to low back pain exceeded $100 billion (in 2005 dollars) and are expected to rise with the aging population. Over the past decade, health care–related spending on low back pain diagnostic and "therapeutic" procedures has skyrocketed, yet patient outcomes (in all age groups) have not improved.

A recent study, analyzing the data of more than 13 years, shows that older adults are more likely to develop recurrent episodes of back pain if they are female, suffer from depressive symptoms, have two or more chronic conditions, or self-report arthritis. Back pain in older adults is associated with dependence in daily living activities, mobility impairment, and poor self-reported health. The association of back pain and physical function has been quantified; the number of months with back pain (resulting in restricted activity) is associated with such markers of frailty as gait speed, chair stands, and foot tap performance. In a study of Medicare beneficiaries 65 years and older, back pain was second only to shortness of breath while climbing stairs in its association with impaired general physical health status. Cross-sectional data from the Framingham Heart Study have shown that back symptoms account for a large percentage of functional limitations in older adults, especially in women. Psychosocial factors, including comorbid depression or anxiety as well as pain related fear avoidance and pain catastrophizing, play an important role in the experience/reporting of back pain and potentially mediate the relationship with subsequent disability.

Additional research is needed to evaluate patterns of back pain, health care utilization, and outcomes over time in older adults. While low back pain is a common problem in older adults, its etiology, natural history, and therapy are not fully understood and often not well defined.

CLASSIFICATION

Back pain is often categorized as acute (lasts < 4 weeks), subacute (lasts between 4 and 12 weeks), or chronic (lasting > 3 months; some definitions require > 6 months). While much of the literature evaluates chronic symptoms, research shows that low back pain is *not* likely constant, but rather, recurrent or episodic. Understanding the various patterns of back pain in older adults, including what precipitates recurrent episodes, is important as prevention and treatment planning may differ.

ETIOLOGY/PRESENTATION OF BACK PAIN

A number of discrete conditions may cause back pain in older adults (**Table 122-1**). These conditions include mechanical causes, lumbar spinal stenosis, sciatica, vertebral compression fractures, osteoporotic sacral fractures, tumors, and infections. Systemic conditions such as malignancy and infections, although rarely the cause of back pain, are more common in older compared to younger age groups. One of the most challenging aspects of assessing and managing back pain is identifying the source(s) of pain in the older adult who often has multiple musculoskeletal comorbidities (eg, trochanteric bursitis, hip osteoarthritis, multilevel lumbar degenerative changes and lumbar stenosis). These conditions rarely occur in isolation and pinpointing which one contributes most to the patient's pain may be difficult, but vital.

TABLE 122-1 DIFFERENTIAL DIAGNOSES FOR BACK PAIN IN OLDER ADULTS

Nonsystemic/mechanical causes of back pain
Lumbar strain (muscle)
Spinal stenosis
Degenerative disease: Spondylosis (discs and facet joints)
Spondylolisthesis
Spondylolysis
Sciatica
Piriformis syndrome
Herniated disc
Osteoporotic vertebral or sacral compression fractures

Diffuse idiopathic skeletal hyperostosis (DISH)
Congenital disease: Kyphosis, scoliosis
Systemic causes of back pain
Malignancy: Multiple myeloma, metastatic disease, lymphoma, spinal cord tumors, retroperitoneal tumors
Infection: Osteomyelitis, septic discitis, paraspinous abscess or septic emboli (sometimes related to bacterial endocarditis)
Inflammatory arthritis: Ankylosing spondylitis, psoriatic arthritis, reactive arthritis, inflammatory bowel disease
Osteochondrosis
Paget disease
Visceral: Aortic aneurysm, prostatitis, nephrolithiasis, pyelonephritis, perinephric abscess, pancreatitis, cholecystitis, penetrating ulcer, fat herniation of lumbar space

The vast majority of low back pain seen in primary care settings is labeled “nonspecific low back pain” as there is no specific attributable disease or spinal pathology. The natural history, associated features, and etiology of back pain in older adults remain poorly characterized. However, one approach to the assessment of back pain in older adults is to evaluate those patients for the historical, physical, and diagnostic imaging features of these discrete conditions, below, and then to appraise the patient with nonspecific low back pain without one of these conditions.

Tumor

The clinician must always be alert to nonmechanical, either referred or systemic, causes of low back pain. Visceral causes of back pain, such as abdominal aortic aneurysms or pancreatic cancer, are usually nonpositional, progressive, and associated with a normal examination of the lumbar spine and hip. Tumors usually present with a gradual onset and progressive course, with persistent worsening of the pain over weeks and months. This insidious onset of pain, which is initially mild but progressive in severity, is quite distinct from the abrupt onset and positional characteristics of mechanical low back pain. Tumor pain is often nonpositional, lasts longer than 4 weeks, and is associated with systemic/constitutional symptoms.

Infection

Although a rare cause of back pain, vertebral and disc infections can be difficult to distinguish from a mechanical cause of back pain; disc infections can cause the same abrupt onset, positional changes, and L4, L5 and L5, S1 neurologic abnormalities seen in mechanical disc disease. Back pain is the most common musculoskeletal complaint seen in endocarditis, due to metastatic infection (abscess or septic emboli). Because the disc is often involved in this condition, the signs and symptoms can mimic mechanical disc disease. Fever can be absent in older patients with infection. The clinician must be alert to a possible infectious cause of back pain for patients with a high risk of endovascular infection (artificial heart valves, indwelling venous catheters, intravenous drug abuse, etc) and in patients with systemic symptoms and signs of inflammation.

Vertebral Compression Fractures

The abrupt onset of severe back pain, especially in a patient with risk factors for osteoporosis, with or without a history of falls, should always call for a spinal x-ray to rule out a vertebral compression fracture (**Table 122-2**). Vertebral compression fracture is the most common type of osteoporotic fracture. Those that occur slowly (especially in the mid and upper thoracic spine) are often asymptomatic. Only approximately 30% to 40% of vertebral compression fractures are symptomatic. Most symptomatic fractures are in the lower thoracic and lumbar spine. Height loss and kyphosis can occasionally trigger suspicion for vertebral fractures.

TABLE 122-2 ■ CHARACTERISTICS OF VERTEBRAL COMPRESSION FRACTURE

Severe pain with lower thoracic and lumbar fracture
High and mid-thoracic fracture often asymptomatic
Pain resolves in 4–6 wk
Increased risk for subsequent fracture

At times, the initial x-ray is normal and the changes of vertebral collapse appear several days to weeks after the onset of pain. As there is no dislocation with osteoporotic vertebral fractures, neurological signs and symptoms are quite rare. Pain is usually localized to the midline spine but may be referred, however, into the chest, abdomen, or leg. Any movement, including rolling in bed, bending, coughing or lifting, usually exacerbates the pain. Pain, and muscle spasm if present, then gradually improve over the next several weeks and resolves in 4 to 6 weeks. Persistent severe pain (symptoms that continue despite the expected normal period of healing) may suggest additional fractures or an alternative diagnosis.

The presence of a vertebral fracture does increase the risk of a subsequent vertebral and nonvertebral (ie, hip) fractures. One study suggests that 19% of patients who sustained a vertebral compression fracture will have another fracture in the next year. The relationship between osteoporosis and vertebral fracture and chronic back pain and disability is still under investigation. Osteoporotic compression fractures that develop slowly over time are often asymptomatic and may not lead to deleterious sequelae. While some studies have shown increased disability in patients with vertebral fractures, a British population-based study found no correlation between minor vertebral deformities and back pain. Functional impairment from vertebral compression fracture appears to be comparable to that related to hip fracture. In the multicenter Study of Osteoporotic Fractures, investigators found an increase in back pain, disability (in six activities of daily living), and height loss if vertebral deformities (wedge, end plate, and crush) were greater than or equal to 4 standard deviations from the mean. Still, using this large cross-sectional study, these investigators suggest that causes other than vertebral deformities are likely causing much of the back pain in this cohort.

Osteoporotic Sacral Fractures

There have been a number of reports of “sacral/pelvic insufficiency fractures” as a cause of back pain. Older patients, usually women, may report persistent pain in the low back, groin, or buttock area, occasionally lasting from weeks to months. The application of pressure to the sacrum is very painful. Associated neurologic defects are rare, however, if present are consistent with sacral radiculopathy. Leg length discrepancy, abnormal positioning of the leg, focal tenderness around the hip/pelvis, or limited range of motion of the leg should raise suspicion for pelvic injury. The pain usually resolves spontaneously in 4 to 6 weeks. Approximately 50% of these patients had a preceding fall, and the majority of patients have old pelvic and vertebral compression fractures on x-ray.

A sacral insufficiency fracture should be considered especially in older adults with risk factors for fracture (ie, osteoporosis, low body weight, glucocorticoid therapy) and with sudden pain in the low back and buttock with sacral tenderness. Plain radiographs of the pelvis, despite low sensitivity for small fractures, should be obtained to evaluate hip, pelvic, and lumbosacral spine fractures. If plain films are negative but clinical suspicion is high, MRI or CT scan may be useful to document minor pelvic fractures. Some advocate for treating patients symptomatically without advanced imaging so long as other important diagnoses have been ruled out and appropriate follow-up has been arranged.

Sciatica

Sciatica is usually defined as pain radiating to one leg below the gluteal fold. It is often felt in the buttock area, radiating into the posterior aspect of the leg down to the ankle. It may, however, be incomplete, as in the calf pain seen in the “pseudoclaudication” syndrome with lumbar spinal stenosis. The natural history of this condition is well defined in younger adults. Fifty percent of these patients have full resolution of symptoms within 6 weeks. While there are no studies of the natural history of sciatica in older patients, many clinicians do find that sciatica, which develops abruptly and occurs in all positions, usually has a good natural history, similar to that seen in younger individuals. Patients who develop sciatica as part of the lumbar spinal stenosis syndrome, with gradual progression of pain with shorter and shorter periods of standing and walking, may have a more prolonged and persistent natural history.

Lumbar Spinal Stenosis

Narrowing of the intraspinal (central) vertebral canal, lateral recess and/or neural foramina is frequently seen on diagnostic imaging tests of the lumbar spine in older individuals. These abnormalities, often caused by spondylosis or degenerative arthritis affecting the spine, have clinical significance only if the typical history of lumbar spinal stenosis is present (**Table 122-3**). Changes in spinal dynamics with movement explain some of the clinical features of lumbar spinal stenosis. Flexion of the lumbar spine decreases the intraspinal protrusion of the disc, decreases the bulge of the

yellow ligaments within the canal, and stretches and decreases the cross-sectional area of nerve roots, resulting in an increase in spinal canal volume in relation to nerve root bulk. Extension of the lumbar spine causes bulging of the disc into the canal, enfolding and protrusion of the yellow ligaments into the spinal canal, and a relaxation and increase of the cross-sectional diameter of nerve roots. Extension of the canal thus produces a decreased volume of the spinal canal in relation to nerve root bulk.

TABLE 122-3 CHARACTERISTICS OF LUMBAR SPINAL STENOSIS

Pain with extended spine
Prolonged standing
Walking
Walking down hill
Pain relieved on flexing spine
Sitting
Leaning on walker or grocery cart
Sciatic pain on walking
Incomplete sciatica—"pseudoclaudication"

These changes in dynamics explain the clinical picture of lumbar spinal stenosis. Positions that extend the spine (standing, walking down hill, prone lying, and extending the back) worsen symptoms, while positions that flex the spine (sitting, bending forward, placing weight on a walker or cart, and lying in a flex position) relieve the symptoms.

Patients with lumbar spinal stenosis present with pain, either in the lower back or legs, which comes on with prolonged standing and walking and is relieved with sitting. Individuals with this condition will often bend their spine more as they walk and find that they can walk further in a grocery store, supported by a cart. The leg pain can present with a classic picture of sciatica (pain radiating from the posterior aspect of the buttock down to the foot) or an incomplete "pseudoclaudication" syndrome, in which the patient feels pain only in the calf while standing and walking.

Lumbar spinal stenosis should not produce pain when going from lying to sitting and should not produce severe pain with bending, stooping, or lifting objects. New back pain/leg symptoms in an older patient and/or neurologic deficits usually warrant imaging to determine structural narrowing of the lumbosacral spine. Plain radiographs of the spine may suggest a diagnosis of lumbar spinal stenosis, however, MRI or CT with myelography help to better define bony anatomy and visualize soft tissues and neural structures. Still, there is little consensus on best criteria to define lumbar spinal stenosis or its severity. Further, radiographic evidence of spinal stenosis is a common incidental finding (up to ~30% in asymptomatic older adults) and should always be correlated clinically.

Mechanical Low Back Pain

The majority of older adults with low back pain do not have tumors, infections, lumbar spinal stenosis, or vertebral compression fractures (**Table 122-4**). They are best described as patients with mechanical back pain of uncertain etiology.

TABLE 122-4 CHARACTERISTICS OF MECHANICAL LOW BACK PAIN

Intermittent sharp back pain
Pain comes on and subsides rapidly
Pain going from lying to sitting and with bending
Asymmetric loss of motion of lumbar spine
Weakness of L4, L5, L5, and S1 innervated muscles

A good deal of back pain in younger individuals is probably caused by displacement of the outer annulus fibrosis or inner nucleus pulposus of the intervertebral disc. The disc does not contain pain fibers: the perivertebral structures with the most sensitive pain fibers are the posterior longitudinal ligament and the dura mater, which lie posterior to the

vertebrae and discs. The sinuvertebral nerve innervates these structures. Irritation of this nerve causes reflex spasms of the paravertebral muscles of the lumbar spine. It is, thus, logical to assume that soft-tissue displacement in this area will cause pain and limitation of some, but not all, of the planes of movement of the lumbar spine, spasm of the paravertebral muscles, and subtle weakness of the muscles innervated by the appropriate nerves roots (L4, L5, and S1—in most cases).

In a young adult's lumbar spine, the central nucleus pulposus often herniates outside the annulus fibrosis and indents the pain-sensitive posterior longitudinal ligament and dura mater, producing pain that often lasts for several weeks and occasionally causing sciatica owing to nerve root irritation. Because the nucleus pulposus loses water content with aging, herniation of this structure is less common beyond the age of 55 years.

Older patients often have a syndrome of sharp pain in the lumbar area, worsened with bending movements, which comes on and subsides rapidly but recurs frequently. On physical examination, these patients often have asymmetric loss of range of motion in the lumbar spine, paravertebral muscle spasm, weakness of the L4-, L5-, and S1-innervated muscles, and pain going from the flexed to the erect position. Clinicians often use the term "unstable lumbar spine" to describe this syndrome, although the evidence for specific mechanical instability is lacking. Patients with this condition often have one intervertebral disc space narrowed and sclerotic changes out of proportion to other disc spaces, and anterior displacement of one vertebra on another (spondylolisthesis). Maneuvers such as going from lying to sitting and bending forward often produce pain. Before considering major interventions, it is important to distinguish this condition, in which pain results from movement of the lumbar spine (eg, lying to sitting), from lumbar spinal stenosis, in which pain results from prolonged extension of the spine (standing and walking).

Diffuse Idiopathic Skeletal Hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH) is characterized by calcification of prevertebral and peripheral ligaments. Ossification of spinal ligaments is often confused with osteophytes, and the condition is frequently mislabeled as disc degeneration or osteoarthritis. Spinal involvement is characterized by the following: (1) the presence of flowing calcification and ossification along the anterolateral aspect of at least four contiguous vertebral bodies, (2) relative preservation of intervertebral disc height in the involved area, and (3) the absence of apophyseal joint bony ankylosis or other features of ankylosing spondylitis.

Most studies have not found any association with DISH and back pain, while other studies have noted an increase in ligamentous tenderness, stiffness, and immobility of the cervical, thoracic, and lumbar spine in individuals with this condition. The condition should be distinguished from disc disease with vertebral osteophytes and is a cause of significant spinal immobility in older individuals.

EVALUATION

The evaluation of the older adult with back pain depends heavily on the history, physical examination, and observation of the patient. The history and physical examination remain the most helpful tools in the assessment of back pain in older adults, particularly because of the high false-positive rate of spinal diagnostic imaging tests in this age group. Laboratory tests and diagnostic imaging studies have a secondary role in the assessment of these patients. The clinician must verify that the clinical presentation of the patient fits the results of the diagnostic imaging tests before proceeding with interventions.

The role of the clinician in assessing and managing back pain in older individuals focuses on (1) identifying those conditions that require immediate attention (eg, infections and tumors), (2) recognizing the usual patterns of pain for defined causes of back pain, (3) assisting the patient with therapy for these specific conditions, (4) educating the patient on the natural history, precipitating events, and therapeutic approaches to nonspecific mechanical low back pain, and (5) establishing realistic expectations, identifying goals of management, and assessing progress toward these goals over time.

History

Patients with a mechanical cause for pain usually have intermittent, positional pain, often with the peak intensity of pain at the episode onset (**Table 122-5**).

TABLE 122-5 HISTORY ITEMS THAT HELP DIFFERENTIATE CAUSES OF BACK PAIN

Abrupt onset of pain
Vertebral compression fractures
Mechanical low back pain
Insidious onset, progressive course, nonpositional pain
Tumor
Infection
Nonspinal visceral pain
Positional attributes
Pain when lying to sitting or bending
Mechanical low back pain
Pain when standing and walking, relieved with sitting
Lumbar spinal stenosis
Nonpositional
Tumor
Infection

Pain that is worse on going from lying to sitting and with bending, that occurs when one suddenly changes position, and that resolves quickly but recurs frequently, suggests mechanical disease of the lumbar spine as a result of soft-tissue displacement. Severe pain in any position, which comes on abruptly and is aggravated by even rolling over in bed, suggests a vertebral compression fracture. A woman with sacral and buttock pain, sacral tenderness, and osteoporosis should be evaluated for a sacral insufficiency fracture. Gradually worsening progressive pain, lasting more than a month, which is nonpositional and associated with systemic symptoms and signs, might suggest tumor. Hip disease can often mimic back problems. Pain that is worse when going from sitting to standing and that causes a limp indicates possible hip disease.

Physical Examination

The clinician must first determine whether the problem is in the hip or back. It can be difficult to distinguish these conditions, as both can give buttock and low back pain. Pain that occurs when going from the supine to sitting position is more apt to be from the back, while groin pain, worsened with weight bearing, favors the hip. A complete examination of the passive range of motion of the hip, done with the patient in the supine position, should reveal 40 degrees of hip abduction, more than 100 degrees of flexion, 50 to 60 degrees of external rotation, and 20 degrees of internal rotation. In addition, a manual muscle examination of the lower extremities, which demonstrates mild weakness of the L4, L5 (hip abductor and great toe extensor) and L5, S1 (hip extensors) innervated muscles of the lower extremities, favors the back as the cause of pain. One recent study demonstrated that the presence of groin pain, a limp, and limited internal rotation of the hip all favored the hip as the cause of pain.

Several findings on physical examination can be useful in determining discrete causes of back pain (**Table 122-6**).

TABLE 122-6 PHYSICAL EXAMINATION FINDINGS THAT HELP DIFFERENTIATE CAUSES OF BACK PAIN

Paravertebral muscle spasm
Mechanical low back pain
Vertebral compression fracture
Asymmetric loss of range of motion of lumbar spine
Mechanical low back pain
Weakness of great toe extensor and hip abductor (L4, L5) and hip extensors (L5, S1)
Mechanical low back pain
Lumbar spinal stenosis

The physical examination of the lumbar spine is an essential component of the assessment of a patient with back

pain (**Figure 122-1**). This is best done while standing. The examiner observes the patient for kyphosis or scoliosis and then palpates for paravertebral muscle spasm. The patient is then brought through the four ranges of motion of the lumbar spine, side flexion to the right, side flexion to the left, forward flexion, and extension, observing for asymmetric limitation of motion or reproduction of the patient's pain by these maneuvers (see **Figure 122-1**). In the supine position, straight leg raise tests can indicate nerve root irritation if positive, but a negative test does not exclude any condition. The hips should be examined by testing the passive range of motion. The examiner should be able to abduct the leg to 40 degrees before the pelvis tilts. There should be 60 degrees of external rotation (heel toward the midline) and 20 degrees of internal rotation (heel away from the midline) of each hip (**Figure 122-2**).

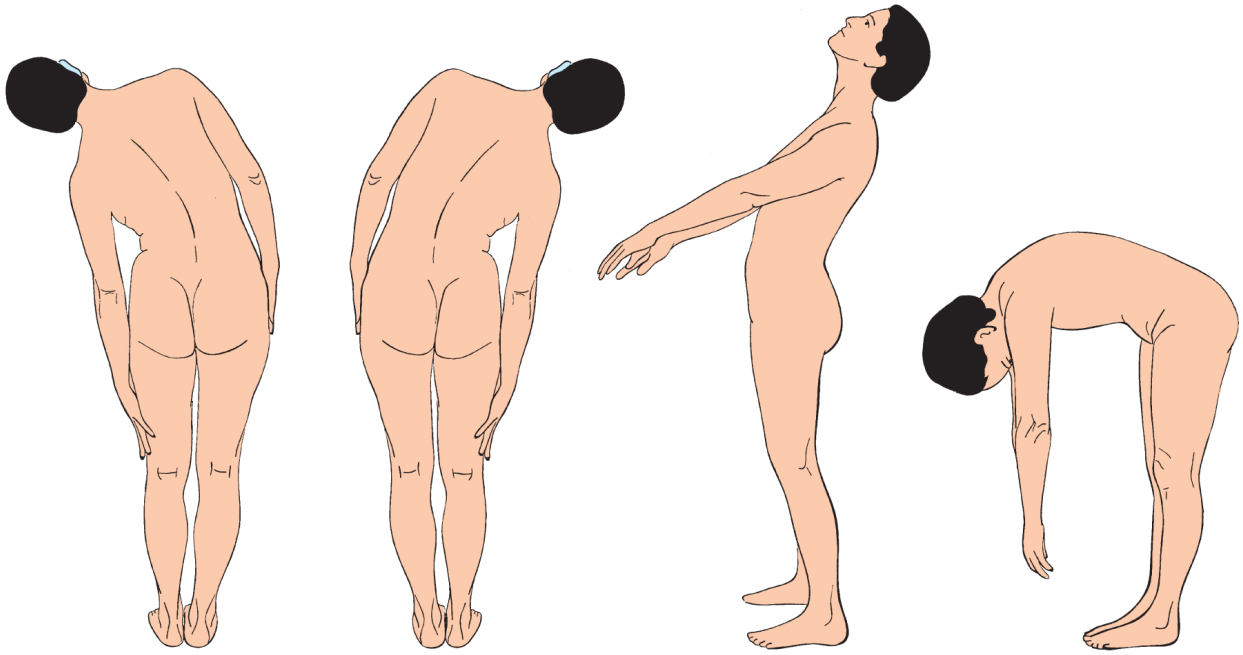


FIGURE 122-1. Range of motion of lumbar spine.

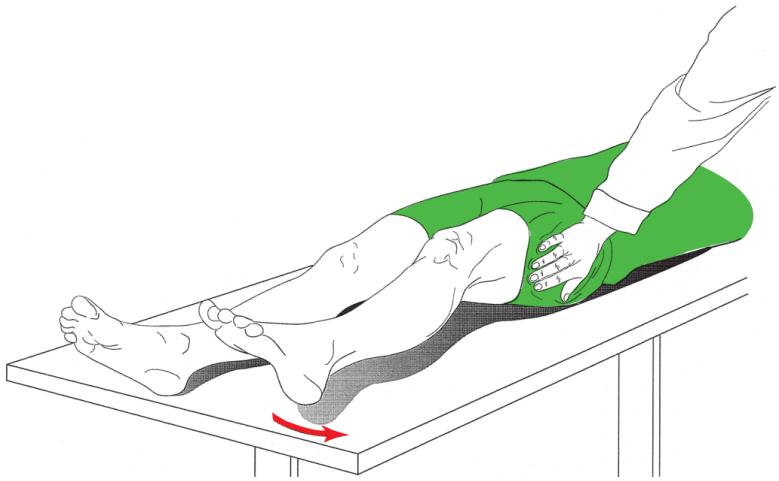


FIGURE 122-2. Resisting abduction of the leg.

Manual muscle testing of the lower extremity gives much useful information, as subtle L4, L5 and L5, S1 weakness is common in patients with mechanical back pain. L4, L5 is tested by resisting the patient's abducted leg at the lateral upper thigh (gluteus medius muscle) (see **Figure 122-2**), by resisting the patient's ability to dorsiflex the foot (tibialis anterior muscle), and by resisting the great toe extensor (extensor hallucis longus) (**Figure 122-3**). L5, S1 (gluteus maximus muscle) is tested by trying to overcome hip extension (trying to pull the leg off the examining table, when the patient has been instructed to hold the leg firmly on the table). One can also test L5, S1 by resisting the patient's ability to evert the foot (peroneus longus and peroneus brevis).

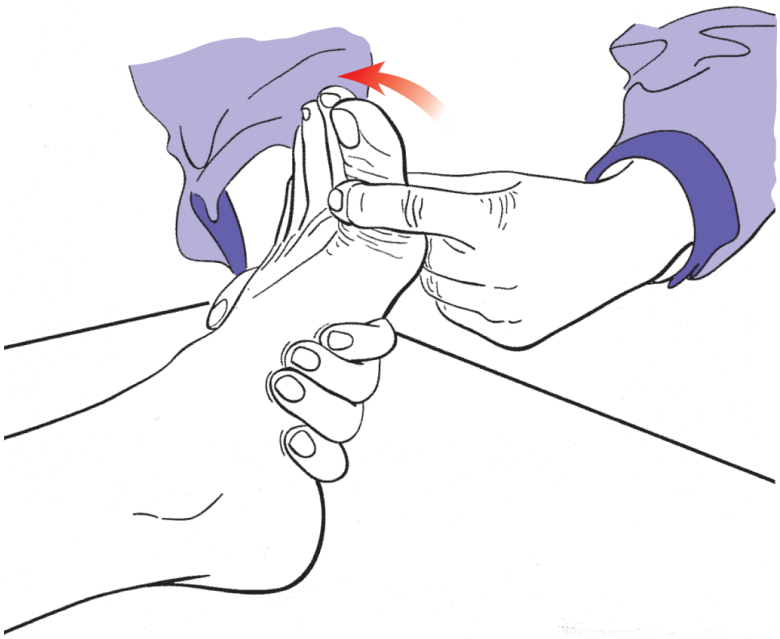


FIGURE 122-3. Resisting great toe extensor.

Most patients with lumbar disc disease or lumbar spinal stenosis will have some abnormalities of the examination of the lumbar spine or of the muscles innervated by L4, L5 or L5, S1. Patients with vertebral compression fractures may have a good deal of tenderness in the lumbar spine but should have no neurologic abnormalities. Patients with osteoporotic sacral fractures will have sacral tenderness, but a normal lumbar spine examination and no lower extremity muscle weakness. Those with sciatica almost always have L4, L5 and L5, S1 weakness. A patient with persistent, severe back pain, but with a normal examination of the lumbar spine, sacrum, and hips and no evidence of L4, L5 or L5, S1 muscle weakness, should be evaluated thoroughly for a possible neoplasm or infection.

New neurologic abnormalities (dermatomal sensory deficits, focal weakness, clonus) associated with abrupt onset back pain may suggest retropulsed bone fragments in the spinal canal or foraminae which should be further evaluated with urgent MRI or CT scan and urgent consultation with a spine surgeon.

Laboratory Tests and Imaging

The interpretation of diagnostic tests in older patients with back pain is a challenge, given the high rate of abnormal tests in asymptomatic individuals in this age group. A CBC and an ESR/CRP are reasonable screening tests if the patient's history and physical examination suggests a tumor or infection. While routine imaging for low back pain in younger populations is not recommended, plain films of the spine may be appropriate in older adults with back pain. A plain x-ray of the lumbar spine is more helpful in the evaluation of older patients than younger ones, as it may demonstrate a vertebral compression fracture, DISH, or spondylolisthesis.

According to the American College of Radiology, the criteria listed in **Table 122-7** should be used to determine who is at higher risk for systemic disease-related back pain and when imaging is appropriate.

TABLE 122-7 ■ RED FLAGS FOR BACK PAIN DUE TO SYSTEMIC DISEASE

Age > 70
Recent significant trauma or milder trauma (age > 50)
Unexplained weight loss or fever
Immunosuppression (such as diabetes mellitus)
History of cancer
Osteoporosis or prolonged use of glucocorticoids
Focal neurologic deficits that are progressive or produce disabling symptoms
Duration of symptoms > 6 wk or more (subacute or chronic)
IV drug use

The clinician must be aware that changes in the lumbar spine are ubiquitous in older individuals and not well correlated with back pain. Kellgren and Lawrence's classic epidemiological study in Leigh, England, found that 89% of the males and 57% of the females between the ages of 55 to 64 years had disc degeneration of the lumbar spine. A 1984 study of lumbar sacral spine x-rays found no association between back pain and Schmorl nodes, the disc vacuum sign, traction spurs, and disc space narrowing between the third and fourth lumbar vertebrae, or between the fifth lumbar and first sacral vertebrae. There was an association between acute low back pain and disc space narrowing, and traction spurs between the fourth and fifth lumbar vertebra. Another study found no correlation between vertebral osteophytes and low back pain but did find increased back pain in individuals with spondylolisthesis (pars interarticularis defect and frontal slippage of one vertebra on an adjacent vertebra).

MRIs of the lumbar spine often demonstrate anatomic abnormalities in asymptomatic individuals, especially in older adults. In a 1994 study of MRIs of the lumbar spine in patients without back pain, only 36% had a normal examination; 52% of these individuals had a disc bulge in at least one level, and 27% had disc protrusions. In another study of asymptomatic individuals, 36% of subjects older than 60 years had a herniated nucleus pulposus, 21% had spinal stenosis, and 93% had degenerative disc disease. A 1998 study found that 56% of asymptomatic individuals had tears of the annulus fibrosis of the lumbar disc. In a VA study of 198 subjects who had had no back pain for at least 4 months, 83% had moderate-to-severe degeneration of the disc, 64% had at least one bulging disc, and 32% had at least one disc protrusion. In individuals older than 65 years, 100% had disc degeneration and desiccation, 83% had a disc bulge, and 38% had facet joint degeneration.

The above findings indicate that the clinician cannot depend on imaging studies to diagnose the cause of back pain in older adults. These studies are used to confirm a diagnosis, indicated by the history, physical examination, and by the clinician's knowledge of applied anatomy.

MANAGEMENT

Back pain in older adults is often inadequately treated for several potential reasons including: a limited evidence base to guide management, lack of physician education, physician concerns about the potential for treatment-related harm, and older adults' beliefs about pain and pain treatments. Other barriers to treatment that are specific to geriatric populations include *age-related* physiologic changes resulting in altered drug absorption and decreased renal excretion; sensory impairments; polypharmacy; and multimorbidity. Additional attitudinal, access and system-level barriers have been identified that also contribute to undertreated pain in vulnerable populations, including older adults.

Management of back pain should begin with a combination of nonpharmacologic and rehabilitative approaches, as described below, along with pharmacologic and then more invasive management strategies if indicated, depending on the circumstance (listed by specific etiology).

Nonpharmacologic Approaches (General Principles)

Interest in nonpharmacologic approaches for managing back pain in older adults is increasing. Nonpharmacologic approaches include cognitive (eg, distraction), acupuncture, mindfulness, massage, self-management programs and/or behavioral (eg, goal setting, exercise, tai chi, yoga) techniques that constitute well-established methods for treating pain (in general). Existing evidence suggests that these therapies are safe, can reduce pain, and in many cases improve patient function. Nearly all studies of nonpharmacologic interventions conducted to date, however, have been for short term (< 6 months). The long-term efficacy and ability of older adults to sustain their use over time remain inadequately defined. Despite this, temporary relief from back pain may offer an opportunity to develop positive expectations and commitments from the patient and provider.

It is important to communicate to older patients that using both nondrug and drug therapies is the standard of care and can be productive, particularly with individuals who may hesitate to engage in nonpharmacologic treatments. Recommending a specific nonpharmacologic modality will depend upon its availability, affordability (eg, Medicare does not cover many of the approaches listed, however), patient preferences, and the physician's ability to accurately describe its benefits and risks. As there are no head-to-head comparisons evaluating the nonpharmacologic approaches, recommending a modality that is accessible and affordable is essential.

Rehabilitative Approaches

Addressing function and fall risk is critically important for all geriatric patients, particularly in those with persistent pain, including chronic back pain. Rehabilitative therapies, including physical therapy (PT) and occupational therapy (OT), can help maintain and possibly enhance functional independence. Geriatric pain management guidelines recommend that all older patients with persistent pain (including back pain) adopt physical activity regimens that include strengthening, flexibility, balance, and endurance exercises. PTs/OTs can help older adults implement individualized home-based treatment programs. Home-based services directed at improving safety and mobility could potentially facilitate involvement in out-of-home activities; these services might indirectly yield dividends such as more time spent socializing with family and friends. Physical therapists can play an important role in developing "function-enhancing interventions" in older adults with mobility limitations.

In addition, PTs can conduct an inventory of existing equipment (eg, does the patient have a functional walker?) and make recommendations about new assistive/mobility devices. OTs can directly observe a patient's ADL functioning in the home and make recommendations about assistive devices that may help to improve ADL functioning. Both paid and family caregivers, especially of older adults with cognitive impairment, can reinforce patient's ongoing use of rehabilitative techniques and should be engaged and empowered to do so. Finally, PTs/OTs can also train caregivers to reinforce concepts learned during treatment sessions, including coaching on fall risk, safety, body mechanics, and pacing.

Rehabilitation health care specialists often use various modalities including both therapeutic exercise and spinal manipulation. There is growing popularity and interest in spinal manipulation (often defined as [low to] high velocity and low amplitude thrust and/or manual mobilization of vertebral joints and/or soft tissue manipulation, performed by either a chiropractor, physiotherapist, or other manual health care practitioner) for both acute and chronic back pain. As of yet, there are no studies proving the mechanism underlying the benefit of spinal manipulation. There are strongest data for patients with acute low back pain (without radiculopathy); however, this population has a favorable prognosis even without manipulation. Most studies have focused on chronic back pain, and often exclude subjects with spinal stenosis, spondylolisthesis (second degree or more), lumbar scoliosis (> 20 degrees or more), previous vertebral fractures (seen more often in older adults), systemic causes of chronic back pain (including ankylosing spondylitis, infection, or metastatic disease), or psychiatric or cognitive comorbidities. In the general population (including younger adults), spinal manipulative therapy and spinal stabilization have shown improvements in both pain and function as compared to various treatments (back school—education, relaxation techniques, postural and tailored back exercises, individual physiotherapy—mobilization, active exercise, massage, education, or general exercise), especially in the short term. While data suggest there is a statistically significant improvement with spinal manipulation, its clinical importance remains uncertain.

ETIOLOGY-SPECIFIC MANAGEMENT

Therapy of tumors and infectious causes of low back pain is straightforward albeit often difficult. Appropriate management of vertebral compression fractures, lumbar spinal stenosis, and mechanical low back pain is less clear.

Vertebral Compression Fractures

The traditional treatment for vertebral compression fractures is activity modification and pain control at the onset of symptoms. Oral analgesics are usually needed for acute pain relief due to vertebral compression fracture. These include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), mild opioids combined with acetaminophen, tramadol, or medications that block serotonin or norepinephrine reuptake. Calcitonin (2- to 4-week course) does have some additional analgesic effect in the acute stage. The choice of first-line agent depends on severity of symptoms and the patient's comorbidities. Muscle relaxants have not been rigorously evaluated in this setting and given the high rate of adverse effects in older adults should be used cautiously. Opioids, when necessary, should be used cautiously given known side effects particularly in older adults (sedation/altered mental status, constipation, nausea). For severe pain, hospitalization for pain management may be warranted.

Despite prior beliefs, complete bed rest is not recommended. Patients should resume physical activity as soon as possible (as pain permits). Physical therapy should focus on gait and core strengthening. Aquatic therapy has been shown to accelerate pain relief and physical activities. In several studies, exercise programs have reduced analgesic use and improved quality of life in older adults with vertebral fractures. Education including management of expectations (eg, that it can take several months for the pain to improve) is essential. Bracing is not usually needed for pain management from osteoporotic compression fractures, although it has been shown to be helpful in acute management

of patients with traumatic vertebral compression fractures. Long-term use of bracing should be avoided as its use may lead to immobility of the spine, weakening of paraspinal and core muscles, as well as potential for disuse osteoporosis.

Long-term management of vertebral compression fractures, related to osteoporosis, focuses on improving low bone density (ie, antiresorptive therapy). Underlying conditions that are present and may contribute to development of vertebral compression fractures (hyperthyroidism, granulomatous diseases, infections) require further, specific management beyond the scope of this chapter. Lifestyle modification, namely, smoking cessation and reducing alcohol use, are important. Fall prevention education is effective and essential especially in older adults who have already experienced a traumatic fall or at risk for falls.

There is much interest in vertebral augmentation (the techniques of vertebroplasty and kyphoplasty) in the management of vertebral compression fractures. In a vertebroplasty, extension positioning opens the cleft within a fractured vertebral body, and bone cement is injected into the vertebral body and stabilizes the fracture in this position. In a kyphoplasty, an inflated bone balloon displaces vertebral trabelate and elevates the superior end plate, allowing some restoration of the height of the vertebral body. The balloon is then removed and bone cement is injected into the vertebral space.

The indications and timing for the use of these augmentation procedures is controversial. Current evidence supporting use of these procedures is of low quality. In the acute setting, although uncontrolled studies show encouraging relief of pain with vertebroplasty, the favorable natural history of the pain from compression fractures, and the potential complications and expense of this procedure, should lend caution to its use. In a nonrandomized trial, the control patients were those who elected not to have the procedure. The pain score was significantly decreased in the vertebroplasty group as compared to the conservative therapy group in the first few days, but there were no significant differences in clinical outcomes at 6 weeks or 6 to 12 months. In a study of patients who had pain for greater than 1 year associated with compression fractures, kyphoplasty was performed on 40 patients, with 20 control patients who elected not to have the procedure. At 1 year, the patients with kyphoplasty had fewer new fractures, fewer back pain-related physicians' visits, and greater improvement in pain scores. Again, neither of these studies were randomized controlled trials. Most experts in this field suggest analgesics, calcitonin, and exercise in the acute phase, and moving on to vertebroplasty or kyphoplasty only if patients have persistent severe pain despite conservative management (and the pain is thought to arise from the fracture).

Lumbar Spinal Stenosis

Conservative nonsurgical therapies, alone and in combination, are warranted prior to attempting surgical treatment. Physical therapy is advocated for this condition, but there is little evidence to justify advocating one treatment regimen over another. The goal of therapy is to increase muscular stabilization (often via strengthening of abdominal muscles) and correction of posture (reduce or prevent lumbar lordosis). In general, stretching, strengthening and aerobic fitness are advocated. Along with physical therapy, analgesic and anti-inflammatory medications (as monotherapy or in combination) are often used.

The choice of nonsurgical treatment is difficult, as there are few randomized controlled trials of these therapies. Epidural steroid injections have been used for more than 50 years for sciatica. While there are a number of uncontrolled studies suggesting a good outcome with these injections for lumbar spinal stenosis, randomized controlled trials have had inconsistent results. A randomized trial of 400 older adults with lumbar spinal stenosis and moderate to severe leg pain and disability showed minimal or no short-term benefit in outcomes (disability and leg pain intensity) between the group who received epidural steroid injections of glucocorticoids plus lidocaine versus injection with lidocaine alone. A placebo group was not included in this study.

The decision to proceed with extensive back surgery on an older patient is always a difficult one. A recent Cochrane review of surgery for degenerative lumbar spondylosis found that "there is still insufficient evidence of the effectiveness of surgery to draw any firm conclusions." On the other hand, the Maine Lumbar Spinal study did show that spinal surgery can be effective. This study is an observational analysis of patients treated by orthopedic surgeons and neurosurgeons in community-based practices throughout Maine. This study followed patients treated surgically or medically, at the choice of the patient and surgeon. In this cohort, patients initially treated surgically demonstrated better outcomes in all measures than those treated nonsurgically. After 10 years, however, the relative difference between surgery and conservative therapy was no longer significant. A recent randomized controlled multicenter trial of an interspinous process decompression system did find that patients who underwent this procedure had a statistically significant improvement in neurogenic intermittent claudication versus controls.

Surgery in older adults is associated with higher adverse events rates, which should be discussed with the patient

along with the understanding of long-term outcomes from surgery. An observational study from four surgical centers found that the most powerful predictors of good outcomes of greater walking capacity, milder symptoms, and greater satisfaction were the patient's report of good or excellent health before surgery, as well as low cardiovascular comorbidity.

In summary, lumbar spinal stenosis should be treated first with a conservative approach including physical therapy, perhaps manipulative therapy, analgesics, and possibly epidural steroid injections. If this approach does not give relief in a reasonable period of time, then a surgical approach, decompressing the stenotic canal space, should be considered. Those patients with high self-reported health and low cardiovascular morbidity seem to achieve the best surgical results.

Mechanical Low Back Pain

The management of back pain in older persons requires a logical, if not yet evidence based, approach to the patient, based on both an anatomical understanding of the most likely cause and precipitants of the older adult's pain. For pain that is exacerbated by spinal movement (lying to sitting, bending, etc), spinal instability is the most likely explanation, and thus attempts to stabilize the spine make the most sense. Stabilization may be achieved by isometric abdominal strengthening exercises, lumbar sacral corsets (avoid using for extended periods of time due to muscle disuse/deconditioning), and back protection maneuvers (lifting with one's knees with the back straight, etc). Spinal fusion is reserved for intractable cases of severe low back pain.

There is no therapy needed or indicated for DISH. The pain from sacral insufficiency fractures resolves in 4 to 6 weeks, and analgesics should suffice. Antiresorptive therapy for osteoporosis should be initiated to prevent future fractures.

Spontaneous sciatica usually improves without therapy in most older adults. Epidural steroids may be helpful in the management of sciatica. Surgery should be considered only if the pain persists despite trials of conservative therapy.

Prolonged bed rest should be avoided in older persons, given the complications of this intervention in this age group. Patients should, however, avoid those activities that appear to precipitate their pain. Firm corsets may be considered to allow patients to stay mobile and active.

Analgesics should be used, though cautiously, in the management of pain, especially if used chronically. There is little evidence that anti-inflammatory drugs are any better than simple analgesics, and these are associated with a high incidence of complications in this age group. Pain that occurs only with movement often does not respond well to analgesics. While narcotics may be very helpful with severe pain, the patient should be watched closely for confusion and constipation. Adjunctive pain therapy, with such agents as tricyclic antidepressants with limited anticholinergic side effects (nortriptyline and disimpramine) and gabapentin, may be helpful. The use of combinations of multiple analgesic classes (at the lowest effective dose) may be effective at reducing pain while keeping side effects to a minimum.

PREVENTION

Since back pain in older adults is often recurrent and, while chronic back pain is often reported in the literature, the symptoms often wax and wane. The older adult can usually identify a precipitating event or certain activities or movements that make the back pain worse or prompt a recurrent episode. Once aware of these movements, the clinician can work with the patient to modify behavior and activity to minimize or avoid such movements. Further it is important to recognize certain risk factors for developing more disabling back pain: being female, having multiple comorbid conditions (including arthritis), reporting depressive symptoms, and having poor grip strength (this may serve as a marker for global muscle weakness) or hip weakness. Obesity is also considered a risk factor for back pain. Several of these risk factors, namely depressive symptoms, muscle weakness and body mass index are potentially modifiable and amenable to intervention via primary care interventions. Back pain is also associated with psychosocial repercussion, including anxiety, depression, and social isolation. Expanding the evaluation and management of back pain from physical to include psychosocial aspects of daily life may provide benefits for older adults who suffer from these conditions.

SPECIAL ISSUES

While back pain in older adults is prevalent, costly, and leads to considerable morbidity, much of the literature has focused on younger populations with this condition. Few trials comparing efficacy and safety of different treatments have included older adults with back pain. Pain management and treatment are particularly challenging because clinical guidelines do not currently exist for back pain in older adults; moreover, guidelines for back pain in younger populations fail to account for decision-making complexities that occur commonly in older populations, such as multiple comorbid conditions, polypharmacy, frailty, and fragmented social support systems.

Therapeutic Alliance and Patient Preference

The patient-physician relationship lies at the center of treatment for older adults with (chronic) back pain. Therapeutic alliance is defined as a constructive collaboration between the patient and provider. Although few studies have addressed the specific contribution of the therapeutic alliance to treatment outcomes in patients with back pain, a positive patient-physician relationship has been associated with improved treatment outcomes among patients receiving general and rehabilitative medical care. Devoting the time to establish mutually agreed-upon treatment goals is an important step in building a therapeutic alliance. Other core elements of the therapeutic alliance include (1) setting realistic expectations about what can and cannot be accomplished, taking into account such immutable factors as patient age, etiology, and duration of the pain; (2) availability of the physician for advice, reassurance, and support during back pain flares; (3) tenacity and commitment on the part of both provider and patient; (4) mutual respect; and finally (5) a reciprocal bond of warmth generated by both parties having an emotional investment in the outcomes of treatment.

Discussing and listening to patient preferences regarding management and goals of care are essential. Management programs can be tailored to the older adult's preferences and abilities; preferably, the patient has identified aspects of the program that are most desirable, realistic, and feasible, thus increasing likelihood of adherence. To motivate older adults to comply with a management program, the environment in which the older patient engages in a therapeutic activity should be appropriate and accessible. In order to reinforce treatment initiation and maintenance, the physician can leverage social supports, for example, family members, home attendants, and community-based agencies.

Comorbidity As noted above, multimorbidity and medical complexity often seen in older adults makes management decisions more difficult and sometimes limits treatment options. Further, it is important to recognize that older adults often have multiple sites of pain. Clinicians should inquire about different concomitant locations of pain (eg, spine, knee, hand, hip, peripheral neuropathy) as this may impact management options, patient priorities, treatment expectations and ultimately achieving outcomes of interest. Mental illness (eg, depression and anxiety) often co-occur with chronic (back) pain and must be acknowledged and managed optimally (and simultaneously) for pain outcomes to also improve.

Care settings Multiple resources exist to help both clinicians and patients manage back pain. We advocate for clinicians to seek out/learn about resources that exist within their respective communities by contacting the local Area Agency on Aging (AoA) to find out if they have lists of relevant programs. Also, for example, many Continuing Care Retirement Communities offer wellness/exercise programs that are run by trained staff.

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Chapter 123

Foot Problems

Arthur E. Helfand, Jeffrey M. Robbins

Learning Objectives

- To recognize the need for foot health as a primary clinical need for the older individual and patients with chronic diseases.
- To identify, recognize, and understand the changes in the foot and its related structures associated with aging, chronic diseases, and focal pathology.
- To identify primary foot and related complications associated with aging and chronic diseases that detract from successful aging and increase disability.
- To define clinical strategies to assess the "at risk" patient and understand primary management options, including service indicators and referral for care.
- To develop management practices that stress assessment, education, prevention, management, and continuing education programs.

Key Clinical Points

1. **Provide a comprehensive clinical assessment of the foot and related structures. This is especially important for those individuals with conditions that pose a high risk for pedal complications such as diabetes mellitus, peripheral vascular disease, peripheral neuropathy, end-stage renal disease, and degenerative joint changes that can limit mobility and affect quality of life.**
2. **Changes in the foot and related structures as a result of aging are common causes of foot pain (podalgia). As a result, painful ambulation (pododynia dysbasia) and limitation in mobility can result. These conditions include hyperkeratotic lesions, onychodystrophy, onychomycosis, heel pain/plantar fasciitis, fat pad displacement and atrophy, hallux valgus (bunion), digiti flexus (hammertoe), ulceration (trophic, diabetic, and neurovascular), and the residuals of rheumatoid, degenerative, and gouty arthritis.**
3. **Provide patient information and education that includes hygienic and preventive components, footwear, and orthotic recommendations.**
4. **Provide information on referrals and coordinated care.**
5. **Utilize a clinical podogeriatric assessment protocol that stratifies risk components and includes Medicare and Medicaid considerations as well as methods to prevent amputation.**

INTRODUCTION

Diseases and disorders of foot and their related structures in the older patient represent a significant health concern in both prevalence and incidence. The immobility that results from local foot conditions and the focal complications of systemic diseases has a significant impact on the individual's ability to maintain independence, retain quality of life, and not become a financial burden for society in general. Two important factors involved in the older patient's ability to remain as a vital part of society are a keen mind and the ability to retain their mobility through ambulation.

The human foot is both a static and mobile organ of function. It provides support for the body at rest and during propulsion and ambulation. It supports our ability to walk upright, which is a specific characteristic of man/woman. The ability to remain mobile and functional in society is a key activity of daily living and may well be the primary catalyst to independence for the older population. The loss of the ability to ambulate due to some foot and/or related problem or change not only produces physical limitations but also has a significant impact on the patient's mental, social, and economic status.

Some of the needs for appropriate foot and related health are related to the measurable outcomes of immobility. They include those related to human body systems and include as examples: sluggish vascular flow, cardiovascular stress, chronic constipation, muscles weakness, weakened bone structure (osteoporosis), incontinence, pressure ulceration, increased agitation, depression, decreased appetite, an increased pneumonia risk, and an increased risk of urinary infection. There are also a number of quality of life changes and include as examples; reduced social contact, withdrawal from surroundings, loss of participation in activities, loss of independent and/or assisted mobility, a decreased desire to eat, a loss of independent or assisted toileting, a loss of independent or assisted bathing and/or dressing, increased problems with sleep patterns, a loss of interest in others, and the loss of the desire to live and to discover life and/or to love. To remain active physically, intellectually, and socially provides a sense of well-being and permits older individuals to live their lives to the end of life with purpose.

ETIOLOGIC AND EPIDEMIOLOGIC FACTORS

There are multiple factors that contribute to the etiology of foot problems in older patients. The primary factors include the aging process itself, years of use and abuse, repetitive stress, neglect, foot deformity, and the presence of multiple chronic diseases, such as diabetes mellitus, peripheral arterial diseases, rheumatoid arthritis and degenerative joint changes, musculoskeletal disorders, neurologic deficits and sensory loss, onychial, and dermatologic conditions. Other significant factors include the degree of ambulation, the duration of prior hospitalization, limitation of activity, prior institutionalization, episodes of social segregation, prior and improper self-care, emotional adjustments to disease and life in general, polypharmacy, and the residuals associated with other risk diseases. Other examples include impaired vision, hearing impairment, obesity, the inability to bend, spinal stenosis, the use of tobacco, dementia, a history of substance abuse (alcohol and other drugs), sensory loss, altered biomechanics and pathomechanics, soft tissue atrophy and plantar fat pad displacement, limited joint mobility, and contractures. Discomfort, pain (podalgia), ambulatory dysfunction, and pain when walking (pododynia dysbasia) become distressing and disabling.

The epidemiology of foot disorders and diseases in the older patient needs to focus on prevention. While primary prevention is the goal for any public health issue, the concepts of secondary prevention (ie, finding diseases and disorders in their earliest manifestations) and tertiary prevention (minimizing complications that arise from diseases and disorders) are equally import for older adults. It is also important to promote positive or optimum health, prevent risk-taking activities that reduce health, and prevent disabling illness after the onset of diseases and disorders, which is significantly important in the geriatric patient.

There are a number of host factors that contribute to the development of foot problems in the older population. Some include prior occupations, congenital and/or genetic defects, degenerative joint disease and other arthritides, morphologic changes in foot structure, rotational changes in the musculoskeletal system and muscular imbalance, residual deformities, personal habits and customs, endocrine diseases such as diabetes mellitus, peripheral vascular (venous and/or lower extremity arterial disease), neurologic deficits, dermatologic and onychial abnormalities, a variation in the patient's response to repetitive and intermittent trauma. The agent factors that contribute to the development of foot conditions include hard flat surfaces for ambulation, trauma, foot covering material and fabrication, foreign bodies, foot to shoe last incompatibilities, and neglect of foot and related symptoms.

In addition, there are a number of environmental factors that relate to the epidemiology of diseases and disorders of the foot and its related structures. Some include social and economic factors, customs and shoe styles, low income, adequate care and referral, nutrition, poor foot health education, cultural barriers, physical changes such as climate, flooring materials and covering, hard surfaces, the health care system and insurance limitations, and the lack of school foot health programs.

In clinically managing the older patient, assessment and care at a time when the progression of diseases and disorders can be modified is a major goal. The best example in older adults is to prevent ulcerations in the older diabetic, treat them early when present, and prevent the potential for amputation that change the quality and longevity of life for the older patient. The prime reasons for podiatric referral are listed in **Table 123-1**.

TABLE 123-1 REASONS TO REFER TO A PODIATRIST

- Signs suggesting generalized disease include neuropathy, vascular disease, infection, and focal neoplastic disease
- In those cases where concomitant therapy is indicated
- Where initial management is not effective
- In the presence of skin, nail, postural, and joint deformities of the foot and related structures
- In the presence of diabetes mellitus, neurosensory, peripheral vascular, and other risk diseases
- In the presence of foot problems combined with walking problems and/or a history of falls
- Where orthotics are indicated
- If the patient is unable to obtain and/or provide foot care
- If the patient complains of a foot problems or has specific questions about care including information on footwear

CHANGES IN THE FOOT IN RELATION TO AGE

The skin is one of the first structures to demonstrate change. There is a loss of hair below the knee and on the dorsum of the foot and toes. Atrophy follows with the skin appearing parchment like and xerotic. Brownish pigmentations are common and related to the deposition of hemosiderin. Hyperkeratotic lesions when present are associated with keratin dysfunction (hypertrophy and hyperplasia), a residual to repetitive pressure, atrophy of the subcutaneous soft tissue, and/or acting as space replacement as the body attempts to adjust to the changing pressure placed on the foot.

Toenails undergo degenerative trophic changes (onychopathy), such as thickening (onychauxis and onychogryphosis) and/or longitudinal ridging (onychorrhexis) related to repeated microtrauma, disease, and nutritional impairment. Deformities of the toenails become pronounced, and complicated by xerotic changes in the periungual nail folds as onychophosis (hyperkeratosis) and tinea unguium (onychomycosis). These conditions are usually long standing, chronic, and very common in older adults, and in the case of onychomycosis, present a constant focus of infection.

Progressive loss of muscle mass and atrophy of soft tissue decrease function and activity which increases the susceptibility of the foot to injury, so that even minor trauma can result in a fracture and a marked limitation of activity. Atrophy of the interossei is a precipitating factor in the development of digital contractures (hammertoes), metatarsal prolapse, atrophy, and displacement of the plantar fat pad.

Peripheral vascular disease and arterial insufficiency produce trophic changes, rest pain, intermittent claudication, coldness, and color variations, such as rubor and cyanosis. There may be a loss of sensation and other changes related to neuropathy, in the diabetic patient and those individuals with a history of spinal cord disease, arthritis of the spine, alcohol, or substance abuse. The presence of hemorrhage subungually or in sub-hyperkeratotic tissue, demonstrates marked angiopathy that can be an early finding in diabetes mellitus, renal disease, retinal, cardiac, or renal pathology. These changes generally predispose the patient to infection, necrosis, and tissue loss. If assessment and continuing care are not provided in a comprehensive manner that includes health education and prevention, the resultant complications may result in wards of society and a loss of the quality of life.

The presence of chronic diseases such as rheumatoid arthritis, degenerative joint disease, gout, diabetes mellitus, lower extremity venous and arterial disease, and a variety of neuromuscular conditions, precipitate degenerative changes in the foot that result in podalgia, gait modification, ambulatory dysfunction, altered mobility states, reduced agility, sensory deficits, and a loss of position sense. Physical disability, patients who are mentally challenged, patients with emotional and mental health issues, and patients in long-term care institutions are also at risk. On average, 90% of the adult population over the age of 65 will demonstrate some evidence of foot pain that alter their independent activity. Foot and related complications also represent a significant factor for many hospital admissions related to complications associated with diabetic and vascular ulceration and infection.

ANATOMIC RELATIONSHIPS

The human foot (**Figure 123-1**) is an organ that is static and mobile. It provides support for the body at rest and during propulsion and ambulation. The ability to walk upright is a specific characteristic or men and women. In addition to its

static and propulsive activity, the foot and its related structures are subject by the changes in society to additional forces and activities. These changes are reflected in our hard, flat walking surfaces, the forces of gravity that are related to the weight and activities of each individual, as well as changes in muscular activity related to function, motion, and disability. In addition, the resiliency of the foot itself, the ability to respond and adapt to morphologic variations, and variations in stress, are additional considerations. The human foot from a morphologic standpoint is basically a modified rectangle that is also three dimensional.

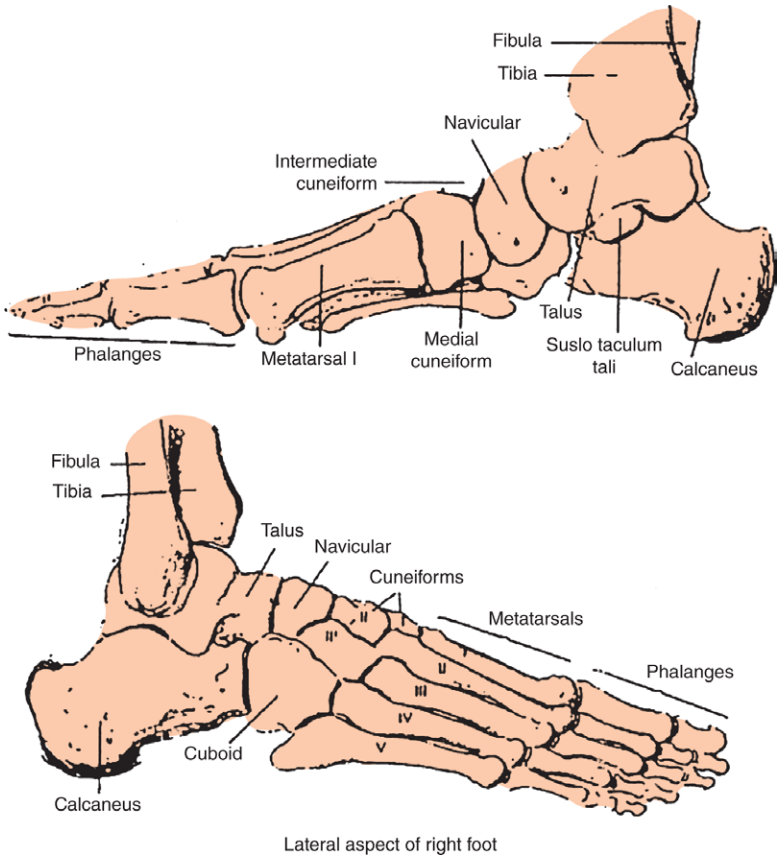


FIGURE 123-1. Anatomy of the foot. (Adapted with permission from Pedorthic Footwear Association. Pedorthic Reference Guide. Columbia, MD; 1992, 1999, 2006.)

The human foot is complex. Each foot has 26 bones (together constituting one-fourth of the body's total), ossicles, ligaments, muscles, tendons, arteries, veins, nerves, and it's covering of skin. The foot normally bears weight on a triangular base with the long sides being the inner and outer longitudinal arches, and the metatarsal arch consisting of the bias along the five metatarsal heads. Weight is initially transferred from the calcaneus to the fifth and first metatarsal heads, statically and functionally.

The talus, with the tibia and fibula comprise the ankle joint. The talus has no muscular attachments and thus is the tendons and muscles, which parallel it, control activity. The talus articulates with the calcaneus. The Achilles tendon attaches to the superior-posterior segment and is a significant structure to foot function. The cuboid is anterior to the calcaneus, and is rectangular in shape that adds to the structural support to the foot. The navicular is anterior to the talus, is coin shaped and provides muscular attachments to aid in function and stabilization. Anterior to the navicular and lateral to the cuboid are three, wedge-shaped bones called the first, second, and third (medial, middle, and lateral) cuneiforms. They help provide stability to the foot. These bones comprise the "rear foot." The arches do not fall. The foot does rotate, pronate, supinate, invert, evert, and elongate and does structurally change in relation to Wolff's law (bone is deposited and resorbed in accordance with the stresses placed upon it) and Davis's law (soft tissue models itself along its imposed demands and is the corollary to Wolff's law). The mid foot consists of the remaining five tarsal bones, that is, the navicular, cuboid, and three cuneiforms.

Anterior to the cuneiforms and cuboid bones are the five metatarsals. Each metatarsal consists of a base, a shaft, and a head. They are anatomically long bones. Anterior to the metatarsals are the phalanges. Each of the lesser toes contains three phalanges. The first or great toe is comprised of two phalanges. The metatarsals and phalanges represent the forefoot. There are two sesamoid bones plantar to the first metatarsal head.

Each osseous structure attaches by ligaments to another to form the joints of the foot. Their functional role is to maintain proximity by keeping the segments of bone articulating with each other. Their properties are strength and rigidity with limited elasticity that permit the joints to maintain some degree of motion or movement. The basic change that occurs in aging bone is a loss of calcium (osteopenia and/or osteoporosis) and in foot ligaments, the transition from elasticity to rigidity. The lateral longitudinal arch is formed by the calcaneus, cuboid, fourth, and fifth metatarsals. It is the lower structural arch. The medial longitudinal arch is formed by the calcaneus, talus, navicular, three cuneiforms, and the first, second, and third metatarsals. It is higher with its summit at the head of the talus and navicular. The pitch of the calcaneus (the angle formed by the plantar surface of the calcaneus and plane of support) determines, to a great degree, the height of that segment. The transverse arches of the foot include the posterior metatarsal arch formed by the bases of the metatarsals and is reasonably firm and the anterior metatarsal arch, formed by the five metatarsal heads, is flexible, and flattens during gait phases, with weight bearing, pronation, and supination.

The most predominant and significant membranous covering of the foot is known as the plantar fascia. It attaches to the plantar posterior segment of the calcaneus or tuberosity, and fans out anteriorly to the metatarsal area. The plantar fascia covers all of the foot muscles, all of the ligaments, and all of the bones on the plantar aspect of the foot. It acts as a spring to aid in function as well as offers protection to plantar structures. It is a very elastic or flexible mass in youth, which becomes waster and rigid with age. The dorsum of the foot does not have a strong fascial attachment. Most of the structures are subcutaneous.

The muscles that control major the functions of the foot have their origin in the leg. The posterior muscles include the tibialis posterior, flexor digitorum longus, flexor hallucis longus, plantaris, and calcaneal or Achilles tendon (formed by the gastrocnemius and soleus muscles). The lateral muscles include the peroneus longus and peroneus brevis. The anterior muscles include the tibialis anterior, extensor hallucis longus, and extensor digitorum longus. As individual's age and chronic disease becomes evident, there is a decrease in muscle strength that can result in ambulatory dysfunction, imbalance, foot drop, and a higher risk for falls.

The muscle on the dorsum of the foot is the extensor digitorum brevis. The muscles on the plantar surface of the foot are protected by the plantar fascia and are layered from superficial to deep. They include the abductor hallucis, flexor digitorum brevis, and abductor digiti quinti minimus in the first or superficial layer. The second layer includes the quadratus plantae, lumbricals, flexor digitorum longus tendon, and flexor hallucis tendons. The muscles of the third layer include the flexor hallucis brevis, adductor hallucis (oblique and transverse heads), and the flexor digiti minimi brevis. The muscles of the fourth layer include the dorsal interossei, plantar interossei, and the tendons of the peroneus longus and tibialis posterior muscles. It is the atrophy of the interossei muscles that are a major factor in the development of hammertoes in the aging patient.

The nerves that control the foot include the lateral sural cutaneous, superficial and deep fibular (peroneal), medial dorsal cutaneous, dorsal digital, tibial, lateral calcaneal, medial plantar, lateral plantar, and saphenous nerves.

The arterial supply to the foot follows the femoral artery, to the popliteal artery, and divides to become the anterior and posterior tibial arteries. The anterior tibial artery becomes the dorsalis pedis artery on the dorsum of the foot, whose terminal branches are the dorsal metatarsal and dorsal digital arteries. The posterior tibial artery becomes the medial and lateral plantar arteries in the foot. The lateral calcaneal artery supplies the lateral segment of the calcaneal area of the foot. The venous return includes the dorsal venous arch, plantar cutaneous venous plexus, medial and lateral plantar veins, and the greater and lesser saphenous veins.

The skin of the foot is composed of a fitted, flexible, elastic inner dermis, covered by a much less sensitive outer epidermis. The skin varies in thickness from 0.5 mm (as in the eyelid) to 4 or 5 mm, in the sole of the foot. The skin of the foot undergoes many changes during the aging process. It becomes thinner, even parchment like, loses its elasticity, usually atrophies, and loses hair. It loses its hydration or water content because there is generally less perspiration and lubrication. The skin loses its suppleness, becomes brittle, dry, and injures easily. This condition accompanied by a diminished blood supply, can be quite serious.

The normal toenail includes the nail matrix, nail bed, nail plate, lunula, eponychium, cuticle, and nail folds. The nail plate is a sheet of keratin and is important in clinical medicine as it reflects the health events of the previous months. The nail plate grows slowly forward until it breaks free of the nail bed at the distal edge. The tissue below the free edge is termed the hyponychium. The matrix is the area under the proximal nail fold, cuticle, and lunula. The arterial supply to the nail bed stems from small arterial branches from the dorsal and plantar anastomoses. Nail growth is affected by age, trauma, chemicals, the environment, and disease.

CLINICAL ASSESSMENT AND MEDICARE CONSIDERATIONS

The clinical management of the older patient with foot and related conditions commences with an understanding of the important principles related to podogeriatric assessment; recognizing primary changes in the aging foot; identifying complications related to systemic diseases and in particular, diabetes mellitus, peripheral arterial occlusive disease; the ability to stratify risk for foot conditions; and degenerative joint changes; understanding Medicare reimbursement policies and serving as the patient's advocate; and being knowledgeable about primary management procedures.

The Pennsylvania Department of Health's Diabetes Prevention and Control Program working with Temple University's School of Podiatric Medicine's Department of Community Health, Aging, and Health Policy and the Pennsylvania Diabetes Academy developed a Comprehensive Clinical Podogeriatric and Chronic Diseases Assessment Protocol (Helfand Index [Appendix, http://www.podiatrym.com/cme/feb04cme.pdf]). The format provides a methodology to assess foot problems associated aging and chronic diseases, stratify those patients most at risk to develop complications, maintain a surveillance instrument related to patient care, and provide a means to evaluate data for outcome measurement that would be valid, accurate, consistent, and relevant. The protocol instrument served as an adjunct to develop prevention and management programs for individual patients, their communities, and as a component for comprehensive geriatric assessment. The protocol's application includes elements of primary, secondary, and tertiary prevention, and stresses a need for patient and professional education as well as the need for appropriate multidisciplinary patient management.

The initial segment includes demographics including the date of visit, identification, the patient's name, age, date of birth, address, phone number(s), fax number, e-mail address, sex, race, weight, height, and social status. Primary physicians, specialty practitioners, and health care facilities are also noted. The date of last visit should be included.

The history of the patients present illness should be noted and include, but is not limited to the following, swelling of feet, painful feet, location, quality, severity, duration, context, modifying factors, hyperkeratosis, onychial changes, bunions, painful toenails, infections, prior ulcerations, prior foot-related surgeries, cold feet, amputations, modifying factors, associated signs and symptoms, and other factors. Additional factors include a prior occupational history, footwear history, environmental concerns, physical activities, and family support.

The past history should also focus on those components that present with pedal manifestations but not limited to the following: cardiac disease, hypertension, arthritis (rheumatoid—degenerative), peripheral arterial and vascular disease, diabetes mellitus (type 1 and 2), thyroid disease (hyper-hypo), Addison disease, hypercholesterol (hyperlipidemia), gout, Paget disease, allergy, family and social status, and a history of smoking and alcohol use. Other factors include the degree of ambulation, imbalance, and fall risk, the duration of prior hospitalizations, functional capacity, and any limitation of activities (ADL [bathing, dressing, toileting, transferring, continence, and feeding] and IADL), prior institutionalization, periods of social segregation, prior care, emotional adjustments to disease, aging, and life in general, multiple medications and drug interactions, as well as complications and residuals associated risk diseases and disorders. The medication history should include current prescriptions, past medications, over-the-counter preparations, and the patient's response.

The systems review should include the following: constitutional; ear, nose, and throat; ocular; skin, hair, and nail; respiratory; psychiatric; hematologic; cardiovascular; musculoskeletal; gynecologic; lymphatic; genitourinary; neurologic; endocrine; gastrointestinal; and immunologic. Current prescriptions and over -the- counter medications should be noted.

As a part of the current Medicare Regulations for coverage, there are a number of diseases and disorders that are noted as special risk conditions in order to qualify coverage for what has been described as "routine foot care" for insurance purposes. The term might better be termed as primary foot care refers to the debridement of hyperkeratotic lesions (heloma and tyloma) and hypertrophic onychodystrophy. Those patients who demonstrate neurosensory and vascular deficits and who present with clinical class findings represent an exemption to the exclusion and become eligible for coverage, within utilization guidelines. Medicare (1971) has indicated that although not intended as a comprehensive list, the following metabolic, neurologic, and peripheral vascular diseases commonly represent the underlying conditions that might justify coverage for "routine foot care." The primary diseases and disorders include but are not limited to the following listed in **Table 123-2A**.

TABLE 123-2A ■ PRIMARY MEDICARE RISK DISEASES

Amyotrophic lateral sclerosis (ALS)
Arteriosclerosis obliterans (ASO), arteriosclerosis of the extremities, occlusive peripheral arteriosclerosis
Arteritis of the feet

Buerger disease (thromboangiitis obliterans)
Chronic indurated cellulitis
*Chronic thrombophlebitis
Chronic venous insufficiency
*Diabetes mellitus
Intractable edema—secondary to a specific disease (eg, congestive heart failure, kidney disease, hypothyroidism)
Lymphedema—secondary to a specific disease (eg, Milroy disease, malignancy)
Peripheral neuropathies involving the feet
*Associated with malnutrition and vitamin deficiency
Malnutrition (general, pellagra)
Alcoholism
Malabsorption (celiac disease, tropical sprue)
Pernicious anemia
*Associated with carcinoma
*Associated with diabetes mellitus
*Associated with drugs and toxins
*Associated with multiple sclerosis
*Associated with uremia (chronic renal disease)
Associated with traumatic injury
Associated with leprosy or neurosyphilis
Associated with hereditary disorders
Hereditary sensory radically neuropathy
Angiokeratoma corporis diffusum (Fabry)
Amyloid neuropathy
Peripheral vascular disease
Raynaud disease

Those diseases identified with an asterisk (*) also must have been seen by their medical physician for management within 6 months prior to their foot care management.

The Department of Veterans Affairs—Veterans Health Administration (2009) and many CMS Medicare Carriers have augmented the initial Medicare listing, listed in **Table 123-2A**, **B**, and **C**.

TABLE 123-2B ■ SPECIALIZED RISKS

Vascular grafts
Joint implants
Heart valve replacement
Active chemotherapy
Renal failure—dialysis
Anticoagulant therapy
Hemorrhagic disease
Chronic steroid therapy

TABLE 123-2C ■ VHA DIRECTIVE 2009-030

Documented peripheral arterial disease
Documented sensory neuropathy

Prior history of foot ulcer or amputation
Visually impaired
Physically impaired
Neuromuscular diseases, eg, Parkinson disease
Severe arthritis and spinal disc disease
Cognitive dysfunction
Chronic anticoagulation therapy
> 70 years old—without other risk factors
Diabetes without foot complications
Obesity

Secondary risk concerns include deficiency of B-complex components, lipidoses, peripheral autonomic neuropathy, acute infective polyneuritis, polyneuropathy associated with collagen vascular disease and malignancy, inflammatory and toxic neuropathy, arterial stricture, and other related vascular changes. Additional factors include, as examples, patients with a history of vascular grafts, joint implants, heart valve replacement, active chemotherapy, renal failure/dialysis, anticoagulant therapy, hemorrhagic disease, chronic steroid therapy, and immunosuppressed states (HIV, AIDS).

There are other diseases and disorders that also present significant complications in the foot and related structures and at some point should be considered in a similar manner. They include but are not limited to the following: acromegaly, Alzheimer disease, degenerative joint disease (osteoarthritis), rheumatoid arthritis, gout, cerebral palsy, coagulopathy, stroke (CVA) and residual paralysis, sarcoidosis, sickle cell anemia, reflex sympathetic dystrophy, chronic obstructive pulmonary disease, hypertension, altered mental status, depression (social, physical, and psychological), Alzheimer disease, dementia, delirium, mental retardation, hemophilia, and Parkinson disease.

The Medicare regulations apply to those individual defined as physicians under Section 1861r of the Social Security Act and include MD, DO, and DPM, as licensed to treat the human foot and its related structures medically and surgically.

The basic dermatologic evaluation should include but is not limited to the following: focal hyperkeratotic lesions, onychauxis, bacterial infection, ulceration, onychomycosis, onychodystrophy, onychocryptosis, cyanosis, xerosis, tinea pedis, verruca, hematoma, rubor, discoloration, and pre-ulcerative changes.

Other clinical findings include as examples: exquisitely painful or painless wounds, slow healing or nonhealing wounds, trophic ulceration, necrosis, changes in texture and turgor, pigmentation (hemosiderin deposition), chronic pruritus, excoriations, neurogenic and/or emotional dermatoses, contact dermatitis, footwear related allergic dermatoses, stasis and atopic dermatitis, eczema, xerosis, recurrent infections (paronychia, tinea pedis, onychomycosis, pyoderma, and/or cellulitis), keratin dysfunction, keratotic lesions with (preulcerative) or without hematoma (such as tyloma [callus], heloma durum [hard corn], heloma millare [seed corn], heloma molle [soft corn], heloma neurofibrosuum [neuritic], heloma vasculare [vascular], onychophosis [callus in the nail groove], and intractable plantar keratosis), poroma, verruca, psoriasis, fissures, hyperhidrosis, bromidrosis, maceration, skin turgor, and tropic changes. Other considerations include seborrheic warts (basal cell papilloma—stucco keratosis), solar keratosis, melanoma, and basal and/or squamous cell carcinoma.

The stratification of risk for mechanical or pressure hyperkeratosis can be summarized by the following classification and grade description: 0 = no lesion; 1 = no specific tyloma plaque, but diffuse or pinch hyperkeratotic tissue present or in narrow bands; 2 = circumscribed, punctate oval, or circular, well-defined thickening of keratinized tissue; 3 = heloma millare or heloma durum with no associated tyloma; 4 = well-defined tyloma plaque with a definite heloma within the lesion extravasation, maceration, and early breakdown of structures under the tyloma or callus layer; 5 = complete breakdown of structure of hyperkeratotic tissue, epidermis, extending to superficial dermal involvement. Many times, keratotic lesions need to be debrided to properly access subkeratotic ulceration in the presence of splinter hemorrhages or hematoma.

Additional primary onychial findings include as examples: onychatrophia (atrophy), onychia sicca (dryness), onycholysis (freeing from the free edge), subungual hyperkeratosis, onychexallis (degeneration), onychodystrophy, onychogryphosis (hypertrophy with deformity), onychia (inflammation), paronychia (bacterial infection), onychitis (inflammation), onychalgia (pain), subungual abscess, subungual heloma (keratosis), subungual exostosis or spur, onychomadesis (freeing from the proximal portion), onychoschizia (splitting), onychyphemia (hemorrhage),

onychomalacia (softening), onychoptosis (shedding), periungual ulcerative granulation tissue, onychodysplasia (involuted or pincer nails), onychorrhexis (longitudinal ridging), Beau's lines (transverse growth cessation), pterygium (hypertrophy of eponychium), Hippocratic nails, koilonychia, leukonychia, onychoclasis (fracture), and diabetic onychopathy. Dystrophic changes also are noted with repetitive microtrauma, stress, and activities related to inappropriate footwear lasts and toe box irritation.

The stratification of risk for onychial structures can be summarized by the following classification and grade description: grade 1 = normal; grade 2 = mild hypertrophy; grade 3 = hypertrophic, dystrophic, onychauxis, mycotic, infected, and onychodysplasia; and grade 4 = hypertrophic, deformed, onychogryphosis, dystrophic, mycotic, and infected.

Coverage for the debridement of onychomycosis also includes documentation of mycosis/dystrophy causing secondary infection and/or pain, which results or would result in marked limitation of ambulation. The specific clinical findings include discoloration, hypertrophy, subungual debris, onycholysis, secondary infection, limitation of ambulation, and pain. In addition, evidence of dystrophy, onychodysplasia, onychauxis, and onychogryphosis are also frequently noted.

The initial foot orthopedic assessment includes an evaluation of the primary deformities that are related to biomechanical and pathomechanical changes that commonly cause pain and contribute to ambulatory dysfunction. They include hallux valgus (bunion), hallux abductor valgus, hallux rigidus and/or limitus, anterior imbalance, Morton syndrome, digiti flexus (hammertoes, claw toes, and mallet toes), bursitis, pes planus, tarsal tunnel syndrome, prominent metatarsal heads and prolapse, pes valgo planus, Charcot joints, pes cavus, bony prominences, rearfoot varus, valgus rearfoot, forefoot spinatus, everted or valgus forefoot, ankle equinus, leg length discrepancies, and other musculoskeletal deformities. The foot type, muscle strength, and ranges of motion should also be noted.

Other considerations include a history of a gradual change in shape or size of the foot, arthropathy, elevated plantar pressure, decreased muscle strength and ranges of motion, atrophy and/or displacement of the plantar fat pad and subcutaneous soft tissue, foot muscle atrophy, tailor's bunion (bunionette), bony prominences, plantar fasciitis, spur formation (including calcaneal), soft tissue inflammation (ie, bursitis, tendonitis, etc), osteopenia, stress fracture, metatarsalgia, Haglund deformity, entrapment syndromes and neuroma, sesamoid displacement, sesamoiditis, contractures, the residuals of arthritis (degenerative, rheumatoid, and gouty), and feet that cannot withstand trauma.

There should be some identification of gait and movement changes that includes a steady or unsteady gait, if the patient is nonambulatory, the use of mobility aids (cane, crutches, or wheelchair), and if the patient is able to reach and see their feet. Gait speed and balance are also important factor. Balance also includes the patient's ability to stand. Ambulatory aids should be noted as well as the patient's ability to adapt to their use. An evaluation of footwear that includes the type of shoe, appropriateness of the shoe last for the patient, fit, size, wear and patterns of wear, shoe lining and wear, the presence of foreign bodies in the shoe, insoles, an orthoses (prescribed and self-purchased). Outsole wear and upper covering distortions should be identified. Footwear should be satisfactory for the patient and compensate for existing deformities. Stockings should be identified as in use or not and as to fabric (cotton, nylon, wool, synthetic, or other material). Footwear should be obtained for their activity, indoor and/or outdoor. Considerations include a broad low heel (maximum of 1.5 in); a shoe that is fastened to the foot by laces, straps, or Velcro; a wide and deep last to accommodate deformities and withstand load bearing; uppers that have some plasticity and/or elasticity for conformity to foot shape; minimal toe stiffening to minimize dorsal trauma; an adequate heel counter; padding around the top line; and a sole that allows for movement with the ground or plane of support, minimizes adherence, and avoids slippage.

The factors that increase pressure and stress should also be considered as factors that increase the risk of ulceration in the older patient. Those factors include body mass, gait (particularly antalgic), ambulatory speed, evidence of repetitive microtissue trauma, change in weight diffusion, and weight dispersion. Pathomechanics that is defined as structural change in relation to function and biomechanics that is defined as forces that change and affect the foot in relation to function should be noted and considered. Imbalance which is defined as the inability to adapt to alterations of stress should consider each of the following: force (alteration in physical condition, either shape or position), compression stress (one force moves toward another), tensile stress (a pulling away of one part against another), shearing stress (a sliding or gliding of one part on the other), friction (the force needed to overcome resistance and usually associated with a sheering stress), elasticity (weight diffusion and weight dispersion), and fluid pressure (soft tissue adaptation and conformity to stress).

Additional complications associated with degenerative joint diseases (osteoarthritis) include pain related to minimal trauma, inflammation, strain, periostitis, myofascitis, decalcification, tendonitis, tenosynovitis, residual deformities, rotational digital deformities, joint swelling, and limitation of motion.

The residual complications related to rheumatoid arthritis cystic erosion, sesamoid erosion and displacement, metatarsophalangeal subluxation and dislocation, interphalangeal subluxation and dislocation, ankylosis, phalangeal reabsorption, talonavicular arthritis, rheumatoid nodules, bowstring extensor tendons, tendon displacement, ganglions, rigid pronation, subcalcaneal, retrocalcaneal, and retroachillies bursitis, ossifying enthesopathy, early morning stiffness, fibrosis, nodules, and contracture. Other inflammatory connective tissue diseases include the residuals of lupus, vasculitis, and polymyositis.

The additional changes related to gout include acute clinical findings such as inflammation, pain or podalgia, swelling, redness, high uric acid levels, limitation of motion, and ambulatory dysfunction. The changes associated with chronic tophaceous gout include deformity, pain, stiffness, soft tissue tophi, atrophy of soft tissue, the loss of bone substance, gouty arthritis, joint deformity, and excessive pain associated with acute episodes and exacerbations of the diseases.

Because there may be reabsorption of bone associated with all joint changes in the older patient, radiographs and other imaging studies are essential to rule out bone infection and neurotrophic joint changes, particularly in the older diabetic.

The primary peripheral vascular assessment evaluation should include coldness, trophic changes, and palpation of the dorsalis pedis and posterior tibial pulses. If pulses are not present, the popliteal and femoral pulses should be identified. Pulses can be evaluated as palpable, audible (with Doppler), inaudible, absent, diminished, normal, or strong. A history of night cramps, intermittent claudication (related to arterial embolus, occlusion, thromboangiitis obliterans (Berger disease) and deep venous thrombosis [DVT]), edema, atrophy, varicosities, and atrophy should be noted. Any amputation or partial amputation should be noted and the etiology identified, particularly related to diabetes mellitus, arterial occlusion, and/or infection.

The peripheral arterial stratification of risk can be noted as follows: 0 = no change, 1 = mild claudication, 2 = moderate claudication, 3 = severe claudication, 4 = ischemic rest pain, 5 = minor tissue loss, and 6 = major tissue loss.

Additional findings associated with peripheral arterial disease (PAD and peripheral arterial occlusive disease—PAOD) include fatigue, rest pain, pain, paresthesia, coldness, decreased skin temperature, gradient temperature, burning, color changes, absent or diminished digital hair, and a history of phlebitis and repeated foot infections. Physical findings include dependent rubor, pallor on elevation, capillary refilling time in excess of 3 seconds, temperature changes, hot spots, xerosis (atrophic, scaly, and dry skin), hair loss, hemosiderin deposition, soft tissue atrophy, and dystrophic nail changes. Advanced findings with the risk of necrosis and need for amputation include blebs, hematoma, delayed venous filling time, prolonged capillary filling time, tissue ulceration (punched-put, painful, and little bleeding) necrosis, and gangrene. Skin temperature can be measured with a radiometer. Nonvascular causes of claudication like pain include arthritis of the hips, restless leg syndrome, peripheral neuropathies, spinal stenosis (pseudoclaudication), or prolapsed intervertebral disc.

Diagnostic studies include Doppler ultrasonography, plethysmography, segmental pressure measurement, ankle-brachial index (< 0.85–< 0.9 = deficit in the foot and < 0.5 = deficit in the toe), treadmill exercise testing (claudication time), duplex ultrasound imaging, magnetic resonance angiography, contrast angiography, oscillometer, and radiography.

The primary neurologic assessment should include the following: Achilles, patellar, and superficial plantar reflexes; vibratory sense (pallesthesia) with a C-128 tuning fork for 10 seconds; response to a loss of protective sensation utilizing a 5.07- to 10-g nylon monofilament at bilateral and multiple sites; sharp, dull; and light touch reaction; joint position; burning; two-point discrimination; and related findings. The response to heat, cold, pain, and two-point discrimination are also important considerations. A tip therm can measure temperature sensation.

With the response to a loss of protective sensation, stratification of risk can be reported as: 0 = no sensory loss, 1 = sensory loss, 2 = sensory loss and foot deformity, and 3 = sensory loss, a history of ulceration, and foot deformity.

The assessment for the evaluation and management of a diabetic patient with diabetic sensory neuropathy, resulting in a loss of protective sensation (LOPS) must include the following criteria (**Table 123-3**).

TABLE 123-3 ■ MEDICARE COVERAGE FOR EVALUATION OF THE PATIENT WITH LOSS OF PROTECTIVE SENSATION (LOPS)

1. A diagnosis of LOPS
2. A patient history of diabetes mellitus
3. A physical examination consisting of findings regarding at least the following elements:

a. Visual inspection of the forefoot, hindfoot, and toe web spaces
b. Evaluation of protective sensation
c. Evaluation of foot structure and biomechanics
d. Evaluation of vascular status
e. Evaluation of skin integrity
f. Evaluation and recommendation of footwear
4. Patient education

The loss of protective sensation can also be stratified by the following example: 0 = no loss of protective sensation; 1 = a loss of protective sensation but without weakness, deformity, preulcer, or a history of an ulcer; 2 = a loss of protective sensation with weakness, deformity, preulcerative keratosis, but no ulcerative history; and 3 = history of ulceration, Charcot foot, or current ulcer.

Additional neurologic clinical findings may also include additional sensory changes such as tingling, clawing sensations, pain, hyperesthesia, and hyperactivity. Motor changes include weakness, atrophy, bowstring tendons, foot drop, and Charcot foot. Autonomic changes include diminished sweating or hyperhidrosis with perfusion. With diabetic patients, pretibial lesions or shin spots should be correlated with peripheral arterial changes, diabetic onychodystrophy, hyperkeratosis, and an intrinsic minus foot. Peripheral neuropathies, multiple sclerosis, poststroke hemiplegia, myopathies, and neoplasms may all present with foot and related symptoms and signs.

There are multiple factors that are related to the assessment of older diabetic patients. The symptoms and signs identified for all of the noted systems apply. Additional considerations include the risk factors associated with diabetic ulceration and include high plantar pressure (walking and/or standing), deformity (degenerative joint changes, biomechanical, and pathomechanical changes), soft tissue atrophy and contractures, neurologic deficit (including a loss of protective sensation, insensitivity, and neuropathy), limitation of arterial flow, and unstable glycemic control. Pes cavus, rocker bottom deformity, and Charcot foot should be noted.

Other clinical findings include fatigue, motor weakness, diminished or lost Achilles and patellar reflexes, blebs, pruritus, excoriation, hair loss, neurotrophic arthropathy, neurotrophic ulcers, disparity in foot size and shape, higher prevalence of infection (bacterial and tinea), necrosis, gangrene, pigmentation, pressure ulceration from repetitive microtrauma, foot drop, diabetic dermopathy (pretibial lesions/shin spots), necrobiosis, dehydration, arthropathy, and diabetic onychodystrophy. Sun-keratotic hematoma, nontraumatic subungual hematoma, or splinter hemorrhages are good indicators of vascular impairment and the potential for ulceration. They are also indicators of small vessel disease that may also be present in the cardiac, renal, and ocular systems. There are also a number of radiographic findings associated with older diabetic patients including thin trabecular bon patterns, decalcification, joint position change, osteophytic formation, osteolysis, osteopenia, osteoporosis, and bone loss associated with osteomyelitis.

There a several classification and stratification scales for diabetic ulceration including the Wagner, University of Texas, and a classification suggested by Sims, Cavanagh, and Ulbrecht. This later outline recognizes risk at a preulcerative level and includes: grade 0 = absent skin lesions; grade 1 = dense callus but not preulcer or ulcer; grade 2 = preulcerative changes; grade 3 = partial-thickness (superficial) ulcer; grade 4 = full-thickness (deep) ulcer but no involvement of tendon, bone, ligament or joint; grade 5 = full-thickness (deep) ulcer with involvement of tendon, bone, ligament, or joint; grade 6 = localized infection (abscess or osteomyelitis); grade 7 = proximal spread of infection (ascending cellulites or lymphadenopathy); grade 8 = gangrene of forefoot only; and grade 9 = gangrene of a majority of the foot.

The assessment process is enhanced by the use of accessible instrumentation such as a C-128 tuning fork; neurologic hammer; percussion hammer; Babinski hammer; goniometer (foot/ankle and toe); biothesiometer or VPT meter to determine vibration perception threshold (VPT); monofilament sensory testing (MFT) devices such as the Semes-Weinstein 5.07 nylon monofilament, Norton monofilament, or the West enhanced sensory test; Tacticon; two-point discriminator; Doppler; dermal thermography with a laser radiometer or similar infrared surface temperature scanner for skin perfusion assessment (85°F = perfusions, 75–85°F = compromised wound health potential, and 74°F or below = poor potential healing); oscillometer; plethyso-analyzer; diagnostic ultraviolet (Wood's) light; and appropriate imaging and laboratory studies.

Medicare also identifies a series of class findings that are required to compliment the "at risk" diseases as a requirement for coverage for primary foot care ("routine foot care"), that is, the debridement of hyperkeratotic lesions and onychial structures. Those finding include patients with sensory or vascular impairment should be noted as follows: A1 = nontraumatic amputation of the foot or integral skeletal portion thereof; B1 = absent posterior tibial

pulse; B2 = advanced trophic changes (such as three of the following subcategories to qualify as one class B finding), B2a = hair growth (decrease or absent), B2b = toenail changes (thickening), B2c = pigmentary changes (discoloration), B2d = skin texture (thin, shiny), B2e = skin color (rubor or redness); B3 = absent dorsalis pedis pulse; C1 = claudication; C2 = temperature changes (coldness); C3 = edema; C4 = paresthesia (abnormal spontaneous sensations in the feet); and C5 = burning.

The presumption of Medicare coverage is applied when the physician (MD, DO, or DPM) rendering the primary routine foot care has identified either (1) a class "A" finding; or (2) 2 of the class "B" findings, or (3) one class B and two class C findings in addition to the primary condition. The identification of a systemic disease with neurologic and/or vascular deficits must include the require class findings for coverage.

The final segment of the assessment process is providing an initial impression and/or diagnosis and indicated referrals for management to include podiatric referral (see **Table 123-1**), medical specialty referral, patient education, special footwear (**Table 123-4**), orthotics, vascular studies, clinical laboratory referrals, radiographic and other imaging studies, and prescriptions as indicated for the management of diseases and disorders of the foot and its related structures.

TABLE 123-4 CRITERIA FOR COVERAGE FOR SPECIAL DIABETIC SHOES

1. The patient must have diabetes mellitus.
2. The patient has one or more of the following conditions:
   a. Previous amputation of the other foot or part of either foot
   b. History of previous ulceration of either foot
   c. Preulcerative callus formation of either foot
   d. Peripheral neuropathy with a history of callus formation of either foot
   e. Foot deformity of either foot
   f. Poor circulation in either foot
3. The physician who is managing the patient's systemic diabetes condition has documented that indications 1 and 2 are met and certifies that the patient is being treated under a comprehensive plan of care for his/her diabetes and that he/she needs special shoes.

All of the assessment components including the focal diseases and disorders of the foot, its related structures, and the pedal manifestations and complications of acute and chronic diseases represent the multiple covariants involved in managing and treating older patients with foot conditions. One mandatory legal key to management includes the requirement for licensure by the individual providing and prescribing indicated medical and surgical care components.

The Department of Veterans Affairs, Veterans Health Affairs has expanded the Medicare guidelines for qualification for basic foot care to include other conditions that place patients at risk for complications and as such deems them as medically necessary. These conditions include those patients who are visually, cognitively or physically impaired as well as those veterans who suffer from severe arthritis, chronic low back pain or who are on chronic anticoagulation therapy (VHA Directive 2009-020).

PRIMARY MANAGEMENT: GUIDELINES AND PRINCIPLES

The management of foot problems in the older patient that are focal or complications of systemic, functional diseases or disorders, require a review of their etiology, symptoms, signs, and clinical manifestations, including the use related diagnostic studies. The associated complications, sequelae, relevant treatment, prognosis, and the overall management of the geriatric patient should reflect a reasonable approach that will reduce pain, improve the functional capacity of the patient, maintain that restored function, and provide for the comfort of the patient in his or her activities of daily living and permit the individual to live life as well as possible to the end of life. Diagnostic strategies include weight-bearing and non-weight-bearing radiographs and other imaging studies. Treatments can include nonsteroidal anti-inflammatory drugs and local steroid injections. Many non-pharmacological interventions can be effective. These include superficial heat with caution, deep heat with extreme caution, therapeutic ultrasound, muscle stimulation, TENS, hydrotherapy and exercise. Shoe modifications can be an important part of care and can include changes to the last, shank fillers, sole wedges, metatarsal bars, rocker soles, Thomas heels, buttressed or flared heels, heel wedges,

excavated heels, heel height adjustment, extra-depth shoes as well as other highly specialized adaptations.

SKIN

A concern for older patients is dryness of the skin and/or xerosis. The etiology is due to a lack of hydration and lubrication; and to some degree is a part of the normal aging and degenerative process. Keratin dysfunction can be associated with xerosis. Fissures develop as a result of stress and repetitive microtrauma, and when present, usually on the heel, present a potential hazard for the development of ulceration. Initial management includes the use of an emollient following hydration of the skin. Twenty percent urea is helpful to aid as a mild keratolytic. Creams and ointments containing lanolin can be utilize as long as the patient does not have an allergy to wool. A plastic or Styrofoam heel cup can be of assistance in minimizing trauma to the heel, reducing the potential for complications. Pruritus is a common in the older adult patient and is usually more severe in the colder weather. It is related to dryness, scaliness, decreased skin secretions, keratin dysfunction, environmental changes, and defatting of the skin that is usually precipitated by the constant use of hot foot soaks. The patient will scratch with excoriations noted on examination. Chronic tinea, allergic, neurogenic and/or emotional dermatoses should be considered as part of the differential diagnosis and treated accordingly. Management consists of hydration, lubrication, protection, topical steroids if indicated, and judicious use of antihistamines in minimal doses to minimize the itching, which is usually the primary complaint. Particular care should be taken in the male patient with a history of prostatic hypertrophy. If excoriations are infected, proper antibiotic therapy should be instituted.

Hyperhidrosis and/or bromidrosis when present should be managed based on the etiology. If local, measures should be undertaken to control the excessive perspiration and odor. Hydrogen peroxide, isopropyl alcohol, and astringents may be used topically. Neomycin powder will help control the odor by reducing the bacterial decomposition of perspiration. Recommendations on footwear and stocking modifications should be considered. Particular care should be provided on colder climates, as dampness can predispose a patient to the vasospastic effects of cold.

Contact dermatitis may be the result of reactions to chemicals used in shoe construction, footwear fabrics, and/or stockings. Tannic acid, nickel, and synthetic fabrics are the common primary irritants. This condition is usually self-limited and presents with bilateral skin lesions. Skin testing can be employed to identify the primary irritant. The general principles of management include removing the cause, mild wet dressings, and the use of topical steroids.

Stasis dermatitis is the residual of venous insufficiency and chronic ulceration. It is more common in patients with dependent edema. Hemosiderin deposition may also be noted with discoloration and induration. Management locally consists of elevation, mild wet dressings, topical steroids, antibiotics as indicated, and supportive measures needed in the management of venous disease. Pyodermias and superficial bacterial infections should be managed locally in a similar manner and when present with tinea, treatment directed toward both etiologies.

Tinea pedis in the older patient may be an extension of onychomycosis that serves as a focus of infection. It is more common in warmer climate and related to hyperhidrosis. Chronic keratotic tinea (dry squamous type) is more prevalent in older patients with scales forming a moccasin pattern on the foot. Interdigital infection demonstrates pruritus, scaling, and fissuring and may macerate with excessive perspiration. The acute vesicular form demonstrates bullous lesions that can rupture and produce raw sensitive skin that makes the patient more prone to secondary bacterial infection. Poor foot hygiene and the inability to bend or see their feet may delay the patient from seeking care until the condition becomes clinically significant and cellulitis is present. In a patient with diabetes or peripheral arterial disease, this complication can be limb threatening. There are a variety of topical medications, such as terbinafine, clotrimazole, butenafine, miconazole, ketoconazole, ciclopirox, naftifine, econazole, sertaconazole, etc that can usually control this fungal infection. Solutions, powders, and/or creams (water washable or miscible) are best when the patient is unable to easily remove an ointment base. Other common dermatologic manifestations that can be demonstrated in the older patient include atopic dermatitis, nummular eczema, neurodermatitis, lichen planus, and psoriasis.

Solitary and/or hemorrhagic bullae are related to shoe trauma, friction, or are related to systemic diseases such as diabetes mellitus. Management is directed toward eliminating pressure, protection, and drainage when appropriate. Supportive dressings and shoe modifications should be utilized as indicated. Gait changes in the older patient magnify many of the foot to shoe last incompatibilities that can result in local foot lesions. Hemorrhagic bullae related to diabetes mellitus are usually indicators of pending ulceration.

Hyperkeratotic lesions, such as tyloma (callous) and heloma (corn) and their varieties, such as hard (durum), soft (molle), vascular (vasculare), neurofibrous (neurofibrosum), seed (millare), and subungual, are usually painful and

secondary to repetitive stress, bony abnormality, deformity, keratin dysfunction, and a lack of hydration and lubrication to the skin. Intractable keratoma, eccrine poroma, porokeratosis, and verruca must be differentiated from these keratotic lesions, although each may present initially as a hyperkeratotic area. The biomechanical and pathomechanical factors that help create these problems are those associated with stress, that is, compressive, tensile, and/or shearing. The loss of soft tissue as part of the aging process and atrophy of the plantar fat pad increase pain and limit ambulation. Contractures, gait changes, deformities, and the residuals of arthritis are all additional factors that need to be considered in management. The incompatibility of the foot type (inflare, straight, or outflare) to the shoe last is another factor to be considered. It is important to recognize that there is usually not one factor, but a multiplicity of conditions including skin tone and elasticity, which results in the development of painful keratotic lesions in older adults. Their management is not routine. As with any other chronic condition in older adults, continuing care is needed to promote ambulation and comfort.

The common sites for the development of hyperkeratotic lesions include dorsal or distal digital, plantar metatarsal heads, marginal calcaneal, and with deformities such as: hammertoes, digital rotations, contractures, hallux valgus, bunion, and/or tailor's bunion (bunionette). These deformities are precipitating factors to foot to shoe last incompatibilities that produce excessive pressure on segments of the foot. Management and treatment should be directed toward the functional needs of the patients and daily living activities. Considerations include debridement, padding, emollients, shoe modifications, last changes, orthoses, and surgical revision as indicated. Materials to provide soft tissue replacement, such as Plastazote, PPT, foam, and silicone produce weight dispersion diffusion as indicated. It is also important to recognize that keratotic lesions of long standing represent a hyperplastic and hypertrophic pathology. Even when weight bearing is removed, they tend to persist for some time. In a sense, hyperkeratotic lesions are a form of body protection to pressure and are symptoms of an abnormal condition. If permitted to remain untreated, enlarge, and condense, they become primary irritants. With pressure such as weight bearing and ambulation, they produce local avascularity, which can precipitate ulceration and their resultant sequelae. Ulcers in the foot usually begin with subkeratotic hemorrhage. Once debrided and managed properly, they usually heal, but may be repetitive, unless adequate measures are instituted to reduce the pressure to the localized areas of stress and ulceration. The application of a topical emollient is also an important home or self-care measure. Even with all measures, the problem may persist due to residual deformity and systemic diseases, such as diabetes mellitus. Thus management and monitoring are similar to any other chronic condition in the older adult and can have a significant impact on the social elements of society, for without mobility and/or ambulation, the older patient is clearly institutionalized in some form.

TOENAILS

The onychial changes that occur with aging are the result of dystrophic changes, systemic complications, infection, long-term disorders, injury, and/or functional modification.

Onychia is an inflammation involving the posterior nail wall and nail bed. It is usually precipitated by local trauma or pressure, a complication of systemic diseases, such as diabetes mellitus, and is the primary clinical sign of impending of infection. Mild erythema, swelling, and pain are the most prevalent findings. Treatment should be directed to removing all pressure from the area and the use of tepid saline compresses. Topical antibiotics can be utilized as a dressing. Lamb's wool, tube foam, or shoe modification should be considered to reduce pressure to the toe and nail. If the onychia is not treated early, paronychia may develop with significant infection and abscess of the posterior nail wall. The infection progresses proximally and deeper structures become involved. The potential for osteomyelitis is greater in the presence of diabetes mellitus and vascular insufficiency. Necrosis, gangrene, and the potential for amputation become reality. Management includes establishing drainage, culture and sensitivity, radiographs and scans as appropriate, saline compresses, and appropriate systemic antibiotics. Follow-up is essential to prevent cellulitis.

Deformities of the toenails are the result of repeated microtrauma, degenerative changes, and/or disease. The continued friction of the toenails over the years, against the inferior toe box of the shoe is sufficient trauma to produce dystrophic change. The initial thickening is termed onychauxis. Onychorrhexis with accentuation of normal ridging, trophic changes, and longitudinal striations are onychopathic when related to disease and/or nutritional etiology. When debridement is not completed on a periodic basis, the nail structure elongates, continues to thicken, and becomes deformed with shoe pressure. Onychogryphosis or "ram's horn nails" is usually complicated by fungal infection. The resultant disability can prevent older adults from wearing shoes. Pain is usually associated with shoe pressure and the deformity. Traumatic avulsion of the nail is a complication. The exaggerated curvature (onychodysplasia pincer

toenails) may even penetrate the skin, with resultant infection and ulceration. Management should be directed toward periodic debridement of the onychial structures both in length and thickness, with as little trauma as possible. The degree of onycholysis (freeing of the nail from the anterior edge) and onychoschizia (splitting) helps determine the level of debridement. With the excess pressure of deformity, the nail grooves tend to become onychophosed (keratotic). Debridement and the use of mild keratolytics and emollients, such as ammonium lactate and 10% to 20% urea preparations provide some measure of home care for the patient. With onycholysis, subungual debris and keratosis develop, which increases discomfort and may generate pain. However, the patient may not present complaints of pain and discomfort due to a loss of protective sensation.

Patients with neurosensory and vascular deficits usually demonstrate some form of onychodystrophy, such as onychorrhexis, onychophosis, deformity, hypertrophy, incurvation or involution, subungual hemorrhage (nontraumatic), onycholysis, (freeing from the distal segment), onychomadesis (freeing from the proximal segment), autoavulsion, and onychomycosis. These individuals are at greater risk of infection, necrosis, gangrene, and possible amputation.

The most common nonbacterial infection of the toenails is onychomycosis. It is defined as a chronic, communicable disease. Culture, KOH microscopic examination, and the clinical presentation are of diagnostic importance. The clinical forms include distal lateral subungual, white superficial, proximal subungual, total dystrophic, and candidal onychomycosis. The superficial white form presents with fungal growth on the superior surface of the nail plate. Left untreated, invasion of the nail bed occurs with trophic changes. With the distal lateral, proximal, and total dystrophic forms, the nail bed is primarily infected, with the possibility of paronychia and subsequent dystrophy. Onycholysis (freeing of the nail from the distal edge) and subungual keratosis occur due to the long-standing chronic nature of this condition in older patients. The posterior nail wall and eponychium demonstrate xerotic changes and hypertrophy, as does the nail plate. *Candida* is most common in patients with some form of chronic mucocutaneous manifestation.

The older patient usually presents with a chronic infection, involving one or more of the nail plates. The entire thickness of the nail plates are usually involved with resultant hypertrophy and deformity due to the delay in management. Pain may be present with paronychia or deformity or diminished due to sensory deficits. Mycotic onychia, paronychia, auto-avulsion, subungual hemorrhage, a foul, musty odor, and degeneration of the nail plate are common findings. The options for treatment include oral antifungals such as terbinafine, itraconazole, and fluconazole and topical medications such as ciclopirox, and two recently FDA-approved preparations, Kerydin and Jublia. A 50% urea-lactic acid combination in gel form will assist to chemically debride the infected nail structures. Due to the chronicity of onychomycosis, matrix involvement enhances hypertrophy and deformity. Multiple prescriptions, diabetes mellitus, and vascular impairment may limit systemic management. Periodic debridement, topical urea, and topical fungicides are the usually indicated for continuing management. Surgical excision may be indicated with excessive pain, as indicated. Onychomycosis must be viewed as a chronic infectious disease, deserving management as any other chronic condition, such as hypertension and/or diabetes mellitus.

Ingrown toenails (onychocryptosis) in the older patient associated with deformity, trauma, and inappropriate self-care. When the nail penetrates the skin, an abscess, and infection result. If not managed early, periungual ulcerative granulation tissue may form that increases the risk of serious complications. Deformity and involution (onychodysplasia) also increase the potential for penetration. In the early stage, a segment of the nail can easily be removed utilizing an English nail splitter and an onychotome, drainage established, saline compresses employed, and antibiotics utilized as indicated. Measures should be taken to prevent the problem in the future. When ulcerative granulation tissue is present, excision, fulguration, desiccation, or the use of caustics is employed to reduce the granulation tissue. In all cases, removal of the penetrating nail is primary. Partial excision of the nail plate and matrix can be completed utilizing regional anesthesia followed by chemical cautery of the matrix area with CP Phenol. With this procedure, postoperative management includes isopropyl alcohol compresses and topical steroid solutions. With aging, changes in the nail plate may occur, which when viewed distally, appear C shaped (onychodysplasia). This abnormal curvature is incurvation or involution. When present, the pressure of the nail plate on the nail bed and folds produces onychophosis (hyperkeratosis in the nail folds) and discomfort, with complaints similar to an ingrown toenail. The condition may precipitate pressure ulcerations and infection. When this condition is severe, early and total removal of the nail plate and matrix should be considered to avoid complications as the patient ages.

Subungual heloma, when present, is usually associated with a subungual exostosis, spur, or hypertrophy of the tufted end of the distal phalanx. Initial treatment consists of debridement and protection of the toe involved, as well as the use of a shoe with a high toe box. Surgical excision of the osseous deformity may be indicated if the condition cannot be managed in a conservative manner. A primary differential diagnosis is subungual melanoma that requires

biopsy and prompt management. In all cases of suspected bone pathology, radiographs properly positioned to isolate the area of pathology will provide an appropriate diagnostic approach.

There are multiple onychopathies that occur in the older adult that are associated with cutaneous and systemic disease. The most common include, but are not limited to psoriasis, mucocutaneous lichen planus, anemia, diabetes mellitus, chronic obstructive pulmonary disease, myocardial infarction, Raynaud disease, hyperthyroidism, hypothyroidism, vasospastic states, endocarditis, cardiac disease, hypertension, malignancy, rheumatoid arthritis, cirrhosis, alcoholism, peripheral arterial diseases, systemic medications, and local contact agents.

PATHOMECHANICS AND BIOMECHANICS

The human foot is primarily a rigid structure that supports heavy physical workloads that are static and dynamic. The foot itself is shaped like a modified rectangle and bears static forces in a triangular pattern. The transmission of weight and force starts at heel strike, proceeds anteriorly along the lateral segment of the foot, medially across the metatarsal heads, to the first metatarsal segment for the push-off phase of the gait cycle. The social activities of life, occupation, and disease produce morphologic variations in both the structure and function of the foot, in keeping with Wolff's and Davis' law as the body adapts to the stress placed upon it. The environment itself, that is, flat and hard surfaces force the foot to absorb shock, creating prolonged periods of micro and repeated trauma.

As individuals age, the problems magnify, by changing stance, gait, and the ambulatory status of older adults. The primary considerations include balance; a shuffling gait; broadening the base of gait an stance; reduced toe clearance; changes related to hip, knee flexion, degenerative joint disease, and obesity; as well as specific gait change including circumduction, festinating, steppage, cerebellar, and sensory ataxic gait. Pain, slow speed, short step length, and a narrow stride and width are also important factors. The stress created on the foot and the inability of the patient to adapt to stress produces inflammatory changes in bone and soft tissue, such as osteitis, periostitis, synovitis, capsulitis, fasciitis, myositis, fibrositis, neuritis, and arthritis. Structural modifications of an external nature need to be considered along with the use of physical modalities and appropriate medication as indicated.

Foot problems of a pathomechanical or biomechanical nature usually arise from the interaction between normal morphologic variations, the capacity to adapt to stress, and the stressors acting on the foot itself. Morphologic variations may be intrinsic, that is, within the foot itself, or extrinsic, such as changes in the physiologic relationship of the legs, knees, thigh, hip and back on the human foot. These changes may be bone and/or soft tissue. The common intrinsic changes include elements such as a hypermobile segment, pes cavus, atrophy of the interossei muscles producing digiti flexus or hammer toes, and the development of hallux valgus, or the so-called "bunion deformity."

The management of pathomechanical and/or biomechanical disorders should be directed toward eliminating the cause and redistributing weight to nonpainful areas of the foot, through weight diffusion and weight dispersion. In addition, the variations in and individual's capacity to adapt to change, particularly when surgical revision is considered, is significant. The primary treatment goals are to relieve pain, to restore maximum function and to maintain that restored function once achieved. Bilateral weight and nonweight bearing radiographic and imaging studies are indicated as patient management needs are considered from both a static and dynamic phase.

The ability to adapt to stress is dependent on two major systems, the neuromuscular and vascular; which may be significantly comprised as part of the aging process and disease. The mechanical stressors are two in nature. The first is macrotrauma, which results from sudden injury, such as a fall, resulting in a fracture. The second might be termed microtrauma, which accounts for the hundreds of thousands of repetitive injuries to the foot from occupational activities, obesity, poor stance, modified gait and foot to shoe last incompatibilities. The systemic stressors are those factors affecting the foot as complications of diseases such as diabetes mellitus, all forms of arthritis, arteriosclerosis, etc. It is also obvious that the foot cannot be divorced or segmented from the body, nor can the foot itself be segmented. It is thus evident that the foot must be considered as a total "end" organ of locomotion and that the resultant mechanical, rotational, and/or positional changes comprise parts of a syndrome or a chain of events of a chronic and progressive process. Once a link in the chain breaks, every effort must be made to prevent further damage and minimize the associated complications of chronic disease. As such, chronic foot problems take years to develop and become significant when they create pain and affect ambulation, the activities of daily living, and the quality of life.

FOOT ORTHOPEDICS

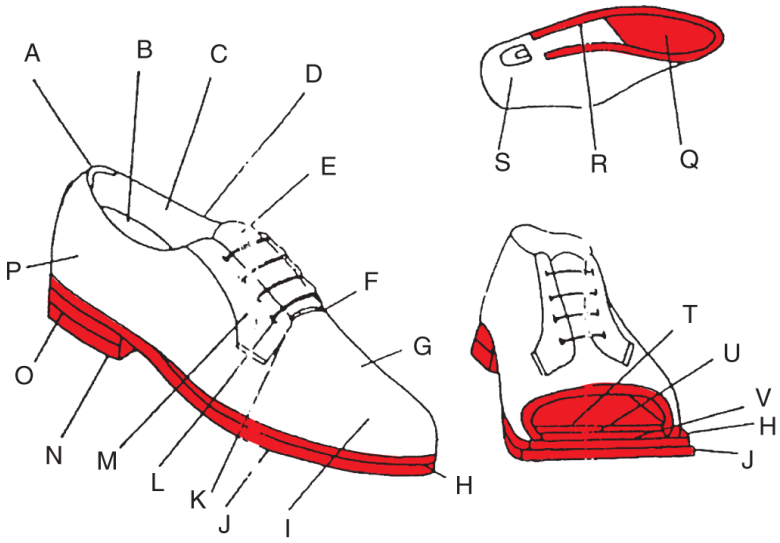
There are varieties of residual foot deformities that can be present in multiple combinations in the older adult. These include but are not limited to hallux valgus, hallux varus, splay foot, hallux flexus, digiti flexus (hammertoe), digiti quinti varus, overlapping toes, under-riding toes, prolapsed metatarsals, pes cavus, pes planus, pronation, hallux limitus, and hallux rigidus. Many of these changes are the result of and related to degenerative joint disease (osteoarthritis), rheumatoid, and gouty arthritic changes.

Conservative modalities include shoe last changes, shoe modifications, orthoses, digital braces, physical medicine, exercises, and mild analgesics for pain. Surgical revision, arthroplasty, and joint replacement are also treatment options that should be considered with chronic pain, limitation of the quality of life, and as indicted. Age itself should not be the singular indication of contraindication for surgical consideration. Other factors must also be given to the patient's overall health, medical condition, mental status and the ability to adapt to change in relation to ambulation, for to have an anatomically corrected joint and a patient that cannot ambulate without pain defeats the treatment needs of older adults. Foot conditions need to be managed medically, physically, mechanically, and surgically, to keep the patient ambulatory and pain free.

Fractures of the foot and toes may be the result of direct trauma and/or stress, related to bone loss. Most uncomplicated and closed fractures that are in good position should be appropriately immobilized as indicated. Open fractures need surgical management. Digital fractures can usually be managed with silicone mold and surgical shoes and supportive dressings, as long as the joints distally and proximally are immobilized.

FOOTWEAR AND ORTHOSES

See **Figure 123-2** for an overview of the anatomy of the shoe. Shoe selection should be based on the functional needs of the patient, a shoe last that conforms to the foot, the complications of other diseases and disorders, shoe size that is based on internal and external measurements, and fabricated of materials that will provide protection, support, and permit maximum foot function. For example, the stylish dress shoe has different social needs than does a shoe for daily use and for walking and exercise.



A. Backstay
B. Heel Pack
C. Quarter lining
D. Top line
E. Tongue
F. Tongue bar
G. Vamp
H. Welt
I. Toe cap
J. Sole
K. Throat line
L. Eyelet row
M. Eyelet facing
N. Heel
O. Heel base
P. Heel foxing
Q. Bottom filter
R. Shank
S. Counter under quarter
T. Sock lining
U. Insole
V. Filter

FIGURE 123-2. Components of a shoe. (Adapted with permission from Pedorthic Footwear Association. Pedorthic Reference Guide. Columbia, MD; 1992, 1999, 2006.)

For the most part, a shoe that provides some flexibility to allow for free mobility usually feels the most comfortable unless there are deformities or other special conditions that require rigidity. The foot is basically a

modified rectangle thus a quadrangular shoe would be the best last, to conform to the shape of the foot. With deformity, special lasts may be indicated. The shoe should have an acceptable heel height to avoid forcing the toes into the end of the shoe. The material of construction should be porous to allow for the evaporation of moisture. There should be some degree of moderate sole friction to avoid slippery and adhesive sole material. This consideration also needs to be evaluated in comparison to flooring surfaces and in particular, high pile carpets. The shoe should be lightweight to reduce energy expenditure on the part of the patient. The wearing of shoes should be socially acceptable in appearance to the patient. Cost is a factor and a reasonable price for the particular patient becomes essential given the limited incomes of older patients. For long-term care patients, these suggestions may well change for the incontinent nursing home patient, a soft washable foot covering may be the most practical solution.

Shoes are constructed over a last or model of the foot. The last may be inflare, straight, or outflare. It is essential that the flare of the foot match the flare of the shoe to avoid a foot-to-shoe-last incompatibility and permit abnormal pressure to develop. Shoes generally consist of an outsole, heel, rand, counter, quarter, vamp, back stay, filler, lining, upper, tip, toe cap, foxing, welting, insole, sock lining, tongue, eyelet, and laces or other closure.

Some of the basic shoe types include standard lasts, basic orthopedic shoes with its long counter and Thomas heel, rigid shank shoes, high top lasts, extra depth shoes, shoes with moldable interiors, custom molded and fabricated footwear, and athletic footwear.

The basic shoe modifications that may be utilized for older patients include medial (for valgus deformity) and lateral (for varus) heel seat wedges. Sole wedges are utilized for alignment and support and to help maintain a better gait pattern. Calcaneal wedges to limit motion and alter gait. Metatarsal bars are utilized to shift or transfer weight from the metatarsal heads to the shaft. In addition, the bar produces a moderate heel rise to push off without additional metatarsal head weight bearing. Examples include the Denver, Hauser, and Comma bar. The Thomas heel and long counter provide improved balance, increase calcaneal support, and increase the stability of the shank area. Long shoe counters are to increase mid-foot support and control foot direction. Heel flares are to increase ankle stability either medially or laterally. The heel may be reversed to provide lateral stability.

A shank filler provides for a total contact shank area, increases stability, and enhances the weight-bearing surface. They can also be utilized for excessive valgus and varus. The spring extension can be utilized to increase push-off. The steel splint or plate is utilized to limit motion, usually at the first metatarsal-phalangeal joint in relation to hallux limitus or rigidus. The rocker bottom, which is an extension of the metatarsal bar, is designed to prevent flexion and extension of the shoe. Shoe elevations can compensate for limb length discrepancies. The solid ankle cushion heel (SACH) improves extension (planter flexion) or ankle motion. The SACH heel can also be utilized with a metatarsal bar, rocker bar, springs or double sole, which then limits some motion. The KEEL heel is utilized to eliminate lateral forces. Steel springs, cork, or wooden buildups may also be employed as indicated.

Internal shoe modifications medial longitudinal pads or cookies, metatarsal pads, balance pads, calcaneal bars, heel pads and lifts, Barton and Thomas wedges, and tongue or bite pads, heel elevations, cushions, and wedges. Excavations and stretching or relasting are also important. Shoe selection and last determination as well as fit are essential for the older patient, particularly when an orthoses is to be utilized.

ORTHOSES FOR THE OLDER PATIENT

Orthoses are utilized to protect, restore, and/or improve function that support, align, prevent or modify deformities. Foot orthotics may or may not include a shoe and/or any modification to make an orthotic functional and effective. Orthoses are prescribed by health care professionals and are fabricated to meet the specific needs of the patient.

The primary prescription objectives include modifying foot function, compensate for existing deformities, weight dispersion, weight diffusion, soft tissue supplementation, shock absorption, support, realignment, improved performance, restriction of motion, enhancement of motion, prevention of injury, reduction of weight load, stabilization, and the relief of pain.

The available orthoses include rigid, semirigid, and flexible forms, utilizing materials such as plastics, Plastazote, Evazote, Aliplast, polyurethane, Sorbothane, Viscolas, cork/rubber, Birkokork, Korex, PPT, Spenco, Poron, leather, silicone latex, laminates, Ortholene, subortholene, polypropylene, polyethylene, proprietary polyolefins, and graphite composites. In addition, replaceable pads, insoles, heel orthoses, functional orthoses, latex shield, silicone molds, and digital orthoses are also utilized as indicated.

The foot orthosis is a form of durable medical equipment that does provide support and compensate for malalignment, which may be present in the older patient. The orthosis is utilized to improve function and provide

support. It may be utilized to evenly redistribute weight, as is the case of the total contact orthoses. It may accommodate painful areas and provide for filler in the post amputation period. For the older patient, correction is many times modified to become compensation and may limit motion, compensate for abnormal foot position, help equalize limb length discrepancy and control position and motion.

The prime diagnostic categories that deserve consideration for the use of orthoses in the older patient, include as examples, but are not limited to the following: heel spur syndrome, calcaneal bursitis, plantar fasciitis, metatarsalgia, hallux valgus, Morton neuralgia, hyperkeratotic lesions including shearing and diffuse tyloma, heloma, and intractable plantar keratosis, myalgia, sesamoiditis, spastic foot, osteoarthritis, rheumatoid arthritis, gouty arthropathy, diabetic osteoarthropathy, hammertoes, plantar ulceration and preulceration, insensitive feet, instability, hallux limitus and rigidus, chronic instability and sprains, pes planus, pes cavus, varus and valgus deformities, podalgia, pododynia dysbasia, neuromotor dysfunction, neurologic deficits and compensation for osseous malformations.

Orthoses may be over the counter, custom made or customized, and modified prefabricated components. They may be full-length, to sulcus, to metatarsal head area or have extensions to compensate for metatarsal length discrepancies. Rigid orthoses are usually fabricated from metal or thermoplastics. With thermoplastics, the degree of rigidity and flexibility can be modified by the thickness and material selection, the weight and functional needs of the patient and the use of soft material as a part of a top cover. Semirigid orthoses are usually fabricated from leather, rubber, cork, polypropylene, and celastic and may include steel springs in the shank area. Soft orthoses usually consist of materials that provide weight diffusion, weight dispersion or is multidensity to encompass both concepts. Materials include Plastazote, Spenco, PPT, Pelite, Aliplast, felt, ground cork/wood flour and latex. Silicone also is not utilized for both plantar orthoses and as digital orthoses in the form of silicone molds. These custom designed digital braces have a significant role to play in the management of the older patient as they provide a great deal of flexibility, are cost effective, can easily be modified and/or changed and custom designed to meet individual patient needs and diagnostic indications.

The general types include calcaneal orthoses such as heel stabilizer/cups, heel protectors and shock absorbing calcaneal seats. The full-length orthoses are usually soft and may have some degree of semi-rigid characteristics for stability. Multi-density and total contact orthoses usually fit this category. Schaffer, Whitman, and Mayer designs are still utilized, based upon the indications and ability of the patient to adapt to this form of shell design. Metatarsal extensions and modifications are incorporated into these primary classifications and include but not limited to the following examples: heel pad, heel spur pad, cutouts for weight dispersion, scaphoid pad, longitudinal arch reinforcement, wedges, Morton's extension, rear foot post, forefoot post, metatarsal pad, and heel lifts.

For the geriatric patient, the usual prescription includes some degree of flexibility to provide both a functional accommodative orthotic. Some of the newer rigid materials, used in a thinner plate, do provide some flexibility and does permit a myotatic reflex to function. Geriatric orthoses usually provide some form of cushioning material that is both weight diffusive and weight dispersive. Keys are also strength, semiflexibility, and resiliency that compensate for change in the multiple systems involved in gait and the changes related to aging and chronic diseases.

The final determination of appropriate form and material depends on the weight of the patient, findings at examination, general functional needs, activities of daily living, and the physiologic adaptability of the patient. Clinical needs and appropriate indications are essential considerations for relief of pain, restoration of a maximum degree of function, and maintaining that level of function, once achieved.

It is important to remember that footwear, as protection and foot covering, needs to be compatible with the foot and the patient's functional requirements. Shoe modifications enhance these requirements. The foot orthosis adds another link in the chain needed to keep the patient pain free and ambulatory. The foot, shoe, and orthoses must function as a unit and as a part of the patient's ambulatory system.

THERAPEUTIC SHOES FOR DIABETICS

The importance of footwear and appropriate orthoses for the older population has been clearly delineated in relation to the "at risk" diabetic under Medicare. The "therapeutic shoe" provisions, as currently projected, demonstrate in this singular disease, the important relationship between shoes and orthoses in the diabetic. It is important to note that this is just one example of need.

At this time, the provisions for coverage indicate that the patient must meet the following criteria (**Table 123-4**).

Following the above a podiatrist or other qualified physician knowledgeable in the fitting of therapeutic shoes and inserts may write the prescription. The footwear must be fitted and furnished by a podiatrist or other qualified

individual such as, pedorthist, orthotist, or prosthetist.

The shoes may be of two types. The first is a depth-inlay shoe to accommodate multidensity inserts and the second is a custom molded shoe that needs to meet additional criteria as follows:

1. Charcot foot with evidence of rocker bottom deformity of severe adduction or abduction of the forefoot.
2. Flail foot not supported by a depth shoe.
3. Major foot deformity not accommodated by depth shoe.

In addition, detailed documentation indicating the inability to support or protect the foot in a standard or depth shoe will be essential to document the foot deformity.

With the depth-inlay shoe, multiple density inserts will be accepted with a future projection for total contact activity achieved by molding to the foot or model. The projections include coverage for three sets of inserts, made at different times, and adjusted to changing needs.

Other shoe modifications under this Medicare provision include the following at this time:

- Rigid rocker bottoms
- Roller bottoms
- Metatarsal bars
- Wedges
- Off-set heels

ULCERATIONS

The management of ulcerations in the older patient depends on the etiology and the related complications associated tissue loss. Risk factors include diabetic neuropathy, peripheral vascular disease, biomechanical and pathomechanical factors, previous history of ulceration, poor hygiene, age, inappropriate footwear, gait abnormalities, ambulatory dysfunction, poor vision, inappropriate and delayed care, inappropriate home care and the use of over-the-counter remedies, and other related systemic factors. General principles include supportive measures to reduce trauma and pressure to the ulcerated area, such as dressings, orthoses, shoe modifications, and special shoes (extra depth and custom molded shoes). The prevention and control of infection, and maintaining a clean, healthy base to permit healing are essential. Issues that need to be considered include perfusion, size, depth or tissue loss, infection, and neuropathy including a loss of protective sensation. The debridement of keratosis when indicated is essential to prevent roofing of the ulcer. The use of physical modalities and measures such as low voltage therapy (contractile currents) and exercises can assist in improving the local vascular supply to the ulcer and in helping to establish a clean base. Pressure ulcers of local origin are usually associated with a bony prominence, biomechanical abnormality, and external trauma or as the result of stress associated with gait change. Atrophy of soft tissue and the residuals of arthritis provide a focus for the development of ulcerations. Tissue loss associated with systemic diseases is usually related to sensory loss, neuropathic joint change, and vascular insufficiency, as with diabetes mellitus and peripheral arterial disease. Management focuses on identifying the underlying diagnosis, local supportive measures, adequate treatment of the related systemic diseases and efforts to minimize the potential for osteomyelitis and amputation risk, and maintaining the ambulatory status of the patient for as long as possible.

Methods to remove pressure from weight bearing areas can be attained by the use of orthoses and/or shoe last changes; the use of pads, bars, wedges, and other modifications; increasing the sole thickness and using shock-absorbing material; and surgical shoes, total contact orthosis, special foot and ankle walkers, and ortho and heel wedge surgical shoes. Older patients who avoid the use of footwear at home, due to their inability to bend, expose themselves to the potential of foreign bodies and foot injury.

DIABETIC AND PERIPHERAL ARTERIAL CONSIDERATIONS

Foot complications relating to diabetes have a significant impact on the quality of life of diabetic patients. The older diabetic presents with a covariant set of syndromes including dermopathy, onychopathy, vasculopathy, neuropathy, and myopathy. The symptoms are similar those of aging in general but appear at an earlier age. Foot complications are also

a major cause of hospitalization and 50% to 75% of these amputations can be prevented when the diagnosis is made early and interventions are instituted that can affect outcomes. Emphasis is placed on preventing lower extremity amputations, which can produce major life style changes and have a significant economic impact on the patient, their families, the health care system, and society in general. Programs such as "LEAP" (lower extremity amputation prevention, Department of Health and Human Services), "PACT" (Prevention, Amputation, Care, and Treatment, Department of Veterans Affairs), and "PAVE" (Prevention of Amputation in Veterans Everywhere Program, Department of Veterans Affairs) are examples of these efforts. Older diabetic patients present the greatest risk for ulceration, infection, hospitalization, and amputation due to the multiple systems involved in the disease. Similar changes can be demonstrated with peripheral arterial disease, hemophilia, cardiac disease, chronic renal failure (dialysis), obesity, poststroke, and chronic obstructive pulmonary disease. Tissue loss in older adults and amputation can terminate the patient's independent life of usefulness to themselves and society.

The pathogenesis of a diabetic foot ulceration in the older patient includes diabetes mellitus itself; trauma (direct and/or repetitive microtrauma); neuropathy—motor (weakness, atrophy, deformity, abnormal stress, high plantar pressure, and hyperkeratosis), sensory (loss of protective sensation), autonomic (anhidrosis, xerosis, fissures, and decreased sympathetic tone); peripheral arterial disease—macrovascular (atherosclerosis and ischemia), microvascular (structural and/or functional); osteoarthropathy (Charcot joints); impaired response to infection; reduced nutrient capillary blood flow; with subsequent ulceration and potential amputation. The risk increases with sensory deficits, altered biomechanics and neuropathy, increased tissue pressure (erythema and subkeratotic hematoma), bony deformity, decreased or absent pedal pulses, prior ulcerative history, and toenail pathology.

Hyperkeratotic lesions form as space replacements and provide a focus for ulceration due to increased pressure on the soft tissues with an associated localized avascularity from direct pressure and counterpressure. Tendon contractures and hammertoes increase pressure. A warm foot with pulsations in an older diabetic with neuropathy is not uncommon. When ulceration is present, the base is usually covered by keratosis that retards and many times prevents healing. Necrosis and gangrene are related to infection with eventual occlusion and gangrene. Foot drop and a loss of position sense are usually present. Pretibial lesions are indicative of this change as well as microvascular infarction. Arthropathy gives rise to deformity, altered gait patterns and a higher risk for ulceration and limb loss.

In addition to the relationship of vascular and neuropathic changes, ulcerations must be related to trauma and in particular, the effects of repeated microtrauma. Hyperkeratosis related to keratin dysfunction, space replacement, bony abnormality, and/or pathomechanics would react to pressure and trauma, which may be mechanical, thermal, and/or chemical in nature. Sub-hyperkeratotic hemorrhage is usually an early clinical sign of tissue breakdown. Regardless of the cause, the general principles of management include a decrease of local trauma by the use of orthotics, shoe modifications, specialized footwear, and efforts to maximize weight diffusion and weight dispersion techniques. Physical modalities, medication, and exercise can be employed to improve the vascular supply to the part, following adequate evaluation by Doppler and other techniques. Appropriate invasive techniques and by pass surgical procedures should be considered. Local debridement of the ulcerative site and adequate home wound care, appropriate antibiotics, topical enzymes, and tissue stimulants should be considered. Radiographs and bone scans should be ordered early on in the management process to deal with infection at its first signs. Culture and sensitivity, appropriate antibiotic therapy, and hospitalization should be considered to prevent, where possible, amputation. Wound care includes medical debridement, special dressings, autologous and epidermal grafts (Apligraf, Dermagraft, Oasis wound management, and biologic dressings), and recognizing limb-threatening infection (deep ulceration, bone and/or joint involvement, systemic toxicity, ischemia, gangrene, and gas gangrene). Negative pressure wound therapy, hyperbaric oxygen, and transcutaneous oxygen measurement are additional considerations.

Asymptomatic diabetic older patients should be evaluated at least twice a year to identify problems at their earliest development. Patients with foot conditions requiring primary management should be followed every 30 to 60 days, depending on the degree of complications. A multidisciplinary care approach, which includes the patient and his/her family, is an essential element in managing older adult diabetics with foot problems.

AMPUTATION PREVENTION

The threat of amputation in at risk groups including those with diabetes, end-stage renal disease, and peripheral vascular disease demands a more prevention-oriented approach. The Department of Veterans Affairs has led the way in this regard with the introduction of the (PACT program, which was initiated in 1993. This program is now known as the PAVE program (VHA Directive 2012-030). This program directed every VHA medical center to establish a

model of care that identified patients at risk for amputation defined as those with diabetes, end-stage renal disease, and peripheral vascular disease at a minimum. Once identified, these "at risk" patients are screened for wound precursors including foot deformity, absent pulses, and loss of protective sensation. A foot risk score (FRS) is then assigned based on this screening as FRS 0 or normal risk, FRS 1 or low risk, FRS 2 or moderate risk, and FRS 3 or high risk. Based on this risk score a referral algorithm is used to provide timely and appropriate referral for follow-up and/or treatment. FRS 0 and 1 patients receive self-foot care education and are then screened at least annually in primary care. FRS 2 and 3 patients are referred for ongoing regularly scheduled surveillance and care by foot care specialists (eg, podiatric physicians).

CONCLUSION

The ability to retain ambulation is directly related to foot health as individuals age. Regardless of the care setting, that is, home, ambulatory facilities, long-term care programs, mental health facilities, assisted living, or other models, all practitioners must think comprehensively, and recognize that team care must be an essential part of the management of the older individual. Foot health education such as programs developed by the Pennsylvania Department of Health (Feet First and If the Shoe Fits), is available to both patients and professionals, and should be employed as a part of all geriatric patient education programs. With the high prevalence and incidence of foot problems in the older patient, the ability to live life to the end of life will depend to a great deal on the ability to remain alert, mobile, and to retain the qualities that make individuals want to live.

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APPENDIX I: COMPREHENSIVE CLINICAL PODOGERIATRIC AND CHRONIC DISEASE PROTOCOL ASSESSMENT (HELFAND INDEX)

DATE OF VISIT _____ MR# _____
PATIENT'S NAME _____ AGE _____
Date of Birth _____ SOCIAL SECURITY # _____
ADDRESS _____
CITY _____ STATE _____ ZIP CODE _____
PHONE NUMBER _____
SEX M F _____ RACE _____ B W A L NA_____
WEIGHT LBS _____ HEIGHT IN _____
SOCIAL STATUS M S W D SEP_____

NAME OF PRIMARY PHYSICIAN/HEALTH CARE FACILITY _____
DATE OF LAST VISIT _____

HISTORY OF PRESENT ILLNESS

- Swelling of Feet
- Painful Feet
- Hyperkeratosis
- Onychial Changes
- Bunions
- Painful Toe Nails
- Infections
- Cold Feet
- Other

- Location
- Quality
- Severity
- Duration
- Context
- Modifying Factors
- Associated Signs & Symptoms

PAST HISTORY

- Heart Disease
- High Blood Pressure
- Arthritis
- *Circulatory Disease
- Thyroid

- Diabetes Mellitus
- *IDDM
- *NIDDM
- Hypercholesterol
- Gout

Allergy	History: Smoking: OH
	Family - Social

SYSTEMS REVIEW

Constitutional

ENT	Card/Vasc	GU
Eyes	Musculo-	Neurologic
Skin/Hair	Skeletal	Endocrine
Respiratory	GYN	GI
Psychiatric	Allergic	Immunologic
Hematologic	Lymphatic	

MEDICATIONS

DERMATOLOGIC

*Hyperkeratosis		Xerosis
Onychauxis	B-2-b	Tinea Pedis
Infection		Verruca
*Ulceration		Hematoma
Onychomycosis		Rubor
Onychodystrophy		*Preulcerative
*Cyanosis	B-2-e	Discolored

FOOT ORTHOPEDIC

*Hallux Valgus	*Hallux Rigidus-Limitus
*Anterior Imbalance	*Morton’s Syndrome
*Digiti Flexus	Bursitis
*Pes Planus	*Prominent Met Head
*Pes Valgoplanus	*Charcot Joints
*Pes Cavus	Other

VASCULAR EVALUATION

*Coldness	C-2	*Claudication	C-1
*Trophic Changes	B-2-a	Varicosities	
*DP Absent	B-3	Other	
*PT Absent	B-1	*Amputation	
*Night Cramps		*AKA BKA FF T	A-1
*Edema	C-3	Atrophy	B-2-d

NEUROLOGIC EVALUATION

*Achilles		Superficial Plantar
*Vibratory		*Joint Position
*Sharp/Dull		*Burning C-5
*Paresthesia	C-4	Other

RISK CATEGORY - NEUROLOGIC

0 = No Sensory Loss
*1 = Sensory Loss
*2 = Sensory Loss & Foot Deformity
*3 = Sensory Loss, Hx Ulceration, & Deformity

RISK CATEGORY - VASCULAR

0 - 0 NO CHANGE
*I - 1 MILD CLAUDICATION
*I - 2 MODERATE CLAUDICATION
*I - 3 SEVERE CLAUDICATION
*II - 4 ISCHEMIC REST PAIN
*III - 5 MINOR TISSUE LOSS
*III - 6 MAJOR TISSUE LOSS

CLASS FINDINGS

A1	Nontraumatic Amputation
B1	Absent Posterior Tibial
B2	Advanced Trophic Changes
B2a	Hair Growth (decrease or absent)
B2b	Nail Changes (thickening)
B2c	Pigmentary Changes (discoloration)
B2d	Skin Texture (thin, shiny)
B2e	Skin Color (rubor or redness)
B3	Absent Dorsalis Pedis
C1	Claudication
C2	Temperature Changes (cold)
C3	Edema
C4	Paresthesia
C5	Burning

ONYCHOMYCOSIS: Documentation of mycosis/dystrophy causing secondary infection and/or pain, which results or would result in marked limitation of ambulation.

Discoloration
Hypertrophy
Subungual Debris
Onycholysis
Secondary Infection
Limitation of Ambulation and Pain

CLASSIFICATION OF MECHANICAL OR PRESSURE HYPERKERATOSIS

GRADE DESCRIPTION

0. NO LESION
1. NO SPECIFIC TYLOMA PLAQUE, BUT DIFFUSE OR PINCH HYPERKERATOTIC TISSUE PRESENT OR IN NARROW BANDS
2. CIRCUMSCRIBED, PUNCTATE OVAL, OR CIRCULAR, WELL DEFINED THICKENING OF KERATINIZED TISSUE
3. HELOMA MILLIARE OR HELOMA DURUM WITH NO ASSOCIATED TYLOMA
4. WELL DEFINED TYLOMA PLAQUE WITH A DEFINITE HELOMA WITHIN THE LESION EXTRAVASATION, MACERATION AND EARLY BREAKDOWN OF STRUCTURES UNDER THE TYLOMA OR CALLUS LAYER

5. COMPLETE BREAKDOWN OF STRUCTURE OF HYPERKERATOTIC TISSUE, EPIDERMIS, EXTENDING TO SUPERFICIAL DERMAL INVOLVEMENT

PLANTAR KERATOMATA PATTERN

LT 5 4 3 2 1 RT 1 2 3 4 5

ULCER CLASSIFICATION

GRADE - 0 - ABSENT SKIN LESIONS
GRADE - 1 - DENSE CALLUS BUT NOT PRE-ULCER OR ULCER
GRADE - 2 - PREULCERATIVE CHANGES
GRADE - 3 - PARTIAL THICKNESS (SUPERFICIAL ULCER)
GRADE - 4 - FULL THICKNESS (DEEP) ULCER BUT NO INVOLVEMENT OF TENDON, BONE, LIGAMENT OR JOINT
GRADE - 5 - FULL THICKNESS (DEEP) ULCER WITH INVOLVEMENT OF TENDON, BONE, LIGAMENT OR JOINT
GRADE - 6 - LOCALIZED INFECTION (ABSCESS OR OSTEOMYELITIS)
GRADE - 7 - PROXIMAL SPREAD OF INFECTION (ASCENDING CELLULITIS OR LYMPHADENOPATHY
GRADE - 8 - GANGRENE OF FOREFOOT ONLY
GRADE - 9 - GANGRENE OF MAJORITY OF FOOT

ONYCHIAL GRADES AT RISK

Grade I	NORMAL
Grade II	MILD HYPERTROPHY
Grade III	HYPERTROPHIC
	DYSTROPHIC
	ONYCHAUXIS
	MYCOTIC
	INFECTED
	ONYCHODYSPLASIA
Grade IV	HYPERTROPHIC
	DEFORMED
	ONYCHOGRYPHOSIS
	DYSTROPHIC
	MYCOTIC
	INFECTED
FOOTWEAR SATISFACTORY	HYGIENE SATISFACTORY
YES NO	YES NO

STOCKINGS: NYLON COTTON WOOL OTHER NONE

ASSESSMENT

PLAN

PODIATRIC REFERRAL
PATIENT EDUCATION
MEDICAL REFERRAL
SPECIAL FOOTWEAR
VASCULAR STUDIES
CLINICAL LAB

IMAGING
Rx

NOTE 1

Practitioners who are permitted by state license to render examination, diagnosis, and treatment must provide foot care services for Medicare reimbursement.

NOTE 2

Services furnished for the evaluation and management of a diabetic patient with diabetic sensory neuropathy, resulting in a loss of protective sensation (LOPS) must include the following:

1. A diagnosis of LOPS
2. A patient history
3. A physical examination consisting of findings regarding at least the following elements:
   a. Visual inspection of the forefoot, hindfoot, and toe web spacess
   b. Evaluation of protective sensation
   c. Evaluation of foot structure and biomechanics
   d. Evaluation of vascular status
   e. Evaluation of skin integrity
   f. Evaluation and recommendation of footwear
4. Patient education

Chapter 124

Fibromyalgia and Myofascial Pain Syndromes

Cheryl D. Bernstein, Jacqueline V. Aredo, Jay P. Shah, Debra K. Weiner

Learning Objectives

- Know the distinguishing elements of the history and physical examination for older adults with fibromyalgia as compared with myofascial pain.
- Describe the three-pronged approach to treating myofascial pain syndromes.
- List the nonpharmacologic and pharmacologic treatments for fibromyalgia that are supported by strong evidence and have an acceptable safety profile for older adults.

Key Clinical Points

1. **Fibromyalgia and myofascial pain are distinct syndromes that may occur independently or coexist.**
2. **Myofascial pain syndromes are diagnosed by eliciting a characteristic history coupled with identification of active trigger points on physical examination.**
3. **Myofascial pain syndromes may present with neuropathic symptoms such as paresthesias and burning and can mimic radiculopathy. As they are treated best using nonpharmacologic strategies, their diagnosis can prevent exposing frail older adults to multiple potential adverse drug effects and unnecessary procedures.**
4. **Older adults presenting with widespread pain should undergo a comprehensive history and physical examination including careful review of their medications. If a potential cause is not elicited, fibromyalgia screening should ensue. The 2010 Revised Fibromyalgia Criteria allow for disease screening without the need for a tender point examination.**
5. **Fibromyalgia syndrome (FMS) is common in older adults and may be the sole cause of pain or a key pain comorbidity. Axial pain is common in FMS, and in older adults with neck, upper, or low back pain, FMS should be screened routinely.**
6. **FMS is associated with a number of nonpharmacologic and pharmacologic treatments with strong efficacy evidence. Older adults should be encouraged about the wide range of effective treatments that are available.**

Fibromyalgia and myofascial pain syndromes (MPSs) are among the most common musculoskeletal disorders from which older adults suffer. These disorders represent opposite ends of the pain spectrum with the discrete character of MPS at one extreme and the widespread symptoms of fibromyalgia at the other. It should be noted that these disorders may coexist in the same patient. Because MPS are so commonplace, patients with fibromyalgia often have coexisting MPS and the converse occurs less frequently. MPS may be acute or chronic, and is associated with taut muscle bands and hypersensitive areas called trigger points. Fibromyalgia syndrome includes symptoms of sleep disruption, fatigue,

and psychological distress in addition to widespread pain. Both fibromyalgia and MPS may result in significant functional impairment and cause suffering and disability comparable to that of rheumatoid arthritis and osteoarthritis. Diagnosis of these disorders is grounded in appropriately targeted history and physical examination; these are the tools required to avoid unnecessary ordering of "diagnostic" tests and foster implementation of appropriate management strategies.

FIBROMYALGIA SYNDROME

Definition and Epidemiology

The gold standard for diagnosing fibromyalgia is clinical evaluation by a specialist. In 1990, the American College of Rheumatology (ACR) developed criteria to help distinguish FM from other rheumatologic disorders associated with widespread pain (eg, systemic lupus erythematosus, rheumatoid arthritis), and these criteria require the performance of a physical examination to identify tender points. In 2010, Wolfe and colleagues put forth new criteria that did not require a tender point exam and queried symptoms other than pain. These criteria were revised in 2011, then converted into a survey questionnaire shown in **Figure 124-1**. There are five parts to the questionnaire: (1) a tally of self-reported painful areas—the Widespread Pain Index, (2) severity of symptoms other than pain, part 1 (fatigue, cognitive symptoms, waking unrefreshed), (3) severity of symptoms other than pain, part 2 (lower abdominal pain, depression, headaches), (4) symptoms duration more than or equal to 3 months, and (5) absence of another disorder to explain pain. The Fibromyalgia Symptom (FS) score (later renamed the polysymptomatic distress scale) is the sum of components 1 through 3. FS scores of greater than or equal to 13 are 96.6% sensitive and 91.8% specific, as compared with the 1990 ACR criteria, which are 81% sensitive and 88% specific.

This is a self-report questionnaire based on the modification of the 2010 ACR preliminary diagnostic criteria for fibromyalgia (0–31 points).

1. Widespread pain index (0–19 points)

Check all areas of pain or tenderness during the past 7 days

- ○ Right jaw
- ○ Left jaw
- ○ Neck
- ○ Right shoulder
- ○ Left shoulder
- ○ Upper back
- ○ Chest
- ○ Right upper arm
- ○ Left upper arm
- ○ Right lower arm
- ○ Left lower arm
- ○ Lower back
- ○ Abdomen
- ○ Right hip or buttocks
- ○ Left hip or buttocks
- ○ Right upper leg
- ○ Left upper leg
- ○ Right lower leg
- ○ Left lower leg

2. Severity of symptoms other than pain, part 1

For each symptom indicate the severity of the symptom during the past 7 days.

	No Problem (0 points)	**Slight or Mild Problem (1 point)**	**Moderate Problem (2 points)**	**Severe Problem (3 points)**
A. Fatigue				
B. Trouble thinking or remembering				
C. Waking up tired or unrefreshed				

3. Severity of symptoms other than pain, part 2

During the past six months have you had the following symptoms?

	No (0 points)	**Yes (1 point)**
A. Pain or cramps in the lower abdomen		
B. Depression		
C. Headache		

4. Symptoms duration ≥ 3 months? 0 points

- ○ Yes
- ○ No

5. Absence of another disorder to explain pain? 0 points

- ○ Yes
- ○ No

FIGURE 124-1. Modified Fibromyagia Criteria 2011: A Survey. This is a self-report questionnaire based on the modification of the 2010 ACR preliminary diagnostic criteria for fibromyalgia (0-31 points).

The authors wish to emphasize that the survey shown in **Figure 124-1** is not meant as a diagnostic tool. The practitioner must evaluate for other causes of widespread pain and obtain a careful history and physical examination to that end. If fibromyalgia is suspected, the patient should be evaluated by a specialist to confirm the diagnosis.

The incidence of fibromyalgia syndrome (the proportion of new cases or first ever episodes) is difficult to measure in part because symptoms seem to ebb and flow over time. According to five large population studies, approximately 10% of the population has widespread pain. Of those with widespread body pain, approximately 2% to 8% meet ACR diagnostic criteria for fibromyalgia. Prevalence estimates vary depending on the study and criteria used for diagnosis. According to these original criteria, women are four to seven times as likely to have fibromyalgia compared to men, with the greatest prevalence in those 60 to 79 years of age. Using the 2011 survey the female-to-male ratio drops to 1.8:1 overall and 3.4:1 in those age 60 and older. This difference likely results from elimination of the tender point examination, which may be too insensitive in men to make the diagnosis. Patients with fibromyalgia also have been estimated to have a two- to sevenfold greater risk of suffering from depression, anxiety, headache, irritable bowel syndrome, chronic fatigue syndrome, systemic lupus erythematosus, and rheumatoid arthritis compared to healthy individuals.

PATHOGENESIS

While recent studies have added to our understanding of the pathogenesis of fibromyalgia, the exact cause is still unknown. Most studies suggest that abnormal central nervous system pain processing, known as central sensitization, plays a key role in fibromyalgia pathogenesis. Abnormal peripheral pain processing, peripheral sensitization, also contributes to fibromyalgia pathogenesis. The cause of sensitization is not known, but a variety of neuroendocrine and biochemical abnormalities are believed to be involved. Potential environmental triggers include acute pain and trauma, viral infections (Epstein-Barr virus, Lyme disease, Q fever, viral hepatitis) and psychological stress. Studies also suggest a “central pain-prone phenotype,” which includes factors such as female sex, early life trauma and family history of pain or mood disorders.

Peripheral Tissue Abnormalities

Early studies of fibromyalgia patients failed to consistently show abnormalities in the peripheral tissues. However, reexamination of this issue has uncovered differences between muscle samples from fibromyalgia subjects and healthy controls. One difference is higher levels of nitric oxide in muscles of fibromyalgia patients that may result in increased cell death. Other abnormalities that have been identified in muscles of fibromyalgia patients as compared with healthy individuals include lower phosphorylation potential and oxidative capacity as evidenced by lower levels of muscle phosphocreatine and ATP, as well as increased substance P, DNA fragmentation, interleukin-1, and perfusion deficits. While the exact meaning of these abnormalities is unclear, the findings suggest an underlying difference in muscle metabolism of fibromyalgia patients as compared to people without fibromyalgia. Further study is needed to establish a relationship between these findings and the pain and fatigue fibromyalgia patients report.

Central and Peripheral Sensitization and Pain Amplification

Abnormalities of peripheral and central pain processing are well established in fibromyalgia. In the periphery, tissue sensitization results from changes in primary nociceptive afferents, increased neuronal excitability, and enlarged neuronal receptive fields. Central sensitization (ie, augmented central pain processing) involves neuroplasticity in the brain and spinal cord. “Windup,” a normal finding of increased pain sensations after repeated exposures to a painful stimulus, is an example of central sensitization. In studies of fibromyalgia patients, the “windup” response is exaggerated compared to controls. Staud and colleagues studied fibromyalgia patients and healthy controls after repeated exposure to heat stimuli. While both groups had higher pain ratings after repeated exposures to heat, the degree of windup and temporal summation was significantly greater in fibromyalgia subjects. In addition, the fibromyalgia subjects had more prolonged after sensations compared with control subjects.

Central sensitization in patients with fibromyalgia also can be contributed to by diminished descending analgesia, or conditioned pain modulation (also referred to as diffuse noxious inhibitory control [DNIC]). Fibromyalgia patients have deficient endogenous pain inhibition in response to noxious stimuli (ie, DNIC) compared to those with chronic

low back pain. These findings support the role of central sensitization in fibromyalgia and are summarized in a review by Phillips and Clauw.

Neuroendocrine and Autonomic Nervous System Abnormalities

Altered activity of the hypothalamic–pituitary–adrenal axis (HPA), and abnormal levels of adrenocortical trophic hormone (ACTH) and urinary cortisol have been demonstrated in patients with fibromyalgia. Evidence suggests that the HPA axis may be less resilient than normal in fibromyalgia patients and that this and other HPA axis abnormalities may underlie the impaired response to stress that many of these patients exhibit. The review by Crofford provides an expanded discussion of the neuroendocrine abnormalities in fibromyalgia syndrome.

Autonomic nervous system dysregulation has been demonstrated in fibromyalgia and associated disorders including chronic fatigue, irritable bowel syndrome, and interstitial cystitis. Measures of heart rate variability and peripheral blood flow suggest high levels of sympathetic activity in fibromyalgia patients compared to controls. Other findings suggesting sympathetic dysfunction include attenuated responses to orthostatic challenge, cold pressor testing, and auditory stimuli. Reduced plasma and CSF catecholamines in response to stress provide further evidence of sympathetic nervous system dysfunction.

Biochemical Abnormalities

While there are no serologic tests to assist practitioners with making a diagnosis of fibromyalgia, a number of biochemical abnormalities have been identified in the context of research studies. Russell and colleagues have identified lower levels of serum serotonin and norepinephrine in patients with fibromyalgia compared to controls. Low platelet serotonin levels have also been identified. While cerebrospinal fluid (CSF) serotonin has not been measured in patients with fibromyalgia, its precursor and metabolic products have been demonstrated to exist at significantly lower levels in the CSF of fibromyalgia patients compared to controls. Norepinephrine's metabolite, methoxyhydroxyphenylglycol, and dopamine's metabolite, homovanillic acid, are also reduced in fibromyalgia patients. Further discussion of the biochemical abnormalities found in fibromyalgia patients is found in the review by Mease.

Abnormal levels of nociceptive neurochemicals have also been found in patients with fibromyalgia. Several studies have shown that substance P, a neuropeptide involved in pain transmission, exists in significantly higher levels in the CSF of fibromyalgia patients compared to those without fibromyalgia (see Russell reference). Nerve growth factor (NGF), which promotes production of substance P, also is elevated in the CSF of fibromyalgia patients.

Functional Imaging of Pain

Researchers have used functional neural imaging including, functional magnetic resonance imaging (fMRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET) to help understand fibromyalgia pathogenesis. Functional MRI measures regional blood flow in the central nervous system in response to environmental stimuli and provides evidence for increased central nervous system activity that corresponds to subjective pain reports. In response to noxious stimuli, fibromyalgia patients show increased activation on fMRI in the anterior cingulate cortex, insula, and secondary somatosensory cortex. SPECT imaging studies consistently demonstrate reduced regional blood flow in the right thalamus of fibromyalgia patients compared to controls. PET studies of fibromyalgia patients have not provided conclusive results.

Voxel-based morphometry uses structural brain MRI images to assess the volume of specific brain regions. Using this technology, decreased regional brain volume has been found in a variety of chronic pain and stress-related disorders. It also demonstrates an increased loss of grey matter in fibromyalgia patients compared to controls. The significance of these findings is not known and may relate to impaired endogenous pain inhibition and cognitive dysfunction.

Genetics

Mounting evidence points to fibromyalgia as a heritable disorder. This evidence includes familial aggregation of fibromyalgia as well as a reduced pain threshold in the first-degree female relatives of fibromyalgia patients, even in those without overt clinical symptoms. Siblings of fibromyalgia patients are nearly 14 times more likely to develop the condition compared to the general population. Genetic studies of families with multiple cases of fibromyalgia reveal a linkage to chromosome 17. Gene polymorphisms in the serotonergic, catecholaminergic, and dopaminergic systems

and a higher prevalence of polymorphisms in the promoter region of the serotonin transporter gene (5HTT) in fibromyalgia patients as compared to healthy controls also have been identified. Physical and environmental exposures are believed to alter gene expression and contribute to the development of fibromyalgia as well.

Clinical Presentation

Patient history Fibromyalgia patients often report that they feel pain "all over." Pain diagrams, on which patients are asked to shade painful areas of a human figure, are helpful in making a diagnosis. For fibromyalgia patients, these diagrams show diffuse shading on the right and left sides of the body as well as above and below the waist. We observe that some fibromyalgia patients shade, circle, or put an X through the entire figure. Patients generally rate their pain as moderate to severe in intensity. Over time, pain will fluctuate in severity but typically does not resolve completely. The quality of the pain may be variably described as deep aching, mild tenderness, or sharp sensations. Symptoms are generally constant throughout the day but often are worse in the morning and the evening. Triggers, including stress, cold weather, illness, and unaccustomed exertion, will likely increase pain. In addition to pain, 75% of patients report stiffness and over 50% report a sensation of swelling. Low back pain and chronic whiplash are relatively common, affecting 20% to 30% of the patients with fibromyalgia.

Fibromyalgia patients are likely to report a wide variety of nonmusculoskeletal symptoms, most commonly fatigue and difficulty sleeping. Sixty percent of patients report psychological and neuropsychological symptoms including anxiety, mental distress, and cognitive dysfunction. Thirty percent of patients report current depression with over 50% of patients reporting a history of depression. Headaches are also common. Uncommon symptoms (< 20% prevalence) include tinnitus, dizziness, vertigo, and Raynaud phenomenon. Using the 2011 ACR criteria, fibromyalgia may coexist in 17% of patients with osteoarthritis, 21% of patient with rheumatoid arthritis and 37% patients with systemic lupus erythematosus. **Table 124-1** lists the symptoms and syndromes commonly associated with fibromyalgia.

TABLE 124-1 FIBROMYALGIA-ASSOCIATED SYMPTOMS AND SYNDROMES

Musculoskeletal
Stiffness
Sensation of joint swelling
Nonmusculoskeletal
Fatigue
Difficulty sleeping
Dysesthesias
Paresthesias
Depression
Anxiety
Stress
Dyspnea
Palpitations
Difficulty concentrating
Tinnitus
Dizziness
Vertigo
Associated syndromes
Headache
Tension type
Cervicogenic
Migraine
Irritable bowel syndrome
Pelvic pain

Restless leg syndrome
Interstitial cystitis
Myofascial pain syndromes
Associated rheumatological disorders
Systemic lupus erythematosus
Rheumatoid arthritis
Sjogren syndrome

Up to 80% of fibromyalgia patients report debilitating fatigue. This complaint encompasses mental fatigue and impaired concentration commonly referred to as “fibro fog,” physical fatigue after exertion, and general sleepiness. In fibromyalgia patients, these symptoms most often occur in the absence of other medical illnesses. Poor sleep quality seen in fibromyalgia patients is known as nonrestorative sleep. Patients awaken feeling unrefreshed even after a full night’s sleep. Other complaints include light sleep, frequent awakenings, and insomnia. As with other aspects of fibromyalgia, the cause of poor sleep and chronic fatigue is not fully known. Studies of sleep architecture in fibromyalgia patients have revealed abnormalities, which may account for daytime fatigue. One such finding is alpha wave intrusion into stage four sleep. In fibromyalgia patients, alpha waves, typically seen in stage one light sleep, are found in stage four slow wave deep sleep. This finding has been associated with reduced production of growth hormone and insulin growth factor which are necessary for muscle repair. In addition, fibromyalgia patients have a relative rapid eye movement (REM) sleep deficiency compared to healthy controls. These abnormalities, while not specific to fibromyalgia, may cause significant fatigue and pain. One large epidemiologic study found that improvements in restorative sleep correlate with resolution of chronic widespread pain.

Clinical Assessment

When evaluating the older adult with widespread chronic pain, the practitioner should be cognizant of multiple rheumatologic disorders that can be associated with widespread pain in addition to fibromyalgia syndrome such as generalized osteoarthritis, pseudogout, gout, rheumatoid arthritis, systemic lupus erythematosus, and polymyalgia rheumatica, as summarized in **Table 124-2**. A careful history and thorough physical examination for synovial and extrasynovial findings can help differentiate these conditions from fibromyalgia. **Table 124-2** lists a number of key features on history and physical examination that may aid in the diagnosis. Other diagnostic considerations include hypothyroidism, vitamin D deficiency, demyelinating polyneuropathies, and paraneoplastic syndromes. A targeted laboratory panel may be helpful in teasing out these differential diagnostic considerations.

TABLE 124-2 ■ DIFFERENTIATION OF OSTEOARTHRITIS FROM OTHER COMMON RHEUMATOLOGIC DISORDERS: HISTORY, PHYSICAL EXAMINATION, AND OTHER DIAGNOSTIC FEATURES

DISORDER	HISTORY		PHYSICAL EXAMINATION		OTHER DIAGNOSTIC FEATURES/COMMENTS
	AM STIFFNESS	LOCATION OF PAIN	SYNOVITIS	EXTRASYNOVIAL DISEASE	
Osteoarthritis	Generally short-lived, eg, < 30 min	Weight-bearing appendicular joints, cervical and lumbar spine, DIPs, PIPs, and first CMC. MCP and wrist involvement go against OA	Absent or mild	None related to arthritis itself.	Since OA is ubiquitous in older adults, x-rays should be used to rule out other disorders, not to diagnose OA.
Pseudogout	Pseudorheumatoid pattern may be associated with prolonged AM stiffness	Knee and wrist are most common locations; disease is often symmetrical	Acute flares are intensely inflammatory	Chondrocalcinosis on x-rays; eye deposits, bursitis, tendonitis, carpal and cubital tunnel syndromes may occur Tophaceous soft tissue deposits uncommon	Chondrocalcinosis may be asymptomatic. Identification of intracellular CPPD crystals offers a definitive diagnosis in acute flares. Acute and chronic forms occur.
Gout	Pseudorheumatoid pattern may be associated with prolonged AM stiffness	Joints of the lower extremities are most often involved, especially first MTP; disease is typically asymmetrical	Acute flares are intensely inflammatory	Tophi may deposit in soft tissues.	Hyperuricemia may be asymptomatic. Serum uric acid cannot diagnose gout. Identification of intracellular monosodium urate monohydrate crystals offers a definitive diagnosis in acute flares
Rheumatoid arthritis	Prolonged, eg, > 30 min. Duration of stiffness is used as one parameter of disease activity	Any synovial joint. The lumbar spine is typically spared.	Present	Not uncommon; rheumatoid nodules can develop in soft tissues. Many other possible manifestations including anemia, vasculitis (skin lesions, peripheral neuropathy, pericarditis, visceral arteritis, palpable purpura), pulmonary disease, etc	Patients may be seronegative. If disease is suspected, patient should promptly be referred to a rheumatologist to retard disease progression.
Systemic lupus erythematosus	Not a prominent feature	Depends on tissues involved—may or may not be limited to joints. Comorbid fibromyalgia is not uncommon	Generally absent; arthralgias are more common than arthritis	Common—eg, anemia, skin rash, pleuritis, peritonitis, pericarditis, nephritis, meningitis, etc	Anyone with suspected SLE should promptly be referred to a rheumatologist.
Fibromyalgia syndrome	Generally short-lived, eg, < 30 min	Typically diffuse. Worst symptoms often involve the axial skeleton.	Absent Joints themselves are not involved, although patients experience pain in joints and soft tissues	Many other disorders may coexist (see **Table 124-3**).	Fibromyalgia syndrome is not a diagnosis of exclusion, but one based upon careful history (see text).
Polymyalgia rheumatica	May be prolonged, lasting several hours	Typically proximal—eg, shoulder girdle, hip girdle, neck. If headaches, jaw claudication, and/or prominent systemic symptoms (eg, fever), consider temporal arteritis	May occur, especially in small joints of hands	Occurs if comorbid temporal arteritis and relates to involvement of arteries (eg, Raynaud phenomenon, bruits, claudication)	Because the erythrocyte sedimentation is very nonspecific, this test should be used to assist with confirmation of a suspected diagnosis. Note that cases of PMR and TA with a normal ESR have been reported.
Vitamin D deficiency	Absent	Typically described as diffuse, deep pain. Bony pain is often present	Absent	Fatigue is a common feature with proximal muscular weakness (pelvic-girdle myopathy). Tenderness with palpation of bony structures	Fatigue and difficulty climbing stairs are common complaints. Gait imbalance and falls may be seen. In severe cases, the profound weakness results in need for a wheelchair. Radiologic findings include fractures and Looser-Milkman pseudofractures (osteomalacia giving a striped appearance to bones). Direct measurement of serum 25(OH)D is the best marker for vitamin D deficiency.
Hypothyroidism	Absent	Diffuse myalgias and arthralgias	Joint swelling may be present with noninflammatory joint effusions. Hand, knee, and wrist involvement. Avascular necrosis, gout, and or pseudogout may coexist	Myalgias, generalized weakness, and carpal tunnel may exist	Fatigue, mental slowing, and depression often seen. Associated symptoms include hair loss, edema, cold intolerance, dry skin, constipation, and weight gain.

CMC, carpometacarpal joint; CPPD, calcium pyrophosphate dehydrate; DIP, distal interphalangeal joint; ESR, erythrocyte sedimentation rate; MCP, metacarpophalangeal joint; MTP, metatarsophalangeal; OA, osteoarthritis; PIP, proximal interphalangeal joint; PMR, polymyalgia rheumatica; SLE, systemic lupus erythematosus; TA, temporal arteritis.

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Elsevier.

The practitioner should review all medications when assessing the older adult with widespread pain. Toxic myopathy is a well-documented side effect of HMG-CoA reductase inhibitors, commonly known as statins. Certain statins are more toxic than others, and the amount of muscle damage is dose-related. Another common cause of drug induced myopathy is chronic high dose corticosteroids (30 mg of prednisone equivalents per day). While steroid myopathy is most commonly associated with weakness, muscle pain may develop over time. Other medications known to be associated with painful myopathies include the antiretroviral agent zidovudine, the antifungal agent voriconazole, and a number of immunosuppressant medications including interferon, cyclosporin, and tacrolimus. Commonly abused drugs including cocaine, heroin, amphetamines, and alcohol also can cause painful myopathies. Symptoms typically begin within weeks to months of drug exposure and resolve with discontinuation.

Treatment

A variety of pharmacologic and nonpharmacologic interventions are available for the treatment of fibromyalgia. Evidence-based guidelines vary, and no singular treatment is accepted as first line. Most experts agree that the most effective approach integrates both pharmacologic and nonpharmacologic strategies. Although response is likely to be modest, we have successfully employed a number of management approaches in our older adult patients with fibromyalgia. Antidepressants and some antiseizure medications may be beneficial, particularly if therapy is aimed at addressing associated symptoms such as disrupted sleep, depression, and/or anxiety (**Table 124-3**). For improving overall function and well-being, most experts agree that nonpharmacologic therapies have greater success and should be considered as essential to any well-formulated treatment plan.

TABLE 124-3 MEDICATIONS USED IN FIBROMYALGIA TREATMENT

DRUG	RECOMMENDED DOSE	COMMENTS
Antiepileptic medications		Titrate slowly
Gabapentin	100–600 mg daily Max dose 1800 mg daily	May cause sedation or dizziness Dose adjustment for renal failure
Pregabalin	150–300 mg daily Max dose of 450 mg	
Tricyclic antidepressants (TCA) Nortriptyline	10–50 mg nightly	Sedation and confusion Avoid in narrow angle glaucoma Recommend baseline ECG to evaluate QT prolongation; if present, avoid use
Serotonin reuptake inhibitors (SSRI) Fluoxetine Citalopram	 20–80 mg daily 20–40 mg daily	SSRIs have superior tolerability compared to TCAs
Serotonin norepinephrine reuptake inhibitors (SNRI) Venlafaxine Duloxetine	 75–100 mg daily 30–60 mg daily	Avoid in those with uncontrolled hypertension Avoid in patients with liver disease Avoid in those with narrow angle glaucoma
Milnacipran	100–200 mg daily	More potent for inhibition of norepinephrine reuptake than duloxetine
Analgesics Tramadol	50–100 mg every 6 h as needed	May cause sedation and confusion Avoid in patients with seizures May cause serotonin syndrome in combination with SSRIs or other antidepressants Dose adjustment for renal failure
Muscle relaxants		Likely to cause sedation

Cyclobenzaprine	5–10 mg nightly	Similar side effects to tricyclic antidepressants

Medications

Antidepressants Antidepressants are among the most widely studied medications for the treatment of fibromyalgia. The analgesic effect of antidepressants may result from increased central nervous system serotonin and norepinephrine, which act to block pain signals from the periphery. In addition to reducing pain, antidepressants may improve sleep and emotional well-being. Those used most commonly are the tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).

Among these classes of antidepressants, tricyclics are the oldest and have the strongest evidence for efficacy in fibromyalgia. Two of the earliest placebo-controlled clinical trials demonstrated modest effectiveness of amitriptyline at doses of 25 to 50 mg nightly. These medications are effective for pain, sleep, bowel, and bladder symptoms. Cyclobenzaprine, a muscle relaxant with structural similarity to the tricyclics, has shown efficacy in several short-term clinical trials. A recent meta-analysis of the literature on cyclobenzaprine has shown effectiveness in treating some symptoms and providing overall improvement but did not show reduction of fatigue or tender points (see Goldenberg reference).

While tricyclic medications may benefit patients with fibromyalgia, side effects may limit their use, even in low doses. The anticholinergic effects of this class are responsible for most of the adverse effects including sedation, confusion, constipation, and palpitations. Impaired mobility and falls have also been described in older adults. TCAs may also prolong the QT interval, which in the worst-case scenario results in torsade de pointes and death. Prior to their initiation, therefore, an ECG should be obtained and if there is evidence of QT prolongation, these medications should be avoided. Secondary tricyclic amines, desipramine, and nortriptyline have fewer side effects but are not as well studied.

The SSRIs and SNRIs may have fewer adverse effects than the TCAs, but there is only modest evidence for their efficacy. The SSRIs increase serotonin levels at lower doses and both serotonin and norepinephrine levels at higher doses. The first double-blind, randomized, placebo-controlled trial of fluoxetine failed to show any benefit compared to placebo. A crossover study found improvement in pain, function, and overall well-being after treatment with fluoxetine 20 mg daily or amitriptyline 25 mg daily compared to placebo, and a combination of both drugs produced a superior result compared to either drug alone. Two studies have evaluated citalopram. While one study failed to show benefit of citalopram, Anderberg and colleagues demonstrated improvement in depression and overall well-being in fibromyalgia patients treated with citalopram (20–40 mg) compared to those in the placebo group. Older SSRIs, like fluoxetine, are less selective for serotonin reuptake and may be more effective as analgesics. Studies also have examined the dual SNRIs for the treatment of fibromyalgia. While the benefits of venlafaxine were found in open-labeled studies, a randomized placebo-controlled trial showed no benefits of low-dose venlafaxine (75 mg daily) over placebo. Duloxetine (60 mg daily) and milnacipran (100–200 mg daily) are FDA approved for fibromyalgia. Both medications reduce pain and fatigue, and improve quality of life. Duloxetine is now available in a generic form. Compared to duloxetine, milnacipran is a more potent inhibitor of norepinephrine reuptake and may be more effective for fatigue and cognitive symptoms. Elevated blood pressure is a concern with both medications and monitoring is suggested. Nausea and orthostatic hypotension are common side effects and may be reduced by taking the medication with food and using slow titration. Withdrawal syndrome may occur with abrupt discontinuation.

Antiepileptics Aside from the antidepressants, very few drug classes have evidence for efficacy in the treatment of fibromyalgia. Recent reviews support for the use of the antiepileptic drugs gabapentin (currently available in generic form) and pregabalin. While the mechanisms of action of antiepileptic drugs are largely unknown, especially for the newest agents, it is believed that they reduce neuronal excitability, decrease ectopic neuronal discharge, and modulate the levels of a variety of neurotransmitters. A large study of pregabalin, which binds to the alpha(2)-delta subunit of the voltage-gated calcium channel, found that fibromyalgia patients experienced significant improvement in pain, fatigue, social functioning, vitality, and general health perception compared to controls (see Crofford reference). Pregabalin was the first medication approved for fibromyalgia syndrome at a dose range of 300 to 450 mg daily. A recent meta-analysis of anticonvulsants for fibromyalgia found mild improvements with pregabalin in pain, sleep and fatigue compared to placebo. While the efficacy of gabapentin to treat fibromyalgia has not been rigorously examined, our clinical experience suggests that even low-dose gabapentin (eg, 100–600 mg/day) may be beneficial for reducing pain and improving sleep. Sedation and dizziness are common side effects of both medications and may contribute to falls in older adults. These are minimized by starting with low bedtime doses and slowly titrating upward. **Table 124-4**

compares the benefits and side effects of the three FDA-approved fibromyalgia medications.

TABLE 124-4 SUMMARY COMPARISON OF FDA-APPROVED DRUGS FOR THE TREATMENT OF FIBROMYALGIA

	EFFICACY OF SX RELIEF					
DRUG	PAIN	SLEEP	FATIGUE	MOOD	HRQOL	SAFETY/TOLERABILITY
Pregabalin	++	++	++	+	++	Dizziness Somnolence Weight gain
Duloxetine	++	++	+	++	++	Headache Nausea Diarrhea Hepatotoxicity
Milnacipran	+	+	++	+	++	Headache Nausea

HRQOL, health-related quality of life.

Analgesics With the exception of tramadol, there are no data that demonstrate efficacy of analgesics for the treatment of fibromyalgia. Tramadol, a weak mu receptor agonist with dual serotonin and norepinephrine reuptake inhibition, is unique in its mechanism and has been shown to be effective in three randomized controlled trials. As with other opioids, prolonged use of tramadol may be linked to abuse and dependence and should be considered judiciously. Because of the sometimes refractory nature of pain in fibromyalgia, these patients not infrequently are treated with more potent opioids, which may result in a number of adverse effects including dysmobility and falls, delirium, increased depression, sedation, nausea, and vomiting. Other concerns with opioid use include reduced receptor availability in fibromyalgia patients, and the risk of developing opioid-induced hyperalgesia. While hyperalgesia may occur with any patient on chronic opioids, it is a particular concern in fibromyalgia patients who are already sensitive to pain. If opioids are being considered, a pain specialist's evaluation is often helpful.

Hormonal supplements and other agents Studies of hormonal supplements for patients with fibromyalgia have had mixed results. Randomized trials of growth hormone demonstrate some benefit in terms of pain and fatigue reduction. Because this medication is quite costly and because the study results cannot be broadly generalized (ie, most patients with fibromyalgia do not have low levels of insulin-like growth factor), it cannot be recommended for routine use. Potential side effects include hypertriglyceridemia, hyperglycemia, anemia, cholelithiasis, and carpal tunnel syndrome. A number of other hormonal supplements have been tried anecdotally including thyroid hormone, dehydroepiandrosterone, and calcitonin but the absence of randomized controlled trials precludes recommending these agents for the treatment of fibromyalgia. Similarly, nutritional supplements, herbal medications, and vitamin therapy are not accompanied by rigorous data to support their use. While some studies and anecdotal reports suggest benefit from guaifenesin, a 12-month randomized controlled trial of this medication showed no benefit for pain or symptom reduction.

For patients with fibromyalgia and vitamin D deficiency, repletion of vitamin D may reduce pain and improve function (see Wepner et al reference). Given the other risks associated with vitamin D deficiency in older adults (eg, falls, osteoporosis), 25-OH vitamin D levels should be checked routinely, not just in those with chronic pain.

There is growing interest in the use of cannabinoid molecules for the treatment of chronic pain. Nabilone, a synthetic cannabinoid has been evaluated in two small trials of fibromyalgia patients. Improvements in pain, sleep, and quality of life were demonstrated. Most treatment guidelines caution against the use of cannabinoids given high frequency of side effects (dizziness, vertigo, and nausea) and the potential for abuse.

Improving sleep and treating fatigue is often difficult. Sleep hygiene education, which includes keeping regular schedules, elimination of daytime naps, establishment of a restful sleep environment and exclusion of caffeine, is helpful for many patients. Benzodiazepines are typically not recommended for long-term use as they have addictive qualities when used for long term and may disrupt the normal sleep cycle. Sedative antidepressants, anticonvulsants, and muscle relaxants including cyclobenzaprine or tizanidine are useful in promoting sleep and improving other fibromyalgia symptoms.

Nonpharmacologic Therapies

Nonpharmacologic therapies for fibromyalgia include cognitive-behavioral techniques, exercise, acupuncture, balneotherapy (ie, bathing) and massage. Systematic review of regular aerobic exercise for fibromyalgia (20 min daily, 2–3 times week) demonstrated improvements in pain, function, aerobic capacity, and well-being. Most therapists recommend individualizing programs based on patient abilities and symptoms. During pain flares, which may occur after physical exertion, programs should be modified but not ceased. Water aerobics also may be beneficial. The evidence supporting strength training is not as robust as that for aerobic exercise. Strength training is beneficial for fibromyalgia patients who are typically deconditioned and may be up to 30% weaker than control subjects.

Data support the benefits of coupling exercise programs with educational sessions and cognitive-behavioral techniques. Lectures on fibromyalgia and the benefits of exercise improve treatment outcomes. Cognitive-behavioral therapy (CBT) is useful for fibromyalgia patients who tend to catastrophize their painful symptoms. Patients can alter pain perception and manage pain flares through the use of coping skills and relaxation techniques. CBT is most useful as part of an interdisciplinary program that includes education and exercise. Both inpatient and outpatient interdisciplinary programs have been found beneficial. Additional studies are needed to demonstrate the full benefit of multidisciplinary treatments.

The benefits of complementary techniques for the treatment of fibromyalgia have also been evaluated. Several randomized controlled trials of acupuncture have shown effectiveness for relieving fibromyalgia symptoms although none have been performed exclusively in older adults. These data are encouraging, however, given the overall safety of this treatment modality. Mind-body movement techniques such as yoga, qigong, and tai chi are promising as fibromyalgia therapies. Two controlled trials of tai chi for fibromyalgia showed improvements in pain, sleep, and function. Similar improvements were found in fibromyalgia patients participating in an 8-week yoga program compared to those receiving standard care. Weak evidence supports chiropractic treatment, massage therapy, interferential current and ultrasound for the treatment of fibromyalgia syndrome. Further studies are needed to determine the potential impact of all these modalities, and to identify potential long-term treatment benefits.

Assessing Response to Treatment

A number of standardized questionnaires are available to assess response to treatment. One of the most efficient and useful is the 20-question Fibromyalgia Impact Questionnaire (FIQ), which takes only a few minutes to complete and quantifies physical function, painful symptoms, and emotional well-being specifically in fibromyalgia patients (**Figure 124-2**, see Burckhardt reference).

Name: _____ Date: / /

Directions: For questions 1 through 11, please circle the number that best describes how you did overall for the *past week*. If you don't normally do something that is asked, cross the question out.

Were you able to:	Always	Most	Occasionally	Never
Do shopping?	0	1	2	3
Do laundry with a washer and dryer?	0	1	2	3
Prepare meals?	0	1	2	3
Wash dishes/cooking utensils by hand?	0	1	2	3
Vacuum a rug?	0	1	2	3
Make beds?	0	1	2	3
Walk several blocks?	0	1	2	3
Visit friends or relatives?	0	1	2	3
Do yard work?	0	1	2	3
Drive a car?	0	1	2	3
Climb stairs?	0	1	2	3

12. Of the 7 days in the past week, how many days did you feel good?

0 1 2 3 4 5 6 7

13. How many days last week did you miss work, including housework, because of fibromyalgia?

0 1 2 3 4 5 6 7

Directions: For the remaining items, mark the point on the line that best indicates how you felt overall for the past week.

14. When you worked, how much did pain or other symptoms of your fibromyalgia interfere with your ability to do your work, including housework?

No problem with work — Great difficulty with work

15. How bad has your pain been?

No pain — Very severe pain

16. How tired have you been?

No tiredness — Very tired

17. How have you felt when you get up in the morning?

Awoke well rested — Awoke very tired

18. How bad has your stiffness been?

No stiffness — Very stiff

19. How nervous or anxious have you felt?

Not anxious — Very anxious

20. How depressed or blue have you felt?

Not depressed — Very depressed

FIGURE 124-2. Fibromyalgia Impact Questionnaire (FIQ).

MYOFASCIAL PAIN SYNDROMES

Background and Epidemiology

Myofascial pain syndrome (MPS) is a condition that describes pain arising from the muscle as well as the surrounding connective tissue, for example, fascia. MPS is characterized by the presence of taut bands of skeletal muscle, which may contain discrete, palpable nodules known as myofascial trigger points (MTrPs; **Figure 124-3**). MPS can be an acute or chronic condition, and the pain is often regional, compared to the chronic, widespread pain characteristic of fibromyalgia. MPS may also be associated with muscle weakness, decreased flexibility, limitations in range of motion, and a diminished quality of life.

MPS is thought to arise from the presence of active MTrPs, which are spontaneously painful. Digital palpation of active MTrPs reproduces and/or exacerbates the patient's spontaneous pain complaint, and often produces referred pain in distinct patterns (**Figure 124-4**). Latent MTrPs, in contrast, are not spontaneously painful, but they produce pain upon palpation, and present with physical findings that are similar to those found with active MTrPs. MTrPs can develop in almost any skeletal muscle, and impair normal muscle functioning in those regions.

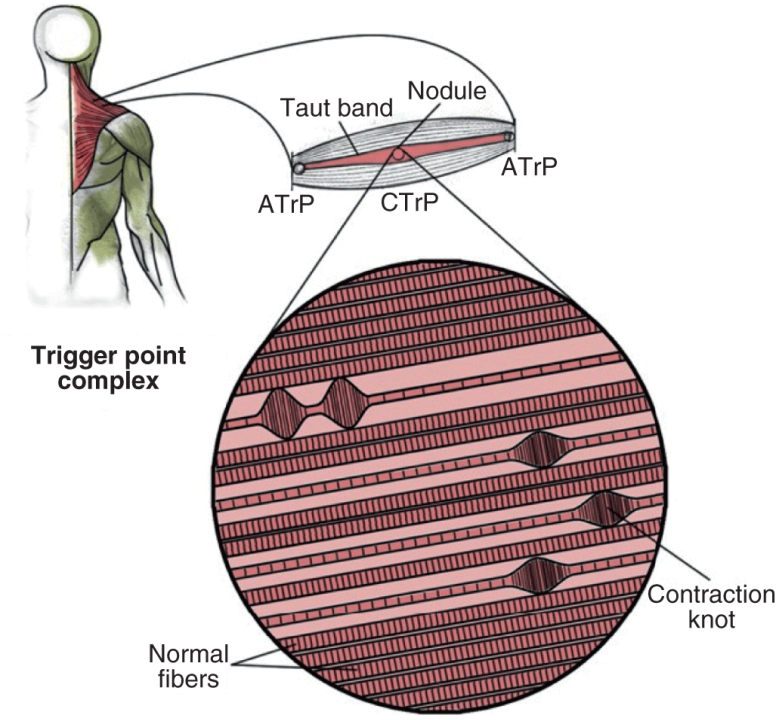


FIGURE 124-3. Schematic of a trigger point complex. CTrP identifies the central trigger point that is found in the endplate zone and contains numerous contraction knots and electrically active loci among normal fibers. A taut band of muscle fibers extends from the trigger point to the attachment (ATrP) at each end of the involved fiber. (Reproduced with permission from Simons DG, Travell JG, Simons LS. *Travell & Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual*, Volume I, 2nd ed. Baltimore: Williams & Wilkins, 1998.)



FIGURE 124-4. Schematic of referred pain patterns. Stimulation of MTrPs (X's) in the right sternocleidomastoid muscle produces major pain referral patterns as indicated by the shaded areas, as well as minor patterns as indicated by the dotted areas. (Reproduced with permission from Simons DG, Travell JG, Simons LS. *Travell & Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual*, Volume I, 2nd ed. Baltimore: Williams & Wilkins, 1998.)

MPS is a prevalent condition in the general population, and is a particularly common source of musculoskeletal

pain in older adults. For example, one study in 2005 showed that 95.5% of older adults (age ≥ 60 years) with chronic lower back pain had physical findings consistent with MPS. MPS may arise independently of other medical conditions or it may co-occur with other conditions such as temporomandibular joint dysfunction, visceral pain syndromes, radiculopathy, and fibromyalgia (**Table 124-5**). Either way, MPS should be addressed as part of a chronic pain patient's treatment regimen, as it is a common component of persistent musculoskeletal pain.

TABLE 124-5 ■ PARTIAL LIST OF DISORDERS ASSOCIATED WITH MTrPs

Primary Myofascial Pain Syndromes
Low back pain
Knee pain
Shoulder/neck pain
Migraines
Tension headaches
Piriformis syndrome
Lateral epicondylitis (tennis elbow)
Secondary Myofascial Pain Syndromes
Radiculopathies, disk pathology
Temporomandibular joint dysfunction
Tendonitis
Carpal tunnel syndrome
Computer-related disorders
Problems associated with whiplash
Spinal dysfunction
Visceral pain syndromes: pelvic pain/urologic syndromes, nonanginal chest pain, hepatic referred pain
Post-herpetic neuralgia
Complex regional pain syndrome
Nocturnal cramps
Phantom pain
Neurogenic pruritus
Tinnitus
Torticollis
Osteoarthritis
Fibromyalgia
Hypothyroidism
Vitamin B_{12} deficiency
Rheumatoid arthritis
Structural anatomic variations: scoliosis, pelvic torsions, leg-length inequality

Compiled from Dommerholt J, Bron C, Franssen J. J Man Manip Ther 2006;14(4): 203-221 and Gerwin RD. Curr Pain Headache Rep 2001; 5(5): 412-420.

Pathophysiology

While substantial advances have been made, a full understanding of the pathophysiology and etiology of MPS and the role of MTrPs is still lacking. MPS frequently arises following direct or indirect muscle trauma. Examples of direct trauma include whiplash, muscle injury, and surgical disruption, whereas indirect trauma usually occurs through muscle overuse or misuse. Both forms of trauma activate afferent nociceptors, which connect to the central nervous system (CNS) via thinly myelinated (group III) and unmyelinated (group IV) nerve fibers, thereby initiating the process of nociception. Several biochemicals may serve as mediators for this activation. A traumatic event itself can also open ion channels along the membranes of free nerve endings, resulting in cation influx and subsequent

nociceptor depolarization.

Electromyography studies have shown that MTrPs display spontaneous electrical activity (SEA) compared to uninvolved surrounding muscle. SEA is associated with dysfunctional motor endplates, and consists of a wave-like pattern of endplate noise (EPN) and irregular spikes compared to the discrete, low-amplitude miniature endplate potentials (mEPPs) found in normal muscle. SEA is thought to occur following an excessive release of acetylcholine from the motor neuron at the neuromuscular junction, which binds to its receptors along the motor endplate, and facilitates Na^+ influx and depolarization. Depolarization of muscle fibers initiates the process of sarcomere contraction, which, when sustained, could contribute to the development of sarcomere contractures in the taut band. Overall, the presence of SEA in MTrPs suggests that there is abnormal activity at the motor endplate, and is highly correlated with both decreased pain thresholds and increased pain intensity.

In 1989, Janet Travell and David Simons proposed their landmark "integrated trigger point hypothesis" in *Myofascial Pain and Dysfunction: The Trigger Point Manual,* a comprehensive guide for understanding and diagnosing MPS. Their hypothesis was founded on the idea of the "energy crisis," in which a muscle injury causes persistent fiber contracture and ATP depletion through an excessive release of Ca^{2+} from the damaged sarcoplasmic reticulum (SR). Ca^{2+} in the sarcoplasm binds to troponin, exposing sites on actin filaments to which myosin may bind and initiate the crossbridge cycle that causes muscle contraction. A new ATP molecule binding to the myosin head is required to dissociate the actin-myosin complex and terminate the contraction. Since ATP is also required to pump Ca^{2+} back into the SR, a diminished ATP supply permits an overabundance of Ca^{2+} in the sarcoplasm, sustained muscle contracture, and propagation of the "energy crisis." The "integrated hypothesis" expands upon this crisis, attributing the initiation of the contracture to aberrant acetylcholine release at the neuromuscular junction. Furthermore, the region surrounding the fiber contracture exhibits capillary compression, reduced blood flow, and local hypoxia. These deficiencies together with the increased metabolic demands of the muscle result in "tissue distress," and the production of substances known to activate and sensitize nociceptors.

Researchers have since followed up on the ideas put forth by Travell and Simons, and have found evidence to support their hypothesis. For example, a number of biochemical substances associated with both pain and inflammation are elevated in the milieu of active MTrPs in human subjects. Shah et al. utilized a novel microdialysis system in order to measure the concentrations of various analytes in active MTrPs, latent MTrPs, and in normal tissue without MTrPs (2008). Shah's group found that the concentrations of substance P (SP), calcitonin gene-related peptide (CGRP), bradykinin (BK), serotonin (5-HT), norepinephrine (NE), tumor necrosis factor-alpha (TNF-α), and interleukins such as IL-1β, IL-6, and IL-8 in the active MTrPs were significantly elevated compared to the concentrations in the latent MTrPs and in the normal tissue. In addition, the pH of active MTrPs was significantly lower than the pH of both the latent MTrPs and the normal tissue, indicating a greater concentration of protons in the active MTrP. In contrast, there were no significant differences between the concentrations of the substances in the latent MTrPs and in the normal tissue. These substances may represent the by-products of "tissue distress" following the events outlined in the "trigger point hypothesis," although a causal relationship remains to be established. In addition, many of these analytes are known to directly activate and/or sensitize nociceptors, and could contribute to peripheral sensitization.

Although several advances have been made in characterizing MTrPs and their relation to MPS, a full understanding of their etiology remains elusive. Simon's "integrated trigger point hypothesis" suggests that adverse events at the muscle fiber level could contribute to MTrP development. Accordingly, the Cinderella hypothesis was proposed, which describes how muscle damage may occur with recurring low- to mid-level exertions. Since small fibers are initially employed to sustain mild exertions and are the last to be derecruited, these "Cinderella" fibers often become overused and metabolically stressed. On the other hand, the larger muscle fibers in the same region will seldom experience activation. This disequilibrium with muscle fiber recruitment may ultimately manifest itself as tissue damage and pain (ie, indirect trauma). One study showed how office workers engaged in 30 minutes of typing developed MTrPs in their upper trapezius muscles, thereby exemplifying the relation between low-level, continuous muscle contractions and MTrP formation. Moreover, poor postural habits may also be common facilitators for MTrP generation through a similar process.

The combination of selective fiber overuse, decreased muscle perfusion, and a distinct biochemical milieu thought to characterize active MTrPs sets the stage for the sensitization of nociceptor terminals. Peripheral sensitization describes the state in which there is a decrease in the normally high threshold for nociceptor activation; therefore, light mechanical stimuli may trigger a response that would not typically be generated. If the environment of an active MTrP consists of substances known to activate and sensitize the receptors along the fibers, one can imagine that sustained activation of nociceptors will affect the response of higher-order neurons as well. Accordingly, sensitization not only

takes place at the nociceptor terminal, but may also occur in the CNS. Central sensitization involves neuroplastic changes in the dorsal horn, resulting in sensitized dorsal horn neurons, apoptosis of inhibitory neurons, operation of previously ineffective synapses, and the expansion of receptive fields. These alterations typically produce clinical findings such as allodynia and/or hyperalgesia. Pain referral is also an indicator of central sensitization, likely occurring through the activation of synapses that were formerly silent.

An active MTrP may induce central sensitization by acting as a source of continual afferent bombardment to the dorsal horn neurons. In addition to sensitizing dorsal horn neurons, MTrP stimulation has been shown to increase the activity of certain brain regions associated with hyperalgesia, such as the primary and secondary somatosensory cortices, the mid and anterior insula, and the inferior parietal cortex. Furthermore, decreased activity in the right dorsal hippocampus, which is involved in descending pain modulation, has also been observed. Therefore, it is important that treatment of an active MTrP takes place shortly after its development in order to prevent persistent pain reinforced by central sensitization. Although many regard central sensitization as an irreversible phenomenon, there is some evidence that MTrP treatment may initiate its reversal.

Despite being distinct conditions, both chronic MPS and fibromyalgia share the process of central sensitization as part of their underlying pathophysiology. Many researchers have proposed a role for MTrPs in initiating and maintaining the chronic, widespread pain found in patients with fibromyalgia. However, several studies have shown that not all patients with fibromyalgia present with MTrPs, casting doubt upon the need for active MTrPs to drive both syndromes. It is also important to keep in mind that most patients presenting with active MTrPs do not complain of widespread pain characteristic of fibromyalgia, but instead seek attention for regional pain that may or may not refer to select areas of the body. Nevertheless, deactivation of MTrPs should be incorporated as part of the treatment plan for the patients with fibromyalgia that also have MTrPs.

Clinical Presentation and Evaluation

MPS may occur in virtually any body location and the accompanying pain may be relatively discrete or cover a large area. Patients may describe MP as dull, aching, or burning. Symptoms may mimic radiculopathy and other neuropathic pain syndromes. The onset of pain may be acute, following muscle injury or strain, or it may be gradual, making the precipitating factor(s) difficult to identify. Myofascial pain may be self-limiting and self-resolving, but is more often than not chronic, persisting well after the inciting injury has healed if the patient has identified such an event.

A number of features of the patient's history may point toward a diagnosis of MPS. These include characteristic exacerbating and relieving factors. Patients with MPS often report that the following factors exacerbate their pain: (1) excessive physical activity, (2) firm pressure over the painful muscle, (3) cold exposure, (4) psychological stress, and (5) acute illness (eg, viral infection). Patients report that the following factors tend to alleviate their pain: (1) mild activity, (2) gentle stretching, (3) gentle pressure (eg, massage), (4) moist heat, and (5) a brief rest period following activity. In addition, patients with MPS frequently complain of abnormalities in addition to pain. Common neurologic and motor dysfunctions include weakness, numbness, paresthesias, changes in gait, and limitations in range of motion. MPS may also be associated with autonomic phenomena, such as piloerection, sweating, and temperature changes. Appetite, mood, and sleep disturbances and decrements in cognitive function can be part of any chronic pain disorder from which older adults suffer, including MPS. Efforts should also be made to address these complaints in order to optimize MPS treatment.

Physical examination is required to elicit the pathognomonic features of MPS, that is, *taut bands* and *trigger points* (MTrPs). A taut band is a group of taut muscle fibers extending from a trigger point to the muscle attachments. Taut bands may or may not contain MTrPs, which are discrete, hyperirritable, palpable nodules. MTrPs may be latent (ie, painful only upon compression) or active (ie, spontaneously painful). Latent MTrPs exist not uncommonly in contralateral muscle groups, perhaps because of compensatory muscle activity (eg, pain in one leg related to myofascial pathology of the tensor fascia lata may cause a relatively antalgic gait with compensatory overuse of the contralateral tensor fascia lata). *Active MTrPs* are those that are responsible for clinical symptoms. These points are always tender and prevent full muscle lengthening. When these points are compressed, a radiating pain pattern is typically, though not always, elicited that corresponds to the pain that the patient reports in the context of the history of present illness. Sometimes a "jump sign" is elicited on physical examination, that is, a general pain behavior response demonstrated by the patient that may include verbal as well as nonverbal expression (eg, crying out, grimacing, withdrawing). The examiner may also appreciate a "local twitch response," that is, an involuntary, transient contraction of a taut band that traverses a MTrP and that occurs in response to stimulation of the MTrP (eg, with needling or snapping palpation).

Accurate diagnosis of MPS requires the use of precise physical examination technique, summarized in **Table 124-6**. Because effective treatment of MPS involves recognition and treatment of the underlying cause (eg, axial and appendicular arthritis, kyphosis, scoliosis, leg length discrepancy, Parkinson disease) before examining the painful muscles, a general physical examination including comprehensive musculoskeletal, neurologic, and mobility examinations must be performed. These examinations must be carried out with an eye toward identifying abnormalities that create muscular dysfunction. Examples in the neurologic examination include abnormalities of resting muscle tone such as Parkinson disease and poststroke changes. Examples in the musculoskeletal examination include decreased range of motion of the hips, knees, cervical spine, and shoulders; scoliosis; kyphosis; and functional leg length discrepancy (ie, discrepancy in the height of the iliac crests, observed when standing behind the patient with the hands on top of the crests). Examination of the patient's gait allows for an integrated assessment of body mechanics. Examination for underlying visceral pathology should also be performed, particularly in the presence of spontaneously painful (ie, active) MTrPs in the pelvic or abdominal musculature.

TABLE 124-6 PHYSICAL EXAMINATION TECHNIQUE FOR EXAMINING THE PATIENT WITH MYOFASCIAL PAIN

1. Perform a general musculoskeletal examination looking for contributors to myofascial pain (eg, spinal malalignment, leg length discrepancy, arthritis).
2. Place the patient in a comfortable and relaxed position.
   a. When examining the upper body, the patient should be sitting with forearms resting in lap.
   b. When examining the lower back, the patient may be standing, sitting, or lying prone. If none of these positions are comfortable, examine side-lying.
   c. When examining the lower extremities, the patient should be lying supine or prone.
3. Place yourself in a comfortable and relaxed position.
   a. When examining the upper body, the examiner should be standing squarely in front of the patient.
   b. When examining the lower back, the examiner should be standing to the side of the patient, allowing for the use of one arm to brace the patient from the front and the other hand to palpate. If the patient is lying, stand beside the patient. If the patient is sitting, stand to the side of the exam table and behind the patient.
   c. When examining the lower extremities, the examiner should be standing at the bedside.
4. When there is unilateral pain, always palpate the nonpainful side first.
5. Assess the movement of the skin over the subcutaneous tissue before palpating the muscles.
6. When palpating taut bands, sweep the examining hand firmly across the involved muscle, in a direction that is perpendicular to the orientation of the muscle fibers and in the same plane as the fibers.
7. When palpating trigger points, palpate firmly over the muscle in a direction that is perpendicular to the orientation of the muscle fibers and in a plane that is perpendicular to the fibers.
8. Physical examination targeting potential visceral pathology of the abdomen and/or pelvis should be performed if myofascial pain of these regions is diagnosed.

The most important aspect of preparing for the muscular examination is ensuring that the examiner and the patient are in a comfortable and relaxed position. When palpating the musculature of the upper body (eg, trapezius, sternocleidomastoid), generally the patient should be sitting, with hands folded in the lap and the examiner should be standing squarely in front of him. When palpating the musculature of the lower back, the patient should be either standing upright or lying down in the prone position, whichever is most comfortable. If none is possible, the examiner should have the patient in a side-lying position or sitting on the examining table with the examiner standing behind the patient. If the patient is standing, the examiner should stand to the patient's side, bracing the front of the body with one arm and palpating the muscles with the other hand. If the patient is unable to stand and the exam is performed lying down, the examiner may palpate the paraspinal muscles by standing at the bedside. When palpating the musculature of the lower extremities, the patient should be lying supine or prone (depending on whether the anterior or posterior muscles are being examined, and which position is most pragmatic/comfortable), with the examiner standing to the side of the patient.

Prior to palpating the musculature, the examiner should assess the movement of the skin over the subcutaneous tissues using very light palpation and simply gliding the skin in a direction of movement that is perpendicular to the orientation of the involved muscle fibers. Patients with chronic MPS commonly have reduced movement of the skin

over the involved region. After palpating the skin, the muscles should be examined. The nonpainful side of the body should be palpated prior to palpating the painful area. This strategy serves two purposes. First, it helps the patient to relax. Second, it allows comparison of normal with abnormal. Palpation of taut bands requires proper orientation of the examiner's hand in relation to the orientation of the muscle fibers. The hand should be placed perpendicular to the orientation of the fibers and the fingers swept firmly across the fibers. This motion allows for the tautness of the fibers to be appreciated. To elicit the radiating pain that is a pathognomonic feature of MTrPs, the examiner should palpate the area firmly.

While a sweeping hand motion is needed to appreciate taut bands, this is not required to appreciate MTrPs. Often, but not always, MTrPs are associated with the finding of a "nodule." The MTrP may be large and easily palpable, or it may be small and difficult to identify; either way, the muscle should be palpated thoroughly to search for the area of greatest tenderness. Depending on the location of the pain, the palpation technique may need to be modified. Travell and Simons offer two other techniques: (1) "pincer palpation," that is, palpation accomplished by grasping and rolling the muscle between the thumb and one or more fingers and (2) "flat palpation," that is, palpation accomplished by deep palpation through intervening tissue and application of pressure primarily in a direction that is perpendicular to the tissue plane. Following successful treatment of MTrPs, taut bands and MTrPs typically resolve, thus baseline examination is critical not only to arrive at a proper diagnosis, but to assess response to treatment.

By definition, patients with MPS have taut bands that are tender compared to the relaxed surrounding fibers, but they may not necessarily present with a discrete nodule. Although some MPS specialists deem the presence of a MTrP as essential for the diagnosis of MPS, others have recognized the pain and associated symptoms and signs linked to the taut band as sufficient indicators of MPS. Therefore, the diagnosis of MPS is often made with or without the presence of a palpable nodule.

Table 124-7 provides a summary of clinical characteristics that are typical of MTrPs.

TABLE 124-7 CLINICAL CHARACTERISTICS OF MYOFASCIAL TRIGGER POINTS (MTrPs)

Diagnostic History
Abrupt onset: due to acute overload, rapid movement, direct trauma, or chilling (exposure to cold temperatures especially when the muscle is fatigued)
Gradual onset: due to chronic overload, muscle fatigue, sustained muscular contraction in shortened position, and repetitive activity
Visceral, viral, metabolic, and endocrine disease, arthritic joints, nutritional deficiencies, anxiety, and emotional distress
Symptoms
Autonomic abnormalities: • Increased vasomotor activity (localized vasoconstriction, pallor during stimulation of the MTrP, rebound hyperemia), lacrimation (tears) • Coryza (nasal congestion, loss of smell) • Increased sudomotor activity (sweating) • Increased pilomotor activity (gooseflesh) • Salivation • Proprioceptive disturbances (imbalance, dizziness, tinnitus)
Motor abnormalities: • Localized dysfunction of involved muscle • Remote dysfunction of muscles at a considerable distance to the MTrP • Stiffness and weakness without atrophy • Disturbance of motor coordination • Restricted range of motion
Sensory abnormalities: • Lowered pain pressure threshold over the MTrP • Referred pain (projection of pain to distant reference zones in specific pain referral patterns characteristic of MTrP location and affected muscle) • Persistence of pain symptoms long outlasting the precipitating event
Other symptoms: • Dermographia in skin overlying active MTrPs

Panniculosis (hypersensitivity of skin and resistance to “skin rolling”)
- Primary sleep disturbance
- Depression
- Visual disturbances

Physical Findings
Point tenderness in the taut band of muscle
Local twitch response (LTR) via manual palpation or dry needling
Exacerbation of pain with firm pressure
Reproduction of usual and referred pain with firm pressure[a]
Increased pain with passive or active stretching of the involved muscle
Jump sign (reflex-like flinching and recoil upon palpation)

[a]Only in active MTrPs.

Data from Simons DG. Review of enigmatic MTrPs as a common cause of enigmatic musculoskeletal pain and dysfunction. J Electromyogr Kinesiol. 2004;14(1): 95–107, and Simons DG, Travell JG, Simons LS. Travell & Simons’ Myofascial Pain and Dysfunction: The Trigger Point Manual, 2nd ed. Baltimore: Williams & Wilkins, 1999.

Some examples of common MPS include cervicogenic headaches, piriformis syndrome, trapezius myofascial pain (sometimes associated with “tension neckache”), pseudotrochanteric bursitis, upper and lower back pain, and postherpetic pain. These syndromes are discussed below.

Cervicogenic headaches Cervicogenic headaches are characterized by neck and pericranial pain and are often associated with structural abnormalities of the cervical spine including osteoarthritis and facet arthrosis. Typically, cervicogenic headaches are unilateral in location and range from moderate to severe in intensity. While cervicogenic headaches lack the pulsating quality of migraine headaches, they may have migraine-associated features such as photophobia, phonophobia, nausea, vomiting, and dizziness. Triggers of cervicogenic headache include a variety of neck postures and movements as well as pressure applied to the cervical paraspinal muscles, the suboccipital muscles, and the trapezius. Palpation of these muscles produces pain, which radiates over the head and may extend to the ipsilateral shoulder and arm.

Making the diagnosis of cervicogenic headache may be difficult especially if structural lesions of the cervical spine are not present. A careful history and examination that clearly implicate the cervical spine and its musculature as the source of the pain are essential for diagnosis. Some studies suggest that diagnostic blockade of cervical structures may be useful in patient evaluation; however, this is not typically needed.

Sciatica mimickers When MPS occurs in the pelvic and buttock regions, the resulting pain and associated limitations in muscle function may closely resemble the dysfunctions associated with sciatica. The piriformis muscle originates from the pelvic surface of the sacrum, passes through the greater sciatic foramen, and inserts into the medial side of the upper end of the greater trochanter. The fibers of the sciatic nerve course through the piriformis. Piriformis syndrome describes the occurrence of sciatica in association with piriformis myofascial pain that results from nerve entrapment by the myofascial taut bands in the piriformis. Patients with piriformis myofascial pain also may describe intense buttocks discomfort without sciatica. Because the piriformis acts to externally rotate the thigh at the hip joint, patients with piriformis myofascial pain sometimes demonstrate external rotation of the leg when standing or lying supine. Palpation of the piriformis can be performed with the patient standing or lying supine. The technique recommended for examining the patient in the supine position is described in **Table 124-8**. Myofascial pain of the piriformis may involve the low back, buttock, and posterior thigh. Typically this myofascial pain is increased by sitting, standing, and walking.

TABLE 124-8 PHYSICAL EXAMINATION IN OLDER ADULTS WITH LOW BACK AND LEG PAIN: DETECTION OF MTrPs, BIOMECHANICAL PERPETUATING FACTORS, AND OTHER PAIN GENERATORS

FINDING	OPERATIONAL DEFINITION	EXAMINATION TECHNIQUE
Functional leg length discrepancy	Pelvic asymmetry	Have patient stand with both feet on floor, shoes removed. Ask him to stand with feet together, and as erect as possible. Kneel behind patient. With palms parallel to floor, and fingers

		extended, place lateral surface of index finger of both hands atop pelvic brim bilaterally. Level of eyes doing the examination should be level with hands. Determine if right and left hands are at different heights.
Scoliosis (lateral/rotational)	Lateral/rotational curvature of thoracolumbar spine	Have patient stand on floor with shoes removed. Stand behind patient. Run index finger along spinous processes (do not lift hand between vertebrae) a series of 3 times. If you do not detect scoliosis, then: Ask patient to bend forward. Determine if there is asymmetry in height of paraspinal musculature.
Sacroiliac joint pain	Pain with direct palpation of sacroiliac joint or with Patrick test	*Direct palpation*: Have patient stand on floor with shoes removed. Stand behind patient. Exert firm pressure over sacroiliac joint, first on one side, then the other. Palpate right joint with right thumb, standing to left side of patient; palpate left joint with left thumb, standing to right of patient. *Patrick (FABER) test*—Have the patient lie supine on the examining table and place the foot of involved side on opposite knee. Then slowly lower the test leg in abduction toward the examining table. If patient reports pain in back (*not* groin, buttocks, or leg), then test is positive. Other commonly performed SI provocation tests include supine distraction and compression; compression in side-lying; Gaenslen maneuver; thigh thrust
Myofascial pain, piriformis	Presence of pain on deep palpation of piriformis	Have patient lay supine on examination table. Have patient flex right hip and knee, keeping sole of foot on table. Cross bent leg over opposite leg; again place sole on table and exert mild medially directed pressure on lateral aspect of knee to put piriformis in stretch. Exert firm pressure (4 kg) over middle extent of piriformis. Repeat examination on opposite side.
Myofascial pain, TFL ± iliotibial (IT) band pain	Presence of pain on deep palpation of tensor fascia lata and/or IT band	Have patient lying supine on examination table. Using thumbs of both hands, exert firm pressure (4 kg) over full extent of TFL and IT band. Repeat examination on opposite side.
Kyphosis	Deformity of thoracic spine creating forward flexed posture	Have patient stand on floor with shoes removed. Ask him to stand fully erect. Inspect posture from the side.
Myofascial pain of paralumbar musculature	Presence of pain on deep palpation of paralumbar musculature	Have patient stand on floor with shoes removed. Stand behind and to left of patient and brace him in front with left arm and palpate full extent of right paravertebral musculature with right thumb. Exert approximately 4 kg of force. Repeat, palpating the left paravertebral musculature.
Myofascial pain of gluteus medius	Presence of pain on deep palpation of gluteus medius	Have the patient either prone or side-lying. Palpate just distal to the iliac crest, following its course on either side of the hip joint.
Vertebral body pain	Presence of pain on firm palpation of lumbar spinous processes	Position yourself behind patient, as for examination of paravertebral musculature above. Using dominant thumb, firmly palpate spinous processes L1–L5.

Hip disease	Pain and restricted motion of hip	*Hip internal rotation*—measure with patient sitting and leg dangling, OR have patient lie supine on examining table with hip and knee bent to 90 degrees. Put the hip into maximum internal rotation and ask patient if he experiences pain. *Hip flexion*—have patient lie supine and pull knee to chest; then have patient let go and examiner should hold leg in maximum flexion, ensuring that pelvis is flush with exam table. American College of Rheumatology clinical criteria for hip OA, ie, self-reported pain in hip + exam consistent with hip OA • Internal hip rotation < 15° + hip flexion < 115° OR • Internal hip rotation > 15° and painful + hip AM stiffness < 60 min *Patrick test*—as above.

Adapted from Weiner DK, Sakamoto S, Perera S, Breuer P. Chronic low back pain in older adults: prevalence, reliability, and validity of physical examination findings. J Am Geriatr Soc. 2006;54:11–20, with permission from Blackwell Publishing.

The gluteus minimus is another muscle in which MPS symptoms may mimic sciatica and, therefore, this muscle should be carefully examined and treated in patients with sciatica. The fibers of this fan-shaped muscle extend from the outer surface of the pelvis and converge onto a tendon, which is attached to the anterior surface of the greater trochanter. The gluteus minimus fibers work with the gluteus medius to abduct the thigh during extension, and to stabilize the pelvis during ambulation. Patients with myofascial pain arising from the gluteus minimus typically complain of hip pain during ambulation, often presenting with a limp, and may also have trouble rising from a sitting position. Because the gluteus minimus is the deepest of the gluteal muscles, it may be difficult for the examiner to palpate taut bands. However, if the patient lies in the supine position or on his/her side and relaxes the gluteal muscles, MTrPs may be located by identifying the areas of greatest, localized tenderness. Palpation of MTrPs in the gluteus minimus may also induce a thigh jerk.

Trapezius MP The trapezius is a very large muscle and, therefore, associated myofascial pain can have a number of presentations. The fibers originate from the occiput, the ligamentum nuchae, and the vertebral spinous processes of the seventh cervical vertebra and all of the 12 thoracic vertebrae and they insert onto the distal third of the clavicle, the acromion, and the length of the spine of the scapula. The upper fibers elevate the scapula, the middle fibers pull the scapula medially, and the lower fibers pull the medial border of the scapula downward. The upper and lower fibers also assist the serratus anterior muscle in rotating the scapula when the arm is raised above the head.

Patients with myofascial pain of the trapezius typically do not complain of limitations in movement, but full rotation of the head and neck to the opposite side is often painful, and opposite side bending may be somewhat restricted. Radiating pain patterns vary according to which of the trapezius fibers contain MTrPs (ie, upper, middle, or lower). MTrPs that occur in the upper trapezius may cause pain that radiates up the posterolateral part of the neck to the mastoid process, causing so-called “tension neckache.” Sometimes this pain may radiate to the angle of the jaw and/or the temple and back of the orbit. Dizziness also may occur. MTrPs of the middle fibers of the trapezius may be associated with a superficial burning pain very close to the spinous processes of the seventh cervical and the third thoracic vertebrae or with aching on the top of the shoulder or acromion process. MTrPs of the lower fibers of the trapezius, typically located along the lower border of the muscle, may refer pain to the high paracervical spinal musculature, the mastoid and the acromion, as well as aching and tenderness of the suprascapular region. Perpetuating factors include anything that causes abnormal biomechanics of the upper body such as a whiplash injury or prolonged computer work in an ergonomically unfriendly workspace.

Upper and lower back pain These syndromes may be caused by myofascial pain of the thoracolumbar paraspinal musculature. Numerous muscles constitute the paraspinal group, including both superficial and deep muscles. The superficial group is collectively referred to as the erector spinae and is the largest muscular mass of the back. It originates from the sacrum, the iliac crest, and the spinous processes of most of the lumbar and the last two thoracic vertebrae and insert into the ribs, the transverse processes of the cervical vertebrae, the thoracic vertebrae, and the mastoid process. The deep group comprises the semispinalis, multifidus, and rotatores. The primary function of the paraspinal musculature is spinal extension. Patients with parathoracic myofascial pain may experience pain that

radiates to the region of the scapula or more medially, and sometimes to the anterior lower chest; patients with paralumbar myofascial pain may experience pain that radiates to the buttocks or the lower abdomen. Precipitation of myofascial pain may be caused by sudden muscular overload (eg, when lifting objects using poor body mechanics), or associated with a vertebral compression fracture. Multiple vertebral compression fractures may also accumulate to cause hyperkyphosis and associated muscular strain. Physical examination typically reveals diminished spinal range of motion.

Upper and lower back pain in the older adult often relates to the presence of axial spondylosis. This spondylosis causes aberrant neuronal input by injuring spinal nerves, disrupting generation of neurotrophic factors, and resulting in muscle shortening and pain. This condition, formally described by Chan Gunn, is referred to as neuropathic myofascial pain. Axial spondylosis is ubiquitous in older adults, thus it is not surprising that myofascial pain commonly occurs in older adults with axial arthritis, even in the absence of frank radiculopathy (eg, myofascial pain of the sternocleidomastoid and trapezius in patients with cervical spondylosis).

Techniques used to examine the lower back to identify MTrPs and associated perpetuating factors are described in **Table 124-8**. Treatment of postural abnormalities is an important component of treating paraspinal myofascial pain. Physical therapy geared toward strengthening of paraspinal muscles is a key component of treatment, not only for the pain itself, but also for reducing the risk of future vertebral compression fractures.

Pseudotrochanteric bursitis This syndrome is caused by myofascial pain that involves the tensor fasciae latae (TFL) muscle. The TFL originates from the outer edge of the iliac crest between the anterior superior iliac spine and the iliac tubercle and inserts into the iliotibial tract. It assists the gluteus maximus in maintaining the knee in extension when a person stands and it also flexes the hip. Patients with TFL myofascial pain experience pain in the region of the hip and thigh, sometimes extending to the knee. The pattern of pain radiation is not uncommonly confused with trochanteric bursitis and is thus sometimes referred to as pseudotrochanteric bursitis. Patients may also complain of poor sitting tolerance, difficulty walking rapidly, and lying on the involved side. They may also have difficulty lying on the opposite side unless a pillow is placed between the knees because of the tight iliotibial band. Physical examination may reveal restricted hip extension and adduction and TFL trigger points. When standing, patients with TFL myofascial pain tend to maintain the hip in slight flexion. Other disorders that should be considered in the differential diagnosis include L4 radiculopathy and meralgia paresthetica.

Postherpetic pain While postherpetic neuralgia is commonly thought of as a purely sensory phenomenon, myofascial pain has been described as a possible component of this disorder. The explanation for this association may be several-fold. The varicella zoster virus (VZV) can directly infect the ventral ventral horn of the spinal cord, but this mechanism is thought to be extremely uncommon. A more likely explanation for myofascial pain in the setting of postherpetic neuralgia lies in axial spondylosis (ie, neuropathic myofascial pain, described above) or in guarding behavior.

We hypothesize that a spinal nerve already vulnerable from spondylosis that has caused muscle shortening may be particularly prone to the generation of MP following an acute insult such as VZV. The myofascial pathology that results may then further exacerbate neuropathic pain by entrapping the spinal nerves as they course through the taut bands of the muscles afflicted by myofascial dysfunction. This results in a feedback loop.

Myofascial pathology may also develop in the setting of postherpetic neuralgia as a result of guarding behavior. That is, the pain associated with reactivation of VZV can be excruciating, causing the patient to move their body in ways to protect the painful area. When this type of behavior occurs over a prolonged period of time, muscles may develop contraction knots that are characteristic of myofascial pain. Whatever the mechanism by which postherpetic neuralgia may be complicated by the development of myofascial pathology, treatment of both the myofascial pathology and the neuropathy may be needed to afford optimal pain relief.

Other Myofascial Pain and Dysfunction Syndromes

Since muscles cover virtually the entire body, any body region may be affected by MPS. Thus, MPS should always be included in the practitioner's list of differential diagnoses for regional pain syndromes. Just as importantly, the practitioner must be aware that MPS may occur in response to visceral disease; when myofascial dysfunction is identified in the abdomen and pelvis, the possibility of underlying visceral pathology must be kept in mind. Sometimes after the visceral pathology has been eradicated, myofascial pain may persist, which further complicates evaluation and treatment.

Some less common causes of MPS include pelvic floor myofascial dysfunction causing chronic pelvic pain in both

men and women, pelvic myofascial dysfunction causing urologic pain (eg, interstitial cystitis and the urgency-frequency syndrome), masticatory myofascial dysfunction causing toothache, abdominal wall myofascial dysfunction causing chronic abdominal pain (eg, following abdominal surgery or a gastrointestinal illness), and intercostal myofascial dysfunction causing postthoracotomy pain. As noted earlier in this chapter, myofascial dysfunction is not always associated with complaints of pain (ie, in the case of latent trigger points). For example, masticatory myofascial dysfunction has been associated with tinnitus and myofascial dysfunction of the trapezius with dizziness. Cervical myofascial dysfunction may also be associated with dizziness, a sense of imbalance and tinnitus, and treatment (as outlined below) may alleviate these symptoms. Thus the practitioner must keep MPS on his list of key differential diagnoses for the older adult who presents with a chief complaint of dizziness. For a more extensive discussion of these and other MP and dysfunction syndromes, the reader is referred to Travell and Simons' *Myofascial Pain and Dysfunction: The Trigger Point Manual*. Another less detailed but very useful introductory text that practitioners may want to consider is *Trigger Point Therapy for Myofascial Pain: The Practice of Informed Touch*, 2005, edited by Finando and Finando; www.InnerTraditions.com

Treatment

In developing a treatment plan for a patient with MPS, it is important to distinguish between precipitating factors that initiate the syndrome versus perpetuating factors that maintain the pain and dysfunction. The examiner should carefully address both factors. Furthermore, deactivation of MTrPs is crucial, as it will eliminate a source of ongoing nociception. It is also important to include appropriate aerobic and strengthening exercises into the program, which may help to inhibit the return of symptoms. The most effective treatment strategies are interdisciplinary, often involving contributions from a variety of healthcare practitioners (eg, physicians, occupational and physical therapists, massage therapists, etc), and are tailored to the individual patient.

Precipitating and perpetuating factors A distinction must be made between *perpetuating factors* and *precipitating factors*. The factors that *perpetuate* myofascial pain in older adults typically are multiple and develop over a long period of time, creating an accumulation of factors that must be addressed as comprehensively as possible to afford an optimal therapeutic response. In the older adult with low back pain, for example, a combination of lumbar spondylosis, degenerative scoliosis, and hip arthritis may contribute to the injury pool. The physical factors that *precipitate* myofascial pain may be overt such as a fall with direct trauma to the piriformis that causes piriformis syndrome or they may be more subtle such as a flare of knee osteoarthritis that alters gait and precipitates tensor fasciae latae pain. Psychological stressors may also precipitate flares of myofascial pain or they may act as perpetuating factors.

The correction of perpetuating factors is arguably one of the most important aspects of MPS treatment. Even if the precipitating factors are addressed, the presence of perpetuating factors may reactivate the patient's original myofascial pain complaint, preventing resolution of pain and dysfunction. Perpetuating factors typically persist over time, and often require behavioral and lifestyle adjustments. As part of the search for perpetuating factors, the practitioner should specifically identify any contributing vitamin deficiencies (eg, B_1, B_6, B_{12}, C, D, folic acid) or hormonal imbalances. Repetitive movements that contribute to muscular dysfunction such as those that occur in wheelchair users and computer operators also should be identified. Proper body mechanics during sitting, standing, walking, and sleeping should be taught by an occupational or physical therapist and efforts to modify repetitive movements and/or other mechanical stressors should be instituted.

Older adults that spend prolonged periods resting in static positions (eg, sitting, reclining, etc) may perpetuate their MPS through inactivity. Efforts should be made to incorporate intervals of light movement or stretching if the patient is able to tolerate such activities, in order to minimize overuse of small muscle fibers (ie, the Cinderella hypothesis).

Direct or indirect acute trauma also should be identified. For example, if a patient has a sudden leg length discrepancy, such as that which may occur following total hip or knee replacement, prescription of a shoe lift by a physical therapist may be helpful. For patients with longstanding leg length discrepancy, a shoe lift may disrupt the patient's established compensatory strategies and lead to mobility dysfunction and falls. In these patients, the muscle dysfunction of the pelvis and lower extremities should be first addressed by a physical therapist before considering an orthotic device.

Abnormal posture should be corrected. This can be particularly helpful for the patient with cervicogenic headaches. In the older adult with severe kyphosis related to multiple vertebral compression fractures, restoration of normal posture may not be possible, and prescription of a walker to unload the spine (ie, alleviate strain on the lower back musculature) should be considered strongly.

To the extent that psychological stressors, anxiety and depression, are playing a role in perpetuating myofascial

pain, cognitive behavioral therapy or other treatments may be useful. Vitamin D deficiency also should be identified and treated given its association with musculoskeletal pain (see Plotnikoff reference) although randomized controlled clinical trials evaluating its efficacy in patients with myofascial pain have not been performed. Patients who do not respond to these approaches in combination with MTrP treatment should be referred to an interdisciplinary pain clinic.

Trigger point treatment The goal of treating MTrPs is to *deactivate* them. There are currently several approaches to MTrP deactivation that may be undertaken that can be roughly categorized into those that are noninvasive and those that are invasive. **Table 124-9** provides a summary for the approach to treating MPS.

TABLE 124-9 APPROACH TO TREATING MYOFASCIAL PAIN SYNDROMES

1. Identify and treat perpetuating factors, eg, correct leg length discrepancy after total joint replacement, inject rotator cuff and provide physical therapy for rotator cuff tendonitis, treat knee osteoarthritis, begin or optimize medications for Parkinson disease, prescribe rolling walker for those with kyphosis.
2. Refer to a physical therapist that is experienced in treating patients with chronic pain for *gentle* stretching and strengthening, treatment of perpetuating factors, and for education regarding activity pacing and flare self-management techniques.
3. Perform trigger point injections or dry needling to achieve a local twitch response.
4. If psychological stressors are identified as a perpetuating factor, refer for cognitive-behavioral therapy.
5. Prescribe systemic analgesics only as adjunctive therapy, not as the primary mode of treatment.
6. Refer patients who do not respond to these treatments for interdisciplinary management in a pain clinic.
7. Prescribe aerobic exercise for cardiovascular fitness and prevention of pain flares.

Noninvasive MTrP Techniques Travell and Simons championed the use of the noninvasive "*spray and stretch*" technique in their *Trigger Point Manual*, due it its ease of application, minimal discomfort to the patient, and overall positive results. This technique involves spraying ethyl chloride on the skin over the muscle containing the region of pain, and then passively and slowly stretching the muscle through its normal length. Spray and stretch is useful for treating many muscles during each session, and is practical since it does not require the precise identification of each individual MTrP. With this technique, the localization and stretching of the taut bands is sufficient to cause MTrP release and improvement in pain and dysfunction. Other noninvasive techniques include *myofascial manipulation*, in which the muscle is passively stretched without the use of a vapocoolant spray, and *MTrP release*, in which increasing digital pressure is applied on a MTrP until the tension is released.

Invasive MTrP Techniques *Dry needling* is a common, minimally invasive technique used to deactivate MTrPs. It involves the insertion of a small-caliber needle (eg, an acupuncture needle or small caliber hypodermic needle) directly into the MTrP, to either a superficial or deep level. The goal of deep dry needling is to induce a LTR, since studies have shown that dry needling treatments are most effective when such a response is produced. Although active MTrPs are typically the primary targets for dry needling treatment, some researchers recommend needling latent MTrPs as well, in order to curtail their development into the active form.

MTrP injections are another type of invasive approach to MTrP deactivation. Also known as "wet needling," this technique involves a process similar to dry needling, but insertion into the MTrP is accompanied by the injection of a local anesthetic, such as bupivacaine, lidocaine, or procaine. Overall, there appears to be no added benefit with injecting an anesthetic into the MTrP—that is, dry needling appears to be just as effective as injection therapy in deactivating MTrPs and relieving pain.

It is thought that the pain relief produced from both wet and dry needling occurs as a function of the mechanical disruption that takes place within the MTrP, resulting in the release of the muscle contracture, and elimination of the nociceptive source. In addition, Ga et al demonstrated that acupuncture dry needling is as effective as MTrP lidocaine injections in reducing pain, and that there was no significant difference in posttreatment soreness between the two treatment groups (2007). Nevertheless, because the use of anesthetic injections preceded the development of the dry needling technique, injections continue to be a popular form of MPS treatment today.

Botulinum toxin A injections as an alternative treatment for deactivating MTrPs. Botulinum toxin exerts its effects by preventing the release of acetylcholine from the motor neuron at the neuromuscular junction, and may inhibit the release of the neuropeptides substance P and calcitonin gene-related peptide from surrounding sensory neurons as well. In this capacity, botulinum toxin A is used to promote relaxation of the contracted fibers within the MTrP, thereby decreasing the afferent drive to the CNS. Dosages typically range from 25 to 200 units, depending on the size

of the muscle to be injected. However, clinical trials have shown mixed results on the efficacy of injecting botulinum toxin A into MTrPs for treating MPS, especially when compared to anesthetic injections. Pain relief may result from mechanically disrupting muscle fibers that is associated with needling, whether wet or dry.

Oral Medications Medications are often considered as potential supplements to the aforementioned treatments for MPS, but most should be used judiciously in older adults. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be helpful when taken in conjunction with therapies that target MTrP deactivation, but produce only limited relief (if any) when used alone. Because of their numerous potential deleterious effects in older adults, we do not recommend NSAIDs for the treatment of MPS in these patients. Clonazepam and amitriptyline have been shown to reduce pain in some types of MPS, but their deleterious side effects outweigh the benefit of pain relief in many older adults. Muscle relaxants like cyclobenzaprine, on the other hand, do not appear to reduce pain related to MPS. We have had some success with low-dose gabapentin (eg, 300 mg twice a day) for the treatment of neuropathic MP, for example, in patients with cervical spondylosis and MP of the paracervical musculature. Medications that target nonpainful symptoms of MPS, such as mood and sleep abnormalities, may help to alleviate those particular disturbances, but require supplemental therapy in order to address the underlying myofascial dysfunction.

Self-Management When educating patients about myofascial pain, the importance of maintaining active involvement in their care (ie, maintaining a home stretching program and eliminating precipitating and perpetuating factors) should be emphasized. An essential element of any physical therapy program for the treatment of MP, therefore, is instruction in a home exercise program that includes a daily stretching routine, identification and elimination of movements that may perpetuate myofascial dysfunction, and techniques to manage pain flares.

Other Treatments A number of other treatments have been tried for MP, including topical medications such as capsaicin, lidocaine, and EMLA cream; repetitive magnetic stimulation; transcutaneous electrical nerve stimulation; biofeedback; massage; ultrasound; laser therapy; traditional Chinese acupuncture and Japanese acupuncture; nerve blocks; cervical spine dorsal root rhizotomy for the treatment of cervicogenic headaches; and many others. The quality of evidence at the present time cannot recommend for or against prescription of any of these treatments.

CONCLUSION

Our understanding of the pathogenesis, diagnosis, and treatment of fibromyalgia and MP syndromes has grown significantly. We now understand fibromyalgia as a central sensitivity syndrome with patients demonstrating increased sensitivity to a variety of stimuli, especially pain. While the pathogenesis of fibromyalgia needs further study, there seems to be a genetic predisposition and a clear familial aggregation. Lower levels of central neurotransmitters and nociceptive chemicals are believed to be involved with fibromyalgia pathogenesis. Data on the pathophysiology of MP supports both central and peripheral sensitization. The chemical milieu of muscles affected by MP is distinct from that of normal musculature.

For both fibromyalgia and MP syndromes, individualized approaches to treatment are recommended. Medications alone do not typically improve function, but may improve mood, sleep, and pain. Stretching and local modalities as well as identification and treatment of perpetuating factors should be considered first line for MP and aerobic exercise is a key component of the approach to treating fibromyalgia. Interdisciplinary treatment programs that include education, CBT, and exercise may be very effective for both fibromyalgia and MP syndromes. Further studies are needed to advance the treatment of older adult patients with these disorders, reduce the associated risk of functional compromise, and improve overall quality of life.

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Chapter 125

Infection: General Principles

Kevin P. High

Learning Objectives

- Identify and address modifiable risk factors for infection in older adults.
- Appropriately order and use culture data in older adults, including knowing when NOT to order cultures of urine and skin.
- Identify the most common causes of fever of unknown origin (FUO) in older adults and modify the FUO work-up versus that used in young adults.

Key Clinical Points

1. **Multiple risk factors including comorbidity, malnutrition, immune senescence, and social determinants of health (eg, nursing home residence, poor access to care) increase the risk of infection in older adults versus young adults.**
2. **Although antibiotic dose adjustments are sometimes necessary for seniors due to declines in renal or hepatic function, the adage of "start low, go slow" should NOT be used to guide initial antibiotic dosing for serious infections in older adults in whom time to effective treatment is a major determinant of outcome. Providing full initial dosing of antibiotics is critical in these situations with changes in subsequent doses to adjust for renal or hepatic function.**
3. **Because asymptomatic colonization (eg, asymptomatic bacteruria) is common in seniors, it is prudent to adopt a practice of "culture stewardship." This concept is akin to antibiotic stewardship to reduce unnecessary antibiotic use, but avoids unnecessary antibiotics by limiting the collection of culture samples to only those clinical conditions where they are of clear benefit. Cultures should only be performed when there is strong evidence of infection (eg, new-onset fever, delirium), and never from skin surface swabs or urine in the presence of a long-term indwelling catheter; cultures in these settings are more often misleading than helpful.**
4. **The causes of FUO differ in old versus young adults most notably with temporal arteritis being the underlying diagnosis in about 1 in every 6 cases of FUO in those age 60 years and over. Temporal arteritis is absent in FUO series in adults less than 50 years of age.**

PREDISPOSITION OF OLDER ADULTS TO INFECTION

A number of factors increase the risk of infection in older adults compared to young adults. The relationships between these risk factors may be very complex leading seemingly similar patients to have markedly different overall risk for clinical infection. For example, many older individuals have latent infection with *Mycobacterium tuberculosis* (ie,

asymptomatic infection) and do not manifest clinical illness despite an aging immune system and the presence of various comorbid conditions. However, superimposing malnutrition, perhaps due to medication- or illness-induced anorexia, may be the final insult necessary to tip the scales toward illness resulting in clinical manifestations. Several well-recognized features associated with advanced age clearly increase risk for clinical infection; these are reviewed in the following paragraphs.

Comorbidities

In older adult individuals, there is an increased incidence of infection and mortality for many infectious diseases likely directly resulting from comorbid conditions (eg, diabetes, renal failure, chronic pulmonary disease, edema, immobility) that accompany advanced age. Comorbidity most often results in reduced innate immunity, that is, responses that are not specific to a given organism or antigen. Critical innate immune components include nonspecific barriers such as skin integrity, cough, and mucociliary clearance, as well as innate immune responses triggered by recognition of patterns of microbial products (eg, endotoxin, lipoteichoic acid) without the need for prior exposure (eg, complement, tissue phagocytes such as polymorphonuclear neutrophils [PMNs] and toll-like receptors [TLRs]). Perhaps the best clinical example in which comorbidity contributes heavily to infection risk is chronic obstructive pulmonary disease (COPD). This disease, most often caused by prolonged exposure to tobacco smoke, has a high prevalence in older adults. The impaired mucociliary clearance, alveolar macrophage dysfunction, and suppressed cough mechanism substantially increase the risk for lower respiratory tract infection in older adults with COPD.

Comorbid diseases in older adults with infection can also be important predictors for worse outcomes. For example, community-acquired pneumonia (CAP) is typically treated on an outpatient basis and rarely causes mortality in patients under age 50 years. However, multiple comorbid conditions and advanced age greatly increase the risk of mortality associated with CAP. In fact, while age itself dominates many CAP prognostic indices, advanced age alone is not a predictor of mortality in those persons older than 75 years of age where comorbidity dominates. Furthermore, cognitive decline and other barriers that reduce adherence to medical regimens often necessitate hospitalization of older adults in circumstances where their younger counterparts are often treated as outpatients, further increasing costs and enhancing the rate of complications.

Waning Immunity

While comorbidities substantially predispose older adults to infection, there are also age-related fundamental changes in the immune response that accompany advancing age (see Chapter 3 on immune function), so called immune senescence. Immune senescence is not merely a global state of reduced immunity, but a dysregulation of immune responses at multiple levels.

The most consistent immune deficit identified in advance age is a reduction in adaptive T-cell responses. There are decreases in naive T-cell subsets, marked depression of cytokine production (particularly IL-2) and important cellular surface receptors (IL-2 receptor and CD28), as well as suppression of T-cell responses by inflammatory cytokines that inhibit T-cell immunity such as IL-10 and prostaglandin E_2.

Although there is little doubt that immune senescence exists, the clinical role of this phenomenon in the predisposition of older adults to infection remains uncertain. In observational studies it is difficult to separate immune changes due to comorbid illness from those of aging itself and longitudinal studies have not been powered to detect differences in clinical infection rates. It does appear that immune senescence markers predict vaccine responses as measured by antibody titers and other surrogate markers, but again, clinical outcomes have not been adequately studied.

Nutrition

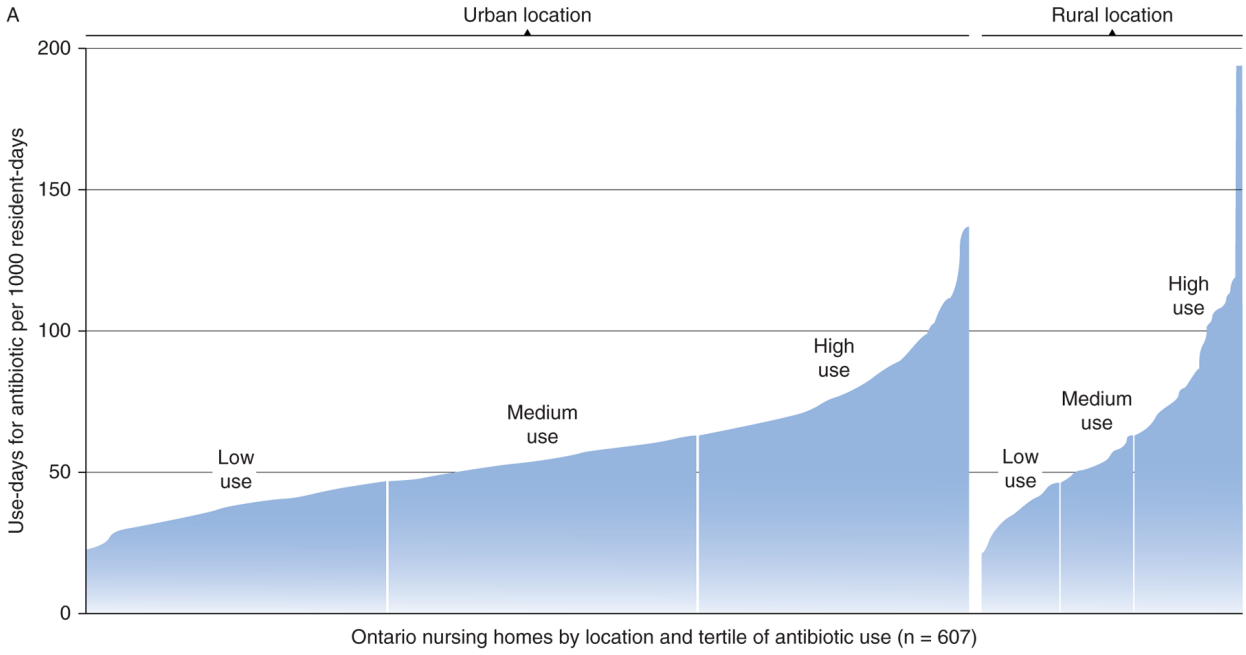
Nutritional status is a major confounder in studies of immunity in older adults. Protein–energy malnutrition (PEM) is present in 30% to 60% of patients older than 65 years of age who are admitted to the hospital, and is linked to delayed wound healing, pressure ulcer formation, CAP, increased risk of nosocomial infection, longer hospital stay, and increased mortality. In community-dwelling older adults, PEM often goes unrecognized, but even mild PEM (ie, seniors with a serum albumin of 3.0–3.5 g/dL) demonstrate poor vaccine responses. Despite strong epidemiologic evidence linking PEM to infection in older adults, the role of nutritional supplements for preventing infection remains controversial. Some studies of long-term care facility residents suggest use of supplements may increase caloric intake, but others indicate meal-time calorie consumption may reciprocally decrease, leading to no real change. Despite this

controversy, there is widespread agreement that adequate nutrition should be encouraged and provided to debilitated older adults, and that adequate nutrition is essential for proper wound healing, and functional recovery from serious infectious diseases.

Specific micronutrient deficiencies are also common in older adults, and have been linked to poor immune function (eg, vitamin B_{12} deficiency and inadequate pneumococcal vaccine responses) and risk of infection (eg, vitamin D deficiency linked to risk of TB and *C difficile* infection). Several micronutrient supplementation trials have been performed that highlight the potential importance of adequate nutrition even in apparently healthy older adults. Vitamin E supplementation (> 200 mg/day) in healthy older adults individuals enhances delayed-type hypersensitivity (DTH) and vaccine responses for a primary T cell–dependent antigen (hepatitis B), but has no effect on T cell–independent vaccine responses (pneumococcal vaccine) or the booster response to tetanus. A word of caution, however, meta-analyses of vitamin E supplementation suggest increased mortality in those taking greater than or equal to 400 mg/day, highlighting the dangers of mega-dose therapy with some vitamins (vitamins A, D, E, and K). Multivitamin/mineral supplements have been examined in healthy, free-living older adults and consistently demonstrate improved serum vitamin levels, but inconsistent results for preventing clinical infection or boosting vaccine responses. Other studies in older adult residents of long-term care facilities suggest zinc (20 mg/day) plus selenium (100 μg/day), or specific commercial formulas may reduce the risk of infection, but more work is required to define the role of vitamin or mineral supplementation for augmenting immune response in the older adult population, and to determine whether there are specific subpopulations that could help identify target groups for therapy.

Social and Environmental Factors

There is increasing recognition that the health of seniors is not only a function of biomedical variables but also socioeconomic status, environment, and delivery of health care services. This “determinants of health” perspective combines biomedical, behavioral, social, and environmental explanations of illness and health (**Figure 125-1**). For example, population-based studies reveal that lower income is associated with higher rates of CAP and invasive pneumococcal infections among older adults. Lower socioeconomic status may predispose to infection for a number of reasons: increased exposure to infectious agents (eg, grandparents raising young children more often), poor nutrition, increased risk of comorbid disease (eg, due to pollution/tobacco exposure), or differential access to care (eg, lower vaccine rates).



The 607 Ontario nursing homes are presented by location (urban or rural) and tertile of antibiotic use (high, medium, or low).

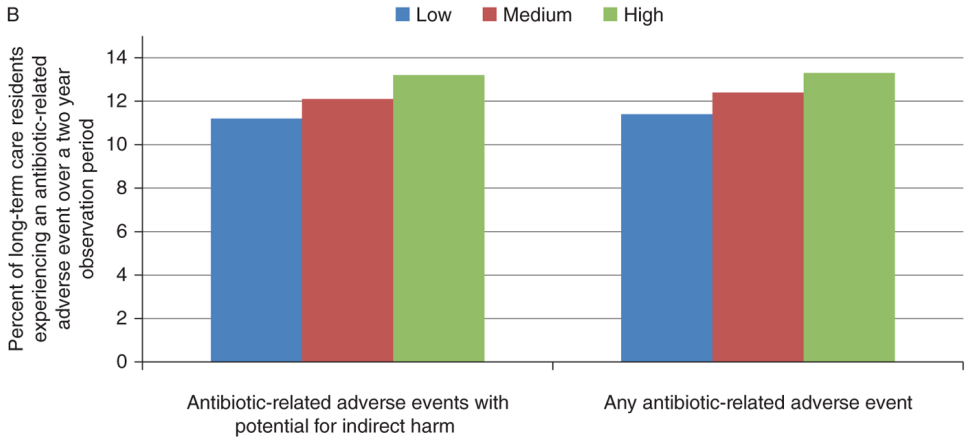


FIGURE 125-1. **(A)** Antibiotic use days vary markedly between long-term care facilities. High antibiotic use is associated with for-profit status, rural location, and smaller size (lower number of beds). (Reproduced with permission from Daneman N, Bronskill SE, Gruneir A, et al. Variability in antibiotic use across nursing homes and the risk of antibiotic-related adverse outcomes for individual residents. *JAMA Intern Med*. 2015 Aug;175(8):1331-1339.) **(B)** Percent of long-term care residents experiencing antibiotic-related adverse events with potential for indirect harm (*C difficile*, diarrhea/gastroenteritis, multidrug-resistant organism infection) or any antibiotic related adverse event (including antibiotic allergic reaction and general adverse medication event). All differences were statistically significant. (Data from Daneman N, Bronskill SE, Gruneir A, et al. Variability in antibiotic use across nursing homes and the risk of antibiotic-related adverse outcomes for individual residents. *JAMA Intern Med*. 2015 Aug;175(8):1331-1339.)

Long-term care residents have a particularly high incidence of respiratory and other infections (mainly urinary and skin infections) that can be explained by the multiple determinants model. The close contact residents have with other residents plays a key role in the spread of respiratory infections such as influenza, or with bacterial infections such as group A streptococcus (ie, *Streptococcus pyogenes*). This combination of frail older individuals and a confined setting can lead to severe outbreaks with high mortality rates. The close proximity of residents, poor adherence to basic infection control measures, and the intense use of antibiotics are factors that lead to the spread of antibiotic resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and multiresistant gram-negative rods. Although the actual infectious threat many of these organisms pose to individual residents is uncertain, the potential reservoir creates a problem when such residents are transferred to acute care hospitals where these organisms can spread to other susceptible hosts.

DIAGNOSIS AND MANAGEMENT OF INFECTIONS IN OLDER ADULT PATIENTS

Presentation of Illness

Infectious diseases frequently present with atypical features in older adults. Serious infections may be signaled by nonspecific declines in function or mentation, or decreased oral intake. Underlying illness (eg, congestive heart failure [CHF] or diabetes) may be exacerbated by infection leading older adult patients to seek medical attention for symptoms related to comorbidity. The most common sign that indicates infection, fever, is often absent in the older adult patient. Several studies show that frail older adults have lower mean baseline body temperatures than the currently accepted normal of 98.6°F (37°C). Animal models of aging demonstrate that temperature elevations in response to compounds that typically raise body temperature (IL-1, IL-6, tumor necrosis factor [TNF]-α) are diminished with advanced age. The decline in basal temperature and blunted response to inflammatory stimuli make it less likely that a frail older adult will achieve a body temperature commonly recognized as fever. It has been suggested that fever in frail older adults should be defined as (1) persistent elevation of body temperature of at least 2°F (1.1°C) over baseline values, or (2) oral temperatures of 99°F (37.2°C) or greater on repeated measures, or (3) rectal temperatures of 99.5°F (37.5°C) or greater on repeated measures. The sensitivity of detecting fever and infection in the nursing home setting has been improved using this definition, and reasonable specificity maintained. The importance of a "normal" or reduced temperature in the face of significant infection cannot be overemphasized. A blunted febrile response often leads to delayed diagnosis and is an indicator of a poor prognosis.

Cognitive impairment may also contribute to the difficulty of diagnosing infection in older adults. Such patients are often unable to communicate symptoms and clinicians should have a lower threshold to pursue objective assessments (eg, laboratory and radiologic evaluations) for infection in cognitively impaired older adults with changes in functional status.

Finally, age- and comorbidity-related changes in anatomy and physiology may confound interpretation of diagnostic evaluations. For example, there is diminished sensitivity of transthoracic echocardiography (TTE) for detecting vegetations on the heart valve in endocarditis in older adults due to calcification of valves and other anatomic changes associated with age. Studies suggest that the sensitivity of TTE of 85% to 90% in adults aged 55 and under is reduced to less than 50% for those over age 70. More frequent use of transesophageal echocardiogram (TEE) is thus often needed in seniors where sensitivity returns to 85% to 90% and specificity is not reduced.

Antibiotic Management and Stewardship

Physiologic changes associated with aging and comorbidities alter drug distribution, metabolism, excretion, and interactions (see Chapter 24). Antibiotic dose reductions are occasionally required in older adults because of changes in renal function or predisposition to important side effects such as changes in mental status (eg, fluoroquinolones). In addition, antibiotic interactions are more frequent because most older adults are taking multiple medications. Digoxin, warfarin, oral hypoglycemic agents, theophylline, antacids, and H_2-receptor antagonists all have significant interactions with commonly prescribed antibiotics. Drug concentrations can increase (eg, enhanced digoxin toxicity associated with macrolides, tetracyclines, and trimethoprim) or decrease (eg, reduced quinolone absorption with concomitant administration of antacids) with concomitant drug administration. These changes and the increased incidence of side effects in older adults often lead clinicians to the dictum of "start low, go slow" when administering new medications in older adults. However, for antibiotics, this is not an appropriate strategy. Altered gastric motility, decreased absorption, increased adipose tissue, and coadministration of other drugs can decrease blood levels of antimicrobials in older adults, and since systemic antibiotics reach tissues via blood flow, poor vascular perfusion to the site of infection, particularly in skin and soft-tissue infections of the lower extremities, may reduce efficacy. Adherence may be limited by poor cognitive function, inadequate understanding of the drug regimen, impaired hearing or vision, and polypharmacy and studies suggest that any regimen requiring greater than twice daily dosing is associated with very poor adherence rates. Finally, there are data that suggest higher antibiotic levels are particularly important for efficacy in older adults where outcomes in serious infection are more dependent on reaching adequate levels earlier than in young adults. This is especially true for antibiotics that are "concentration dependent" (ie, the higher the concentration in relation to the minimal inhibitory concentration [MIC], the better the antibiotic kills, such as fluoroquinolones).

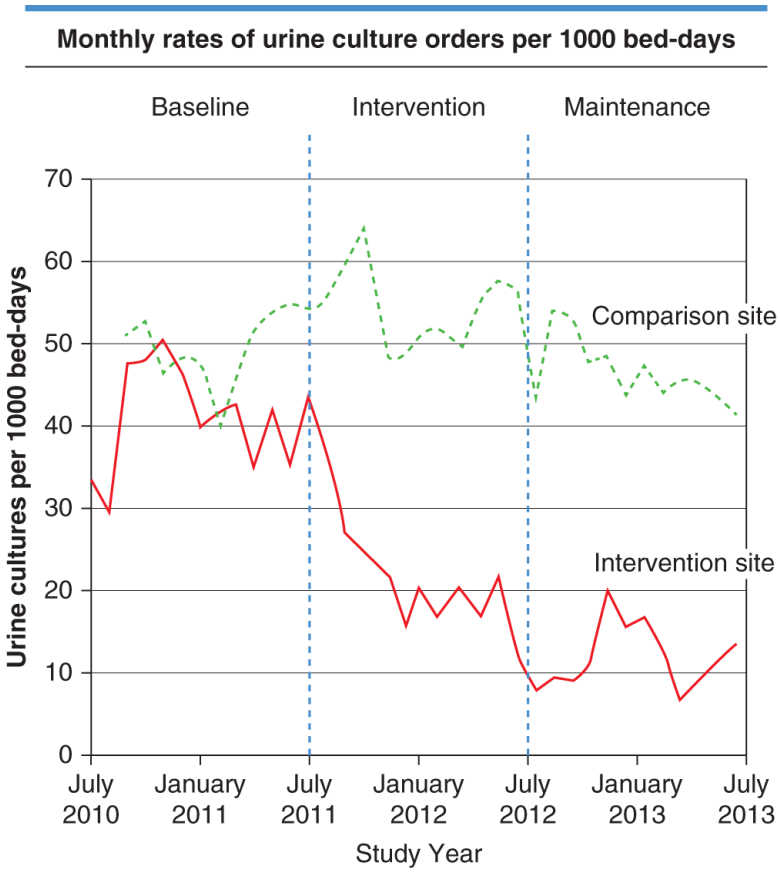
Many ethical dilemmas surround antibiotic use in frail older adults and terminally ill patients. The 1998 American Medical Association (AMA) Council of Ethical and Judicial Affairs included antibiotics, along with mechanical ventilation, as "life-sustaining" treatment. Others argue that antibiotics are part of ordinary care, even those who are designated to be receiving "comfort measures only." While every clinical situation is unique, and no blanket recommendation can be made for the use or nonuse of antibiotics in the terminally ill, it seems prudent to include

antibiotic administration in the discussion of advanced directives as a potentially life-sustaining intervention, and to treat it no differently than any other medical intervention such as surgery or mechanical ventilation.

Although older adults are at the greatest risk for infections treated by outpatient parenteral antibiotic therapy (OPAT) (eg, for treatment of endocarditis or osteomyelitis) OPAT has been frequently underused in older adults primarily due to the fact that Medicare did not cover the cost of OPAT and older adults frequently had to be admitted to nursing homes or stay in acute care hospitals to obtain appropriate therapy. With the institution of Medicare Part D in 2006, OPAT is now covered, although navigating the system to obtain reimbursement for both the antibiotic and the necessary supplies for administration takes considerable knowledge and effort.

Older adults represent an important population in whom antibiotic stewardship can be most effective. Older nursing home residents have some of the highest rates of multidrug resistant organism (MDRO) colonization and infection. Residents at especially high risk for colonization and infection with MDROs include those with indwelling devices (eg, urinary catheters, G-tubes) and those with marked functional impairment. This is perhaps not surprising as those same residents are more likely to receive antibiotics. However, high levels of antibiotic use in a nursing home are more a characteristic of the nursing home than the type of patient in that nursing home (**Figure 125-1*A***). Further, high levels of antibiotic use have harmful effects on residents—even individual residents that don't receive antibiotics—just by being in a high-risk milieu, where MDROs are common. **Figure 125-1*B*** demonstrates that high antibiotic use nursing homes place residents at higher risk for antibiotic-related adverse events (*Clostridium difficile*, diarrhea or gastroenteritis, antibiotic-resistant organism infection, allergic reaction, or general medication adverse events).

An important concept in the fight to reduce antibiotic resistance is limiting the number of unnecessary cultures obtained—such as reducing swab cultures of pressure ulcers and urine cultures in those with indwelling catheters. Such cultures will *always* be positive, and the information does *not* correlate with clinically relevant cultures (eg, bone biopsy under an ulcer or blood cultures in those with an indwelling urinary catheter and sepsis). This approach of "culture stewardship" provides an important early step in reducing antibiotic use and can be very effective (**Figure 125-2**). Additional means to reduce inappropriate antibiotic use in long-term care settings include comprehensive educational programs and in-nursing home consultation by infectious diseases specialists.



Shown are the intervention vs comparison sites across the 3 study periods ($P < .001$).

FIGURE 125-2. Impact of criterion-driven culture orders on the number of urine cultures obtained for hospital inpatients and nursing home patients. (Reproduced with permission from Trautner BW, et al. Effectiveness of an antimicrobial stewardship approach for urinary catheter-associated asymptomatic bacteriuria. *JAMA Intern Med*. 2015;175[7]:1120–1127.)

CLINICAL SYNDROMES IN OLDER ADULTS

A complete review of all the clinical infectious syndromes seen in older adults is beyond the scope of this chapter, and many individual infections are covered elsewhere in this textbook. Common infections not covered elsewhere are reviewed in the following sections.

Infective Endocarditis

Although in the middle twentieth century infective endocarditis (IE) was primarily a disease of young and middle-aged adults associated with postrheumatic fever and congenital valvular lesions, it has become a disease of older adults associated with degenerative valvular disorders and prosthetic valves (prosthetic valve endocarditis [PVE]). Furthermore, temporary and permanent pacemakers, pulmonary artery catheters, and other invasive devices are more frequently used in older adults and predispose subjects to IE.

Native valve IE in young adults is typically caused by streptococci, staphylococci, and occasionally by HACEK organisms (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, Kingella*). These same organisms predominate in older adults, but comorbidities and prosthetic devices change the profile of causative agents; gastrointestinal (GI) and genitourinary (GU) organisms such as enterococci and gram-negative rods become more common in native valve IE. Coagulase-negative staphylococci are a frequent cause of PVE, both from contamination at the time of surgery and from occult or documented bacteremia during the hospital stay. Other nosocomial bacteremias, often with more resistant organisms (eg, *Enterobacter* spp.), can also result in PVE.

Endocarditis is difficult to diagnose in the older adult patient. Fever and leukocytosis are less common (55% and 25%, respectively, for older adults versus 80% and 60%, respectively, for younger patients). As stated above, the prominence of degenerative, calcific valvular lesions and prosthetic valves lowers the sensitivity of TTE. TEE is more sensitive, and improves the diagnostic yield by 45% over that of TTE. Age alone is not a major risk for mortality in IE, with a 2-year survival of 75% for IE in all age groups unless major comorbidities exist—these determine prognosis at any age.

Antibiotic treatment of IE is directed at identified pathogens or the most likely causes if blood cultures are negative (**Table 125-1**). Therapy is administered intravenously for 2 to 6 weeks. Combination regimens with aminoglycosides are particularly problematic in the older adult patient because of toxicity (both renal and ototoxicity), but is occasionally unavoidable in certain circumstances (eg, enterococcal IE). Surgical therapy is required only when specific criteria are met, primarily recurrent embolic events or worsening heart failure.

TABLE 125-1 ■ SUGGESTED EMPIRIC ANTIMICROBIAL THERAPY FOR COMMON INFECTIONS IN OLDER ADULTS

INFECTION	THERAPY	COMMENTS
Community Acquired		
Outpatient Therapy		
Acute sinusitis	Amoxicillin	Amox/clav or new macrolide (clarithromycin or azithromycin) if refractory; new macrolide if penicillin allergic
Acute exacerbations of chronic bronchitis	Amoxicillin-clavulanate or resp-FQ	Infectious exacerbations only; new macrolide if penicillin allergic. Resp-FQs have been shown to extend the time between acute exacerbations and therefore may be preferable in those with frequent, infectious exacerbations
Pneumonia	[Azithromycin or clarithromycin + 2nd gen cephalexin or amox/clav] *or* resp-FQ	Review and update immunization status—particularly new recommendation for pneumococcal conjugate vaccine
Cellulitis	Amox/clav *or* cephalexin	If pustules/skin abscesses *S aureus* more likely than *Streptococcal* spp. About half of all *S aureus* will be community-acquired

		MRSA; include TMP-SMX or minocycline if suspected. New IV drugs for MRSA (eg, oritivancin, dalbavancin) may change management in near future with single or two-dose IV regimens
Infected neuropathic ulcer	Amox/clav	Initial outpatient treatment of diabetic foot infection; for penicillin-allergic patient, use cephalosporin if allergy is not severe, use clindamycin + ciprofloxacin for severe allergy
Symptomatic UTI	FQ, TMP-SMX	Uncomplicated cystitis or pyelonephritis
Bacterial diarrhea	FQ	Oral rehydration is key—most will resolve without antibiotics. DO NOT USE ANTIBIOTICS IF SHIGA TOXIN IS POSITIVE (due to risk of HUS/TTP)
C difficile diarrhea	Metronidazole or vancomycin	Use vancomycin if WBC > 15,000 or creatinine > 1.5 times baseline. Fidaxomicin is FDA approved and is equivalent to vancomycin for cure, but reduces relapse rate (cost is a major consideration keeping fidaxomicin from being first-line therapy)
Inpatient Therapy		
Pneumonia	[Ceftriaxone + azithromycin or clarithromycin] *or* resp-FQ alone	Seriously ill (intensive care unit) combination therapy may be best; consider *Legionella* in seriously ill; consider *Pseudomonas* if severe COPD (FEV_1 < 30% predicted) or structural lung disease
Pyelonephritis (no catheter)	3rd gen cephalosporin *or* FQ	
Sepsis from urologic source (with catheter)	3rd gen cephalosporin + ampicillin or vancomycin	Catheter-related sepsis due to urologic source is often polymicrobic; have to consider enterococcal species, in addition to gram-negative bacilli. Early catheter exchange improves outcome
Acute bacterial meningitis	Ceftriaxone + vancomycin	Vancomycin needed because of small percent of ceftriaxone-resistant *S pneumoniae*; give dexamethasone with or prior to antibiotics if Gram stain of CSF reveals bacteria. Add ampicillin if *Listeria* infection suspected (alcoholism, unpasteurized dairy consumption, preceding GI illness)
Intra-abdominal infection	[Ampicillin/sulbactam + gentamicin] *or* [ampicillin + gentamicin + metronidazole] *or* pip/tazo *or* carbepenem	Surgery nearly always indicated for appendicitis, cholecystitis, ischemic colitis, abscess drainage, but rarely required for diverticulitis; tigecycline for patients with significant β-lacatam allergy
Native valve endocarditis	Penicillin + nafcillin	Vancomycin for penicillin-allergic patient
Prosthetic valve endocarditis	*Early* (< 60 days)—vancomycin + 3rd generation cephalosporin *Late* (> 60 days)—vancomycin	Treat pacemaker and implantable defibrillator devices similarly
Infected diabetic foot ulcer	Ticar/clav *or* pip/tazo	3rd gen ceph and clinda for penicillin allergy; tigecycline for significant β-lactam allergy
Cellulitis	Ampicillin/sulbactam	Add clinda if high suspicion for GAS or vancomycin if MRSA suspected; vancomycin + FQ for β-lactam allergy
Septic shock syndrome; with no obvious focus	Carbepenem; add clindamycin if GAS suspected	Aggressive supportive care—sepsis bundles/protocols; consider intravenous immunoglobulin if streptococcal toxic shock syndrome
Nursing Home Acquired		
Infected pressure ulcer	FQ + clindamycin (PO); ticar/clav *or* pip/tazo (IV)	Pressure-relieving devices, nutrition, debridement essential; culture/x-ray to identify osteomyelitis or MRSA; NEVER do swab culture of surface to identify organism(s)—only surgical cultures of value

Pneumonia	Resp-FQ *or* ceftriaxone + azithromycin or clarithromycin	Consider tuberculosis (primary or reactivation); choose empiric coverage of *Pseudomonas* (eg, change ceftriaxone to cefepime) if heavy antibiotic exposure in last 3 months and/or structural lung disease (eg, COPD with FEV_1 < 30% predicted); add vancomycin if MRSA colonized
Sepsis due to urinary source	Ciprofloxcin (PO) or ceftriaxone (IM/IV)	Add enterococcal coverage if catheter present
C difficile colitis	Metronidazole or vancomycin	See comments above regarding vancomycin vs metronidazole. Close attention to infection control as nosocomial spread documented; spores not killed by alcohol-based antispetics, must wash hands with soap/water
Nosocomial/Hospital Acquired		
Pneumonia	Cefepime *or* carbepenem *or* pip/tazo + vancomycin or linezolid	Decision influenced by numerous factors: underlying medical conditions, mental status, respiratory support, prior antibiotic exposure, aspiration; risk of MRSA usually elevated in nosocomial pneumonia, thus vancomycin usually justified at initial therapy and can be dropped if no MRSA isolated
Catheter-associated urosepsis	Vancomycin plus 3rd gen ceph or FQ	Culture to guide subsequent therapy
Intravenous catheter-associated infection (cellulitis, phlebitis, abscess, bacteremia)	Vancomycin	If immunocompromised, add cefepime or ceftazidime; surgery required for septic thrombophlebitis
C difficile–related diarrhea	Metronidazole or vancomycin	See comments above regarding vancomycin vs metronidazole. Discontinue the implicated antimicrobials if possible; attention to infection control and hand washing as noted above
Postoperative wound infection; incision/deep with cellulitis, abscess, or bacteremia	Cefazolin (mild infection) Vancomycin + 3rd gen ceph (severe infection)	Reopen and explore wound; definitive therapy guided by cultures

2nd gen, second generation; 3rd gen, third generation; amox/clav, amoxicillin-clavulanate; carbepenem, imipenem-cilastatin or meropenem; ceph, cephalosporin; clinda, clindamycin; COPD, chronic obstructive pulmonary disease; FQ, fluoroquinolone; GAS, group A streptococci (*S pyogenes*); HUS/TTP, hemolytic ureic syndrome/thrombotic thrombocytopenia purpura; MRSA, methicillin-resistant *S aureus*; pip/tazo, piperacillin-tazobactam; resp-FQ, respiratory fluoroquinolone (gatifloxacin, levofloxacin, moxifloxacin); ticar/clav, ticarcillin-clauvulanate; TMP-SMX, trimethoprim-sulfamethoxazole; vanco, vancomycin; UTI, urinary tract infection.

Antibiotic prophylaxis is available for bacterial endocarditis for all "at-risk" patients and should be provided for dental, upper respiratory tract, GI, or GU procedures. Although the evidence supporting this practice is relatively weak, it has become the standard of care. Current recommendations for IE prophylaxis are available in sources listed in the references.

Bacteremia and Sepsis

Bacteremia rates are much higher in older adults than in younger patients, comprising up to 14% of all admissions in some geriatric units. Older patients with bacteremia are less likely than younger patients to have systemic signs such as fever, chills, or diaphoresis. Bacteremia in older adults is more likely to arise from a gastrointestinal or genitourinary source than in young adults. Thus, the causative agent is more likely to be a gram-negative rod.

Despite a similar initial cytokine response to that of young adults with sepsis, the prognosis of sepsis in older adults is worse. The 28-day mortality for sepsis in young adults is 26% to 33% versus 35% to 42% in adults older than age 65 years. Nosocomial gram-negative bacteremia carries a mortality rate of 5% to 35% in young adults, but 37% to 50% in older adults. A major contributing factor is reduced physiologic reserve because of age and comorbidities that reduce the ability of older adults to recover from a septic episode.

Antibiotic management of bacteremia and sepsis in older adults is similar to that of younger adults, and the

importance of initially broad coverage must be emphasized. Mortality is greatly reduced if an antibiotic that covers the eventually isolated organism is included in the initial regimen, whereas waiting to identify the organism and switching the antibiotic once identified has little to no effect on overall survival. Thus it is imperative to include coverage for MRSA, resistant gram negative rods, enterococci and other resistant organisms when there is a high clinical suspicion for resistant organisms in an older adult, in particular nursing home residents represent a high-risk population.

Prosthetic Device Infections

As the prevalence of the US population older than age 65 years has increased, permanent implantable prosthetic devices have become quite common. Prosthetic joints, cardiac pacemakers, artificial heart valves, intraocular lens implants, vascular grafts, penile prostheses, and a variety of other devices are primarily placed in older adults. Foreign bodies provide a conducive environment for bacterial colonization and inhibit host immune factors, often leading to infection. While it is impossible to review all prosthetic device infections in this chapter, several general concepts can be stated. Prosthetic device infections are usually categorized by causative agents that typically present early (< 60 days from implantation) or late (> 60 days). Early infections are primarily caused by contamination at the time of surgery or events associated with the implantation hospitalization (eg, bacteremia caused by IV or urinary catheters). Thus, the causative organisms for early prosthetic device infections are primarily skin and nosocomial flora. Coagulase-negative staphylococci predominate; *S aureus* and diphtheroids are common as well. Gram-negative bacilli, fungi, or polymicrobial infections are rare causes of early infection except when the material itself or associated products such as dressing material are contaminated. Late infections tend to be caused by the same organisms that cause community-acquired bacteremia in the older adult population, and bacteremic seeding of the device is likely the mode of infection in these cases. Staphylococci, including coagulase-negative staphylococci, are the exception to this rule, playing a major role in prosthetic device infections in both the early and late periods. Thus, empiric antistaphylococcal therapy is imperative in either early or late prosthetic device infection.

It is difficult to cure prosthetic device infections (ie, eradicate the organism) with the device in place. However, in some instances, early antibiotic intervention combined with aggressive surgical debridement may result in cure without removing the device. Because prosthetic device infections often include biofilms and occur in the setting of other factors that limit antibiotic efficacy (eg, poor circulation), it is preferable to use bactericidal antibiotics, and combinations with a second agent that penetrate these areas well (eg, rifampin) may be most effective when trying to cure infection with a device remaining in place. If early, aggressive therapy is ineffective in controlling the infection, it is imperative that the device be removed. In prosthetic joint infection (the clinical entity of device-related infection most well-studied) two-stage procedures, where the device is removed and antibiotics given for an extended period (usually 6 weeks) with delayed reimplantation have the highest success rate. However, for life-saving devices, such as mechanical valves or implantable defibrillators, this is not an option.

Prevention of prosthetic device infection is facilitated by the use of clean air systems and/or personal isolator systems in the operating room. Although there are limited data for efficacy, typical antimicrobial prophylaxis for clean surgery is appropriate; prophylaxis other than at the time of surgery remains unproven. However, perioperative antimicrobial prophylaxis for dental, GI, and GU procedures is indicated for prosthetic valves and is frequently employed for vascular grafts, particularly within the first few months after placement. There is no evidence to demonstrate benefit for prophylaxis in patients with prosthetic joints, intraocular lens implants, intracoronary artery stents, cerebrospinal fluid shunts, breast implants, or other less-commonly used prostheses. The American Dental Association (ADA) recommends “considering” antibiotic prophylaxis for patients with prosthetic joint at “high risk,” which the ADA define as joints within 2 years of placement, immunosuppressed patients (including immune compromise as a result of diabetes mellitus, rheumatoid arthritis, and malnourishment), or those with a previous joint infection.

Tuberculosis

It has long been established that advanced age is a major risk factor for developing tuberculosis (TB), and even with the increasing populations of young adults at risk due to the HIV epidemic and increasing immigrant populations, older adults still comprise approximately one-fourth of all TB cases reported in the United States. Tuberculosis often presents differently in older adults than in young adults. Several studies have demonstrated that, when compared to young adults, older adults are less likely to present with fever, night sweats, cough, or hemoptysis, and more likely to present with nonspecific symptoms of dizziness, nonspecific pain or mental “dullness,” a prior history of tuberculosis, and a concomitant diagnosis of underlying cancer. Radiographic and laboratory differences also occur with older

adults being more likely to have widespread pulmonary parenchymal infiltrates whereas young adults are more likely to have isolated upper lobe infiltrates, and older adults are more likely to have evidence of malnutrition (ie, reduced serum albumin).

The most important issue of TB management in older adults remains the challenge of diagnostic testing. Using the tuberculin skin test (TST) in classic studies, William Stead and colleagues at the University of Arkansas defined the prevalence of TST positivity in older adult residents of long-term care facilities, the risk for reactivation of *M tuberculosis* with and without prophylactic therapy, and the survival of older adults in each of these situations. Overall conclusions from these studies suggest that the sensitivity of the TST to detect latent infection declines with age, that TB is rare (< 0.2%) in older residents in whom the TST is never positive, that TST positive individuals develop clinical disease 2% to 5% of the time (this is increased two- to threefold if the TST represents a recent conversion), and that isoniazid (INH) prophylaxis in TST positive subjects reduces the risk of clinical disease to < 0.3% for most subjects (the exception being those who are TST positive and previously had active tuberculosis—in those cases, isoniazid therapy reduced the risk from 2–5% to 1.5–2%). The benefits of isoniazid prophylaxis are long-lasting with improved survival in TST-positive treated subjects (vs untreated TST positive subjects) apparent at 1.5 years and persisting up to at least 8 years.

From these data it is clear that identifying TST positive older adults is important for preventing active tuberculosis through INH prophylactic treatment. Confounding issues, however, surround interpretation of the TST. In the most recent guidelines from the American Lung Association, a TST is considered positive if greater than 5 mm induration in HIV-positive persons, recent TB contacts, those with fibrotic changes on chest radiograph consistent with prior TB, and immunosuppressed patients (including those on ≥ 15 mg/day of prednisone for at least 1 month); greater than 10 mm is considered positive for recent immigrants, injection drug users, residents and employees of healthcare facilities (including nursing homes), and persons with high-risk conditions (silicosis, diabetes mellitus, chronic renal failure, leukemia/lymphoma, head and neck or lung cancer, weight loss ≥ 10% of ideal body weight, and status post gastrectomy); for all other persons, a TST greater than 15 mm is considered positive.

Equally as important to appropriate interpretation is the need to do “two-step” initial testing in those who will undergo serial testing (such as residents of long-term care and health care workers). Some people infected with *M tuberculosis* may have a negative reaction to initial testing if many years have passed since they became infected. This false positive skin test may be revealed by a positive reaction to a subsequent TST that is “boosted” by the first test. If this is not recognized at the time of initial testing, a subsequent positive may incorrectly be interpreted as a skin test conversion (going from negative to positive). For this reason, the “two-step method” is recommended (**Figure 125-3**) in those who will undergo periodic testing thereafter (eg, nursing home residents, health care workers).

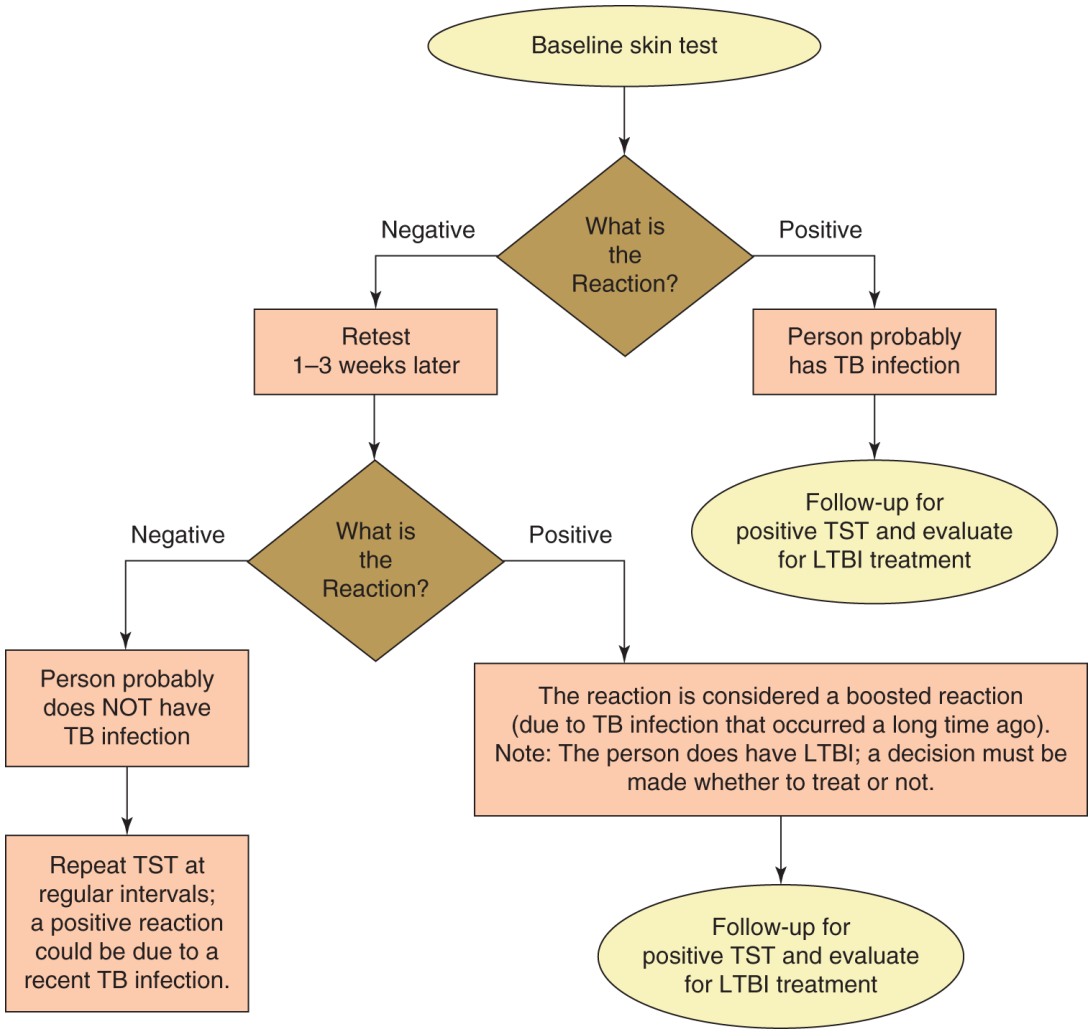


FIGURE 125-3. Interpretation of "two-step" tuberculin skin testing (TST) in nursing home residents and others (eg, healthcare workers) who will undergo repeat TST. LTBI, latent tuberculosis infection; TB, tuberculosis. (Reproduced from Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Centers for Disease Control and Prevention.)

New diagnostic tests for tuberculosis have been developed and include quantitation of interferon-γ release assay (IFGA) from whole blood measured after ex vivo *M tuberculosis* antigen stimulation. Unfortunately, these newer assays have only demonstrated modestly improved sensitivity or specificity and not in older adults. The pooled sensitivity from multiple studies appears to be 71% for TST versus 76% for IFGA. The specificity for the three tests is 66% and 97%, respectively. None of the tests appears to be useful for the following response to therapy with the specificity increase for the IFGA being most useful in those who have received Bacillus Calmette–Guérin (BCG) immunization.

The treatment of tuberculosis in older adults does not differ from that of young adults, but older adults are more susceptible to adverse effects and drug-durg interactions. Latent disease (TST positive only without clinical signs and symptoms), if not previously treated, should be treated with 9 to 12 months of INH, whereas patients with clinical illness should initially receive four drugs (usually INH, rifampin, pyrazinamide, and ethambutol), pending culture and susceptibility testing. The duration of therapy depends on many factors including the site of infection, susceptibility test results, and clinical response.

Fever of Unknown Origin

Fever of unknown origin (FUO), classically defined as temperature more than 101°F (38.3°C) for at least 3 weeks and undiagnosed after 1 week of medical evaluation, has different causes in older adults than in young adults (**Table 125-2**), and these differences influence the diagnostic work-up. The cause of FUO can be determined in virtually all cases and approximately one-third of cases will have treatable infections (eg, intra-abdominal abscess, bacterial endocarditis, tuberculosis, or occult osteomyelitis). In contrast to young adults, connective-tissue disease (CTD) is a more frequent cause of FUO in adults older than age 60 years. A compilation of several recently published series

suggests that 25% of all FUOs in the older adult patient are caused by CTDs. However, the CTD most likely to cause FUO in young adults, systemic lupus erythematosus (SLE), is absent in series of older adults and replaced by temporal arteritis (TA) and polyarteritis nodosa (PAN). Neoplastic disease accounts for another 20%, most often a result of hematopoietic malignancies (eg, lymphoma and leukemia). Importantly, however, multiple myeloma, a disease much more likely in older adults than in young adults, is almost never a cause of FUO. Drug fever is a common cause of FUO in older adults, and granulomatous angiitis, deep venous thrombosis with or without recurrent pulmonary emboli, and hyperthyroidism occasionally cause FUO in older adults.

TABLE 125-2 FEVER OF UNKNOWN ORIGIN (FUO) IN THE OLDER PATIENTS

MAJOR CAUSES	% OF CASES[a]
Infections	35
Intra-abdominal abscess	12
Tuberculosis	6
Infective endocarditis	10
Other	7
Collagen vascular disorders	28
Temporal arteritis/polymyalgia rheumatica	19
Polyarteritis nodosa	6
Other	3
Malignancy	19
Lymphoma/other hematologic	10
Solid tumors	9
Other (pulmonary emboli, drug fever)	10
No diagnosis	8

[a]Percentages represent pooled data from three studies of FUO in the older patient.

A reasonable approach to FUO in older adults can be inferred from the most likely causative entities. A thorough history and physical examination; basic laboratory evaluations of complete blood counts with differential, serum chemistries and hepatic enzymes, thyroid function studies, erythrocyte sedimentation rate (ESR), placement of a purified protein derivative (PPD) skin test, a chest x-ray, and initial blood and urine cultures should begin the search. If the diagnosis continues to be elusive and the ESR is elevated, temporal artery biopsy even in the absence of typical history or objective physical findings should be strongly considered. If the source remains obscure, or if there is a low suspicion for temporal arteritis, abdominal imaging with computed tomography (CT) or magnetic resonance imaging (MRI) should be performed. Further invasive diagnostic procedures, such as bone marrow and liver biopsy, or laparoscopy, should be considered in specific cases, but are low yield unless there are significant clues for involvement (eg, cytopenias or hepatomegaly).

IMMUNIZATION OF OLDER ADULTS

Immunization recommendations for older adults are constantly being updated. The latest consensus recommendations can be found online at the Centers for Disease Control and Prevention (CDC) website at www.cdc.gov/nip/publications/ACIP-list.htm.

Pneumococcal Vaccine

Although many studies of pneumococcal vaccine have failed to reach statistical significance indicating benefit, the confidence intervals of negative studies have not ruled out benefit, particularly when only invasive disease end points (ie, bacteremia and meningitis) were selected. Some of the lack of clear benefit may be a result of waning of efficacy

at the extremes of old age (> 85 years), unrecognized immune compromise in many older adults, and the fact that the pneumococcal vaccine is really 23 different vaccines (ie, 23 serotypes) and failure of any one serotype is considered a failure of the vaccine. Despite these ongoing scientific discourses, pneumococcal immunization for persons age 65 years and older has become standard practice, and is recommended for all seniors in this age group as well as for many patients under age 65 years with comorbid conditions. Two vaccines are available: a 23-valent polysaccharide vaccine (PPSV23) and a 13-valent pneumococcal conjugate vaccine (PCV13). In 2014, recommendations for pneumococcal vaccination in older adults from the ACIP were revised (**Figure 125-4**). Whereas previously only PPSV23 was recommended for healthy seniors, the ACIP now recommends that both PCV13 and PPSV23 be given sequentially—PCV13 given first followed by PPSV23 6 to 12 months later. For those who have already a first dose of PPSV23, repeat immunization with PCV13 is recommended, as long as approximately 1 year has passed since PPSV23 administration. Another dose of PPSV23 should follow 6 to 12 months later and approximately 5 years after the most recent dose of PPSV23—a minimum interval of 5 years between PPSV23 doses should be maintained. Studies of revaccination demonstrate that adverse events are uncommon and mild. Thus, when the pneumococcal immunization history is unknown, the vaccine should be administered.

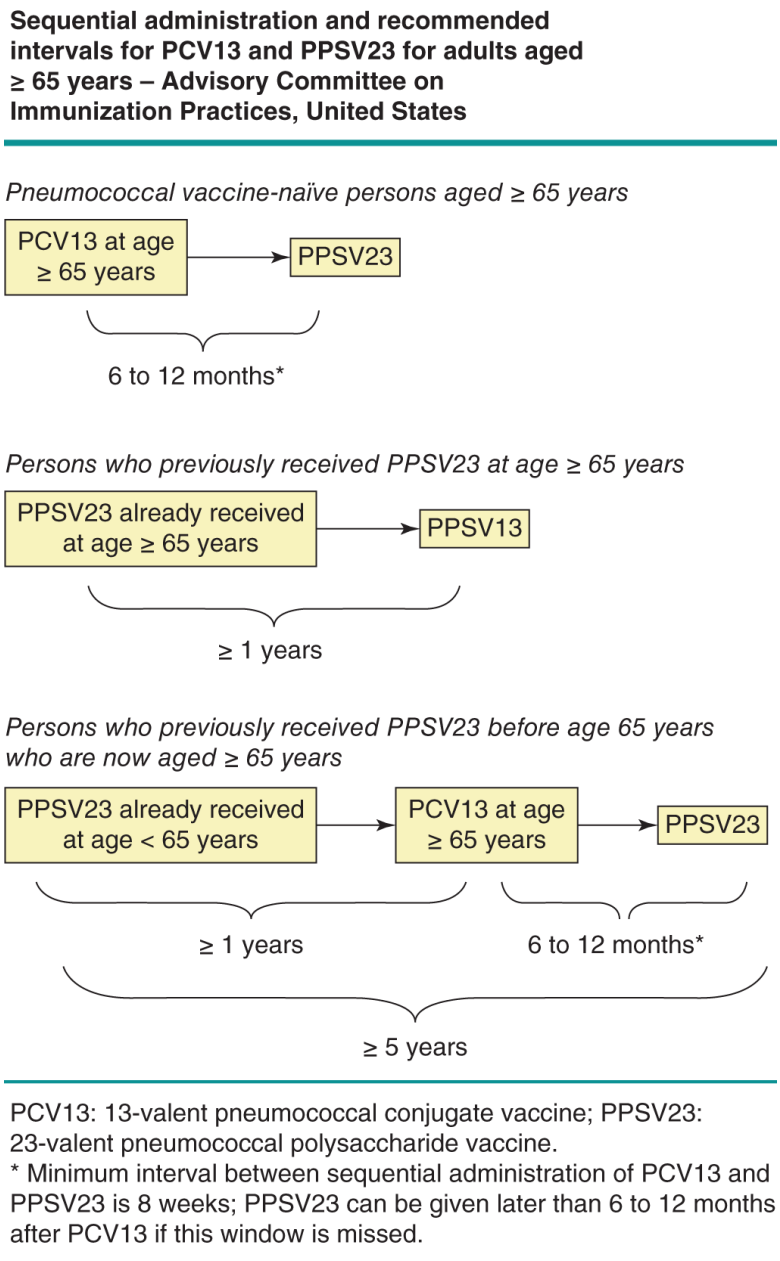


FIGURE 125-4. Algorithm for pneumococcal vaccine sequencing per current Advisory Committee on Immunization Practices recommendations. (Reproduced with permission from Tomczyk S, Bennett NM, Stoecker C, et al. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged ≥65 years: recommendations of the Advisory Committee on

An important demonstration of the power of vaccines can be found in the use of the pneumococcal conjugate vaccine in young children to secondarily reduce the risk to older adults through herd immunity. Widespread use of pneumococcal conjugate vaccine in children reduces carriage in children of vaccine serotypes and thereby exposure of older adults to these organisms. Since introduction of the conjugated-pneumococcal vaccine, given only to children in prior years, invasive pneumococcal disease due to vaccine serotypes has substantially declined in adults aged more than 65 years because of reduced transmission to seniors by children.

Implementing current pneumococcal vaccine recommendations remains the greatest obstacle to prevention of fatal *S pneumoniae* disease in older adults. According to CDC estimates, only 40% to 50% of eligible older adults receive pneumococcal vaccine. Many unvaccinated older adults diagnosed with invasive pneumococcal disease saw a medical practitioner within the prior 6 to 12 months. The CDC and its Advisory Committee on Immunization Practices (ACIP) have outlined several strategies for improving vaccine administration including (1) age-based: review immunizations in all persons at age 50 years, vaccinating those with qualifying comorbid conditions; (2) organizational (eg, standing orders): routine administration in older adults and at-risk patients in office, nursing home, and hospital settings by a blanket order for all patients (this is the single most effective strategy); (3) community-based: public health promotions focusing on underserved, often inner-city populations and community outreach programs (senior centers, civic organizations, etc); and (4) provider-based: physician-reminder systems (chart checklists, computer "flags," prehospital discharge, etc).

Influenza

The current influenza vaccine is a killed virus that is modestly immunogenic with estimated efficacy rates of 60% for illness and 50 to 60 percent for mortality. Annual influenza immunization reduces rates of respiratory illness, hospitalization, and mortality in the older adult population, and current ACIP recommendations are for all persons over the age of 6 months to be immunized just prior to influenza season each year. Medical personnel and caregivers for high-risk patients should be immunized to reduce transmission to those at increased risk for complications.

There are multiple formulations of influenza vaccine (see Chapter 130 detailed information regarding influenza and the influenza vaccine), but readers should be aware that high dose influenza vaccine was recently shown to be significantly more effective than standard dose vaccine in older adults for preventing influenza-like illness (relative efficacy, 24.2%; 95% confidence interval [CI], 9.7%–36.5%) and serious events possibly related to influenza reducing overall events by 17.7% (95% CI, 6.6%–27.4%), serious pneumonia by 39.8% (95% CI, 19.3%–55.1%), and all-cause hospitalizations by 6.9% (95% CI, 0.5%–12.8%).

Zoster

Zoster is much more common, and the devastating effects of postherpetic neuralgia much more frequent in older adults than in young adults (see Chapter 128). In 2006, the FDA approved a vaccine that reduces the risk of zoster by about 50% and the risk of clinically significant postherpetic neuralgia by about 60%. The FDA approved the vaccine for use in those age 50 and over without a prior history of zoster. The ACIP, however, recommends the vaccine for all adults age 60 and over due to the greater incidence of postzoster complications in those over 60, and regardless of prior zoster history citing the safety of the vaccine and the unreliability of a zoster history. Several newer and more effective zoster vaccine formulations are in development, but not yet approved at the time of this writing.

Other Vaccines

The older adult population is the group most at risk for tetanus in the United States, with older women being particularly susceptible because of a lower likelihood of receiving boosters associated with minor/moderate trauma. Subprotective levels of tetanus antibody (< 0.01 U/mL) have been found in 43% to 61% of men and in 48% to 71% of women older than age 50 years. A complete vaccine series is indicated for persons with an uncertain history of tetanus immunization and for those who have received fewer than three doses. Boosters should be given at 10-year intervals, or more frequently with high-risk injuries such as burns, puncture wounds, or extensive soft-tissue injury.

Similarly, pertussis is often propagated by adults with incomplete immune protection though diagnosed much more frequently in children. Pertussis protection wanes with age after vaccination in childhood and until recently, the pertussis component in tetanus/diphtheria boosters (Td) was not recommended for adults. However, this has changed and all adults, including those 65 years and over, should receive an acellular pertussis formulation (TdaP) at least once

as one of their scheduled tetanus boosters.

Hepatitis vaccines may also be considered for older adults under certain circumstances. Hepatitis B vaccine is indicated for all persons at risk for percutaneous or mucosal exposure to infected blood or body secretions. Older adults may have comorbidities (eg, renal failure) that place them at risk, but they also commonly volunteer at health care facilities and should be considered at risk if they engage in any patient contact. Hepatitis A vaccine is indicated in more limited circumstances such as chronic hepatitis C, travel, and for men who have sex with men. Unfortunately, the efficacy of hepatitis A and B vaccines in older adults is unknown, but may be much lower than in young adults. Age-related declines in antibody titers to levels below those considered protective begin as early as age 35 years and by age 70 less than half of adults administered the hepatitis B vaccine, and only two-thirds of those given the hepatitis A vaccine will produce serum antibodies to levels considered protective.

TRAVEL RECOMMENDATIONS FOR OLDER ADULTS

Older adults are among the most widely traveled members of our society. Many countries require cholera and yellow fever vaccines prior to entry. However, the yellow fever vaccine is a live-virus vaccine and data suggest that older adults are six times more likely than young adults to experience a serious adverse event. Furthermore, although still quite rare, reactions requiring hospitalization or resulting in death are 3.5- and 9-fold higher in adults age 65 to 74 and older than 75 years, respectively, when compared to young adults. Because the incidence of yellow fever in travelers is very low, particularly when travel is limited to urban centers, a compelling case to administer the vaccine should be elicited prior to administering yellow fever vaccine in older adults. Often the most compelling reason is that countries may deny access to those who cannot prove recent immunization, but a physician's letter of exemption is often acceptable.

Hepatitis A immunization is strongly encouraged for individuals anticipating prolonged travel (usually longer than 3 weeks) in areas where water and sanitary conditions are uncertain. Similarly, typhoid vaccine may be indicated for travel for extended periods of time to rural areas with poor sanitation. Other considerations include rabies (particularly when traveling to rural areas of southeast Asia, where stray dogs are commonly encountered), hepatitis B, Japanese encephalitis, and meningococcal vaccines (particularly for travel to sub-Saharan Africa).

Malaria chemoprophylaxis can be difficult in older adults. Side effects are more common for many agents (eg, mefloquine may produce dizziness, change in mental status, and bradycardia or prolonged QT intervals), and coadministration may be difficult in those taking cardiac medications or with significant heart disease. There are multiple alternative regimens for malaria prophylaxis but recognition of current resistance patterns are critical. Clinicians are directed to the CDC website (www.cdc.gov/travel) for the most up-to-date information.

Diarrhea occurs in 25% to 50% of travelers to developing countries. Primary treatment consists of fluid and electrolyte replacement, but antimicrobial therapy with a quinolone is indicated when diarrhea is accompanied by fever, bloody stools, or is prolonged. Antimotility agents are safe when coadministered with antibiotics.

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Chapter 126

Pneumonia

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Learning Objectives

- Identify the critical differences in presentation, etiology, and management of pneumonia in older adults versus young adults.
- Determine risk factors for infection due to antibiotic-resistant organisms.
- Integrate pneumonia prevention measures into routine care of older adults.

Key Clinical Points

1. **The diagnosis of pneumonia in older adults may be more complex due to the physiologic changes which occur with age and accumulation of comorbidity. Both promote subtle and/or atypical clinical presentations with fever, productive cough, and other classic signs being less common in older adults.**
2. **It is important to categorize older patients with pneumonia based on functional status, which predicts severity of illness and changes the likelihood of specific pathogens, including multidrug resistant organisms.**
3. **Known risk factors for infection due to resistant pathogens include functional impairment, recent hospitalization, previous antibiotic treatment, the presence of indwelling devices, and severe illness. It is important to know local resistance rates to adapt antibiotic treatment choices.**
4. **An interdisciplinary approach to management is critical with a goal of preserving and/or recovering function.**
5. **Prevention measures, which diminish the incidence and severity of pneumonia in older adults, should be employed; these include immunization versus influenza and pneumococcal disease and optimized management of comorbidities.**

INTRODUCTION

In developed countries, pneumonia is a major cause of mortality and the most frequent cause of infectious death, as well as the leading cause of severe sepsis and septic shock. The incidence of pneumonia increases with age and is associated with high morbidity, mortality, and health care costs. Pneumonia in older adults affects a heterogeneous spectrum of patients; the assessment of clinical, cognitive, functional, and social issues is key to achieving correct ascertainment of most likely pathogens and thus initial antibiotic management, clinical decision making, and subsequent care planning.

DEFINITION

Pneumonia can be defined from three different points of view: the clinician, researcher, and pathologist. Pneumonia is

clinically defined as the combination of symptoms (fever, chills, cough, pleuritic chest pain) and signs (hyper- or hypothermia, increased respiratory rate, dullness upon percussion, crackles, wheezing, pleural rub) associated with an opacity (or opacities) on a chest x-ray. In epidemiological or clinical trials, the presence of two or more of these symptoms, one or more of the physical signs, and a new opacity on the chest x-ray not due to other conditions (such as congestive heart failure, vasculitis, pulmonary infarction, drug reactions or atelectasis) is typically required for a diagnosis of pneumonia. From the pathologist point of view, pneumonia is an acute inflammatory process of the lung parenchyma in response to an infectious agent that affects the structures of the distal airways. The pneumonic process can predominantly develop in the alveoli (alveolar pneumonia), the interstitial space (interstitial pneumonia), or both (mixed pneumonia or diffuse alveolar damage). Alveolar pneumonia is predominantly exudative inflammation. Interstitial pneumonia is normally referred to as proliferative or productive, with inflammation in the stromal space and production of fibrous tissue, respectively. The histology of pneumonia depends on the state of progression, etiological agent, and host conditions, such as immune deficiency.

Pneumonia can also be defined in terms of the characteristics of the host, place of acquisition, and severity. As these circumstances are related to the etiology, we will address them in the etiology section.

EPIDEMIOLOGY

The epidemiology of pneumonia is difficult to determine and even more so in older population; data differ across continents, states, and hospitals. It is estimated that pneumonia has an incidence of 2 to 10 cases per 1000 inhabitants per year. The risk is higher in males, and in both sexes increases dramatically with age. According to European and American registries, the incidence of pneumonia is 25 to 40 cases per 1000 inhabitants per year with a mortality rate of 7% to 35% in patients older than 65. This increased vulnerability associated with age is presumed to be due to physiologic changes in the immune response that occur during aging and a higher burden of associated chronic diseases that are cumulative with age.

Pneumonia causes more than 4 million annual outpatient visits in the United States. There are more than 1 million hospitalizations due to pneumonia each year and 600,000 occur in adults over 65 years. Between 10% and 20% of hospitalized patients require admission to the intensive care unit (ICU). The mean length of stay in the hospital is 5 days, and the overall 30-day mortality rate is 23%. Mortality depends on the severity of the pneumonic episode, as well as age and associated risk factors. This ranges from 1% to 2% in young patients without comorbidity, to 25% to 50% in older adults with a severe comorbidity. The 30-day mortality rate is three times higher among those over 85 years old, compared to the group of patients aged 65 to 74 years. In the United States, more than 50,000 deaths per year are attributed to pneumonia and 85% occur in patients over 65 years old. The 30-day readmission rate is approximately 20%. Total cost of care for patients with pneumonia is over 17 billion dollars a year in the United States. The cost of treatment is mainly in seniors as total cost is primarily driven by hospitalization—responsible for 80% of economic resources devoted to this disease.

The presence of indwelling devices (nasogastric tube, urinary catheter), comorbidity (chronic obstructive pulmonary disease [COPD], diabetes, cancers, liver disease, heart disease, renal disease), tobacco use, malnutrition, splenectomy, and age extremes (older patients or children < 5 years) is associated with an increased risk of pneumonia. In older adults, other risk factors have also been described, such as swallowing disorders, use of sedatives and the presence of disability and baseline functional status. Vaccination and the use of angiotensin-converting enzyme inhibitors (which may protect by stimulating cough mechanisms) are protective factors.

Summarizing briefly, when compared to young adults, pneumonia in older adults is associated with increased risk of morbidity, mortality and functional impairment, with a higher percentage of admissions, more often to the ICU, a longer length of hospital stay, and increased use of health resources.

PATHOPHYSIOLOGY

Pneumonia is most frequently produced by the microaspiration of flora that colonizes the oropharynx and sinuses. A high percentage of silent oropharyngeal microaspiration has been demonstrated in older adults with community-acquired pneumonia (CAP). This microaspiration occurs in up to half of older patients hospitalized for pneumonia. A systematic review showed microaspiration risk factors include male gender, dementia, lung disease (COPD), and administration of certain drugs (antipsychotics, proton pump inhibitors); angiotensin-converting enzyme inhibitor use

was protective. Taylor et al. simplified aspiration risk factors as presence of chronic neurologic disorders, esophageal disease, decreased level of consciousness, and history of vomiting.

Other less common forms of infection are (1) direct inhalation of the infectious agent, as with the tubercle bacillus, influenza, and other respiratory viruses and fungi; (2) hematogenous spread is less common, except in the case of staphylococcal pneumonia after a viral influenza infection; (3) contiguous spread of infection from a subphrenic abscess, esophageal rupture, or other anatomic breach; and (4) iatrogenic contamination (eg, through an endotracheal tube).

The probability of infection depends on the aspiration volume, the virulence of the bacteria and the host's defense mechanisms. Several factors have been described as causing a higher risk of pneumonia in older adults, such as physiological changes associated with age, increase and severity of underlying diseases, and an increase in the number of hospitalizations. Age-associated changes in the respiratory system are a decrease in rib cage mobility and respiratory muscle strength, increases in "dead" space and residual volume, a decrease in the sensitivity of the respiratory centers to hypoxemia and hypercapnia and modifications in the airway receptors. Changes in the immune system associated with aging, or immunosenescence, consist of a progressive reduction in the immune response that affects all components of both the innate and adaptive immune system (see Chapter 3). The most significant changes are alterations in mucosal barriers, favoring invasion by microorganisms; reduction of native T cells and the differentiation and proliferation of T cells; alteration of T-cell subtypes (↓CD4+/↑CD8+); B-lymphocyte deficiency and impaired production of specific antibodies; cytokine imbalance (↓ IL-2, IL-1, and IFN and ↑ IL-4, IL-6, IL-8, IL-10, and TNF). These modifications involve a greater risk for infection and rapid progression of infection, a poor response to vaccines, a lesser subjective sensation of shortness of breath and increased susceptibility to bronchial and respiratory failure.

ETIOLOGY

A microbiologic diagnosis is generally difficult to establish, even when complex and invasive diagnostic methods are employed. The etiology is usually monomicrobial and, overall, the most common agent is *Streptococcus pneumoniae* (20%–65%) and should always be taken into account when choosing initial antibiotic coverage. With an increase in age, there is a reduction in the frequency of microorganisms conventionally known as *atypical* (*Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*), and there is a relative increase in the incidence of pneumonia due to *Haemophilus influenzae* and gram-negative bacilli (GNB). In a smaller percentage of cases, it appears that viruses are involved (12%–18%), and the strongest causative associations have been drawn with particularly influenza virus, respiratory syncytial virus (RSV), and human metapneumovirus (HPV); these three organisms may account for 8% to 14% of pneumonias in older adults—particularly during seasonal outbreaks.

Pneumonias are often classified by the etiologic agent (pneumococcal pneumonia, staphylococcal pneumonia, etc.), but this approach is not very practical from a clinical point of view, as the causative pathogen is generally unknown at the time of diagnosis and is often never established. Therefore, initial treatment must be established empirically and may not be modifiable based on a microbiologic diagnosis. In clinical practice, it is more useful to consider other aspects to select initial therapy such as the immunocompetence of the host, the place of acquisition, the presence of risk factors for resistant microorganisms and the severity of the acute episode.

Differentiation depending on the immunocompetence of the host is essential, as this frequently points to a totally different etiologic spectrum. The type of immunosuppression, intensity, and duration influence the etiology, management and prognosis. Neutropenia favors pneumonia due to *Staphylococcus aureus* (SA), enteric GNB such as *Pseudomonas aeruginosa* (Ps), and fungi (especially *Aspergillus* spp, *Mucor* or *Candida*). Cellular immunodeficiency, as in an advanced HIV infection, transplant patients, or those receiving immunosuppressive therapy, predisposes to bacterial pneumonia with a much larger spectrum than in immunocompetent patients, including Ps, SA, *L pneumophila*, tuberculosis, invasive fungal infections, *Pneumocystis jiroveci*, viral pneumonia due to *cytomegalovirus* or respiratory syncytial virus, helminths, or protozoa.

Depending on the place of acquisition, pneumonia is classified as either community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP). CAP is pneumonia that presents outside the hospital setting (and may be further differentiated into health care–associated pneumonia [HCAP]—see commentary below). HAP occurs after more than 48 hours of hospital stay or during 10 to 14 days after a hospital discharge. This differentiation is important due to the spectrum in microbial etiology. The microorganisms most frequently isolated in HAP are enteric GNB (*Klebsiella pneumoniae*, *Escherichia coli*, Ps, *Serratia marcescens*, and *Enterobacter* spp), followed by gram-positive cocci (SA).

In severe HAP, Ps and *Acinetobacter* spp are the most common among gram-negative bacteria. Viruses and fungi are isolated less frequently, but must be taken into account in immunocompromised patients. The etiology may vary depending on the period of time pneumonia develops. In early HAP (within 5 days), the most common etiology is enteric GNB (*E coli, K pneumoniae*, *Proteus,* and *Serratia*), *H influenzae,* SA, and *S pneumoniae*. In late HAP (more than 5 days), A*cinetobacter* spp, Ps, and methicillin-resistant SA (MRSA) increase in frequency. There are additional, specific risk factors associated with certain microorganisms that can guide the clinician toward a specific diagnosis in HAP. These risk factors can be useful when deciding the antibiotic treatment to establish (**Table 126-1**).

TABLE 126-1 SPECIFIC RISK FACTORS FOR HOSPITAL-ACQUIRED PNEUMONIA

MICROORGANISM	ASSOCIATED RISK FACTORS
Multidrug-resistant pathogen	• Previous antibiotic treatment • Hospitalization > 5 d in the previous 90 d • Increased resistance rate in the hospital • Residence in a nursing home • Home intravenous treatment (including antibiotics) • Chronic dialysis • Active wound care • Contact with a patient infected by a multidrug-resistant pathogen • Immunosuppressive disease and/or immunosuppressive therapy
Bacilli gram negative	• Underlying disease • Functional impairment
Pseudomonas, Multidrug-resistant bacilli	• Recent intensive care unit admission • Previous antibiotic treatment • Chronic corticosteroid therapy • Structural lung disease • Late-onset nosocomial pneumonia
Legionella spp	• Chronic corticosteroid therapy • Hematologic cancer • Contact with contaminated water • Previous cases of nosocomial pneumonia caused by *Legionella* spp
Staphylococcus aureus	• Recent intensive care unit admission • Previous influenza • Colonization or prevalence of methicillin-resistant strains • Traumatic brain injury • Coma • Diabetes mellitus • Renal failure
Aspergillus spp	• Chronic corticosteroid therapy
Anaerobic organisms	• Poor oral hygiene • Decreased level of consciousness • Manipulation of the airway • Recent abdominal surgery

Health care–associated pneumonia (HCAP) can be defined as the one that occurs in patients who meet one of the following criteria: (1) hospitalization for 2 days or more in the preceding 90 days; (2) residence in a nursing home or

extended care facility; (3) home infusion therapy (including antibiotics); (4) chronic dialysis within 30 days; (5) home wound care; or (6) family member with multidrug-resistant pathogen. However, this concept is currently under some scrutiny. Evidence provided by two large retrospective observational studies that included patients from the United States showed that those who met one of these criteria had a higher prevalence of pneumonia caused by MRSA or resistant GNB, such as Ps. These results have not been confirmed in studies carried out in European countries. Further, it has been documented that up to 50% of patients with pneumonia attending the emergency department may met criteria for HCAP and only 10% to 30% of these patients have infections caused by resistant bacteria. Therefore, the use of such criteria with high sensitivity and limited specificity may lead to excessive utilization of broad spectrum antimicrobials, unnecessary costs and an increased prevalence of resistant bacteria. Finally, the concept of HCAP does not take into account the severity of the disease, and it is well known that resistant bacteria appear most frequently in patients with severe disease. In conclusion, though widely employed and specifically identified in many guidelines, the HCAP concept lacks the necessary precision to identify a profile of patients at risk of infection by resistant organisms, and therefore an etiologic approach is recommended by many authors based on individual risk factors for infection caused by resistant organisms and severity of disease.

The etiology of CAP is influenced by comorbidities, basal functional status, severity of the acute episode, antimicrobial treatment received and contact with the hospital setting or place of residence. Therefore, an etiologic approach can also be recommended according to risk factors for resistant microorganisms and severity of disease. Several scales have been developed to rule out infection by multidrug-resistant microorganisms (MDRO). Shorr et al. proposed a scale that includes four items: recent hospitalization (4 points), admission from long-term care (3 points), hemodialysis (2 points), and critical illness (1 point). When the total score is zero, there is a high negative predictive value (84%) for MDRO. Aliberti et al. documented that independent MDRO risk factors were living in a nursing home and previous hospitalization in the last 90 days. Another study found that patients with clinical signs of severe pneumonia and presence of two risk factors (immunosuppression, hospitalization in the previous 90 days, severe dependence quantified with a Barthel index less than 50, and taking antibiotics within the previous 6 months) were associated with a higher frequency of MDRO (2% vs 27%).

It has been published that the probability of Ps or MRSA infection is increased in severe CAP, defined as a pneumonia that requires admission to an ICU or has a risk class V according to the Pneumonia Severity Index (PSI). If we consider the approach proposed by Ewig in Europe and by Brito and Niederman in the United States, when making an empirical treatment decision, the key would be the initial clinical severity status and the prior functional status. Thus, when there are at least two factors for multidrug resistance (severe pneumonia, hospitalization in the previous 90 days, residence in a nursing home, severe basal dependence for daily living activities, immunosuppression, or taking antibiotics during the previous 6 months), empiric coverage of MDRO is warranted.

Risk Factors for Uncommon Microorganisms

Colonization of the oropharynx may favor pneumonia due to unusual microorganisms through microaspiration. This is more common in older adults compared to younger patients. Risk factors for less common pathogens are shown in **Table 126-2**.

TABLE 126-2 RISK FACTORS FOR INFECTION BY LESS COMMON PATHOGENS

MICROORGANISM	RISK FACTORS
Pseudomonas aeruginosa	• Severe COPD with $FEV_1 < 35\%$ • COPD > 4 cycles of antibiotic treatment in the last year • Bronchiectasis with previous colonization • Nasogastric enteral feeding • Intensive care unit admission
Enterobacteriaceae and/or anaerobic organisms	• Functional impairment • Risk factors for aspiration • Dysphagia • Gastroesophageal reflux • History of vomiting

	• Cerebrovascular diseases • Dementia • Periodontal disease • Poor oral hygiene
Extended spectrum β-lactamase producing *Enterobacteriaceae*	• Previous antibiotic • Hemodialysis • Long-term indwelling urinary catheter • Residence in long stay center • Recent hospitalization • Diabetes mellitus • Recurrent urinary tract infections
S aureus resistant to methicillin	• Undergoing care for bedsores or wounds • Clinically serious illness + recent hospitalization + prior intravenous antibiotics + institutionalization • Previous colonization • Superinfection of pneumonia virus influenza during influenza epidemic

Bacterial colonization depends on multiple factors such as age, comorbidity, basal functional status, bacterial load, antimicrobial use, presence of devices, indwelling devices and prior contact with health centers or nursing homes. Etiologic studies show an increased incidence of pneumonia due to *Enterobacteriaceae* in relation to age. El-Solh et al. identified *Enterobacteriaceae* and anaerobes as the most frequently isolated pathogens in institutionalized patients with aspiration pneumonia with the basal functional status as main determining factor. This study concluded that functional impairment is associated with more frequent colonization by GNB, especially *Enterobacteriaceae*. Another important aspect to consider in suspected infection by *Enterobacteriaceae*, is whether they may produce extended-spectrum β-lactamase (ESBL). A recent study with the aim to determine the sensitivity of strains isolated from patients hospitalized with pneumonia, in both the United States and Europe, showed that 20% and 35% of isolated *Klebsiella* spp (the main *Enterobacteriaceae* involved in pneumonia) were ESBL-producing in each geographical area.

Despite recognized classical risk factors for anaerobic infection, the role of anaerobes in pneumonia in seniors is not well known because anaerobic cultures or other detection methods are rarely used in studies.

The frequency of Ps in older adults is low (1%–2%). Chronic respiratory disease and a nasogastric tube use stand out as the main risk factors. This microorganism should be suspected in severe COPD (FEV_1 < 35% predicted), multiple previous antibiotic treatments, admission to ICU and/or presence of bronchiectasis and prior colonization with this organism.

Finally, it is known that colonization by SA is more frequent when there has been a prior episode of influenza. The probability of MRSA is more frequent in patients admitted in the ICU, with a history of intravenous antibiotic treatment at home or undergoing ulcer care. Shorr et al. proposed a scale to predict MRSA infections with low risk if the score is less than or equal to 1 (2 points: recent hospitalization or ICU admission; 1 point for each of the following: < 30 or > 79 years of age, prior exposure to intravenous antibiotics, dementia, cerebrovascular disease, being a female with diabetes, coming from a residential care home). MRSA infection should be suspected with the presence of pneumonia with bilateral radiological infiltrates with cavitation or in the presence of risk factors, and primarily in patients with severe disease. If the older patient has been living in a nursing home during the previous year, it is important to know the prevalence of MRSA in that institution.

Viral etiologies are increasingly recognized with wider utilization of PCR-based respiratory virus panels. In particular, influenza and RSV cause substantial morbidity and mortality in older adults. In the context of outbreaks in institutionalized patients, pneumonia can be caused either by primary viral agents or by a bacterial superinfection from *S pneumoniae*, SA, and *H influenzae*. Other respiratory viruses, such as parainfluenza, metapneumovirus, adenovirus, rhinovirus, and coronavirus usually cause less severe respiratory infections in immunocompetent adults.

Finally, there are a number of epidemiologic factors that predispose patients to CAP caused by certain specific agents (**Table 126-3**). **Figure 126-1** depicts an etiologic approach for older patients based on severity of illness, risk factors, and basal functional status to help guide the most appropriate empiric selection of antibiotic coverage.

TABLE 126-3 CLINICAL AND EPIDEMIOLOGIC CONDITIONS RELATED TO SPECIFIC PATHOGENS

CLINICAL AND EPIDEMIOLOGIC CONDITION	ETIOLOGY
COPD, tobacco addiction	*S pneumoniae, H influenzae, C pneumoniae, L pneumophila*
Bronchiectasis, cystic fibrosis	*P aeruginosa, S aureus*
Alcohol intoxication	*S pneumoniae, K pneumoniae, anaerobes, S aureus*
Prison inmates	*S pneumoniae, M tuberculosis*
Contact with birds, fowl, and farm animals	*Chlamydophila psittaci*
Contact with rabbits	*Coxiella burnetii*
Contact with bats or residence in an endemic area	*Histoplasma capsulatum*
Flu epidemic	Virus *influenza, S pneumoniae, H influenzae, S aureus*
Septic mouth, aspiration	Polymicrobial, anaerobes
Advanced HIV infection	*S pneumoniae, H influenzae, P jiroveci, M tuberculosis*
Intravenous drug users	*S aureus*, anaerobes
Steroid treatment	*S aureus, Aspergillus* spp, *L pneumophila*
Comorbidities (diabetes, liver disease, renal failure)	*S pneumoniae, H influenzae*, gram-negative bacilli
Recent antibiotic use	*S pneumoniae* resistant, *P aeruginosa*
Exposure to air conditioning, cooling towers	*L pneumophila*
Travel to Southeast Asia	*B pseudomallei*, avian influenza virus

COPD, chronic obstructive pulmonary disease.

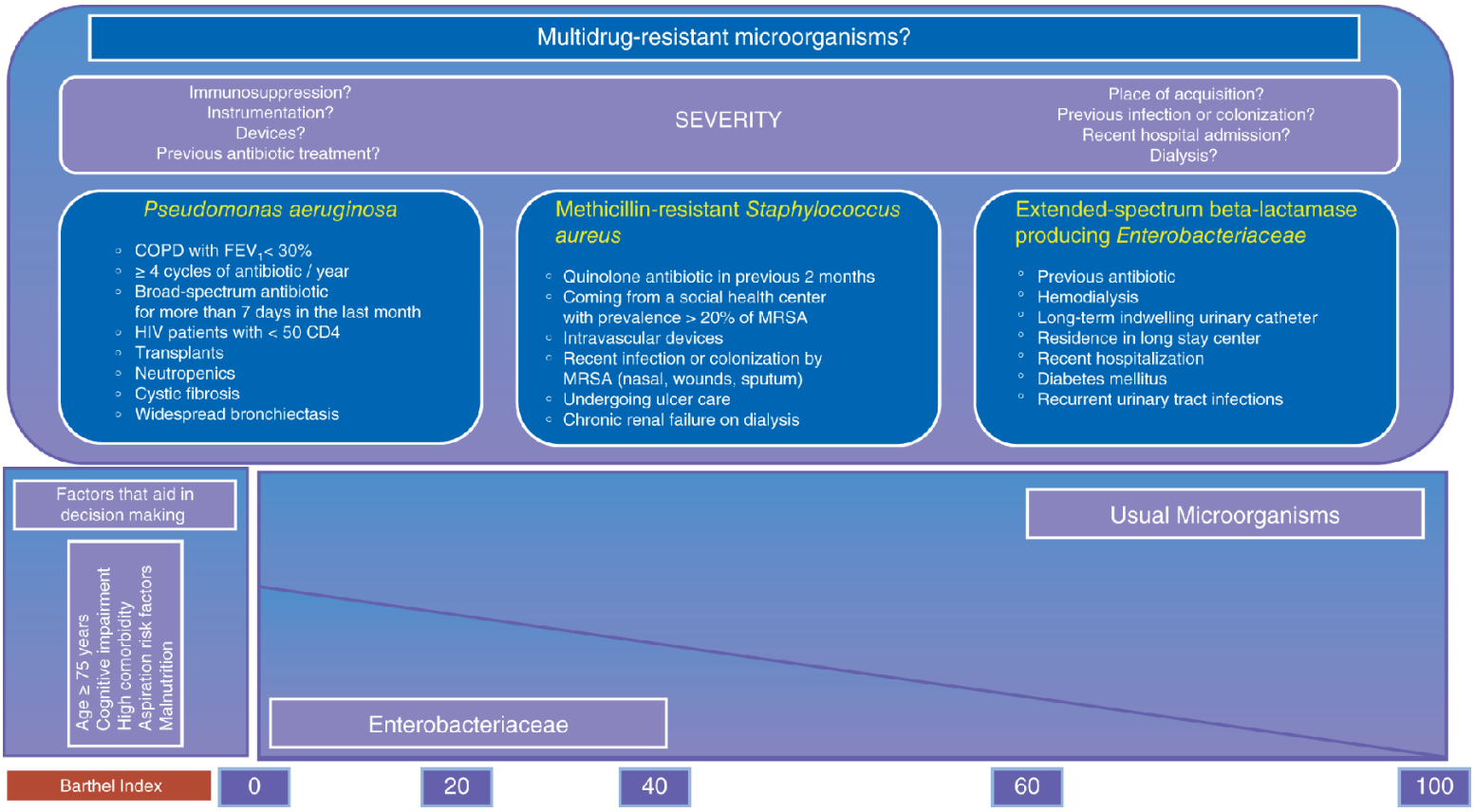


FIGURE 126-1. The Pneumonia Severity Index (PSI) is used to calculate the need for admission and probability of death due to pneumonia based on specific patient characteristics, physical exam findings and laboratory findings at presentation. Age is a major driver of the PSI.

PRESENTATION

Clinical diagnosis of pneumonia in older adults is complex and may be subtle. Symptoms and signs of infection in the adults differ from younger patients. Asymptomatic or atypical clinical presentations such as exacerbation of chronic diseases are more frequent presenting manifestations in older adults. Absence of fever, hypoxemia, or respiratory symptoms do not rule out a pneumonia diagnosis. The most common atypical manifestations are altered mental status or behavior, acute functional impairment, falls, dizziness, loss of consciousness, generalized weakness, anorexia, dehydration, or incontinence. Such presenting symptoms are most frequently associated with the presence of cognitive impairment.

EVALUATION

Initial Evaluation

At the time of initial assessment of the older patient with pneumonia stratification by severity of illness should be performed based on the level of consciousness, respiratory, and hemodynamic parameters, taking into account medical, functional, and/or cognitive situations. Nonspecific complaints or atypical clinical presentation are associated with a lower level of acuity and therefore a delay in the initial assessment and early antibiotic administration in the emergency department. Older adults less frequently have fever, tachycardia, and/or elevation of leukocytes compared with younger patients. These changes may hinder an appropriate diagnosis of sepsis and impact adequate early therapeutic treatment. A recent study has shown that the undisturbed vital signs such as normal heart rate and temperature in older patients with suspected infection delays antibiotic administration and increases the likelihood of hospitalization with the need for intensive care. Therefore, respiratory rate and altered level of consciousness may be the only initial signs of severity in older patients with suspected infection and should trigger evaluation for pneumonia.

Diagnostic Evaluation

After the initial stratification of severity status, tests should be performed to diagnose pneumonia and its etiology. The diagnosis of pneumonia based on physical examination has poor sensitivity and specificity; therefore, the diagnosis should be confirmed by performing a chest x-ray.

The diagnostic tests performed in older adults should not differ from those in younger patients. In daily clinical practice, the chest x-ray is usually enough to rule in the diagnosis of pneumonia in most older patients. However, radiologic signs may not be obvious in up to 30% of the cases and this is more frequent in patients with dehydration and neutropenia. Therefore, in patients with suspected pneumonia and first chest x-ray without pathologic signs, a second study is recommended after 24 to 48 hours. Computerized tomography (CT) is very accurate for the diagnosis of pneumonia although it is usually reserved either for patients with atypical chest x-ray patterns or as a second step in those cases without response to initial treatment. The role of other imaging tests is evolving. Bedside ultrasound can support suspicion of pneumonia and allows evaluation of suspected pleural effusion as well as guidance for a possible thoracentesis. Other procedures, such as bronchoscopy, CT-guided biopsy, biopsy by thoracotomy, or videothoracoscopy, do not differ from indications in younger adults, except for the logical consideration of the patient's life expectancy, desires, and the risks and contraindications related to comorbidities.

Regarding laboratory tests, C-reactive protein and white blood cell counts are not helpful for assessing the severity of illness in older patients with pneumonia. The inflammatory response may be impaired as a consequence of immune senescence and thus may underestimate the severity of the process. Procalcitonin (PCT) has not shown good sensitivity in older populations for the diagnosis of acute bacterial infection, although it may be useful for severity assessment.

Serum lactate value greater than or equal to 2 mmol/L is a predictor of 30-day mortality in older adults. MR-proADM is a peptide produced by the endothelium, derived from proadrenomedullin, which is released in a state of physiological stress. It has been evaluated in observational studies and seems to perform well as a prognostic marker in respiratory infection.

A microbiologic diagnosis should be sought in older adults with pneumonia via blood cultures, Gram stain and culture of respiratory samples and the detection of bacterial antigens in urine (pneumococcal and *Legionella* immunochromatographic test). European guidelines recommend the performance of blood cultures in all hospitalized patients. United States guidelines reserve blood cultures for the most severe patients, such as those with cavitary infiltrates, leukopenia, alcoholism, severe liver disease, asplenia, positive antigenuria test for pneumococcus, or pleural

effusion. Blood cultures have low clinical impact when performed in unselected patients with CAP. However, given the high frequency of atypical clinical presentation in older patients, blood cultures may contribute both to the confirmation of diagnostic suspicions, when potential pulmonary pathogens are isolated, and to the reconsideration of the patient's primary causative agent and therefore it is the opinion of this author that blood cultures should be obtained in all older adults with pneumonia. Adequate sputum cultures can be obtained in about a third of patients, even higher when performed by invasive methods. The importance of Gram stain and sputum culture is reflected in its influence in the modification of the initial antibiotic treatment. The presence of SA, *Klebsiella pneumoniae*, or Ps in Gram stain of the purulent sputum requires consideration when choosing the antibiotic treatment. Likewise, absence of organisms with the morphology of these agents in high-quality respiratory samples has a high negative predictive value, allowing the narrowing of antimicrobial therapy. In older patients with significant functional impairment it is often difficult to obtain quality sputum specimens, and an increase in frequency of oropharyngeal colonization by GNB, SA, and MDRO suggests there may be lower specificity of Gram stain and culture of respiratory specimens from such patients.

Detecting pneumococcal and *L pneumophila* bacterial antigens in urine by immunochromatographic techniques has been an important advance in the identification of these two microorganisms. The sensitivity of pneumococcal antigen is estimated at over 60%, with specificity greater than 90% in adult patients, including patients with chronic bronchitis and pneumococcal colonization. It also has diagnostic value in the pleural fluid and test performance is not altered by prior antibiotic treatment or pneumococcal vaccination. However, the test remains positive until 3 months after the resolution of pneumonia, which limits the utility in patients with recurrences or in the assessment of treatment response. The urinary antigen test for legionellosis only detects *L pneumophila* serogroup I, with a sensitivity greater than 90%. This is recommended in all patients with suspected clinical or epidemiologic concern for legionellosis or in the case of severe pneumonia without another clear etiology.

Test for viral detection in nasopharyngeal aspirates should be used in epidemiologic studies and in those patients diagnosed with influenza who are candidates for antiviral treatment. The best use of these tests has not been defined as many viruses that can cause illness are not represented on widely used viral panels (decreasing sensitivity) and a positive test may not provide sufficient evidence of an alternate diagnosis to allow the clinician to stop antibacterial therapy (limited specificity).

Risk Stratification

The assessment of severity status is essential to designing an individualized care plan for older patients with pneumonia; age, comorbidity, microbial etiology, and early administration of appropriate antibiotic therapy all influence mortality. Previous studies have showed that older pneumonia patients with moderate-severe basal functional dependence have an increased risk of mortality in the short- and long-term compared to those who are independent.

Several short-term prognostic scales have been published, helpful for assessing severity status, and therefore the decision making for hospital admission. The PSI (**Figure 126-2**) and CURB-65 (**Table 126-4**) are risk stratification scales with similar predictive power for 30-day mortality although they have certain limitations. The PSI gives excessive weight to age and relative to hypoxemia and it does not take into account other factors associated with adverse outcomes such as COPD, functional status, social factors, proper oral intake of the patient or the capacity for good adherence. CURB-65 has the limitation of not including the evaluation of hypoxemia and functional status. In fact, studies have suggested oxygenation as the best prognostic indicator in older adults. Neither of these two scales is very useful in assessing the need for ICU admission.

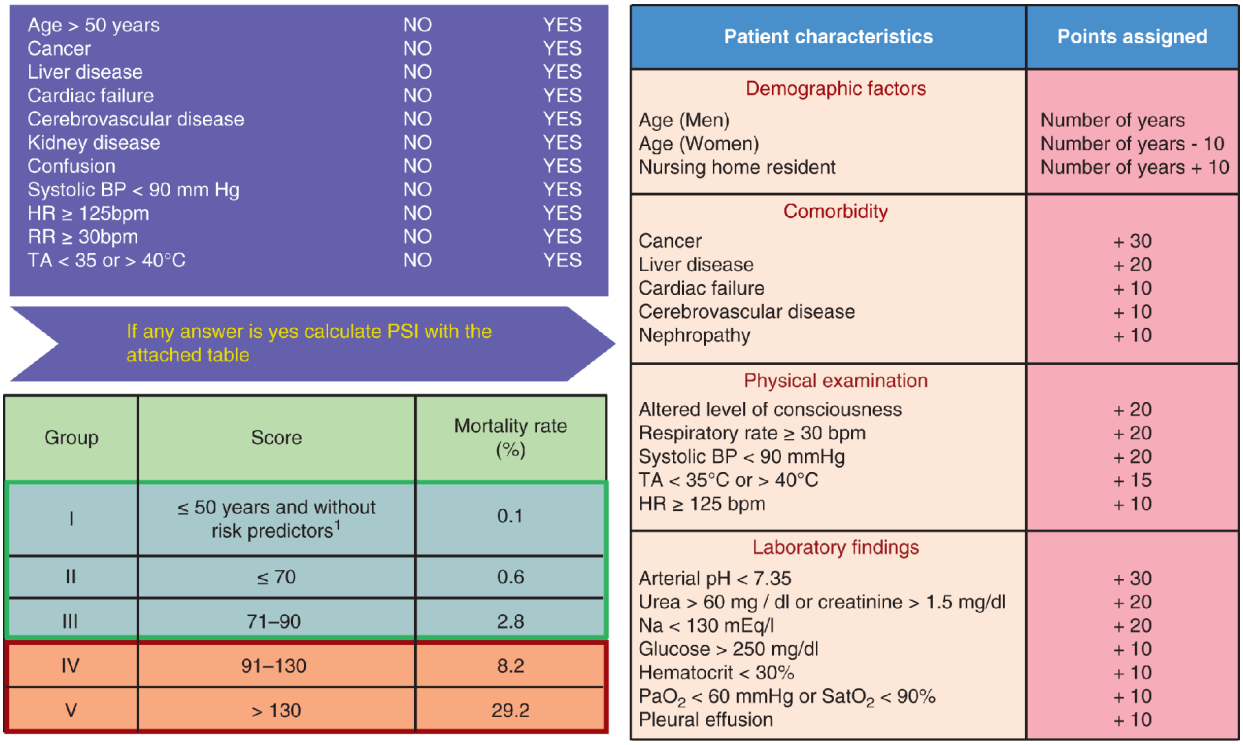


FIGURE 126-2. Pneumonia severity should be assessed according to the clinical situation, biomarkers, and risk stratification scales. In severe cases, the possibility of infection by resistant microorganisms is increased; therefore, expanded antimicrobial therapy should be considered, especially when a risk factor is present. Infection by resistant pathogens should be considered, and likelihood of infection by *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, or extended-spectrum β-lactamase-producing *Enterobacteriaceae* specifically assessed to choose antibiotic coverage. Colonization of the oropharynx by *Enterobacteriaceae* is more likely in those with severe functional dependence.

TABLE 126-4 ■ PROGNOSTIC SCALES: CURB-65

A Point is Applied for Each Item Present	
C	Confusion
U	Urea plasmatic > 44 mg/dL (BUN > 19.6 mg/dL)
R	Respiratory rate ≥ 30 bpm
B	Systolic BP < 90 mm Hg or diastolic BP ≤ 60 mm Hg
65	Age ≥ 65 years old
Score	Stratification
0 or 1	Low mortality (0.7%–2.1%). Possible outpatient treatment
2	Intermediate mortality (9.2%). Consider hospital treatment
3	High mortality (14.5%). Hospital admission.
4–5	Mortality of > 40%. Admission. Consider intensive care unit

In clinical decision making related to ICU admission, other scales have been developed, such as Severity of Community Acquired Pneumonia (SCAP), SMART-COP, or American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) (**Tables 126-5** to **126-7**). SCAP identifies patients who require monitoring and more aggressive treatment and it is very useful for predicting hospital mortality and/or the need for mechanical ventilation or inotropic support. SMART-COP is useful to decide on a more aggressive treatment, without necessarily predicting ICU admission.

TABLE 126-5 ■ PROGNOSTIC SCALES: SEVERITY COMMUNITY ACQUIRED PNEUMONIA (SCAP)

MAJOR CRITERIA	MINOR CRITERIA
pH < 7.30 (13 points)	C: confusion (5 points) U: BUN > 30 mg/dL (5 points)
Systolic blood pressure < 90 mm Hg (11 points)	R: breaths per minute > 30 (9 points) X: multilobar/bilateral chest x-ray (5 points) O: PaO_2 < 54 mm Hg or PaO_2/FiO_2 < 250 mm Hg (6 points) 80: Age ≥ 80 years (5 points)

Low risk: 0–1 (< 10 points); intermediate risk: 2 (10–19 points); high risk: 3–4 (> 20 points).

TABLE 126-6 PROGNOSTIC SCALES: SMART-COP

S Systolic BP < 90 mm Hg (2 points)	**C** Confusion (1 point)
M Multilobar affectation (1 point)	**O** Oxygenation age-adjusted[b] (2 points)
A Albumin < 3.5 g/dL (1 point)	**P** pH < 7.35 (2 points)
R RR age-adjusted[a] (1 point)	
T Tachycardia ≥ 125 (1 point)	

[a] **< 50 years: ≥ 25/min; ≥ 50 years: ≥ 30/min.**
[b] **< 50 years: PaO_2 < 70 mm Hg or oxygen saturation ≤ 93% or PaO_2/FiO_2 < 333;**
≥ 50 years: PaO_2 < 60 mm Hg or oxygen saturation ≤ 90% or PaO_2/FiO_2 < 250.
0-2 points: low risk for vasopressor support or intensive respiratory support.
3-4 points: moderate risk for vasopressor support or intensive respiratory support.
5-6 points: high risk for vasopressor support or intensive respiratory support.
≥ 7 points: very high risk for vasopressor support or intensive respiratory support.

TABLE 126-7 PROGNOSTIC SCALES: ATS/IDSA

Major Criteria
Need for mechanical ventilation
Septic shock
Minor Criteria
Systolic blood pressure < 90 mm Hg requiring fluid
Multilobar involvement (≥ 2 lobes) or progression
Respiratory rate ≥ 30 bpm
Confusion
Urea ≥ 45 mg/dL
$PaO_2/FiO_2 \leq 250$
Leukopenia < $4000/mm^3$
Thrombocytopenia < $100{,}000/mm^3$
Hypothermia (temperature < 97°F or 36°C)
Metabolic acidosis
Lactate > 3 mmol/L or > 27 mg/dL
Hyponatremia
Hyperglycemia in nondiabetic
Alcohol intake

ICU admission if one major or three minor criteria are met.

The detection of frailty and vulnerability by screening scales, such as Identification Senior at Risk (ISAR) or Triage Risk Screening Tool (TRST), or comprehensive geriatric assessment, is particularly valuable to predict short-

term adverse outcomes and decision making about diagnostic and therapeutic procedures and the most appropriate site of care.

There are other independent and dynamic factors that influence prognosis regarding the infection itself and the systemic inflammatory response. Therefore, the probability of bacteremia, the presence of sepsis, severe sepsis or septic shock, and the inclusion of biomarkers should be taken into account in the decision-making process. As discussed previously, sepsis may be underdiagnosed in older adults due to physiological changes with aging.

Site of Care

Clinical guidelines recommend the use of prognostic scales, mainly PSI and CURB-65, for admission decision making. Patients with PSI greater than or equal to III or CURB-65 greater than or equal to 2 meet criteria for hospital admission. The SCAP, SMART-COP, or ATS/IDSA scales can be helpful when deciding on ICU admission. In addition, other issues should be considered regarding site of care such as functional, cognitive, and social factors that may affect the final location.

Alternatives to Conventional Hospitalization

There are different units that can treat patients with CAP. A short stay unit (SSU) is a safe and cost-effective alternative to conventional hospitalization for patients with CURB-65 of 2 or PSI of III. In those seniors living in a nursing home, site of care depends on the characteristics of the center, but if appropriate care can be rendered without moving the patient, it is preferable. Several studies have shown the same mortality, adjusted by functional status, among patients treated in the hospital or in nursing home. Transfer to hospital should be under the following circumstances: worsening of underlying disease, immunosuppression, clinical signs of severe pneumonia, oral intolerance, difficulties in completing the treatment in the facility, complications evident on radiography, or individual assessment (eg, need for specific isolation or high risk of morbidity and mortality without advanced directive).

Considerations for Discharge

Clinical stabilization is considered present when vital signs have normalized, mental status is baseline, and oxygen requirements have improved. The criteria that should be met to discharge the patient include: heart rate less than 100 bpm, respiratory rate less tham 24 breath per minute, axillary temperature less than 37.2°C (< 98.96°F), systolic blood pressure greater than 90 mm Hg, oxygen saturation greater than 90%, good awareness and tolerance of oral therapy. Most patients with pneumonia usually stabilize between the third and fourth hospital day. However, this period of time may increase up to 7 days in the frail older adults.

Specific Recommendations for Antibiotic Selection in Older Adults

Table 126-8 outlines empirical treatment recommendations according to site of care, functional status and severity. **Table 126-9** reflects the treatment of choice depending on the suspected etiology. Regarding HAP, treatment depends on start time (early or late) and the patient's individual risk factors (**Table 126-10**). **Table 126-11** shows the dosing information for the main antimicrobials used to treat pneumonia.

TABLE 126-8 TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA IN THE ELDERLY

	SCENARIO	TREATMENT
Patient without frailty	Outpatient treatment	Amoxicillin/clavulanate or second-generation cephalosporin + Azithromycin or fluoroquinolone
	Inpatient treatment	Amoxicillin/clavulanate or ceftriaxone or cefotaxime or ceftaroline + Azithromycin or fluoroquinolone
	Severe pneumonia	Ceftriaxone or cefotaxime or ceftaroline or ertapenem + Azithromycin or fluoroquinolone ± Linezolid[a] or vancomycin[a] ± Antipseudomonal β-lactam[b] ± Oseltamivir[c]
Patient with frailty	Prefrailty[d]	Amoxicillin/clavulanate or ceftriaxone or cefotaxime or ceftaroline + Azithromycin or fluoroquinolone
	Frail	Ertapenem or Amoxicillin/clavulanate[e] or Ceftriaxone + clindamycin[e]

[a] If there are risk factors for Staphylococcus aureus.
[b] If there are risk factors for infection by Pseudomonas aeruginosa.
[c] Assess if influenza is epidemic in the community.
[d] Be particularly cautious rating risk factors of microaspiration and multiresistant bacteria.
[e] Consider local resistance rates of Enterobacteriaceae to amoxicillin-clavulanic and ceftriaxone; and anaerobes to clindamycin.

TABLE 126-9 DIRECTED ANTIBIOTIC TREATMENT IN PNEUMONIA FOR SPECIFIC PATHOGENS

MICROORGANISMS	TREATMENT
Enterobacteriaceae/anaerobes	Ertapenem or Amoxicillin/clavulanate[a] or Ceftriaxone + clindamycin[a]
Extended-spectrum β-lactamase producing *Enterobacteriaceae*	Ertapenem
Staphylococcus aureus methicillin resistant	Add linezolid or vancomycin to chosen treatment
Pseudomonas aeruginosa	Piperacillin/tazobactam or Imipenem or meropenem or Cefepime + Levofloxacin or ciprofloxacin or Amikacin or tobramycin

[a]

Consider local resistance rate of Enterobacteriaceae to amoxicillin-clavulanic and ceftriaxone and anaerobes to clindamycin.

TABLE 126-10 EMPIRICAL ANTIBIOTIC TREATMENT FOR HOSPITAL-ACQUIRED PNEUMONIA (HAP)

Group I Early HAP (< 5 d) without risk factors	Ceftriaxone or cefotaxime or ceftaroline or Fluoroquinolone
Group II Late HAP (≥ 5 d) or with risk factors	Ceftazidime or cefepime or imipenem or meropenem or piperacillin/tazobactam + Ciprofloxacin or levofloxacin or amikacin or tobramycin ± Linezolid or vancomycin

TABLE 126-11 DOSAGE OF THE MAIN ANTIBIOTICS USED IN PNEUMONIA

ANTIBIOTIC	DOSE	DOSE IN RENAL INSUFFICIENCY (mL/min)	
Amikacin	15–20 mg/kg/24 h	60–80: 9–12 mg/kg/24 h 30–40: 4.5–6 mg/kg/24 h 10–20: 1.5–3 mg/kg/24 h	40–60: 6–9 mg/kg/24 h 20–30: 3–4.5 mg/kg/24 h < 10: 1–1.5 mg/kg/24 h
Amoxicillin-clavulanate IV	2 g/6–8 h	30–50: 1 g/8 h < 10: 500 mg/24 h	10–30: 500 mg/12 h
Amoxicillin-clavulanate PO	2/0, 125 g/12 h	30–50: 500 mg/8 h < 10: 500 mg/24 h	10–30: 500 mg/12 h
Azithromycin IV/PO	500 mg/24 h	No adjustment required	
Cefditoren PO	400 mg/12 h	30–50: 200 mg/12 h	< 30: 200 mg/24 h
Cefepime IV	2 g/8 h	30–50: 2 g/12 h < 10: 1 g/24 h	10–30: 2 g/24 h
Ceftriaxone IV	1–2 g/12–24 h	> 10: not required	< 10: máximo 2 g/24 h
Ciprofloxacin IV	400 mg/12 h	30–50: not required	< 30: 200 mg/12 h
Ciprofloxacin PO	500 mg/12 h	30–50: not required	< 30: 250 mg/12 h
Ertapenem IV/IM	1 g/24 h	< 30: 500 mg/24 h	
Imipenem IV	1 g/6–8 h	30–50: 250–500 mg/6–8 h	< 30: 250–500 mg/12 h
Levofloxacin IV/PO	500 mg/12–24 h	20–50: 250 mg/12–24 h < 10: 125 mg/24 h	10–20: 125 mg/12–24 h
Linezolid IV/PO	600 mg/12 h	No adjustment required	
Meropenem IV	1 g/8 h	30–50: 1 g/12 h < 10: 500 mg/24 h	10–30: 500 mg/12 h
Moxifloxacin IV/PO	400 mg/24 h	No adjustment required	
Piperacillin/tazobactam IV	4/0, 5 g/6–8 h	20–50: 2/0, 25 g/6 h	< 20: 2/0, 25 g/8 h
Tobramycin IV	4–7 mg/kg/24 h	60–80: 4 mg/kg/24 h 30–40: 2, 5 mg/kg/24 h 10–20: 1, 5 mg/kg/24 h	40–60: 3, 5 mg/kg/24 h 20–30: 2 mg/kg/24 h

IM, intramuscular; IV, intravenous; VO, oral.

Given the heterogeneity of older patients and individual risk factors for specific microorganisms, two questions should drive antibiotic treatment choice. First, does the patient have a severe pneumonia or risk factors for unusual microorganisms? And second, does the patient meet the definition of frailty? If the answer to both questions is "no," therapeutic regimens commonly used in younger adults apply; if the patient has severe pneumonia and/or risk factors for less common pathogens, resistant microorganisms are more likely, and broadening antimicrobial treatment should be considered.

The issue of frailty is more complex. Mildly frail seniors (ie, independent or nearly independent for all basic ADLs) at baseline may suffer acute functional and/or cognitive impairment with pneumonia. In this case, monitoring of clinical, functional, and cognitive areas, and interventions to restore function to the previous baseline should be paramount and part of the overall treatment plan. The same antibiotic choices as those used for independent patients suffice.

In moderate-severe frailty, the invasive diagnostic and therapeutic procedures depend on individual goals and the site of care. Furthermore, these patients usually have severe comorbidity and polypharmacy, making them more vulnerable to the occurrence of adverse drug reactions. In addition, there may be important risk factors that determine specific etiologic risk (MDRO or MRSA colonization, aspiration risk, etc). Antibiotic choices in such patients must include broader coverage in addition to routine pathogens.

The first antibiotic dose should be administered as soon as possible because a shorter interval to effective therapy is associated with decreased length of hospital stay and mortality, both in nonsevere patients and in those who present with severe sepsis or septic shock. Combination therapy is indicated in patients that meet criteria for ICU admission; β-lactam and a macrolide or fluoroquinolone is superior to fluoroquinolone monotherapy. If influenza is circulating in the community, oseltamivir should be added, even if more than 48 hours have passed since symptom onset, and treatment against *S aureus* provided until cultures suggest otherwise. In patients with risk factors, empiric MRSA treatment is advisable while awaiting conventional cultures and nasopharyngeal swabs—specific treatment against MRSA should be suspended if these are negative.

Intracellular pathogens are less common in older patients compared to younger patients, and the need for coverage of atypical pathogens is currently a point of discussion. In some studies, the incidence of "atypical pneumonia" can reach 50% and mixed infections may represent 10% to 15% of cases. There is some controversy, except for *L pneumophila*, regarding the benefit of atypical pathogen coverage; American guidelines recommend adequate coverage of atypical pathogens in all cases, while the British guidelines limit it to patients requiring hospitalization. For *L pneumophila*, recent studies show similar rates of causality in nonsevere pneumonia and those requiring hospitalization. Therefore, if it is not possible to rule out infection due to *Legionella*, a macrolide or respiratory quinolone should be given with a β-lactam. In case of suspected pulmonary tuberculosis, quinolones should not be prescribed due to their tuberculostatic activity and the possibility of delaying the diagnosis of pulmonary tuberculosis.

Finally, it should be emphasized that aging produces certain pharmacokinetic and pharmacodynamic modifications of drugs. Doses and intervals must be adapted to the older patient's body weight (or body mass index) and renal function, and modified by drug interactions. Under-dosing antibiotics has severe consequences and should be avoided as vigorously as over-dosing to ensure the best outcome and reduce the risk of emergence of antibiotic-resistant pathogens.

Switch From Intravenous to Oral Antibiotics and Duration of Therapy

After reaching clinical stability, a switch from intravenous to oral antibiotic formulations is safe and reduces length of hospital stay with equivalent outcomes. The presence of bacteremia does not extend the required duration of intravenous antibiotic therapy. Isolation of a causative organism should prompt deescalation to specific, narrowed coverage, but when no organism is isolated, it is advisable to complete therapy using and oral equivalent with respect to the spectrum of activity.

Meta-analyses suggest 7 days of antibiotic treatment is sufficient to cure pneumonia even in older adults. However, there are exceptions, and treatment should be extended in cases of infection by *Legionella*, resistant GNB, or MRSA. In addition, there are clinical situations that may also involve an extension of the duration, such as persistent fever over 72 hours, persistence of more than one criterion of clinical instability, inadequate initial coverage, or the occurrence of complications.

Treatment Failure

Treatment failure is defined as the absence of clinical stability after 3 to 4 days of antibiotic treatment or the occurrence of clinical deterioration, respiratory failure or septic shock in the first 72 hours. This situation is associated with a fivefold increase in mortality. However, reaching clinical stability may take longer without implying a therapeutic failure in older patients with severe pneumonia or concomitant serious comorbidity such as severe COPD or untreated heart failure.

Possible causes of treatment failure include resistant microorganisms, involvement of unusual pathogens, lack of optimized treatment for comorbidity, or the existence of an undiagnosed concomitant process (eg, pulmonary embolism, neoplasm).

When treatment failure is suspected antibiotics should be changed if culture data suggest a pathogen resistant to antibiotics being given, comorbidity treatment optimized, and new imaging studies may be of value. Broadening the antimicrobial spectrum should follow, and risk factors for unusual pathogens reevaluated or the possibility of infection by fungi, mycobacteria, *Nocardia*, and other unusual pathogens reconsidered.

Concomitant Treatment

In conjunction with antibiotic treatment, other therapeutic measures should be carried out such as proper oxygenation (including initial appraisal of noninvasive mechanical ventilation, especially in patients with respiratory failure), fluid balance and the correction of electrolyte disturbances, glycemic control, management of associated comorbidities, nutritional support if needed and the prevention of thromboembolic events. Early physical and cognitive stimulation is very important, even for inpatients; early mobilization is recommended, if possible from the first day of admission, seating the patient out of bed for a minimum of 20 minutes and subsequent progressive mobilization recommended.

Palliative Treatment

Pneumonia is a common complication in older patients with advanced dementia and limited life prognosis, often being the final cause of death. The identification of these patients is very important in order to provide adequate palliative treatment, since in this patient profile clear benefits of intravenous antibiotic therapy have not been proven. Withholding antibiotics may be very appropriate for some patients and palliative treatment only considered individually.

PREVENTION

Given the high incidence, morbidity, and mortality of pneumonia in older adults, preventive measures, especially vaccination, are critical. This becomes even more important in institutionalized older adults, where “herd” immunity plays a major role in reducing risk. Vaccination against influenza and pneumococcus is recommended for all patients aged 65 and older. Despite the existence of a reduced response to vaccination, particularly in frail seniors, risk of infection, mortality, and associated complications are lower in patients vaccinated against influenza and pneumococcus compared with those unvaccinated. Recently, conjugate vaccine (PCV13) has been recommended in addition to polysaccharide for all adults aged 65 years and older. According to the Advisory Committee for Immunization Practices (AICP), PCV13 should be given first with PPS given at least 8 weeks later.

In older adults at risk of aspiration pneumonia, oral care may reduce pneumonia, though efficacy in the highest risk groups (eg, nursing home residents) has not been demonstrated. Oral hygiene should be performed daily by mechanical cleaning (brushing and sponging of the mucosa and lips twice a day and floss once a day), rinsing with chlorhexidine gluconate in cases of gingivitis, saliva substitutes if there is xerostomia, and weekly oral evaluation. If partial or full dental prostheses are present, they should be brushed and left in a cleaning solution for 10 minutes and rinsed using the same procedure as in patients with teeth. Postural measures for feeding (elevation of the head of the bed and remaining in that position until 2 hours after completion of the intake) make sense, but have not been proven to reduce risk in rigorous trials.

There is increasing data on pharmacological interventions that act on the swallowing reflex such as those involved in the thermoregulatory centers and the cough reflex. It is important to avoid all medications that could potentiate aspirations, such as sedatives, and especially antipsychotics. The use of proton pump inhibitors that produce achlorhydria and stomach bacteria is an issue of debate, but should be clearly justified if given. Treatment of hypertension and heart failure may include the use of angiotensin-converting enzyme inhibitors, and in seniors at risk for pneumonia, the stimulated cough reflex may reduce risk. Other preventive measures that can reduce infections in

seniors include optimizing treatment of comorbidities (eg, diabetes mellitus, heart failure) and improving nutritional status.

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Chapter 127

Urinary Tract Infections

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Learning Objectives

- Differentiate asymptomatic bacteriuria (ASB) and symptomatic urinary tract infection (UTI) in older adults.
- Apply specific considerations and guidelines for evaluation of UTI in older adults residing in long-term care facilities.
- Recognize the limitations of current guidelines for diagnosis and treatment of UTI in both community-dwelling older adults and residents of long-term care facilities.
- Identify which older adults are at greatest risk for developing a UTI with a resistant organism.
- Utilize strategies to limit unnecessary antibiotic use in older adults with suspected UTI.

Key Clinical Points

1. **ASB and UTI are the most common reasons antibiotics are prescribed for older adults in both the community and health care settings.**
2. **Distinguishing ASB and symptomatic UTI is problematic. Many older adults do not present with localized genitourinary symptoms required by guidelines to diagnose a symptomatic infection and the baseline prevalence of bacteriuria is high.**
   a. **Clinicians should NOT screen older adults for ASB and those with ASB should NOT be treated with antibiotics. Only in older adults undergoing invasive urologic procedures should ASB screening be considered.**
   b. **In either community-dwelling or long-term care resident older adults with vague, nonspecific symptoms (eg, periods of altered perception, disorganized speech, lethargy, change in odor or color of urine), observation for 24 to 48 hours for the evolution of symptoms with hydration and alternative diagnoses should be considered and does NOT lead to worse outcomes in those eventually proven to have UTI when compared to empiric, immediate antibiotic therapy. If symptoms persist and no other identifiable cause is found, urinary dipstick testing for the presence of leukocyte esterase and nitrite should be performed and if positive, culture and treatment considered. A urinary dipstick negative for both leukocyte esterase and nitrate has been shown to have a negative predictive value of 88% to 100%.**
3. **Clinicians in outpatient and inpatient settings do not often use guidelines aimed at reducing unnecessary antibiotic prescriptions.**
4. **Use of antibiotics to treat UTI is associated with the development of uropathogens with resistance to commonly used antibiotics.**

INTRODUCTION

Urinary tract infection (UTI) is the most frequently encountered bacterial infection in older adults. While the presence of bacteria in the urine in older adults is usually asymptomatic and considered a colonization state, symptomatic infection is associated with morbidity and, rarely, mortality. Optimal management of UTI in this population is

challenging in the face of diagnostic uncertainty, concerns with excess antimicrobial use, and increasing antimicrobial resistance in both the community and long-term care (LTC) setting. In addition, the heterogeneity of the older adult population means approaches may vary for different groups. The impact and management of urinary infection differs for older adults in the community and in those residing in long-term care facilities (LTCFs). There are also unique considerations for the subgroup of older adults with chronic indwelling catheters. The discussion in this chapter is relevant to individuals without long-term indwelling catheters, unless otherwise stated.

DEFINITIONS

UTI is both one of the most commonly diagnosed infections in older adults and one of the most difficult infections to accurately diagnose. Several formal definitions of UTI have been developed; however, there is not a single accepted definition that both professional societies, and clinicians agree upon. The uncertainty surrounding the definition of UTI, particularly in older adults, poses significant diagnostic challenges for providers caring for this population. Definitions of bacteriuria, pyuria, and asymptomatic bacteriuria (ASB) are more universally agreed upon. Bacteriuria implies the presence of bacteria in the urine. Pyuria is generally defined by the presence of 10 or more white blood cells (WBC/mm^3) per high-power field (hpf) in a urine sample, suggesting inflammation of the genitourinary tract. ASB is broadly defined as the presence of bacteria in the urine, with or without pyuria, in the absence of genitourinary signs or symptoms. In asymptomatic women, the accepted definition for ASB is defined as two consecutive voided urine specimens with isolation of the same uropathogen in quantitative counts greater than or equal to 10^5 colony forming units/milliliter (cfu/mL). In asymptomatic men, ASB is defined as a single clean-catch voided urine specimen with 1 uropathogen isolated in quantitative counts greater than or equal to 10^5 cfu/mL. A single *catheterized* urine specimen with one uropathogen isolated in a quantitative count greater than or equal to 10^2 cfu/mL defines ASB in both asymptomatic women and men. Symptomatic UTI is broadly defined when both pyuria and bacteriuria are present in the context of a patient with at least two signs and symptoms of a genitourinary tract infection (ie, dysuria, with or without frequency, urgency, suprapubic pain/tenderness, costovertebral angle pain/tenderness or hematuria). Acute uncomplicated cystitis is defined as a symptomatic UTI that is limited to the lower urinary tract (ie, bladder, urethra) in otherwise healthy adults without structural or functional abnormalities of the urinary tract. Complicated UTI is defined as infection of the upper tract (eg, pyelonephritis), or symptomatic UTI in patients with either functional or structural genitourinary abnormalities, urinary catheters, or in patients with systemic illness such as chronic kidney disease, diabetes, or other immunodeficiency; there is debate as to whether all adults aged 65 years or more with symptomatic UTI should be categorized as having complicated UTI. Recurrent UTI is defined as three or more symptomatic UTIs within a 12-month period or two or more symptomatic UTIs in a 6-month period following clinical resolution of each UTI with antimicrobial treatment. Catheter-associated UTI (CAUTI) refers to patients with an indwelling urethral, suprapubic, or intermittent catheterization with signs or symptoms compatible with UTI (ie, new onset or worsening of fever, rigors, altered metal status, malaise, or lethargy with *no* other identified cause; flank pain; costovertebral angle tenderness; hematuria; pelvic discomfort; OR dysuria, urgency or frequency in patients whose catheters have been removed within the previous 48 hours with no other identified source of infection), along with greater than or equal to 10^3 cfu/mL of one or more bacterial species in a single catheter urine specimen (**Table 127-1**).

TABLE 127-1 ■ COMMON DEFINITIONS

Asymptomatic bacteriuria	Broadly defined as a urinary pathogen isolated in appropriate quantitative counts from a urine culture in adults without genitourinary tract signs or symptoms. In older women: Two consecutive clean-catch midstream urine samples growing at least 10^5 colony-forming units/mL with no more than two species of microorganisms or a single *catheterized* urine specimen with one uropathogen isolated in a quantitative count $\geq 10^2$ cfu/mL. In older men: One clean-catch midstream urine samples growing at least 10^5 colony-forming units/mL with no more than two species of microorganisms or a single *catheterized* urine specimen with one uropathogen isolated in a quantitative count $\geq 10^2$ cfu/mL.
Pyuria	Presence of $\geq$ 10 white blood cells (WBC/mm^3) per high power field (hpf) in a urine specimen.
Leukocyte esterase	Component of a urinary dipstick that is used to detect a substance that suggests there are

	white blood cells in the urine.
Nitrite	Component of a urinary dipstick used to indicate that bacteria may be present in significant numbers in the urine.
Uncomplicated UTI	Symptomatic bladder infection in immunocompetent women without structural or functional urologic abnormalities.
Complicated UTI	Symptomatic bladder infection in adults with structural or functional abnormalities, urinary catheters, or systemic illness.
Recurrent UTI	≥ 3 confirmed urinary tract infections within a 12-mo period or ≥ 2 symptomatic UTIs in a 6-mo period following clinical resolution of each infection with antimicrobial treatment.
Catheter-associated UTI	Signs or symptoms of a UTI in adults who have an indwelling urethral or suprapubic catheter, perform intermittent catheterization, or in those whose catheters have been removed within the previous 48 h *and* ≥ 10^3 cfu/mL of ≥ 1 bacterial species in a single catheter urine specimen.

UTI, urinary tract infection.

EPIDEMIOLOGY

UTI is common in older adults and is responsible for more than 8 million outpatient and emergency department visits in the United States each year. It is one of the most frequently listed diagnoses among hospitalized patients 50 years or older in the United States, accounting for almost a quarter of infectious disease hospitalizations in this age group.

ASB in Older Adults

The prevalence of ASB increases with age and is more prevalent in those residing in LTCFs. In healthy, older adult women, ASB ranges from approximately 5% to 20% in women aged 65 to 90 years, but increases to nearly 45% in women over the age of 90 years. Bacteriuria is uncommon in younger men, but increases significantly with age, especially in men with prostatic hypertrophy. The rate of ASB is approximately 5% in men living in the community, but increases to 20% in men over age 80 years. ASB is highly prevalent in LTC settings, with multiple studies documenting rates for men and women to be approximately 15% to 50%. The rate of ASB in this population is likely to be higher than current estimates, as adults with urinary incontinence and dementia are more likely to have ASB, but also more likely not to be included in research studies given the difficulty of obtaining a urine specimen. Almost 100% of chronically catheterized older adults develop bacteriuria within 1 month of catheterization. ASB often resolves spontaneously, without antibiotic treatment. large cohort study evaluating the prevalence of ASB in older men and women living in the community reported that almost 30% of individuals with ASB at baseline had negative urine cultures at 6 months, whereas among those adults that were negative for ASB at baseline, 6% developed bacteriuria at 6 months. Another large prospective study found that more than 30% of older adult women had spontaneous resolution of ASB over a 6-month interval, whereas 30% of women initially without bacteriuria developed ASB during this time period. In a study of 209 initially nonbacteriuric older men at a VA hospital, 10% had at least one episode of bacteriuria during a mean of 2.8 years of follow-up, and 75% of these episodes resolved spontaneously.

UTI in Older Adults

The incidence of UTI in postmenopausal women is 0.07 per person-year according to a large population-based study. Accurately estimating the prevalence of UTI, however, is challenging, as the definition of UTI varies significantly across the literature. For example, a prospective population-based study of healthy older adult women in Brazil described the prevalence of UTI to be approximately 17% over a 2-year period; however, “foul-smelling urine” was included as a symptom in their definition of UTI, even though this is not a commonly used criterion to define urinary infection according to most professional societies. In LTC residents, the rate of UTI appears to remain high with an estimated rate of 0.15 per patient-year for older women and 0.11 per patient-year for older men. One study of nursing home residents with advanced dementia reported that 27% of older adults were diagnosed with UTI over a 2-year period.

PATHOPHYSIOLOGY

The urinary tract (ie, urethra, bladder, ureters, and kidneys) is presumed to be sterile in a normal host. However, this premise particularly changes in older adults as those with increasing disability tend to become colonized, therefore leading to the high rates of ASB. In most adults, a variety of host factors prevent contamination of the urinary tract from pathogenic organisms. The process of urination is the most effective defense mechanism for preventing bacterial invasion of the urinary tract from gastrointestinal microorganisms. Other mechanisms include acidity of urine, peristaltic activity of ureters, a competent vesicoureteral valve, and a variety of other mucosal and immunologic barriers. UTI most often occurs by an ascending route. Organisms colonize the periurethral area and ascend up the urethra into the bladder, and sometimes kidneys. Renal infection is determined by virulence characteristics of the infecting organism or the presence of genitourinary abnormalities such as obstruction or reflux in the host. Rarely, infection may be hematogenous rather than ascending, with urinary infection secondary to bacteremia from a nonurinary source (this is particularly a consideration when *Staphylococcus aureus* is isolated in patients without an indwelling catheter).

Risk Factors in Older Adults for UTI

Older adults may be at higher risk for development of UTI due to a variety of host factors associated with aging such as a decline in B- and T-cell function. Environmental factors play a large role, as older adults are more likely to have been exposed to the health care system, either through hospitalization or residence in a LTCF, increasing their exposure to virulent nosocomial organisms. Hospitalization often leads to genitourinary instrumentation, and placement of an indwelling catheter has consistently been shown to be a strong risk factor for development of symptomatic UTI in both men and women. Older adults are more likely to have structural or functional abnormalities (eg, benign prostatic hypertrophy in men and cystoceles in women), which lead to urinary stasis by impairing normal voiding and thus, inhibit the host from “flushing” out pathogenic organisms. However, having a high postvoid residual (PVR) has not consistently been shown to increase the risk of developing a symptomatic UTI in either ambulatory women or in LTC residents. A large prospective cohort study of ambulatory women aged 55 to 75 did not find PVR greater than 200 mL to be significantly associated with developing UTI compared to women with residuals less than 50 mL. Another prospective surveillance study in both male and female residents of six Norwegian nursing homes, did not find a significant difference in mean PVR between residents who developed UTI compared to those that did not (79 vs 97 mL, $p = 0.26$). They also concluded that having a PVR of 100 mL or greater was not associated with an increasing risk of developing UTI. In older adults, the most common risk factor associated with developing UTI is having history of UTI. A case-controlled study of postmenopausal women found over a fourfold increase in developing UTI in those women with at least one infection before menopause compared to those with no prior history (odds ratio [OR] 4.20; 95% confidence interval [CI], 3.25–5.42). In postmenopausal women, sexual activity, urinary incontinence, and estrogen deficiency have all been associated with developing UTI, although the extent to which they increase the risk is debated, as studies have demonstrated conflicting results. Declining estrogen levels is associated with increased colonization of the vagina with potential uropathogens. Postmenopausal women are less likely to have lactobacilli colonizing the vagina, and more likely to have *Escherichia coli* and *Enterococci* spp. These changes in vaginal flora, together with the higher pH in the absence of lactobacilli, are similar to changes observed in younger women with recurrent UTI, and have been suggested to facilitate urinary infection in older women. However, a systematic review that included four randomized controlled trials evaluating oral estrogen replacement to placebo, did not find evidence that use of oral estrogens reduced the recurrence of UTI in this population. Certain comorbidities have been linked to developing UTI in older adults. Diabetes mellitus appears to have the strongest association across all age groups. In a cohort of postmenopausal women, those with a diagnosis of diabetes mellitus were almost three times as likely to develop UTI compared to women without diabetes (OR, 2.78; 95% CI, 1.78–4.35). Older adults with diabetes are also at an increased risk for having UTI from a more uncommon uropathogen (eg, *Pseudomonas* spp, *Proteus* spp) and more likely to develop upper tract disease (eg, pyelonephritis). In a cohort of outpatient male veterans with UTI, the most common comorbidities were diabetes mellitus (34.6%), prostate hypertrophy (33%), and history of prior UTI (30.8%). Other comorbidities that have been associated with UTI include cerebrovascular disease, Alzheimer disease, and Parkinson disease.

PRESENTATION AND EVALUATION

Asymptomatic Bacteriuria

It has been well documented that clinicians should not screen older adults for ASB and those with ASB should not be treated with antibiotics. Four prospective randomized studies evaluating treatment of ASB in older adults demonstrated no differences in morbidity or mortality in those treated with antibiotics compared to those who did not receive treatment. Furthermore, persistent asymptomatic colonization of the urinary tract is not associated with an increased risk of development of renal failure or hypertension. Thus, the US Preventative Services Task Force (USPSTF), Society for Healthcare Epidemiology of America (SHEA), Infectious Diseases Society of America (IDSA), and American Geriatrics Society's Choosing Wisely campaign all recommend against screening and treating for ASB in this population. Only in older adults undergoing invasive urologic procedures should ASB screening be considered (**Table 127-2**).

TABLE 127-2 SUMMARY OF RECOMMENDATIONS FOR SCREENING AND TREATMENT OF ASB IN OLDER ADULTS

PROFESSIONAL SOCIETY	RECOMMENDATION
Infectious Diseases Society of America	• Screening for and treatment of ASB is not recommended for the following persons: (1) diabetic women, (2) older women living in the community, (3) older, institutionalized subjects, (4) persons with spinal cord injury, and (5) catheterized patients while catheter remains in situ.
US Preventative Services Task Force	• Recommends against screening for ASB in men and nonpregnant women.
American Geriatrics Society, Choosing Wisely	• Recommends against using antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.

ASB, asymptomatic bacteriuria.

Presentation and Evaluation of Symptomatic UTI

The presentation of UTI varies significantly in the older population and is particularly dependent on a person's age, medical comorbidities (eg, diabetes, cerebrovascular disease, Parkinson disease, etc), structural or functional urinary tract abnormalities, demographics (ie, long-term care facility or community-dwelling), and presence of a urinary catheter (eg, urethral or suprapubic). The wide variety of presentations and uncertainty in the definition of what constitutes a symptomatic UTI makes it one of the most challenging infections to accurately diagnose and effectively treat.

Community-Dwelling Older Adults

Presentation In older, cognitively intact adults, the presentation of a symptomatic UTI is similar to that of younger adults and generally begins with the presence of new or worsening genitourinary symptoms. Acute uncomplicated UTI, otherwise known as cystitis, is the most common presentation of symptomatic UTI in older women, and usually manifests as dysuria with or without frequency, urgency, suprapubic pain, or hematuria. However, it is still unclear if other more nonspecific, generalized symptoms are indicative of symptomatic UTI in this group. A study conducted in a community clinic compared symptoms of premenopausal women (age < 55) and postmenopausal women (> 65 years and older) presenting with UTI. UTI in this study was defined as identification of an uropathogen equal or more than 10^3 cfu/mL in a midstream urine culture in women with symptoms of cystitis (eg, frequency, urgency, hematuria, painful voiding, and urination, new onset of incontinence, pain in the lower abdomen). The investigators determined that in premenopausal women, local genitourinary symptoms such as frequency and dysuria were the most prominent symptoms, whereas in postmenopausal women, urgency, nocturia, incontinence, and generalized nonspecific symptoms (low-back pain, low abdominal pain, constipation, cold and chills) predominated. However, urinary urgency and incontinence often occur in older women without a urinary infection, as does bacteriuria, making it unclear if all of the patients in this study did have a symptomatic UTI that would have benefited from antibiotic therapy. Further studies are needed to determine if nonspecific symptoms correlate with a symptomatic infection that would benefit from treatment with antimicrobials in this population. Patients with upper tract disease (eg, pyelonephritis) typically have additional symptoms such as fever, chills, nausea/vomiting, and flank pain.

Evaluation and diagnosis In younger women, the diagnosis and treatment of UTI is usually based on urinary symptoms alone, without the need for confirmation with laboratory testing. Use of a urinary dipstick (to evaluate for

leukocyte esterase and nitrite), urinalysis, and urine culture are not routinely recommended in patients with reliable histories. In older adults, this is problematic because of the high prevalence of chronic urinary symptoms (eg, incontinence, urgency, nocturia), which may complicate the diagnosis. Diagnosing and treating UTI with antibiotics without further evaluation for bacteriuria and pyuria in this age group often leads to overtreatment with antimicrobials, especially in those with known chronic urinary symptoms. To address this issue, a recent study evaluated five different management strategies for evaluation and treatment of UTI in adult women aged 18 to 70 years old. The investigators hypothesized that delaying use of antibiotics until diagnostic evaluation for UTI was performed, would lead to a decrease in overall antibiotic usage, without delaying symptom control. Patients were randomized to one of the following five strategies: (1) empiric immediate antibiotics; (2) delayed antibiotics (> 48 hours); (3) antibiotics if two or more symptoms were present (cloudy urine, offensive urine odor, moderate to severe dysuria, or nocturia); (4) dipstick (antibiotics offered if [a] nitrites or leukocytes and [b] trace blood was detected); or (5) symptomatic treatment until microbiology results became available and then antibiotics targeted to culture results. The investigators found no differences in symptom duration, severity of frequency symptoms, or severity of unwell symptoms (eg, abdominal pain, restricted activities, and feeling unwell) between the antibiotic management strategies. However, empiric delayed prescriptions (strategy 2) and use of urinary dipstick testing with a delayed prescription as backup (strategy 4) helped to reduce overall antibiotic use. These results suggest that waiting for laboratory confirmation of UTI (eg, urine dipstick and urine culture) does not lead to worse outcomes or significant morbidity and may reduce unnecessary antibiotics. A limitation of this study was that the researchers did not recruit women over the age of 75 and the mean age in each treatment group ranged from 39 to 45 years. However, another prospective cohort study, which included women up to the age of 89, reported similar findings. In this study, outpatient adult women presenting with a possible UTI, were asked to delay antibiotic treatment for as long as possible. Over half of women who delayed antibiotic treatment did not ultimately require antibiotic therapy, and 71% of them reported clinical improvement or cure without any antibiotic therapy. No adults in this study developed worsening disease (pyelonephritis or bacteremia) as a consequence of delaying antibiotic treatment. Therefore, it is reasonable to delay empiric antibiotics in women whose diagnosis of UTI is unclear, especially in women with chronic urinary symptoms, while awaiting further diagnostic testing. In most cases, evaluation for symptomatic UTI in patients with new localized genitourinary symptoms should begin with a urinary dipstick to evaluate for the presence of nitrite or leukocyte esterase. If either nitrite or leukocyte esterase is positive, it is reasonable to obtain a specimen for urine culture and consider initiating empiric oral antibiotics. Urine culture is preferred to confirm the presence of bacteriuria in sufficient quantities and to help guide antimicrobial therapy. In older adults with chronic incontinence, frequency or urgency, and no localized genitourinary signs or symptoms, urinary testing with dipstick, urinalysis, or urine culture should not routinely be performed. Instead, providers should encourage hydration, review medications for potential side effects (eg, diuretics, antipsychotics), and consider other etiologies. In frail older adults with cognitive impairment, if UTI is suspected based on change in mental status (ie, periods of altered perception, disorganized speech, lethargy) and/or change in character of urine (ie, hematuria, change in odor or color), clinicians should recommend symptomatic treatment (eg, hydration, review medications) and observe closely for 24 to 48 hours as both of these signs can occur in other conditions as well. If symptoms persist or new localized genitourinary symptoms develop, a urinary dipstick can then be performed. If urinary dipstick is positive, and further testing with a urinalysis and urine culture reveal bacteriuria plus pyuria, treatment with antimicrobials for symptomatic UTI may be indicated (**Figure 127-1**). In all cases, a clean catch voided urine specimen collected to minimize contamination is preferred. Women should use an antiseptic cloth to first clean the inner folds of the labia, wiping from front to back. A second wipe should then be used to clean the opening of the urethra. Attempts should be made to collect a midstream urine sample, if possible. Although uncommon, symptomatic sexually active women who present with dysuria without pyuria and/or bacteriuria should be evaluated for a sexually transmitted infection (STI). If history is suggestive of a possible STI, screening for chlamydia, gonorrhea, trichomoniasis, HSV, and HIV is warranted.

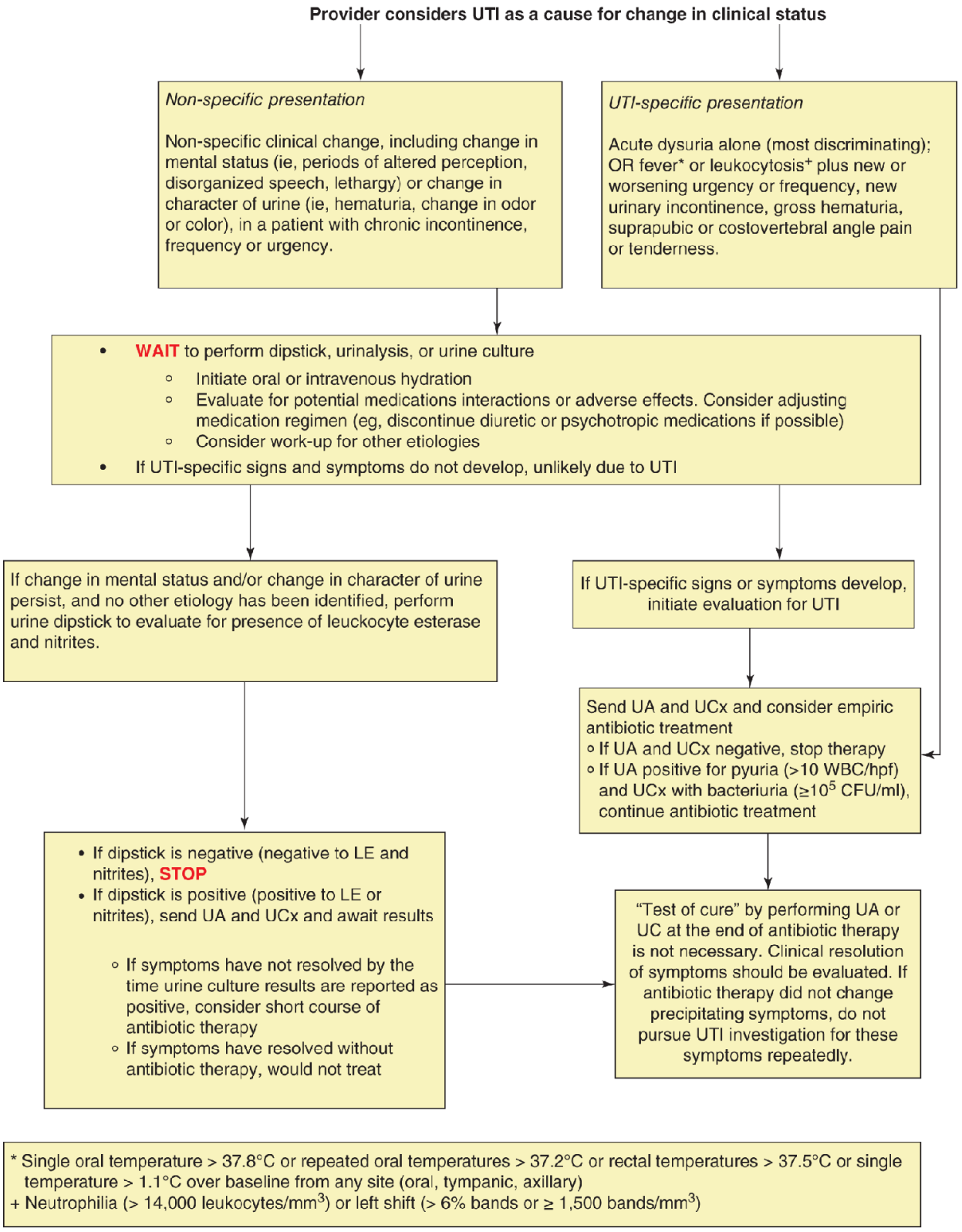


FIGURE 127-1. Urinary tract Infection (UTI) assessment and treatment algorithm. UA, urinalysis; UCx, urine culture.

Long-Term Care Residents

Presentation The presentation of symptomatic UTI in LTC residents is much more elusive. Residents in LTCFs often do not present with typical signs or symptoms of a genitourinary tract infection (eg, dysuria, frequency, flank pain) and, similar to community-dwelling older adults, many have chronic urinary symptoms such as urinary incontinence, frequency, nocturia, and urgency making it difficult for providers to distinguish which patients have a symptomatic UTI that would benefit from treatment. Furthermore, residents in LTCFs often suffer from advance cognitive

impairment and are unable to verbally communicate genitourinary symptoms suggestive of a symptomatic UTI. In a study of suspected UTI in residents of LTCFs with advanced dementia, the most common symptom for suspected UTI was change in mental status (44.3%). Other symptoms of suspected UTI in this group included change in character of the urine, fever, declining functional status, and hematuria. Whether or not nonspecific symptoms such as mental status change or change in functional status should be used to define symptomatic UTI in older adults, particularly LTC residents or residents with cognitive impairment, is still debated. To date, there have been no studies linking delirium or change in functional status alone to symptomatic UTI in adults without an indwelling catheter. Fall, another more common reason for suspected UTI in this population, has not consistently been associated with bacteriuria and pyuria. In a cohort of nursing home residents, 80% of fall episodes presumed to be caused by UTI were not associated with bacteriuria plus pyuria. Thus, in patients whose only sign of a UTI is a fall, clinicians should consider alternative etiologies before pursuing diagnostic evaluation of UTI, only send urine studies after considering alternative diagnoses, and wait to initiate empiric antibiotics.

Evaluation and diagnosis The absence of an agreed upon definition for symptomatic UTI in LTC residents makes the diagnosis particularly challenging. Several consensus guidelines have been published over the past several decades in attempts to help clinicians appropriately prescribe antibiotics for UTI in this population. The McGeer and Loeb criteria, published in 1996 and 2001, respectively, recognized the differences in establishing a clinical diagnosis of infection in LTCFs compared to other settings. The McGeer criteria identified criteria for infection surveillance purposes and the Loeb criteria were developed to help clinicians identify patients that would benefit from empiric antimicrobial therapy. Both guidelines, however, still require the presence of localized genitourinary symptoms in adults without an indwelling catheter (**Table 127-3**). Although these consensus guidelines have been adapted by many professional societies and health care agencies, clinicians are either unaware of the guidelines, or do not use them when deciding to treat patients with antibiotics. In one study, a survey was administered to nurses and providers (ie, physicians, physician assistants) caring for residents in LTCFs, to determine awareness of the most commonly used consensus criteria for diagnosing and treating UTI. Only 64% of providers were aware of the McGeer criteria and only 55% of these providers actually used them in clinical practice. Nurses were more likely to be aware of and actually use the guidelines when evaluating patients suspected of having a UTI compared to physicians. Another large study of nursing homes in the United States did not find evidence that providers considered the Loeb criteria when considering whether to prescribe antibiotics. Only 10.2% (range of 0%–38.9%) of UTI cases treated with antibiotics were found to be appropriate according to the Loeb minimum criteria for initiation of antibiotics. Furthermore, even in nursing homes that had increased adherence to the Loeb minimum criteria, the overall rate of antibiotic prescriptions remained the same because providers cited other indications for initiating antibiotic therapy. A significant weakness of both consensus criteria is that they are largely based on expert opinion, and many of the recommendations used to construct the guidelines are extrapolated from data in younger adults. To further investigate the effectiveness of the McGeer and Loeb criteria in diagnosing UTI, investigators conducted a prospective study of nursing home residents in Connecticut, evaluating the predictive values for the McGeer and Loeb criteria using laboratory confirmed UTI (bacteriuria plus pyuria) as the primary outcome. Although bacteriuria plus pyuria alone are not diagnostic of symptomatic UTI, the combination indicates urinary tract inflammation of the host and is necessary for diagnosis of a clinical infection. In this study, the sensitivity of both the McGeer criteria and Loeb criteria were low at 30% and 19%, respectively. To help improve diagnostic accuracy, the same investigators attempted to identify clinical features that were predictive of bacteriuria plus pyuria in nursing home residents. They found that dysuria alone predicted 39% of cases of with confirmed bacteriuria plus pyuria; however, when used in combination with other symptoms such as change in mental status or change in character of the urine, the predicted probability increased to 63%. This predicted probability is higher than both the McGeer and Loeb criteria, which both had positive predictive values of 57%. In 2012, an expert consensus panel for SHEA proposed revised guidelines for infection surveillance definitions specifically in LTCFs. The new guidelines expanded the definition of UTI and included a new requirement for microbiologic confirmation with urine culture (**Table 127-4**). Although these guidelines are intended for all patients in LTCFs, including those with cognitive impairment, they still require localizing genitourinary signs and symptoms. Thus, applying the guidelines to patients with advanced dementia remains challenging. As in community-dwelling older adults, LTC residents with vague, nonspecific symptoms (eg, periods of altered perception, disorganized speech, lethargy, change in odor or color of urine) should first be observed for 24 to 48 hours for the evolution of symptoms, hydration should be optimized, and alternative diagnoses should be considered. Providers should consider holding medications such as antipsychotics and/or diuretics, if possible, to see if symptoms improve. If symptoms persist and no other identifiable cause is found, urinary dipstick testing for the presence of leukocyte esterase and nitrite should be performed. The

urinary dipstick is convenient, easy to administer, often available in LTCFs, and results are available almost immediately. The sensitivity and specificity for a positive dipstick test in older patients has been shown to be 82% (95% CI, 74%–92%) and 71% (95%, CI 55%–71%), respectively, for diagnosis of bacteriuria plus pyuria. A urinary dipstick negative for both leukocyte esterase and nitrate has been shown to have a negative predictive value of 88% to 100% in residents of LTCF. In patients with nonspecific symptoms and a negative dipstick for leukocyte esterase and nitrites, clinicians should consider other potential etiologies and suspend further evaluation of UTI. Empiric antibiotics directed at UTI is unlikely to be beneficial. If either leukocyte esterase or nitrites are positive, additional testing in with urinalysis and urine culture may be appropriate **(Figure 127-1)**. Every attempt to obtain a clean catch urine is recommended. In patients with severe dementia or urinary incontinence, and whom clinicians determine have a high probability of UTI, in-and-out catheterization for urine collection should be performed if a voided specimen cannot be obtained. For residents without an indwelling catheter and who can provide a voided urine specimen, at least 10^5 cfu/mL of no more than two species of microorganisms is required for the diagnosis of symptomatic UTI. For specimens collected by in-and-out catheterization, at least 10^2 cfu/mL of any number of organisms is the recommended quantitative count. Lower quantitative counts should be interpreted as contamination with colonizing periurethral organisms.

TABLE 127-3 MCGEER AND LOEB CONSENSUS CRITERIA FOR DIAGNOSIS OF UTI IN LONG TERM CARE RESIDENTS WITHOUT AN INDWELLING CATHETER

MCGEER CRITERIA 1996	LOEB CRITERIA 2001
Three of the following must be met: 1. Fever ≥ 38°C or chills 2. New or increased burning pain on urination, frequency, or urgency 3. New flank or suprapubic pain or tenderness 4. Change in character of the urine (eg, new bloody urine, foul smell, or amount of sediment) 5. Worsening of mental or functional status (may be new or increased)	1. Acute dysuria alone or 2. Fever ≥ 37.9°C or 1.5° increase above baseline temperature *plus* ≥ 1 of the following new or worsening symptoms: a. Urgency b. Frequency c. Suprapubic pain d. Gross hematuria e. Costovertebral angle tenderness f. Urinary incontinence

TABLE 127-4 2012 SHEA/CDC SURVEILLANCE DEFINITIONS FOR UTI IN LTC RESIDENTS WITHOUT AN INDWELLING CATHETER

≥ 1 of the following signs or symptoms:

1. Acute dysuria or acute pain, swelling, or tenderness of the testes, epididymis, or prostate

or

2. Fever[a] or leukocytosis[b] and ≥ 1 of the following:
   a. Acute costovertebral angle pain or tenderness
   b. Suprapubic pain
   c. Gross hematuria
   d. New or marked increase in incontinence
   e. New or marked increase in urgency
   f. New or marked increase in frequency

or

3. ≥ 2 of the following:
   a. Suprapubic pain
   b. Gross hematuria
   c. New or marked increase in incontinence

d. New or marked increase in urgency

e. New or marked increase in frequency

AND

At least 10^5 cfu/mL of ≤ 2 species of microorganisms in a voided urine sample or at least 10^2 cfu/mL of any number of organisms in a specimen collected by an in-and-out catheter.

[a]Single oral temperature > 37.8°C or repeated oral temperatures > 37.2°C or rectal temperatures > 37.5°C or single temperature > 1.1°C over baseline from any site (oral, tympanic, axillary).

[b]Neutrophilia > 14,000 leukocytes/mm^3 or left shift (> 6% bands or ≥ 1,500 bands/mm^3).

Older Adults With Indwelling Urinary Catheters

Presentation Catheter-associated urinary tract infection (CAUTI) is the most common health care–associated infection and the most common indication for antibiotic prescriptions in this population. In LTCFs the prevalence of indwelling urethral catheters is approximately 7% to 10%. In the acute care setting, the overall CAUTI incidence rate is 14.7/1000 device days. CAUTI is difficult to accurately diagnose, as older adults with catheters often present with nonspecific symptoms such as fever (33.3%) and mental status changes (13.3%). Furthermore, almost all adults with a chronic catheter will have bacteriuria and pyuria making it difficult to distinguish between catheter-associated asymptomatic bacteriuria (CA-ASB) and CAUTI in patients with nonspecific symptoms.

Evaluation and diagnosis In 2009, the IDSA updated its current guidelines for diagnosis, treatment, and prevention of CAUTI in adults in an effort to reduce the amount of unnecessary antibiotic treatment in this population. These guidelines include patients with indwelling urethral catheters, indwelling suprapubic catheters, or intermittent catheterization. According to the guidelines, CAUTI is defined as patients with a catheter who develop symptoms or signs compatible with UTI, such as new onset or worsening of fever, rigors, altered mental status, malaise, or lethargy with *no* other identifiable cause; flank pain; costovertebral angle tenderness; acute hematuria; pelvic discomfort; OR dysuria, urgency, or frequency in patient whose catheters have been removed in the previous 48 hours with no other identified source of infection, along with greater than or equal to 10^3 cfu/mL of one or more bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose catheter has been removed in the previous 48 hours. The 2012 SHEA guidelines for diagnosis of CAUTI are similar, although require the presence of a urinary catheter specimen culture with at least 10^5 cfu/mL of any organism(s). Similar to residents without a catheter, CA-ASB should not be screened for, except in patients undergoing urologic instrumentation or procedures. The presence or absence of odorous or cloudy urine alone should not be used to differentiate CA-ASB from CAUTI (**Table 127-5**).

TABLE 127-5 DEFINITIONS FOR UTI IN RESIDENTS WITH AN INDWELLING CATHETER

IDSA GUIDELINES 2009	SHEA/CDC GUIDELINES 2012
≥ 1 of the following: 1. New onset of ≥ 1 of the following with no other identifiable cause: a. Worsening fever b. Rigors c. Altered mental status[a] d. Malaise e. Lethargy 2. Flank pain 3. Costovertebral angle tenderness 4. Acute hematuria 5. Pelvic discomfort 6. Dysuria, urgent or frequent urination, or suprapubic pain or tenderness in those whose catheters have been removed	**≥ 1 of the following:** 1. Fever,[b] rigors, or new-onset hypotension, with no alternate site of infection 2. Either acute change in mental status[a] or acute functional decline,[c] with no alternate diagnosis and leukocytosis[d] 3. New-onset suprapubic pain or costovertebral angle pain or tenderness 4. Purulent discharge from around the catheter or acute pain, swelling, or tenderness of the testes, epididymis, or prostate
Plus	***Plus***

≥ 10^3 cfu/mL of ≥ 1 bacterial species in a single catheter urine specimen *or* in a midstream voided urine specimen from a patient whose catheter has been removed within the previous 48 h	≥ 10^5 cfu/mL of ≥ 1 of any organism from a urinary catheter specimen

CDC, Centers for Disease Control; IDSA, Infectious Diseases Society of America; SHEA, Society for Healthcare Epidemiology of America.

[a]Acute onset of inattention, disorganized thinking, altered level of consciousness, or fluctuating changes in mental status from baseline.

[b]Single oral temperature > 37.8°C or repeated oral temperatures > 37.2°C or rectal temperatures > 37.5°C or single temperature > 1.1°C over baseline from any site (oral, tympanic, axillary).

[c]New ≥ 3 point increase in total activities of daily living score from baseline (bed mobility, transfer, locomotion within LTCF, dressing, toilet use, personal hygiene, eating).

[d]Neutrophilia > 14,000 leukocytes/mm^3 or left shift (> 6% bands or ≥ 1,500 bands/mm^3).

MANAGEMENT

Microbiology of UTI

The most frequent organism isolated from urinary cultures in both asymptomatic and symptomatic ambulatory olderly women is *Escherichia coli*, accounting for 75% to 95% of infections. In uncomplicated UTI, over 95% of infections are due to a single organism. For older women with uncomplicated infection, the spectrum of virulence factors in urinary *E coli* isolates is similar to younger women. Pyelonephritis strains are associated with P fimbriae, and have an increased frequency of other virulence characteristics including capsule type, adhesins, and proteins such as iron binding proteins and hemolysins. Other organisms occasionally isolated from this population include other Enterobacteriaceae (eg, *Klebsiella pneumoniae*, *Proteus mirabilis*) and *Enterococcus* spp. Rarely, *Pseudomonas aeruginosa* or group B and D streptococci will be isolated. Common skin flora in this group usually signify contamination, especially if multiple organisms are present. Risk factors for non-*E coli* UTIs in community-dwelling older adults include male gender, severe clinical presentation (eg, symptoms more than 7 days, documented or reported fever, nausea or vomiting, flank pain), those with a history of UTI in the past 12 months, history of diabetes mellitus, previous failure of TMP/SMX for treatment of UTI, or in patients with functional or anatomical abnormalities. Similar to community-dwelling older adults, *E coli* remains the most frequent organism isolated from urine specimens in residents of LTCFs. In a cohort of LTC residents, the most common organisms isolated in urine cultures with bacterial growth of more than 10,000 cfu/mL were (1) *E coli* (53.6%), (2) *Proteus* spp (14.6%), (3) *Klebsiella* spp (13.9%), (4) *Enterococcus* spp (4.5%), (5) *Staphylococcus* spp (4.1%), and (6) *Pseudomonas* spp (2.6%). Less common causes of UTI in this group include *Acinetobacter*, *Candida* spp, and methicillin-resistant *S aureus* (MRSA). In older adults with MRSA detected in urine culture, staphylococcal bacteremia as a potential source should be considered. Long-term care residents, especially those with a chronic urinary catheter, are also more likely to have polymicrobial bacteriuria, with more than one organism isolated in 10% to 25% of bacteriuric subjects.

Treatment for UTI

Pharmacologic therapies for community-dwelling older adults Treatment of UTI for community-dwelling older adults generally follows the same diagnostic algorithm used in younger adults. However, a urine culture should be obtained to guide treatment, as older adults are at higher risk for harboring multidrug resistant organisms (MDROs). Fluoroquinolones (FQs) are the most prescribed antibiotic for treatment of UTI in community dwelling older adults. FQs are often preferred by providers for treatment of UTI given their relatively low side effect profile, high oral bioavailability, and easy dosing schedule (usually 1–2 doses per day). A randomized control trial of ciprofloxacin or trimethoprim/sulfamethoxazole (TMP/SMX) enrolled both ambulatory older patient and nursing home residents and reported 10 days of ciprofloxacin was superior to 10 days of TMP/SMX and had fewer adverse effects. However, widespread use of FQs, especially for treatment of UTI, has led to high rates of FQ resistance in this age group, particularly in LTCFs. Resistance rates vary across institutions, but often exceed 30% in most clinical settings, thus they are no longer recommended as first line empiric treatment. For older adult women with acute uncomplicated cystitis, the International Clinical Practice Guidelines issued by the European Society for Microbiology and Infectious Diseases and the IDSA recommend as first line treatment either nitrofurantoin monohydrate/macrocrystals, 100 mg twice daily for 5 days OR TMP/SMX, 160/800 mg for 3 days. Fosfomycin (3 g as a single dose) is an acceptable alternative, although few studies have demonstrated inferior efficacy compared to nitrofurantoin or TMP/SMX for

treatment of uncomplicated UTI. TMP/SMX or fosfomycin may be preferred in older adults because of a shorter treatment course compared to nitrofurantoin (1 or 3 days vs 5 days). In men, UTI is usually considered complicated, and most experts would recommend treatment for a 7- to 14-day course, although a more recent study conducted in male veterans found shorter-course treatments for UTI (< 7 days) to be as effective compared to longer duration of treatment (> 7 days). Treatment of UTI associated with acute bacterial prostatitis generally requires at least a 14-day course in patients with mild symptoms who respond promptly to treatment, but in more severe cases, most experts recommend treatment for at least 28 to 42 days. Second-line antibiotics for empiric treatment of UTI or for patients whose organisms are sensitive to the following antibiotics include (1) amoxicillin/clavulanate 500/125 mg orally twice daily for 3–7 days; (2) cefpodoxime 200 mg orally twice daily for 3–7 days; or (3) cefixime 400 mg orally for 3 to 7 days. In younger patients, most episodes of acute uncomplicated pyelonephritis can be treated on an outpatient basis. Although age more than 60 years has been described to be a relative indication for hospitalization in patients with acute pyelonephritis, outpatient management in those with mild to moderate illness, adequate social support, and clinical stability, is likely to be as safe and as effective compared to hospitalization. Older adults with pyelonephritis who present with persistent vomiting, progression of uncomplicated UTI, suspected sepsis, uncertain diagnosis, evidence of urinary tract obstruction, and have significant frailty should be hospitalized. FQ are the only oral antibiotic recommended for empirical treatment of acute uncomplicated pyelonephritis. However, increasing resistance of FQ limits the use of this drug in many clinical settings and experts do not recommend empiric FQ use in areas with resistance noted to be higher than 10%. Nitrofurantoin and fosfomycin should not be used because of inadequate renal penetration. In all cases of pyelonephritis, urine culture and sensitivity testing should be obtained (**Table 127-6**).

TABLE 127-6 COMMONLY USED ORAL ANTIBIOTICS FOR TREATMENT OF UTI

ANTIBIOTIC	STANDARD DOSE FOR CRCL[a] > 60	SIDE EFFECTS	COMMENTS
Trimethoprim + sulfamethoxazole	Uncomplicated UTI: 800/160 mg orally twice daily for 3 d Complicated UTI: 800/160 mg orally twice daily for up to 14 d	GI intolerance Elevation in serum creatinine (~ 20%)	First-line treatment for uncomplicated UTI Significant interaction with warfarin (increases INR) and sulfonylurea (increases risk of hypoglycemia)
Nitrofurantoin monohydrate/ macrocrystals	Uncomplicated UTI: 100 mg orally twice daily for 5 d	GI intolerance Pulmonary toxicity (rare)	First-line treatment for uncomplicated UTI, *E coli* resistance remains low (< 10%) Not appropriate for short-course therapy or for treatment of pyelonephritis Avoid if CrCl < 40
Fosfomycin trometamol	Uncomplicated UTI: 3 g single oral dose Complicated UTI: 3 g oral dose every 2–3 d, up to 21 days	GI intolerance (diarrhea ~ 10%) Headache, dizziness Vaginitis	Treatment for complicated UTI is not FDA approved May have lower efficacy compared to other antibiotics Low resistance to ESBL[b] gram-negative rods and VRE[c]
Ciprofloxacin	Uncomplicated UTI: 250 mg orally twice daily for 3 d Complicated UTI: 500 mg orally twice daily for 7–14 d	Generally well tolerated Higher risk of *C difficile*-associated colitis Tendon rupture (rare)	Second-line treatment due to high resistance rates (>30%) Preferred oral treatment for pyelonephritis Significant interactions with antacids and vitamins, may decrease absorption
Amoxicillin + clavulanate	500/125 mg orally twice daily for 3–7 d	GI intolerance Rash	Second-line treatment due to high resistance rates

[a]Creatinine clearance.

[b]Extended spectrum β-lactamase.
[c]Vancomycin resistant enterococci.

Pharmacologic therapies for long-term care residents There are no current consensus guidelines for treatment of UTI specifically for older adults in LTCFs. Therefore, most clinicians follow the same guidelines used in younger outpatient adults. Although in most cases, this algorithm is appropriate, there are few circumstances for which clinicians might need to deviate from these guidelines. First, antibiotic resistance is generally much higher in LTC settings compared to the community population. Thus, it is imperative that clinicians become familiar with local resistance rates and guide empiric antibiotic regimens based on resistance patterns. Urine culture results should always help adjust antibiotic choices. Second, alterations in antimicrobial pharmacokinetics such as increased volume of distribution and decreased renal clearance are often observed in older adults; thus, providers should be cognizant of a patient's glomerular filtration rate (GFR) when dosing antimicrobials. Third, older adults often must manage polypharmacy and drug-drug interactions should always be evaluated. For instance, TMP/SMX, along with many other antibiotics, has significant interactions with anticoagulants and thus, close INR monitoring is recommended in patients receiving warfarin. In most cases, warfarin dosages will need to be decreased by at least 50% through the entire duration of antimicrobial therapy. Nitrofurantoin, another first line antimicrobial choice for UTI, is listed on the American Geriatric Society's Beers Criteria for potentially inappropriate medication use in older adults. Potential for pulmonary toxicity and lack of efficacy in patients with CrCl less than 60 mL/min are listed as possible negative consequences when used in this population. However, nitrofurantoin has consistently lower rates of resistance to *E coli*, making it a good empiric antibiotic choice for UTI caused by this organism. Furthermore, more recent data suggest that nitrofurantoin can be safely administered to patients with a creatinine clearance of at least 40 mL/min and is as effective as other antimicrobials for treatment of uncomplicated UTI. When highly resistant organisms, such as vancomycin-resistant *enterococci* (VRE) and extended-spectrum β-lactamase (ESBL) producing organisms, are suspected, fosfomycin is usually the most effective treatment (0% resistance) followed by nitrofurantoin (15% resistance). ESBL producing organisms are usually resistant to TMP/SMX, FQs, and amoxicillin/clavulanic acid. Duration of antibiotics in this age group is unknown. Some experts suggest longer treatment, categorizing all LTC residents as having complicated UTI. In 2001, SHEA recommended a 7-day course of antibiotics for women with cystitis, although this recommendation is based mostly on expert opinion. A recent systematic review found no differences in short-term outcomes in patients receiving short courses (3–6 days) and longer courses (7–14 days) suggesting shorter courses of antibiotics for UTI are likely to be sufficient in most circumstances. Longer courses are reasonable if there is a delay in response to treatment.

Parenteral Therapy

If patients are severely ill, or clinically worsening despite receiving adequate oral antibiotics, parenteral therapy is indicated. Broad empiric coverage with either piperacillin/tazobactam, a fourth-generation cephalosporin (eg, cefepime or ceftazidime), or a carbapenem (eg, meropenem or doripenem) should be started. Aminoglycosides, such as gentamicin or tobramycin, are sometimes added to β-lactams for synergy and to broaden coverage; however, they are more toxic than other available antibiotics, especially in older adults with renal insufficiency. Studies, however, have shown that ototoxicity and nephrotoxicity with aminoglycoside therapy is unlikely when therapy duration is limited to 48 to 72 hours.

Suppressive Antibiotics

Prolonged suppressive antimicrobial therapy may be considered when there is persistent or recurrent morbidity attributable to urinary infection. Such circumstances are uncommon, but might include recurrent invasive infection in the presence of an underlying genitourinary abnormality that cannot be corrected, persistent infected stones where suppressive therapy may prevent further stone enlargement, frequent symptomatic recurrences from a prostatic source, or with chronic renal failure. Antimicrobial selection for suppressive therapy is individualized, based on susceptibilities of the infecting organism and tolerance. Deciding whether to use antibiotic prophylaxis must be determined based on the frequency of UTI, severity of symptoms, and adverse effects of chronic antimicrobial use such as development of *Clostridium difficile* colitis and various adverse drug reactions. For many older adults, these risks are likely to outweigh any benefit and suppressive therapy is seldom indicated.

PREVENTION

Prevention of UTI plays an important role in halting the growing trend of antibiotic resistance seen in urinary isolates. Nonpharmacologic therapies, such as cranberry containing formulations, are an attractive option for many older adults given their relatively low risk profile. Cranberry juice has been used as a home remedy for prevention and treatment of UTI for decades, although the evidence to support this intervention as a prevention strategy is currently debated. Cranberry proanthocyanidin (PAC) is the active ingredient in cranberry that is thought to inhibit adherence of P-fimbriated *E coli* to uroepithelial cell receptors. A recent Cochrane review evaluating use of cranberry containing products (ie, juice, tablets, or capsules) did not find significant evidence that any of these products prevented UTI in women compared to placebo, water, or no treatment. A potential concern with many of the studies included in the review, was that older adults were unable to drink the amount of cranberry juice containing adequate amounts of PAC thought to be needed to prevent UTI. The necessary volume of a cranberry supplement is an important issue in older adults, particularly for those with cognitive impairment, as adherence to a large amount of fluid, is likely to be low. A recent study examining cranberry capsules containing 36 to 108 mg of PAC found a trend toward a decrease in bacteriuria plus pyuria in LTC residents, suggesting formulations with higher doses of PAC may be beneficial, although further studies are needed. A systematic review and meta-analysis of only randomized controlled trials, did conclude that cranberry products reduced UTI recurrence in women with at least three UTIs in a 1-year period (risk ratio [RR] 0.53, 95% CI 0.33–0.83). Although evidence to suggest cranberry products help to prevent UTI is still unclear, there appears to be minimal risk associated with this intervention and thus, may be a safe alternative to other forms of prevention in certain patients. Given the issues of volume and glucose load for a cranberry juice supplement and size and cost of cranberry capsules, further investigation of cranberry supplements in older adults is warranted prior to recommending either product as a prevention strategy.

In older adults, declining estrogen levels are thought to lead to declining levels of lactobacilli in the vaginal tract and thus, increase colonization of the perineal area with organisms such as *E coli*. In a randomized control trial, researchers hypothesized that replacement of lactobacilli with oral formulations (eg, *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14*) would be noninferior compared to daily antibiotic prophylaxis with TMP/SMX in preventing recurrent UTI. They could not conclude that lactobacilli was noninferior to antibiotics (number of symptomatic UTIs after 12 months of prophylaxis was 2.9 for TMP/SMX and 3.3 for lactobacilli, with a treatment difference of 0.4 clinical recurrences [95% CI, –0.4 to 1.5]); however, they did find lower rates of antibiotic resistance in the group assigned to lactobacilli. Topical estrogen appears to be a safe and potentially effective method for prevention of UTI in postmenopausal women. A systematic review and meta-analysis evaluated the evidence regarding use of vaginal estrogens as a prevention strategy for recurrent UTI in postmenopausal women. Both randomized controlled trials included in this study found that vaginal estrogen (vaginal cream containing 0.5 mg of estriol or vaginal ring with 2 mg estradiol) significantly reduced the risk of UTI in postmenopausal women (RR 0.25, 95% CI 0.13-0.50), and (RR 0.64, 95% CI 0.47-0.86), respectively. However, their pooled effect was not significant (RR 0.42, 95% CI 0.16-1.10).

Prevention of Catheter-Associated UTI

The most effective strategies for prevention of CAUTI are to avoid catheterization and, when an indwelling catheter is indicated, to discontinue the catheter as soon as possible. Medicare patients have the highest rate of CAUTI. In 2008, the Centers for Medicare and Medicaid Services (CMS) began a policy of refusing to pay hospitals for additional costs related to CAUTI. Although this policy was enforced as an attempt to reduce the number of CAUTIs, surveillance studies have not shown a significant decline in rate of CAUTIs since its implementation, and the rate of inappropriate catheter use is still estimated to be around 20% to 50%. The Healthcare Infection Control Practices Advisory Committee as part of the Centers for Disease Control (CDC), issued guidelines in 2009, aimed to help providers with the prevention, diagnosis, and management of persons with CAUTI, particularly hospitalized patients and residents of LTCFs. In older adults that require catheter placement, recommendations include insertion of catheters aseptically by trained personnel, use of the smallest diameter catheter as possible, hand washing before and after catheter manipulation, maintenance of a closed catheter system, avoiding irrigation unless the catheter is obstructed, keeping the collecting bag below the bladder and maintaining good hydration in residents. Uses of antimicrobial-coated catheters have been shown delayed bacterial colonization and thus reduce the incidence of bacteriuria. However, a randomized controlled trial evaluating the use of two antibiotic-coated catheters did not find significant benefit in prevention of CAUTI. These catheters are more expensive and thus are likely not beneficial in most clinical settings. Use of a

computerized clinical decision support intervention for reducing the duration of catheter use has been shown to be effective in limiting the duration of catheters and CAUTIs in hospitalized patients, although this intervention may be more difficult to implement in LTCFs.

SPECIAL ISSUES

Outcomes

Most healthy older adults with symptomatic UTI respond well to antibiotic therapy. However, bacteriuria is associated with significant morbidity, often related to antibiotic use, which promotes the development of multidrug resistant bacteria and overgrowth of organisms such as *C difficile*. Presence of an indwelling catheter, age, and medical comorbidities influence outcomes. CAUTI was associated with a significantly higher mortality in hospitalized adults aged 65 years or more compared to UTI in noncatheterized patients (19.2% vs 10.5%, $p < .05$). In a retrospective cohort study of residents with UTI in LTCFs in the United States, risk factors that appeared to increase the risk of hospitalization included advancing age, Hispanic or African-American race, diabetes mellitus, Parkinson disease, dementia, and stroke. Factors that decreased the risk of hospitalization in this same cohort included, the ability to walk, physician visit at the time of admission to a LTCF, and maintaining or improving mobility in those with severe mobility problems. One of the most serious complications of UTI is the development of bacteremia as a consequence of persistent infection causing hematologic spread. Older adults are more likely than younger adults to develop gram-negative bacteremia as a consequence of UTI. The mortality in patients with bacteremic UTI has been described to be between 14% to 33%. However, adults with bacteremia as a result of UTI compared to bacteremia from other etiologies tend to have better outcomes. In a cohort of bacteremic adults from a Veterans Affairs medical center, the mortality rate from bacteremia attributed to the urinary tract as the source (OR, 0.3; 95% CI 0.1-0.9) was lower than bacteremia from other sources.

Antibiotic Resistance

Antibiotic resistance is a large problem in the community, LTC, and acute hospital settings. UTI remains the most common reason antibiotics are prescribed in older adults, despite increased awareness of emerging resistance as a result of overtreatment. A substantial proportion of antibiotics are prescribed for asymptomatic infection or presentations without localizing urinary symptoms, fostering the development of increasingly resistant organisms.

Antibiotic resistance in the community Antibiotic resistance is no longer limited to the hospital setting. Primary care providers are responsible for a significant number of antimicrobial prescriptions in community-dwelling older adults and recent antibiotic use in the primary care setting has been shown to the be the most important risk factor for development of an infection with a resistant organism. Adults who receive an antibiotic for UTI are over four times more likely to develop a resistant organism within 1 month compared to adults not prescribed an antimicrobial agent. Although the risk is greatest at 1 month, resistance persists for up to 12 months in many patients. In one study of community-dwelling older women in Brazil, 32% of *E coli* isolates from urine cultures of patients with UTI were resistant to TMP/SMX and 42% of isolates from patients with ASB were resistant to TMP/SMX. Another larger study in London analyzed over 11,000 *E coli* isolates from urine cultures and found resistance to trimethoprim to be as high as 40%, although this study included both community and hospitalized patients. A population-based cohort study in Minnesota found the incidence of resistant *E coli* urinary isolates to FQ plus TMP/SMX in adults aged 80 years old or more to nearly double over a 4-year period (274–512 per 100,000 person-years, $p < 0.05$). TMP/SMX is still recommended as a first choice for empiric antibiotic selection among episodes of uncomplicated cystitis. This may be problematic given the increasing resistance rates, especially in adults who received an antibiotic prescription within the previous 12 months. FQs are no longer recommended as first line empiric treatment of UTI because of documented resistance rates of common uropathogens, consistently higher than 30% in most areas. Despite the increasing awareness of drug resistant pathogens in the community, overuse with antimicrobials for treatment of UTI remains. Community dwelling older adults may believe that antibiotic resistance is a hospital acquired condition and may not fully understand the risks associated with each antibiotic prescription. Primary care providers may feel that increasing resistance to antibiotics is largely out of their control. Further studies assessing patient and community physician understanding of antibiotic resistance, particularly as it relates to UTI, are needed.

Antibiotic resistance in LTCFs Over the past several years, increased awareness has been placed on infection control

practices and antibiotic stewardship programs in LTCFs, although inappropriate use of antibiotics remains high in this setting. Prevalence rates of colonization with antibiotic-resistant bacteria have been reported to be higher than 50% in some LTCFs. Observed cases of bacteriuria in LTC residents is associated with increased use of antibiotics and with isolation of multidrug resistant gram-negative rods. Among all urinary isolates of residents in five nursing homes in Connecticut, 26% were resistant to TMP/SMX, 40% were resistant to FQs, and 25% were resistant to cefazolin. The resistance rates to FQ in only *E coli* isolates was much higher at nearly 60%. *E coli* isolates were highly sensitive to nitrofurantoin (93%), although its sensitivity to all organisms was much lower at 68%. Similar to the community setting, high antibiotic prescriptions driving increasing resistance rates continues to be prevalent despite increased awareness. Qualitative studies have characterized some variables which drive inappropriate antimicrobial use in this setting. When antimicrobial therapy is prescribed, often, nursing personnel are evaluating patients and communicating their findings to physicians. Physicians may not assess patients directly.

Nursing personnel (ie, nurses and nurses' aides) are critical to identifying patients that are suspected of having UTI, requesting urine studies to be sent, and suggesting that antibiotic therapy may be warranted. Intervention studies developed to improve antimicrobial use for urinary infection in LTCFs have been reported. A comparative study in 24 nursing homes evaluated a diagnostic and treatment algorithm based on the consensus recommendations for initiating antimicrobial therapy for UTI. The assigned 12 nursing homes to receive the intervention, which included small group interactive sessions for nurses, videotapes, written material, outreach visits, and one-on-one interviews with physicians, were compared to 12 nursing homes allocated to usual care. They saw a small but significant decrease in antibiotic prescriptions for suspected UTI, but overall total antimicrobial use was similar. There are still opportunities for improvement in antimicrobial prescribing practices in LTC residents. These studies are urgently needed to help prevent the further antibiotic resistance.

CONCLUSION

UTI is the most common infection occurring in older populations. The management of UTI for older ambulatory individuals is similar to younger populations, and determined by the presentation as either acute uncomplicated urinary infection or complicated urinary infection. Treatment of symptomatic UTI requires optimal use of urine culture for diagnosis, appropriate antimicrobial selection, and appropriate duration of therapy. In the LTCF, the very high prevalence of ASB interferes with ascertainment of symptomatic infection, especially in residents without localizing genitourinary symptoms. Bacteriuric older individuals who present with clinical decline without localizing findings should not be assumed to have a urinary source, despite a positive urine culture. A critical approach to diagnosis, investigation, and treatment is necessary. Further characterization of symptomatic presentations of urinary infection in the functionally disabled older population, together with evaluation of management approaches such as nontreatment with observation compared with empiric antimicrobial treatment, is needed.

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Chapter 128

Human Immunodeficiency Virus Infection

Amy C. Justice

Learning Objectives

- Identify seniors at risk for HIV infection and include HIV testing in appropriate situations.
- Recognize HIV-associated non-AIDS conditions (HANA) that commonly afflict those aging with HIV.
- Integrate the principles of geriatrics (eg, management of multimorbidity and polypharmacy) into the care of HIV-infected patients.
- Recognize and address social isolation issues in those aging with HIV.

Key Clinical Points

1. **HIV is often unrecognized in older adults because of provider bias that older adults are not at risk and dismissal of clinical clues (frequent pneumonia, weight loss, progressive cognitive decline) as typical of older age.**
2. **HIV treatment has turned HIV into a chronic disease that one ages with over many decades. More than 50% of all people living with HIV in the United States are age 50 or greater.**
3. **While AIDS-associated conditions have declined markedly, comorbid illnesses occur more frequently than in age-matched, HIV-uninfected control populations leading to early multimorbidity, polypharmacy, and functional decline even in those with HIV controlled by antiretroviral therapy.**
4. **In those above 70 aging with HIV, social isolation is very common. Many have been estranged from family and have had friends die earlier in life; there are a number of social and clinical implications (eg, recognition of depression, need for support services in the community).**

DEFINITION

Human immunodeficiency virus (HIV) is a retrovirus that infects and destroys helper T cells leaving untreated patients vulnerable to opportunistic infections and cancers. HIV-1 is the most common subtype and is distributed worldwide. HIV-2 is primarily found in West Africa.

EPIDEMIOLOGY

One of the most amazing success stories of our lifetime is the transformation of HIV infection from a rapidly fatal disease to a chronic health condition. As a direct result of suppression of the HIV virus with antiretroviral therapy, transmission rates have also dropped. However, with one exception occurring in very exceptional circumstances (ie, bone marrow transplant), we have yet to cure anyone of HIV infection. As a result, a growing wave of people living, and aging, with HIV infection (**Figure 128-1**) are reaching middle and advanced age. As of 2010, 52% of those living

with HIV infection in San Francisco and 42% of those in New York City were 50 years of age or older. As of 2011, 70% of HIV-infected individuals receiving care within the national US Veterans Administration Healthcare System were 50 years of age or older. Across the United States, the percentage of adults living with HIV infection who are 50 years of age or older grew from 17.4% in 2001 to 36.2% in 2010.

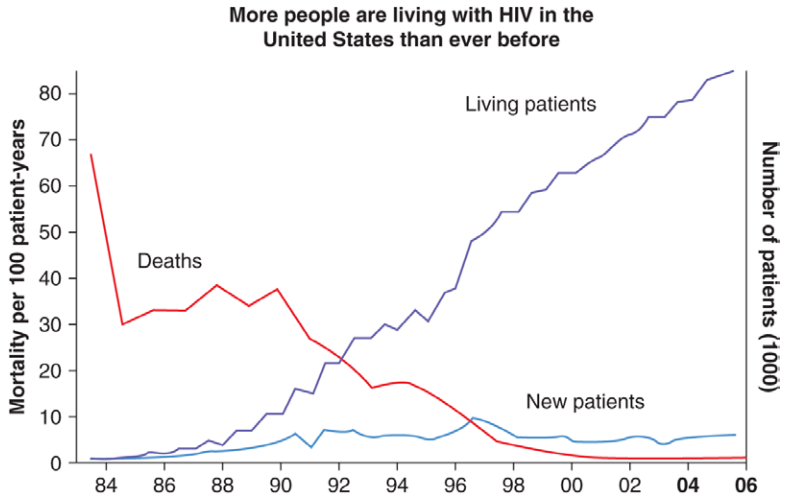


FIGURE 128-1. More people are living with HIV in the United States than ever before. (From www.aids2012.org.)

With increased prevalence, transmission rates are also likely to increase within this age group—especially among those who live in areas with relatively high geographic prevalence including Florida, New York, and Washington, DC. In addition to high local prevalence, ongoing risk behaviors and delayed diagnosis and treatment further enhance the risk of transmission. Those aging with HIV are more likely than other aging individuals to use various psychoactive substances including alcohol, marijuana, cocaine, and opioids which can both interfere with antiretroviral adherence and increase unsafe sexual encounters. Use of sildenafil (Viagra) and related medications to treat erectile dysfunction and enhance sexual performance may increase sexual risk behavior. Additionally, older men are less likely to use condoms and postmenopausal women may be less likely to request that they be used as they face no risk of pregnancy. Age-associated erectile changes may make condom use difficult, and age-associated declines in immunity may place older individuals at higher risk of transmission with each exposure. Finally, older individuals appear to present later in the course of HIV disease compared to younger individuals, extending the period of highest infectivity due to unsuppressed HIV-1 RNA.

Of note, research in age and aging with HIV is still in its infancy. To date, research has focused on comparing outcomes among persons aged 50 years and older to their younger counterparts and to age matched uninfected comparators. A threshold of 50 years of age for aging research is supported in HIV for both sociological and medical reasons: People aged 50 years and older with HIV often feel marginalized because of age and this group experiences a shortened survival and greater burden of comorbid disease. However, since most gerontological studies use a threshold of 65 years of age or even older thresholds, it will be important to study effects of HIV among those of more advanced age. In some cases interactions between HIV and comorbidities associated with aging may only become apparent at more advanced ages. This may be particularly true for neurocognitive disorders, cancer, lung disease, and cardiovascular disease.

Future research will need to differentiate people aging with HIV who have maintained suppressed HIV-1 RNA versus those with continued detectable virus. Susceptibility to HIV-associated non-AIDS conditions varies by level of viral suppression, and in some cases, by level of CD4 recovery after antiretroviral therapy (ART). We do not have a very clear idea of what happens among those in their seventh or eighth decade of life compared to similar aged uninfected individuals. Individuals who are diagnosed early in their disease process, achieve and maintain excellent HIV-1 RNA suppression, do not gain excess weight after ART initiation, and avoid ongoing substance use are likely to experience a very different aging trajectory from those who do not.

Importantly, the study of HIV infection among aging individuals may provide a template for improving the management of complex chronic disease more generally especially among special populations of aging individuals—people of color, sexual minorities, those with few socioeconomic resources, and those aging with heavy substance use histories. These groups are often ignored or understudied when more common conditions of aging are addressed.

PRESENTATION

Little is known about the presentation of acute HIV infection in older patients. In younger patients, acute infection may be completely asymptomatic or present as a flu-like syndrome. Like older HIV-uninfected individuals, older people with HIV infection underreport symptoms compared with younger individuals, and this underreporting may be especially pronounced in older black patients. In addition, the symptoms associated with HIV infection are also common among older patients without HIV infection.

Among those persons 50 years of age and older who are chronically infected with HIV and in care, the most common self-reported symptoms are fatigue, peripheral neuropathy, problems sleeping, muscle or joint pain (myalgias or arthralgias), problems with having sex, and cognitive difficulties. Prior to the start of antiretroviral therapy, people with HIV infection have lower body mass indices and lower cholesterol values than demographically matched controls. Common laboratory abnormalities include leucopenia, anemia (predominantly normocytic), transaminitis, and hyperproteinemia. Thus, unless the clinician has a high index of suspicion in the older patient, or routinely screens for HIV infection, it may be difficult to identify HIV-positive individuals. HIV-infected women enter menopause at a median age of 46 years compared to the median of 51 years among uninfected women. HIV-infected women also tend to experience more pronounced symptoms during menopause. Hypogonadism is also prevalent among men infected with HIV. Like the symptoms, signs, and laboratory abnormalities discussed above, most of the diagnoses made in older people with HIV are not unique to HIV infection.

EVALUATION

Physicians and their older patients are both likely to underestimate the risk of HIV infection. The patient may be misinformed or in denial. The physician may mistakenly believe that the patient has not had unprotected sex with multiple partners or used injection drugs—even in the remote past. Every major medical facility caring for those with HIV infection can recount multiple stories of older patients undergoing extended and expensive work-ups over the course of several months or even years until someone sends a test for HIV infection. Nationally, the median CD4 cell count at presentation for HIV has improved but these improvements have lagged by 50 to 100 cells for those 50 years of age and older.

Screening

Because untreated individuals who are unaware of their HIV infection are more likely to infect others and because benefit from antiretroviral treatment is less among those presenting with advanced disease, timely detection and treatment of HIV infection among older infected individuals is a growing concern. The Centers for Disease Control and Prevention and the US Preventive Services Task Force (USPSTF) currently recommend that clinicians screen adolescents and adults aged 15 to 65 years and all pregnant women, including those who present in labor and whose HIV status is unknown. They also recommend that younger adolescents and older adults should be screened if they are known to be at increased risk. All of these recommendations are grade A recommendations (USPSTF).

The Centers for Disease Control and Prevention goes further to say that opt-out screening (screening after notifying the patient that an HIV test will be performed unless the patient declines) is now recommended in all health care settings. Specific signed consent for HIV testing is no longer required. General informed consent for medical care is considered sufficient to encompass informed consent for HIV testing.

Regardless of age, any patient reporting any of the following: multiple sexual partners and unprotected sex; a prior diagnosis of a sexually transmitted disease (gonorrhea, syphilis, chlamydia, or trichomonas); or illicit drug use is at high risk for HIV infection and should be tested. Note that in some cases, an individual in a monogamous relationship may present with a sexually transmitted disease because their partner has more than one partner. These individuals are at risk for HIV as well and should be tested. While, intravenous drug use is a risk factor in itself; illicit drug use, IV or otherwise, is associated with risky sexual behavior. Hazardous alcohol use is also an important risk factor for unprotected sex with multiple partners. Because older patients may not spontaneously report these behaviors and conditions, physicians should routinely ask (**Table 128-1**).

TABLE 128-1 THE VETERANS AGING COHORT STUDY (VACS) INDEX

COMPONENT	LEVEL	POINTS

Age (years)	< 50	0
	50–64	12
	≥ 65	27
CD4 (cells/mm^3)	≥ 500	0
	350–499	6
	200–349	6
	100–199	10
	50–99	28
	< 50	29
HIV-1 RNA (copies/mL)	< 500	0
	500–99,900	7
	≥ 1×10^5	14
Hemoglobin (g/dL)	≥ 14	0
	12–13.9	10
	10–11.9	22
	< 10	38
FIB-4	< 1.45	0
	1.45–3.25	6
	> 3.25	25
eGFR (mL/min)	≥ 60	0
	45–59.9	6
	30–44.9	8
	< 30	26
Hepatitis C coinfection		5

HIV Testing

HIV testing should be conducted as part of a diagnostic workup in any patient with unexplained anemia, pancytopenia, peripheral neuropathy, oral candidiasis, herpes zoster, recurrent bacterial pneumonia, anal cancer, or any of the more traditional AIDS-associated conditions (*Pneumocystis carinii* pneumonia, Kaposi sarcoma, atypical mycobacterium, tuberculosis, non-Hodgkin lymphoma). Finally, any patient for whom more common causes of debilitating fatigue or weight loss have been eliminated should be tested for HIV.

The blood test that has been used for more than a decade is simple, accurate (sensitivity and specificity > 99.9%), and widely available. It involves two steps. The first step is a screening enzyme immunosorbent assay for HIV antibody. If this test is positive, a western blot is used to confirm the diagnosis. If the first test is negative, the patient is considered uninfected. Even in low-risk populations such as blood donors, the false-positive rate of these combined tests is low (< 0.001%). This somewhat cumbersome test is being replaced at many sites with a dual antigen-antibody test with similar accuracy. If positive, a confirmatory antibody test (not the traditional Western blot) is performed. If that test is negative, a quantitative PCR is then performed to document acute HIV infection. Of note, the diagnosis of acute HIV infection requires antigen detection testing since antibody will not yet be detectable.

When an individual tests positive, it is important to inform them of these results with as much care as you would any other life-changing diagnoses like that of cancer or diabetes. It is particularly important that you facilitate their integration into a clinical practice with substantial experience in the treatment of HIV infection. Comanagement may be needed if the patient has a substantial burden of age-related comorbid conditions or frailty.

Of note, home tests that employ a mouth swab (OraQuick In-home HIV test) or pricking your finger (Home Access HIV-1 Test System), akin to home glucose monitoring, are now readily available. While the blood test requires sending the sample in for centralized lab analyses and calling in for results, the mouth swab test results are available within 20 minutes and completely anonymous. Of note, the accuracy of the mouth swab test is not as high as the other

tests because the level of antibody in oral fluid is lower. This may result in delayed diagnosis. Up to 1 in 12 people who are infected may test negative with this test.

Life Expectancy/Staging/Prognosis

After acute infection, the natural history of HIV infection is usually one of progressive immunodeficiency reaching a symptomatic threshold within approximately 8 to 12 years after infection. If infection goes untreated, survival from the time of first AIDS-associated diagnosis is on the order of 1 to 2 years (median). Survival with current multiclass, combination antiretroviral therapy confers between 20 to 30 additional years of survival depending upon CD4 cell count and age at treatment initiation. Those who achieve HIV-1 RNA suppression before experiencing substantial CD4 cell count loss (ie, never experience a CD4 count below 500 cells/mL) appear to experience a near normal life expectancy so long as they maintain HIV-1 RNA suppression. Prognosis is poorer among those who present late for care, fail to adhere to their treatment regimen, and/or develop widely resistant virus.

Older individuals appear to adhere more effectively to antiretroviral therapy and are quite successful at achieving HIV-1 RNA suppression, but experience a slower improvement in CD4 cell count. They may also be more susceptible to short- or long-term adverse drug effects from antiretroviral therapy.

Age, CD4 cell count, level of HIV-1 RNA suppression after ART initiation, and routine markers of organ system injury including hemoglobin, creatinine, aspartate transaminase, alanine transaminase, platelet count, and hepatitis C status all confer additional information about prognosis. These clinical biomarkers have been organized into a widely validated prognostic index, The Veterans Aging Cohort Study (VACS) Index (http://medicine.yale.edu/intmed/vacs/welcome/vacsindexinfo.aspx see **Table 128-1**), which is predictive of all-cause mortality, HIV-specific and non-HIV causes of death, hospitalization, fragility fractures, functional performance, and neurocognitive performance. Changes in the VACS Index reflect response to antiretroviral therapy more completely than do isolated changes in CD4 cell count and HIV-1 RNA.

MANAGEMENT

Selection and Initiation of Antiretroviral Treatment

Once patients are diagnosed with HIV infection, initiation of antiretroviral therapy becomes a pressing concern both for the personal benefit of the patient and to prevent any further transmission of the virus. Older individuals experience higher HIV-1 RNA viral loads and a more rapid decline in CD4 cell count prior to treatment and experience delayed diagnosis and treatment compared to younger patients.

All individuals infected with HIV experience dramatic and sustained benefit from lifelong antiretroviral therapy. Standard regimens require multiple medications from multiple medication classes. The most common regimens require at least three daily medications, either a nonnucleoside reverse transcriptase inhibitor or a protease inhibitor and two nucleoside reverse transcriptase inhibitors. New classes are recently available and others are under development. Many patients in the United States now take a single coformulated tablet once a day. These newer medications have reduced adverse effects and increased rates of successful viral suppression. They also appear to be more tolerate of minor variations in adherence. In many settings 80% to 90% of those newly initiating ART achieve suppression of the HIV-1 RNA to below 50 copies/mL. and most are able to sustain this level of suppression for many years. There is a growing consensus that treatment should begin immediately after diagnosis, regardless of CD4 cell count. This strategy is likely cost effective as it minimizes risk of HIV transmission, AIDS defining illnesses, and later emergence of HIV-associated non-AIDS conditions.

There are now many antiretrovirals from which to choose and this selection should be informed by consultation with an experienced HIV care provider in light of an HIV-1 RNA viral resistance profile and careful consideration of preexisting organ system injury, mental illness, or, in the case of abacavir, genetic susceptibility to toxicity. Patients require close follow-up for the first several months of therapy to ensure that HIV-1 RNA suppression is achieved and that no concerning adverse events occur. After the first 6 to 12 months of therapy, if viral suppression is achieved, the patient has a CD4 count well above 350 cells/mL, and there are no active issues, patients may be monitored less frequently. While selection of antiretroviral regimens should be informed by an experienced HIV provider, once patients have achieved HIV-1 RNA suppression, their care might be managed by a primary care provider or geriatrician with consultation as needed.

Weight gain after ART initiation is common, clinically significant, and occurs even among those already

overweight or obese, likely due to the decreased metabolic demand that results from effective viral suppression. While some weight gain may be beneficial among those who are underweight or normal weight, because weight gain is associated with incident hypertension, hyperlipidemia, diabetes, and hepatic steatosis, those who are overweight or obese should be counselled to reduce caloric intake or increase exercising to avoid gaining weight after ART initiation.

Chronic Disease Management

Even for the patient achieving and maintaining HIV-1 RNA suppression, aging with HIV is not the same as aging without HIV infection. Chronic HIV infection is a complex disease in which it is often impossible to tell whether a new condition is the result of HIV, HIV treatment, or comorbidity (and/or treatment for the comorbidity). In many cases, the likely answer is that there is no single etiology but rather the conditions results from a combination of some or all of these factors.

No one is immune from HIV infection. Nevertheless, HIV infection occurs more commonly among the homeless, members of inner-city minority or sexual minority populations, or those suffering from psychiatric illness compared with the general population of people 50 years of age or older. General medical comorbidities such as hypertension, diabetes, hepatitis C, and obstructive lung disease are common in these populations. Depression and severe mental illnesses such as psychosis and posttraumatic stress disorder are also more common among older people with HIV infection than among the general population of people 50 years of age or older. Older people with HIV infection may have multiple reasons to have cognitive dysfunction, whether from cognitive diseases of aging (multi-infarct dementia or Alzheimer disease) or from HIV (minor cognitive motor disorder or HIV-associated dementia).

As noted above, people aging with HIV infection are at higher risk for a number of age associated chronic diseases also associated with HIV (HANA conditions). While they do not appear to experience any one of these conditions dramatically earlier than demographically similar uninfected individuals, they do appear to experience a greater overall burden of disease from multiple conditions as reflected in greater polypharmacy, higher levels of physiologic frailty as measured by the VACS Index, decreased functional performance, and more substantial neurocognitive issues.

As a group, patients infected with HIV who are aged 50 years or older are also more likely than uninfected demographic counterparts to have consumed hazardous amounts of alcohol, use illicit drugs (especially marijuana, cocaine, and opioids), and smoke cigarettes. These behaviors increase risk of liver, lung, and heart disease. They also increase risk for a number of common cancers and contribute to neurocognitive dysfunction.

Among patients who continue to drink hazardously and or to use illicit drugs, adherence to antiretroviral therapy and ongoing organ injury are likely to be important issues. Patients should be asked directly about alcohol, cigarette, and illicit drug use, and encouraged to stop or curtail ongoing use. Any patient reporting current drug or alcohol use should be questioned closely regarding treatment adherence and monitored for signs of organ system injury.

More than half of HIV-infected patients smoke. Smoking increases the risk of pulmonary disease, cancer, cardiovascular disease, and fragility fractures, and impairs immune response to ART. It clearly increases risk of mortality. Recent analyses suggest that smoking is associated with a greater number of lost life-years than that associated with treated HIV infection.

Thus, it is important to encourage patients to stop smoking. The average successful patient will attempt quitting several times before succeeding. There are many excellent programs available to assist patients in quitting including online help programs. The use of nicotine replacement therapies may facilitate quitting. Early data suggest greater quit rates with varenicline, but greater adverse events.

Surprisingly little is known about the chronic effects of marijuana among middle-age and older individuals but what is known among younger individuals suggests that chronic use is likely to impair antiretroviral adherence and cognitive functioning and may contribute to obesity. There are no established pharmacologic treatments for marijuana use, but cognitive behavioral therapy or brief motivational interviewing would likely be helpful.

Even moderate levels of alcohol consumption may be harmful among those aging with HIV infection. This is, in part, because HIV infection alters the absorption of alcohol resulting in higher blood levels of alcohol among those with untreated HIV infection compared with uninfected individuals for the same amount of alcohol consumed. It remains to be seen if this difference persists after successful ART. Of note, on-going alcohol use may also impair efforts to stop smoking, to maintain a healthy body weight, or to successfully treat depression. Cognitive behavioral therapy or brief motivational interviewing can be effective alone or in combination with pharmacotherapy for those who drink at higher levels.

HIV-Associated Non-AIDS Conditions

After ART initiation, the incidence of AIDS conditions as defined by the Centers for Disease Control and Prevention drops dramatically and conditions such as Kaposi sarcoma, if present at diagnosis, may resolve without additional treatment. However, the Strategies for Management of Antiretroviral Therapy (SMART) trial demonstrated that viral suppression through ART also decreases incident non AIDS conditions including liver disease, kidney disease, lung disease, and cardiovascular disease, there are conditions for which those with HIV infection appear at greater risk even after adjusting for all established risk factors. The list of these conditions continues to grow and includes cancers associated with viral infections (eg, Hodgkin lymphoma, anal cancer, liver cancer), lung cancer, cardiovascular disease, liver cirrhosis, chronic obstructive lung disease, and renal failure. A hallmark of these conditions is that they are more common among those with unsuppressed HIV-1 RNA and/or lower CD4 cell counts compared with HIV infected individuals with suppressed HIV-1 RNA or higher CD4 cell counts and most are less common after ART initiation.

While the evidence for the association of these conditions with HIV infection compared with demographically and behaviorally similar uninfected individuals continues to grow, the mechanistic explanation for this association is likely complex. Potential mechanisms include immune dysfunction, dysregulation, and suppression; chronic inflammatory stimulation due to reservoirs of HIV-1 RNA replication and to chronic microbial translocation; hypercoagulability; and direct effects of viral proteins. Thus the biomarkers most relevant to studying this phenomenon have yet to be established and likely depend, to some degree, upon the condition in question.

Polypharmacy

Once people with HIV initiate ART, typically in their third or fourth decade of life, polypharmacy (being on five or more chronic medications) becomes the norm a full decade before those without HIV experience this syndrome. Further, due to the sensitivity of many antiretrovirals to drug-drug interactions and substantial preexisting organ system injury among those with HIV, those with HIV infection may be particularly susceptible to the harms associated with polypharmacy. These harms include decreased medication adherence and increased serious adverse drug events including organ system injury, hospitalization, geriatric syndromes (falls, fractures, and cognitive decline), and all-cause mortality.

In addition to antiretroviral medication, common medication classes among HIV-infected individuals with polypharmacy include antihypertensives, diuretics, statins, antidepressants, antacids, and nonopioid analgesics. Many of these medications have well established drug-drug interactions with commonly prescribed antiretrovirals. Of note, HIV-infected individuals are also experiencing an increasing rate of chronic prescription opioid and benzodiazepine use as has been documented in the general population. Of equal concern are medications taken over the counter and dietary supplements, which are almost never accurately documented in the medical record and may be particularly problematic. Recent IDSA guidelines recommend review of the complete medication lists with thoughtful consideration and discussion with the patient to try to prioritize medications and simplify regimens whenever possible.

It will also be important to attempt to keep the number of total medications (for HIV and non-HIV conditions) down in order to avoid drug-drug interactions and cumulative toxicity and to screen regularly for evidence of liver, kidney, and bone marrow toxicity. Antiretroviral treatment timing and choice should be made balancing the individual’s cumulative organ system frailty and their likely risk of adverse events against the substantial benefit of early and aggressive HIV treatment.

Hepatitis C

A large proportion of those with HIV infection in the United States are also infected with hepatitis C. The recent availability of highly effective and less toxic treatment for hepatitis C raises additional issues. HIV-infected individuals with hepatitis C coinfection experience more rapid progression of liver cirrhosis and a heighted risk of hepatocellular cancer. Recent data have demonstrated that suppression of HIV-1 RNA with antiretroviral treatment slows progression of liver disease among those coinfected with hepatitis C. Unlike HIV infection, hepatitis C can be cured. Given the substantial risk for cirrhosis, liver failure, and hepatoma among these individuals, it would seem appropriate to consider treating coinfected individuals earlier rather than later in the course of their disease.

Finding a Balance

The challenge for the aging patient with HIV infection and their provider is to balance screening and treatment for high risk, modifiable conditions including cancer, hypertension, hyperlipidemia, hepatitis C, and substance use against

harm from polypharmacy. Whether or not a particular primary care practice is appropriate for an individual with HIV depends upon the individual's life expectancy, the frequency and impact of the condition, the degree to which outcomes associated with that condition can be modified by timely medical intervention, and the risk associated with the intervention. For example, colon cancer screening via colonoscopy has a slight risk of perforation at the time of screen and a substantial risk of discomfort for the patient. Patients need to live at least 5 to 7 years after their screening for the benefit of the screening in decreased risk of death from colon cancer to outweigh the risk of perforation and the pain and discomfort of the procedure. Conversely, more aggressive screening for anal cancer may be indicated because of the increased incidence of this condition among those with HIV infection. Thus, it would be unwise to apply all "age appropriate" primary care guidelines for those without HIV to those with HIV infection without careful consideration for the individual's prognosis, preferences for care, and personal risk of these conditions.

Finally, multimorbidity is the norm among those aging with HIV infection (**Figure 128-2**). Because of the overlapping complications and comorbid medical and psychiatric disease experienced by most patients with HIV infection, comprehensive care requires a team approach. No one specialist or generalist can hope to stay on top of optimal care in all these domains. HIV specialists need to turn to generalists and geriatricians when determining the best way to manage overlapping comorbid medical disease and to psychologists, psychiatrists, and social workers when managing psychiatric diseases. The management of alcohol and drug abuse also requires the insights of generalists familiar with the medical complications of these behaviors and of psychiatrics, psychologists, and social workers familiar with methods of managing these behaviors. In turn, generalists and geriatricians will need careful guidance from HIV specialists in determining when to start antiretroviral treatment, choosing optimal drug combinations, and determining when to stop or change therapy. For those who must manage patients far from specialty services, frequent telephone conferencing with specialists in HIV and with those experienced in the management of comorbid conditions is recommended.

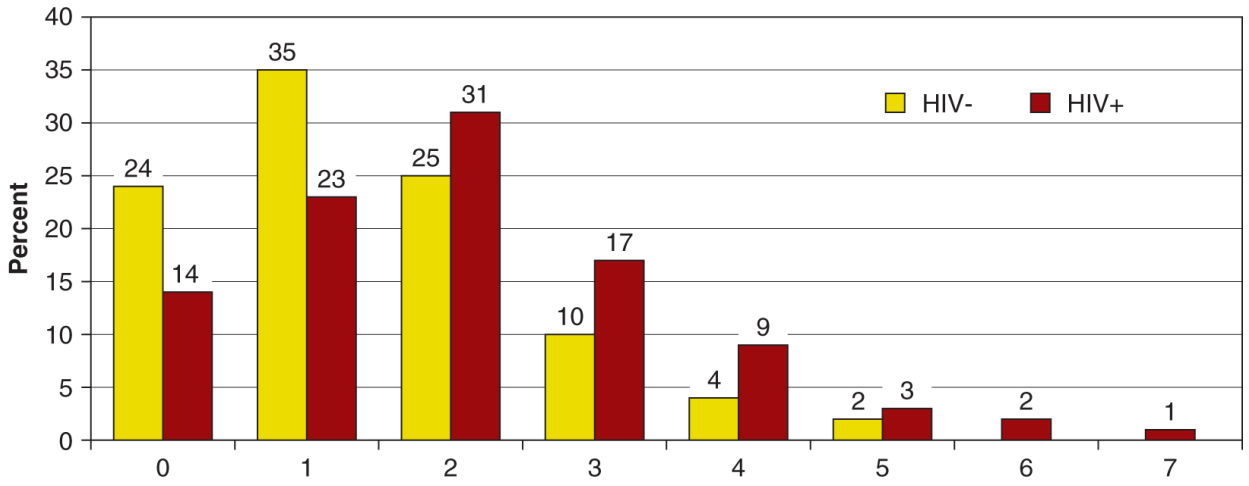


FIGURE 128-2. Multimorbidity is the norm among those aging with HIV infection. Comparison of comorbid disease counts by HIV status. Conditions counted were diabetes, obstructive lung disase, liver disease, anemia, obesity, kidney disfunction, and hypertension. (Adapted from Salter ML et al. *Clin Infect Dis*. 2011;53(12):1256–1254.)

PREVENTION

HIV can be transmitted from one human to another when blood, semen, preseminal fluid, rectal fluids, vaginal fluids, or breast milk come into contact with a mucous membranes or damaged tissue or are directly injected into the bloodstream. The most common causes of transmission are unprotected sexual contact (risky sex) and sharing used needles during injection drug use ("dirty" needles). Transmission can also occur during pregnancy, childbirth, breast feeding, accidental needle punctures (medical occupational exposures), blood or blood product transfusion. HIV is not spread by air, water, mosquitoes or ticks, saliva, tears, sweat, casual contact, drinking fountains, or toilet seats.

The single most effective means of preventing HIV transmission is early diagnosis and treatment of those infected with HIV. This is because HIV-1 RNA viral suppression through antiretroviral therapy dramatically alters the risk of transmission given an exposure. It is also because people who are aware of their HIV status are more likely to alter their risk behaviors by using condoms, decreasing sexual activity, etc. Other means of prevention include pre-exposure

prophylaxis (PrEP) for individuals known to be at very high risk of transmission (eg, serodiscordant couples) and use of condoms.

SPECIAL ISSUES: HEALTH POLICY IMPLICATIONS

Health care systems are seeing an increasing proportion of older HIV-infected individuals presenting for care. These trends reflect in part new seroconversion at more advanced age and, in part, late presentation for care. Based on CD4 count at presentation among European and North American cohorts, older individuals present at a later stage of disease progression than do their younger counterparts and later presentation is associated with poorer clinical response to ART. Older people with HIV infection are dramatically more likely to experience social isolation (**Figure 128-3**). Further, people aging with HIV are substantially more likely to be hospitalized, to experience MICU admission, and polypharmacy. Those with HIV are also more likely to have other chronic viral infections including hepatitis C, hepatitis B, CMV, and HPV. How these patients and their many transitions between inpatient and outpatient care, general medical care and specialty care, and skilled nursing facility care will best be managed in the future remains to be seen. What is nearly certain is that they will place new demands on parts of the health care system including short- and long-term nursing facilities that have previously not managed those with HIV infection in any substantial numbers.

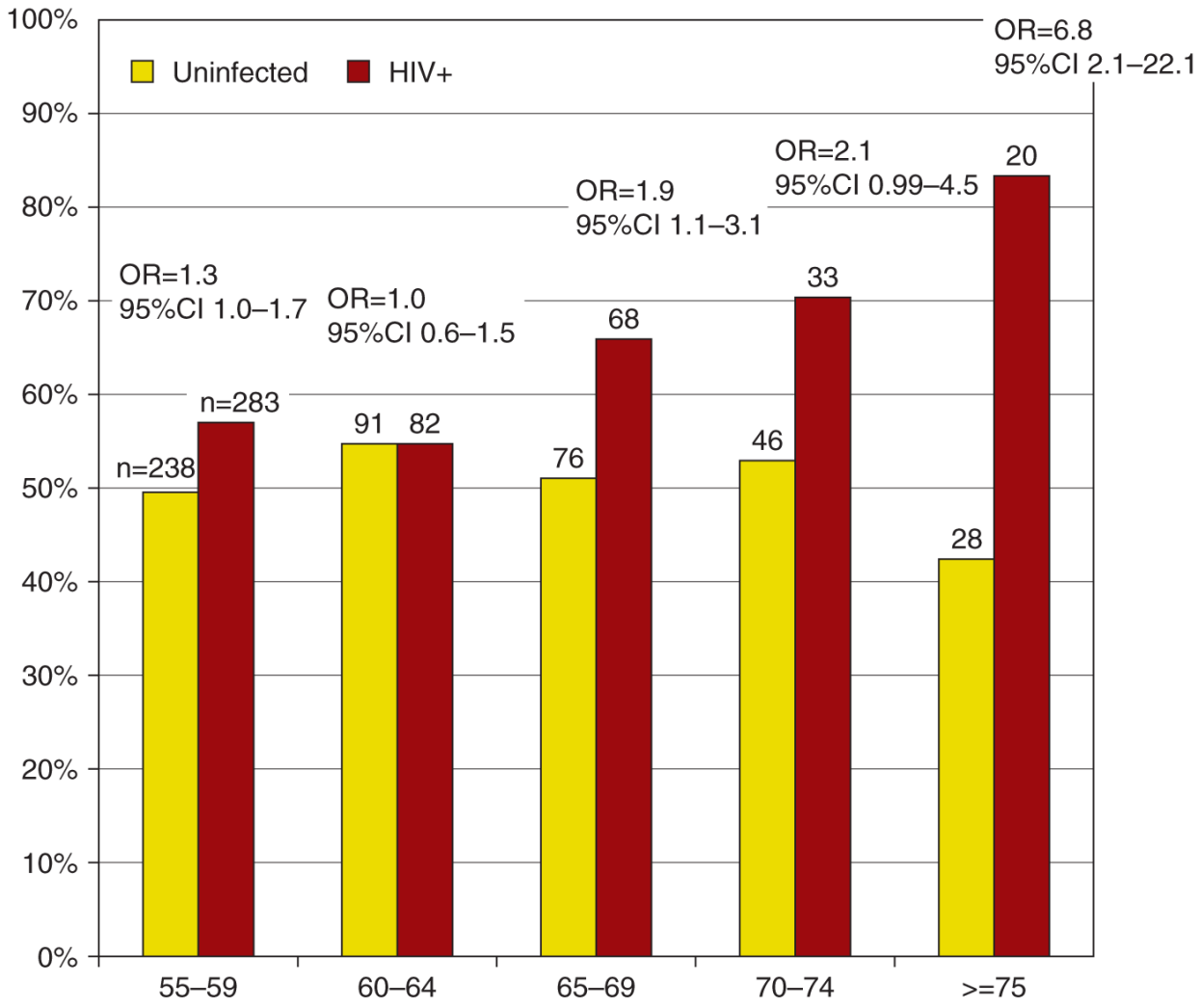


FIGURE 128-3. Social isolation by HIV status and age in the Veterans Aging Cohort Study (VACS). (Adapted from Greyson SR et al. *J Am Geriatr Soc*. 2013;61(9):1456–1463.)

Geriatricians should actively consider screening patients for HIV infection, especially if they live in areas of high local prevalence. Geriatricians will also be increasingly needed to comanage effects of aging and cumulative frailty; comorbid medical and psychiatric conditions; and polypharmacy. They will also need to advise administrators in

skilled nursing facilities and nursing homes on how to appropriately care for these patients.

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Chapter 129

Herpes Zoster

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Learning Objectives

- To understand the impact of aging on the incidence of herpes zoster and postherpetic neuralgia (PHN).
- To recognize typical and atypical presentations of herpes zoster in older adults.
- To know when to order microbiological testing for the diagnosis of herpes zoster and what tests to order.
- To employ the appropriate use of different treatments for the management of herpes zoster and PHN.
- To summarize Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC), recommendations for the use of the zoster vaccine.

Key Clinical Points

1. **All cases of herpes zoster are caused by the reactivation of endogenous varicella-zoster virus (VZV) from latent infection of dorsal sensory or cranial nerve ganglia and not by exogenous transmission of VZV from an individual with herpes zoster or varicella.**
2. **Increasing age and impaired cellular immunity are the strongest risk factors for herpes zoster; other risk factors include white race, female sex, psychological stress, and physical trauma.**
3. **Increasing age is the strongest risk factor for postherpetic neuralgia (PHN); other risk factors include the presence of prodromal pain, severe pain during the acute phase of herpes zoster, and greater rash severity.**
4. **Although the diagnosis can be made on clinical grounds in the majority of cases with a typical dermatomal vesicular rash and pain, laboratory diagnostic testing is indicated when differentiating herpes zoster from HSV, for suspected organ involvement, and for atypical presentations, particularly in the immunocompromised host; polymerase chain reaction (PCR) of vesicular fluid is the preferred diagnostic test.**
5. **The goal of the treatment of herpes zoster in older adults is to decrease the length of the acute attack and to reduce pain by the use of early antiviral therapy (acyclovir, famciclovir, valacyclovir), scheduled analgesia, and if the pain is not adequately controlled, adjunctive agents.**
6. **Lidocaine patch 5%, gabapentin, pregabalin, opioids, and tricyclic antidepressants constitute first-line therapies for the management of PHN.**
7. **Zoster vaccine is recommended for all immunocompetent adults 60 years of age and older by ACIP for the prevention of herpes zoster and PHN.**

DEFINITION

Herpes zoster is a neurocutaneous disease that is caused by the reactivation of varicella-zoster virus (VZV) from a latent infection of dorsal sensory or cranial nerve ganglia following primary infection with VZV earlier in life. Herpes zoster is characterized by unilateral, dermatomal pain and rash. Postherpetic neuralgia (PHN) is pain 90 or more days

after rash onset.

EPIDEMIOLOGY

VZV Transmission

Varicella-zoster virus is a double-stranded DNA herpesvirus that is transmitted from person to person via direct contact or airborne or droplet nuclei when a virus-naive individual is exposed to the vesicular rash of varicella or herpes zoster. These exposed individuals may then develop varicella. Health care workers and staff in nursing homes and hospitals and children who have not received the varicella vaccine may not have had VZV primary infection and are potentially at risk for varicella. However, nearly all older adults are seropositive and latently infected with VZV. The exposure of a latently infected individual to herpes zoster does not cause herpes zoster or varicella. All cases of herpes zoster are caused by the reactivation of endogenous VZV.

Herpes Zoster Incidence and Risk Factors

In general population studies from North America and Europe, the estimated incidence of herpes zoster in persons older than age 65 years varies from approximately 10 to 14 cases per 1000 per year. The lifetime incidence of herpes zoster is estimated to be about 20% in the general population and may be as high as 50% among those surviving to 85 years or older. Current population figures and herpes zoster incidence data yield estimates of about 1 million new cases of herpes zoster each year in the United States.

The cardinal epidemiological feature of herpes zoster is its increase in incidence with aging and with diseases and drugs that impair cellular immunity. The increase in the likelihood of herpes zoster with aging starts around 50 to 60 years of age and increases into late life in individuals older than 80 years of age (**Figure 129-1**). Immunocompromised patients at risk for herpes zoster include persons with human immunodeficiency virus (HIV) infection, Hodgkin disease, non-Hodgkin lymphomas, leukemia, hematopoietic stem cell or solid organ transplant, systemic lupus erythematosus, and those taking immunosuppressive medications. Other risk factors include white race, female sex, psychological stress, and physical trauma.

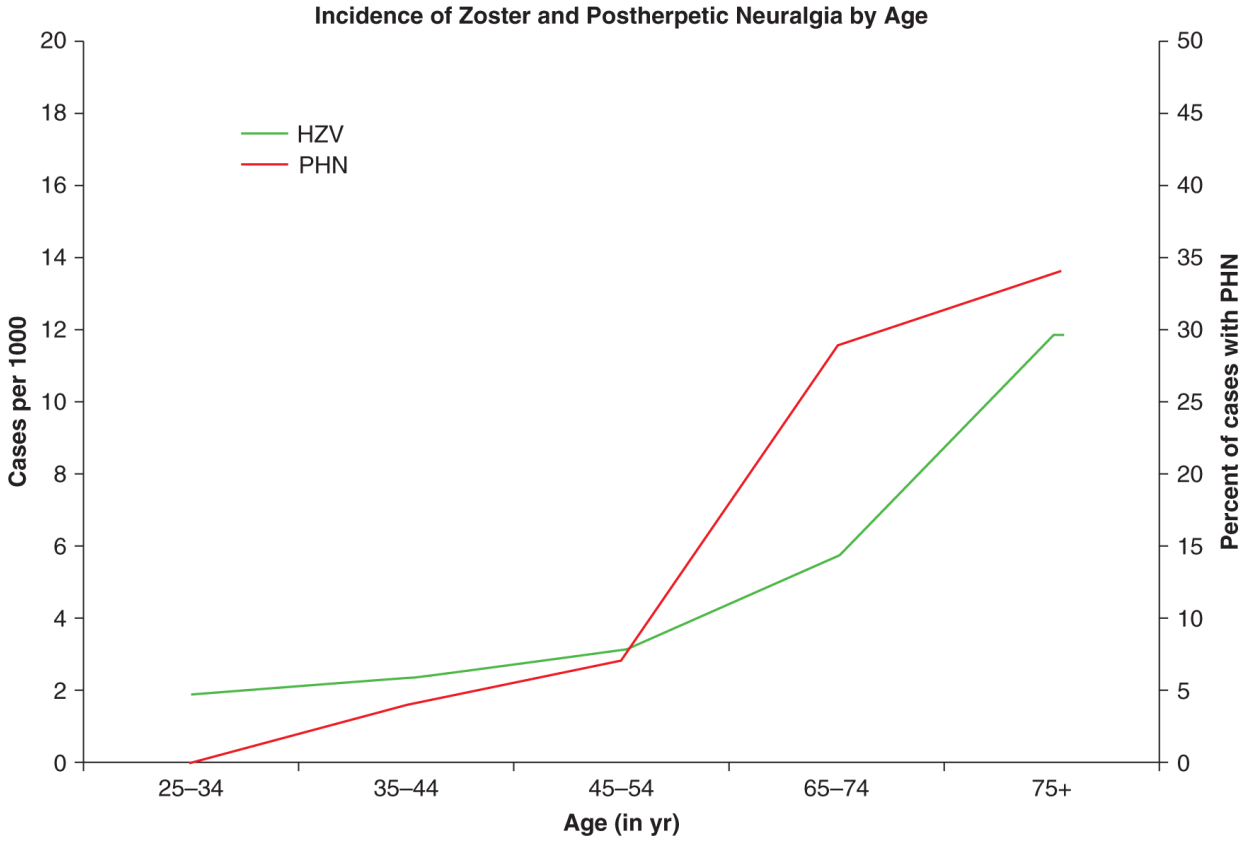


FIGURE 129-1. Incidence of zoster and postherpetic neuralgia by age. (Data from Donahue JG, Choo PW, Manson JE, et al. The incidence

of herpes zoster. *Arch Intern Med*. 1995;155:1605–1609; Choo PW, Galil K, Donahue JG, et al. Risk factors for postherpetic neuralgia. *Arch Intern Med.* 1997;157:1217–1224.)

Postherpetic Neuralgia Incidence, Prevalence, and Risk Factors

Exact data on the incidence and prevalence of PHN are not available because of variable definitions and inadequate data in medical records and administrative databases. In the placebo group of the Shingles Prevention Study, the incidence of PHN was 0.74 cases per 1000 person-years for subjects between 60 and 69 years and 2.14 for subjects older than 70 years (**Figure 129-1**). The figure illustrates that the rate of increase of PHN cases associated with aging is greater than the rate of increase of herpes zoster cases. Investigators have estimated that the prevalence of PHN ranges from 500,000 to 1 million in the United States.

Like herpes zoster, the most important epidemiological feature of PHN is its marked increase in incidence and severity with aging. Other risk factors for PHN include the presence of prodromal pain, severe pain during the acute phase of herpes zoster, greater rash severity, more extensive sensory abnormalities in the affected dermatome, and, possibly, ophthalmic nerve involvement. As the age of a patient and severity of the episode of herpes zoster increase, PHN becomes more likely.

PRESENTATION

VZV reactivates in the affected sensory ganglion and spreads in the peripheral sensory nerve, causing prodromal symptoms that frequently precede the rash by several days. These prodromal symptoms are located in the involved dermatome and range from a superficial itching, tingling, or burning to severe, deep, boring, or lancinating pain, paresthesia, or hyperesthesia. The pain can be constant or intermittent. The prodrome may be mistaken for many other conditions in older adults, including pleurisy, a myocardial infarction, cholecystitis, appendicitis, renal colic, a collapsed intervertebral disk, glaucoma, trigeminal neuralgia, or unappreciated trauma. The prodromal symptoms usually last a few days, although they have been reported to last more than a week. Zoster sine herpete is a condition when patients experience acute dermatomal neuralgia without ever developing a skin eruption.

When VZV reaches the dermis and epidermis, the initial cutaneous presentation of herpes zoster occurs as a unilateral, dermatomal, red, maculopapular eruption. Vesicles generally form within 24 hours and evolve into pustules, which dry and crust in 7 to 10 days. The rash usually heals over in 2 to 4 weeks. In normal individuals, new lesions may continue to appear for 1 to 4 days and occasionally for as long as 7 days. The T1 to L2 or V1 dermatomes are most commonly involved (**Figure 129-2**). Atypical rashes may occur in older persons. The atypical rash may be limited to a small patch located within a dermatome or may remain maculopapular without ever developing vesicles.

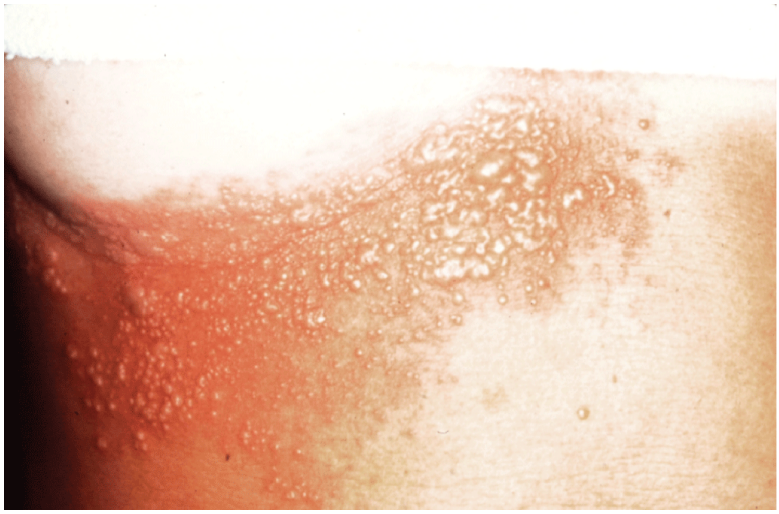


FIGURE 129-2. A patient with herpes zoster illustrates a range of lesions (eg, large pustules, erythematous papules, and crusting).

Herpes zoster–associated acute neuritis produces dermatomal neuralgic pain in many older adults. Some older patients never develop pain while others may experience the delayed onset of pain days or weeks after rash onset. The neuritis is described as burning, deep aching, tingling, itching, or stabbing. A subset of patients may develop severe

pain, especially those with trigeminal nerve involvement. Acute herpes zoster pain can interfere with all activities of daily living but interference is greatest for instrumental activities of daily living, as well as sleep, general physical activity, and leisure activities. As overall pain burden increases, patients experience poorer physical, role, and emotional functioning.

The most feared complication of herpes zoster among older adults is PHN. PHN patients describe the quality of their pain as burning, throbbing, stabbing, shooting, sharp, aching, gnawing, tiring, or tender. The pain may be spontaneous and/or stimulus-evoked. Spontaneous pain may be constant aching or burning and/or brief, intermittent shock-like sensations. Stimulus-evoked pain consists of allodynia or hyperpathia. Allodynia is pain elicited by an innocuous stimulus and is particularly problematic. A cold wind, clothes, or bed sheets against the allodynic skin may cause debilitating pain. Hyperpathia is an exaggerated pain after a mildly painful stimulus. A minor bump of the affected dermatome against an object can cause severe pain that lasts for hours. Patients may experience discomfort that is not described as pain such as numbness or itching. Postherpetic itch can be maddening and appears to be mediated by damage and dysfunction of peripheral and central itch-specific neurons.

PHN greatly interferes with the functional status and quality of life of older adults. Patients can suffer from a variety of constitutional symptoms including chronic fatigue, anorexia, weight loss, and insomnia. PHN is associated with depression and social isolation in older adults. Reduced quality of life and interference with activities of daily living (ADLs) increase significantly as pain severity increases. Instrumental and basic ADLs are all compromised by PHN. For example, the patient with allodynic skin may be forced to avoid bathing or clothing around the affected area. Instrumental ADLs commonly affected include traveling, shopping, cooking, and housework. Studies using standardized pain scales and measures of function and quality of life such as the SF-36, SF-12, EuroQol, and Nottingham Health Profile have shown that PHN significantly interferes with multiple ADLs, reduces health-related quality of life (HRQL), and impairs mental and physical health.

Other complications include ocular inflammation in the setting of ophthalmic herpes zoster, cranial neuropathies, myelitis, visceral involvement, and motor paralysis. VZV-induced damage to the cornea and uvea and other eye structures can cause corneal anesthesia and ulceration, glaucoma, optic neuritis, eyelid scarring and retraction, visual impairment, and blindness in patients who did not receive antiviral therapy. Ophthalmic herpes zoster is also associated with stroke occurring weeks to months after the onset of the rash. Involvement of the third division of cranial nerve V can produce lesions and pain in the mandibular area of the face and in the mouth. Cranial nerve VII and VIII involvement, or Ramsey Hunt syndrome, is characterized by facial palsy in combination with herpes zoster lesions of the ipsilateral external ear, ear canal, tympanic membrane, or hard palate. Symptoms include tinnitus, vertigo, deafness, problems with balance, and facial paresis. Involvement of cranial nerves IX and X may produce pharyngeal or laryngeal lesions and resulting pharyngitis or laryngitis. Motor paralysis, from VZV-induced destruction of motor neurons in the anterior spinal horn or motor radiculitis corresponding to the extension of VZV infection from the involved sensory ganglion, involves muscle groups with innervation that is contiguous with that of the affected dermatome. Painful Bell palsy in an older adult strongly suggests herpes zoster.

EVALUATION

In patients who present with prodromal pain and no rash, herpes zoster is often confused with other causes of unilateral, localized pain in older adults. One diagnostic clue to the presence of prodromal pain is localized cutaneous sensory abnormalities (eg, hyperesthesia, dysesthesia) in the affected dermatome. Herpes zoster is easily diagnosed when an older adult patient presents with the typical dermatomal vesicular rash and pain. During the rash phase, herpes simplex has the most similar presentation to herpes zoster. Evidence supporting herpes simplex includes a presentation in a younger population, multiple reoccurrences of lesions, and the absence of chronic pain. The lesions themselves are more difficult to distinguish, particularly when herpes zoster occurs in areas commonly affected by simplex (eg, oral, genital, buttock lesions). The differential diagnosis also includes contact dermatitis, burns, and vesicular lesions associated with fungal infections but the history and examination usually makes the distinction clear.

The diagnosis of herpes zoster may need laboratory diagnostic testing when differentiating herpes zoster from HSV infection is necessary, for suspected organ involvement, and for atypical presentations, particularly in the immunocompromised host. The preferred diagnostic test is polymerase chain reaction (PCR) because it is highly sensitive and specific and results are available within hours of specimen receipt. The best specimen is vesicle fluid, which contains abundant VZV. Lacking vesicle fluid, acceptable specimens include lesion scrapings, crusts, tissue biopsy, or cerebrospinal fluid.

MANAGEMENT

Acute Herpes Zoster

The principal goal of the treatment of herpes zoster in older adults is to decrease the length of the acute attack and to reduce or eliminate pain. Patients should be instructed to keep the rash clean and dry to decrease the chances of developing bacterial superinfection. Cool compresses, calamine lotion, cornstarch, or baking soda may help to reduce local symptoms and speed the drying of the vesicles.

Antiviral Therapy

The guanosine analogs, acyclovir, famciclovir, and valaciclovir, are phosphorylated by viral thymidine kinase to a triphosphate form that inhibits VZV DNA polymerase and VZV replication. Valaciclovir and famciclovir are prodrugs, which have greater bioavailablity, resulting in higher blood levels and a less frequent dosing schedule. Randomized controlled trials indicate that oral acyclovir (800 mg five times a day for 7 days), famciclovir (500 mg every 8 hours for 7 days), and valaciclovir (1 g three times a day for 7 days) reduce acute pain and the duration of chronic pain in older patients with herpes zoster who are treated within 72 hours of rash onset. The most common adverse effects are nausea, vomiting, diarrhea, and headache. The effectiveness of antiviral agents has not been evaluated for treatment after 72 hours have elapsed since the onset of rash. An exception to the 72-hour threshold for treatment is made for patients who have ophthalmic zoster or patients that continue to have new vesicle formation. Topical antiviral therapy is not an effective treatment.

Analgesics

Acute herpes zoster pain requires the use of standardized pain measures, scheduled analgesia, and close monitoring to adjust dosing and detect adverse effects. Opioid and nonopioid analgesia are a standard of care for the acute pain syndrome. The choice of treatment will depend on the patient's pain intensity, comorbidities, and preferences. Patients with mild pain may be managed with acetaminophen or nonsteroidal agents. Patients with moderate to severe pain usually require treatment with an opioid analgesic (eg, oxycodone).

Corticosteroids

The anti-inflammatory effects of corticosteroids have been postulated to reduce herpes zoster symptoms but there remains controversy over their use. Randomized, controlled clinical trials demonstrated that corticosteroids do not prevent PHN when compared to placebo or acyclovir. These findings, the risk of VZV dissemination, and the adverse effects of corticosteroids in older adults argue against the routine use of these agents in herpes zoster. However, clinical trials have shown reductions in acute pain and one randomized controlled trial showed benefits in improvement in time to uninterrupted sleep, return to routine activities, and cessation of analgesic medications among patients with no relative contraindications to corticosteroids. In the trial, prednisone was administered orally at 60 mg/day for days 1 to 7, 30 mg/day for days 8 to 14, and 15 mg/day for days 15 to 21. Therefore, corticosteroids may be useful in reducing moderate to severe acute pain unrelieved by antiviral agents and analgesics. Corticosteroids are used to treat VZV-induced facial paralysis and cranial polyneuritis to improve motor outcomes and provide pain relief. If prescribed, corticosteroids should always be used in conjunction with antiviral agents.

Adjuvant Agents

If moderate-to-severe herpes zoster pain is inadequately relieved by antiviral agents in combination with oral analgesic medications and/or corticosteroids, then other therapies to consider include gabapentin or pregabalin or neural blockade. The use of these anticonvulsant agents must be balanced against adverse effects of sedation, dizziness, ataxia, and peripheral edema. A randomized controlled trial of antiviral therapy, oral analgesics, and a single epidural block with bupivacaine and methylprednisolone compared to antiviral therapy and oral analgesics alone showed that neural blockade reduces acute pain but does not prevent PHN.

Ophthalmic zoster with ocular involvement requires ophthalmological consultation. Oral antiviral and analgesic therapy is the mainstay of treatment as it is for herpes zoster presenting on the rest of the body but other ocular therapies may be necessary. These treatments are best managed by an ophthalmologist and include antibiotic

ophthalmic ointment to prevent bacterial infection of the ocular surface, topical steroids to reduce ocular inflammation, mydriatics as needed for iritis, and ocular pressure-lowering drugs as needed for glaucoma.

Postherpetic Neuralgia

Oral and topical pharmacotherapy Based on evidence of effectiveness from clinical trials and safety in older adult populations, tricyclic antidepressants (TCAs), gabapentin, pregabalin, lidocaine patch, and opioids are considered first-line therapies because one or more high-quality randomized controlled trials demonstrated efficacy with these agents (**Table 129-1**). Gabapentin, pregabalin, the topical lidocaine patch 5%, and the topical capsaicin patch 8% are approved by the FDA for the treatment of PHN.

TABLE 129-1 MEDICATION FOR MANAGING POSTHERPETIC NEURALGIA

MEDICATION	ADVERSE EFFECTS	BEGINNING DOSE	TITRATION
Lidocaine 5% patch	Dysesthesia, vesicular rash, ulcerations, edema, or erythema at the application site	Maximum of 3 patches daily for a maximum of 12 h	None needed
Gabapentin	Somnolence, dizziness, ataxia, peripheral edema, and cognitive impairment	100–300 mg at night	Increase by 100–300 mg/d every 1–7 d as tolerated in divided doses up to three times a day, maximum 3600 mg daily
Pregabalin	Somnolence, dizziness, ataxia, peripheral edema, and cognitive impairment	50–150 mg daily two to three times a day	Increase to 300 mg/d, given in 2 or 3 divided doses within 1 wk; maximum dose generally 300 mg in older adults
Tricyclic antidepressant nortriptyline	Dry mouth, sedation, constipation, and less risk for cognitive impairment and orthostatic hypotension	10–25 mg qhs	Increase by 10–25 mg daily Every 3–7 d as tolerated; maximum dose 75–150 mg daily
Opioid oxycodone (dosage given for morphine equivalents)	Constipation, nausea, sedation, impaired cognitive function, and falls	2.5–15 mg every 4 h as needed	After 1–2 wk, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed
Tramadol	Constipation, nausea, sedation, impaired cognitive function, orthostasis, and falls	25 mg once daily	Increase by 25–50 mg daily in divided doses every 3–7 d as tolerated; maximum 300 mg daily in patients older than 75 y of age
Capsaicin 8% patch	Burns, increase in blood pressure, avoid contact with eye, mucous membranes	Apply patch to most painful area for 60 min; specialized application procedure	None needed

Topical treatments The topical lidocaine patch 5% reduced PHN in randomized vehicle-controlled trials. In one trial, which also included other neuropathic pain patients, the percentage of patients who obtained 50% reduction in pain was 31% with the lidocaine patch compared to 8% with placebo patch. Up to three patches may be applied over the affected area for 12 hours a day. It may take up to 2 weeks for these treatments to reach full effectiveness. Systemic lidocaine toxicity has not been reported from topical lidocaine.

Capsaicin, a *trans*-8-methyl-*N*-vanillyl-6-nonenamide, is known to deplete substance P, an endogenous neuropeptide that is involved in the transmission of nociceptive impulses from the sensory nerve endings to the central nervous system. Topical capsaicin is available in creams, gels, or lotions in concentrations from 0.025%, 0.075%, and 0.25% and as an 8% patch. The lower dose formulations were shown to have a statistical benefit in studies but clinical effects were small. Combined data from randomized, controlled trials of the 8% patch showed the percentage of patients with a 30% or greater reduction in pain score was 45% with the 8% patch compared with 36% with the control (P = 0.0035). Many patients are unable to tolerate the burning that capsaicin causes. Nonetheless, topical capsaicin may be considered as a backup therapeutic option in PHN because it may be effective in individual

circumstances. The patch requires application in a clinic by personnel who are trained in the proper application.

Gabapentin and pregabalin Gabapentin is an anticonvulsant that has become a popular treatment partly because two randomized, placebo-controlled studies showed a significant clinical benefit in pain relief with gabapentin and partly because of the favorable side effect profile. In those trials, 41% to 43% of patients on gabapentin reported moderate or better pain improvement compared to 12% to 23% of those on placebo. Patients who do not have at least partial relief at 1800 mg are unlikely to benefit from higher doses of gabapentin. Frail older patients often need smaller doses because of problems tolerating higher doses. Doses should be adjusted for creatinine clearance. Adverse effects include somnolence, dizziness, ataxia, and peripheral edema. Cognitive impairment may also occur in older patients.

Pregabalin is an anticonvulsant that is similar in structure and action to gabapentin. In placebo-controlled trials, the proportion of patients with more than 50% decrease in mean pain scores was 50% in the pregabalin group compared to 20% in the placebo group. The adverse effect profile of pregabalin is similar to gabapentin with dizziness, somnolence, peripheral edema, dry mouth, and gait disturbances as the most common adverse effects. The drug has few drug-drug interactions, can be given less frequently than gabapentin, and has a relatively rapid onset of action. Other anticonvulsants (eg, phenytoin, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, valproate) are possibly useful but cannot be considered first-line agents because of limited data for efficacy and/or significant adverse effects.

Tricyclic antidepressants TCAs modulate nerve transmission. Multiple randomized controlled trials of TCAs demonstrated significant pain relief in patients with PHN with 44% to 67% of patients treated with TCAs reporting moderate to good pain relief compared to 5% to 19% of placebo of control drug recipients. In the only head-to-head comparison, nortriptyline demonstrated equivalent efficacy and was better tolerated when compared to amitriptyline in a PHN. Nortriptyline and desipramine are preferred over amitriptyline because they have less anticholinergic effects, resulting in less dry mouth, sedation, constipation, cognitive impairment, and orthostatic hypotension. Tricyclic antidepressants are contraindicated in patients with QT prolongation, familial histories of long-QT syndromes, atrioventricular block, bundle-branch block, or a recent acute myocardial infarction. An ECG looking for QT prolongation or heart block should be evaluated before initiating therapy and with each change in dose. Caution is necessary in the concomitant administration of TCAs and selective serotonin reuptake inhibitors (SSRIs). Tricyclic antidepressants are metabolized by the cytochrome P450 D26 enzyme system and SSRIs, especially fluoxetine, inhibit P450 D26 so toxic TCA plasma concentration could result.

Opioid and opioid-like analgesics In a randomized, crossover trial showing significant pain relief with oxycodone, 67% of patients expressed preference for oxycodone compared to 11% of the placebo recipients. In another crossover study of PHN comparing opioid analgesics, TCAs, and placebo, controlled-release morphine and TCAs provided statistically significant benefits on pain relief. Patients preferred treatment with opioid analgesics compared to TCAs and placebo despite a greater incidence of side effects and more drop-outs during opioid treatment.

Although oxycodone has been shown to be an effective treatment, equianalgesic doses of other opiates are likely to be as effective. The most frequently reported adverse effects were constipation, nausea, and sedation. Impaired cognitive function, falls, and fractures are also more likely to occur in older patients prescribed opioids. Starting at a low dose and slowly increasing the dose may reduce the probability of serious side effects. We start all patients receiving opioids on an aggressive bowel regimen. Tramadol is a mu-opioid agonist and a norepinephrine and serotonin reuptake inhibitor. One randomized controlled trial in PHN found that 77% of subjects on tramadol versus 56% on placebo reported greater than 50% reduction. The adverse effects of tramadol include all the opioid adverse effects noted above as well as orthostatic hypotension, increased risk of seizures in patients with a history of seizures, and risk for serotonin syndrome in patients who use serotonergic medications, especially SSRIs and monoamine oxidase inhibitors.

Combination pharmacotherapy Many PHN patients do not respond to single drug therapy but there are relatively few data on optimal combinations of drugs. Combination therapy may augment a partial response to a single drug or produce better analgesia at lower doses of drug. However, combination therapy in older adults increases the risk of adverse effects and makes it difficult to determine which medication is responsible for adverse effects or benefits. In one study of combination therapy that included 22 patients with PHN, investigators studied the effects of morphine alone, gabapentin alone, or morphine-gabapentin combination in a randomized, double-blind, active placebo-controlled, four 5-week period crossover trial. The results showed that gabapentin and morphine combined achieved modestly better pain relief at lower doses of each drug than either as a single agent. However, the combination was associated with higher levels of sedation, dry mouth, and cognitive dysfunction than the maximal tolerated dose of each single agent. A similarly designed trial of combination therapy with nortriptyline and gabapentin also showed that

better pain relief with the combination than either drug alone.

For patients with PHN who do not have an adequate response to any of the front-line medications, other drug and nondrug treatments deserve consideration. These patients should be referred to a pain specialist or pain center for consideration of more complex drug combinations, risky second-line medications, or invasive treatments.

Other Treatments

Noninvasive treatments Transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS), acupuncture, cold application, and psychological treatments may be useful in some patients and have little risk, although their effectiveness in PHN has not been tested in controlled clinical trials. PHN patients who are good candidates for a trial of PENS or TENS are those that may be experiencing associated myofascial pain in addition to neuropathic pain. The presence of myofascial pathology is indicated by taut muscle bands (ie, a group of tense muscle fibers extending from a trigger point to the muscle attachments) and trigger point(s) (ie, a hyperirritable spot in skeletal muscle that is painful on compression) in the affected dermatome.

Invasive treatments Patients who remain in severe pain and have failed all other therapies can be considered for invasive interventions which include neural blockade, spinal cord stimulation, and central nervous system drug delivery. Neural blockade techniques include sensory nerve, plexus, and sympathetic nerve blocks as well as epidural and intrathecal blockade with lidocaine-like drugs and/or corticosteroids. Spinal cord stimulation requires implantation of an electrode in the thoracic or lumbar epidural space and the placement of a percutaneous electrical stimulator. Central nervous system drug delivery systems place the drug (eg, morphine) as close as possible to central pain receptors in the spinal cord corresponding to the affected dermatome. In general, the risks of these interventions outweigh any potential benefits in older adults with PHN.

PREVENTION

Zoster Vaccine

The zoster vaccine is a live attenuated virus vaccine that significantly boosts VZV-specific cellular and humoral immunity in older adults. This boost in VZV-specific cellular immunity by the zoster vaccine forms the scientific rationale for using the vaccine because cellular immunity to VZV declines with age. The clinical rationale for the zoster vaccine lies in the facts that herpes zoster causes substantial morbidity, antiviral therapy does not prevent PHN and must be initiated within 72 hours of rash onset for maximum benefit, and PHN treatments are incompletely effective and often poorly tolerated by older adults.

The Shingles Prevention Study was a randomized, double-blind, placebo-controlled trial to determine if the zoster vaccine would decrease the incidence and/or severity of herpes zoster and PHN among older adults. The study randomized 38,546 community-dwelling persons aged 60 years old or older to vaccine or placebo and followed them for herpes zoster and adverse events for a median of 3 years. The vaccine reduced incidence of herpes zoster from 11.12 to 5.42 cases (51.3%) per 1000 person-years for an NNT of 59 over the 3.12 years of the study. The vaccine reduced the incidence PHN from 1.38 to 0.46 cases (66.5%) per 1000 person-years for an NNT of 362 over the duration of the study. The zoster vaccine also reduced the pain burden of illness (a pain severity by duration measure) caused by herpes zoster by 61.1%. Two large cohort studies of the use of zoster vaccine in “real world” practice settings showed very similar results for vaccine efficacy for incidence of herpes zoster. Reactions at the injection site are more frequent among vaccine recipients but are generally mild.

Based on these findings, the Advisory Committee on Immunization Practices (ACIP) of the CDC recommends the vaccine for the prevention of herpes zoster and PHN in immuncompetent adults 60 years of age and older. The vaccine is contraindicated in persons with anaphylactic reactions to gelatin or neomycin; with leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic system; on immunosuppressive therapy, including high-dose corticosteroids (> 20 mg/day of prednisone or equivalent) lasting two or more weeks; and with AIDS or other clinical manifestations of HIV, including persons with CD4+ T-lymphocyte values less than or equal to 200/mm^3 undergoing hematopoietic stem cell transplantation (HSCT) or receiving recombinant human immune mediators and immune modulators. The zoster vaccine can be given simultaneously with other inactivated vaccines given at another site including influenza, pneumococcal polysaccharide, and pneumococcal conjugate vaccines.

The exact duration of the protection against herpes zoster by the zoster vaccine is unknown. In the short-term

persistence substudy of the Shingles Prevention Study, 7320 vaccine and 6950 placebo recipients were followed through year 7 after vaccination. Vaccine efficacy for herpes zoster and pain burden persisted through year 5 after vaccination. In the long-term persistence substudy of the Shingles Prevention Study, 6867 subjects were followed up to 11 years after vaccination and compared to historical controls. Vaccine efficacy for herpes zoster and pain burden persisted through year 8 after vaccination. Currently, there is no recommendation for a booster dose of the vaccine.

A large randomized placebo controlled trial in 50- to 59-year-old individuals showed vaccine efficacy of 69.8%. Based on the results of this trial the FDA licensed the vaccine for use in immunocompetent adults 50 years of age and greater. The ACIP retained the recommendation to vaccinate at 60 years of age and over because zoster vaccine administration should be timed to achieve the greatest reduction in burden of herpes zoster and its complications, which is in persons over 60 years old. Given that there is insufficient evidence for long-term protection offered by the herpes zoster vaccine, persons vaccinated under 60 years of age may not be protected when the incidence of herpes zoster and its complications are highest. Conversely, neither the FDA nor the ACIP set an upper age limit on the use of the vaccine. These individuals are at highest risk for herpes zoster and PHN and reduction of herpes zoster pain severity and duration occurs in the “old-old” even when herpes zoster is not prevented.

The efficacy of the zoster vaccine in individuals who have already had herpes zoster is unknown. However, older adults with prior herpes zoster ask for the vaccine because they do not want to experience zoster again and herpes zoster recurs in immuno competent individuals. The ACIP recommends the zoster vaccine for persons older than 60 years of age whether or not they report a prior episode of herpes zoster.

In summary, the incidence of herpes zoster and PHN increases greatly with aging so the majority of herpes zoster cases occur among older adults. Acute herpes zoster pasin, other herpes zoster complications (eg, ophthalmic zoster), and PHN interfere with functional status and lower quality of life in older people. Although not perfect, clinicians now have several tools to prevent and treat these conditions. Those tools include the zoster vaccine, early antiviral therapy, careful acute pain management, and a number of neuropathic pain treatments. The systematic application of these interventions will markedly reduce the suffering of older adults from herpes zoster and PHN.

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Chapter 130

Influenza and Respiratory Syncytial Virus

H. Keipp Talbot

Learning Objectives

- To understand the biology of influenza virus that leads to “drift” and “shift” in surface protein structure and their impact on vaccine formulation and the emergence of influenza pandemics.
- Recognize clinical situations where there is a need for diagnostic testing to confirm a specific viral etiology (influenza or respiratory syncytial virus [RSV]) in symptomatic older adults and recommend the specific tests appropriate in different clinical scenarios.
- Identify appropriate interventions to control outbreaks of influenza or RSV in a nursing home.
- Recognize the appropriate use of antiviral therapies for influenza in seniors.

Key Clinical Points

1. **The influenza virus has a segmented RNA core that encode key proteins on the viral surface including hemagglutinin and neuraminidase. Annual mutations in the RNA lead to “drift” in these proteins requiring annual reformulation and administration of the vaccine.**
2. **When entire segments of the influenza RNA recombine in animals, it can lead to an antigenic “shift” and result in a pandemic as there may be little or no immunity in the population.**
3. **Detection of influenza virus by direct antigen testing is insensitive (as low as 20%) in older adults, and a negative test does not rule out influenza infection. Reverse transcriptase polymerase chain reaction (RT-PCR) is more than 90% sensitive. Similarly, RSV is best detected by RT-PCR.**
4. **RSV is clinically indistinguishable from influenza in older adults—both may present subtly or primarily as an exacerbation of underlying chronic illnesses.**
5. **Antiviral therapy with neuraminidase inhibitors is indicated for treatment of influenza and as chemoprophylaxis for nursing home outbreaks. Supportive care is currently the only treatment for RSV.**
6. **Influenza immunization is recommended for all older adults. A high-dose vaccine is more effective than a standard-dose vaccine in seniors.**
7. **Immunization of staff reduces influenza mortality for nursing home residents.**

INFLUENZA

Viruses are an important threat to the health of older adults. Each year, it is estimated that influenza alone is associated with the death of 36,000 older adults in the United States. Despite immunization, outbreaks of influenza occur regularly in nursing homes and other long-term care facilities. This section of the chapter summarizes the biological, epidemiological, and clinical features of influenza that are relevant to older adults, with a particular emphasis on prevention.

Clinically Relevant Biologic Characteristics of Influenza Virus

To properly understand the impact of influenza in older adults, it is important to be familiar with several key characteristics of the virus. The structure of influenza consists of an envelope with a central nucleic acid core comprised of single-stranded RNA that encodes key structural proteins of the virus including hemagglutinin and neuraminidase on the envelope. There are three types of influenza viruses A, B, and C. However only A and B are clinically relevant. Influenza A viruses are characterized by the structure of the hemagglutinin, a surface protein that binds glycoprotein on the surface of respiratory epithelial cells, allowing the virus to enter by forming an endosome and then using the protein making machinery of the cell to replicate itself. Annually new mutations occur resulting in small changes in the hemagglutinin ("antigenic drift") hence the reason why influenza vaccine needs to be reformulated and given annually. The other surface projection, neuraminidase, cleaves terminal sialic acid residues from carbohydrate moieties on surfaces of infected cells, promoting the release of virions that go on to infect other cells. As discussed below, this is a key target for neuraminidase inhibitors (eg, oseltamivir, zanamivir), thus preventing the influenza virus from replicating.

An important feature of influenza is the segmented structure of the RNA at the core of the virus, with each of eight segments coding for a structural or enzymatic component of the virus. This gives the virus the potential to recombine with influenza viruses of animal origin, forming a virus with a novel genotype and hemaglutinnin to which there is no preexisting immunity. This is known as "antigenic shift" and was responsible for pandemics in 1957–1958, 1968–1969, and 2009. Of note, the highest mortality rates occurring in the 1918–1919 and the 2009 pandemics were not in older adults, but in younger adults, perhaps due to cross protection from the many influenza strains to which older adults were exposed over a lifetime. However, mortality in interpandemic periods is highest in those at the extremes of age. At present, there are only three hemaglutinins (H1, H2, H3) and two neuraminidases (N1, N2) that have developed a stable lineage in humans.

General Epidemiology of Influenza

Epidemics of influenza occur annually between November and April in the Northern Hemisphere. In any given season, there may be several strains circulating, hence the annual influenza vaccine contains multiple influenza strains.

Important Host Considerations in Older Adults

During the interpandemic period, older adults and particularly residents of long-term care facilities are equally likely to contract influenza as young, healthy adults, but are among those at highest risk for complications of influenza. Rates of hospitalization for influenza in older persons range from 136 to 508 per 100,000 persons versus 10 to 25 for those 5 to 49 years of age. The presence of chronic conditions, such as chronic lung disease, congestive heart failure, conditions that predispose to aspiration (eg, stroke), and metabolic disease, increase the risk for complications following infection with influenza. Many of these conditions occur predominately in older age groups. Moreover, studies that have assessed complications have found that age older than 65 years alone is independently associated with increased risk for influenza complications.

Based on our current understanding, the cause of death as a result of influenza in older adults in the interpandemic period includes viral pneumonia, a bacterial infection complicating the influenza infection, myocardial infarction, stroke and exacerbation of underlying comorbid conditions. Infection with influenza virus predisposes to *Streptococcus pneumoniae* or *Staphylococcus aureus* infection, which most often results in bacterial pneumonia. Deficits in innate immunity (phagocytes, natural killer cells) and acquired immunity (T-cell function, cytokine activity, antibody response) are all felt to play a role, as discussed in Chapter 3.

Clinical Presentation

Young, healthy individuals with influenza characteristically present with a sudden onset of fever, cough, myalgia, sore throat, and headache. Fever and cough have been shown in a systematic review to be the best predictors of influenza in the general population. In older adults, the presentation maybe more subtle with cough and change in baseline temperature predominating. Often times, older adults present with worsening of comorbid conditions such as a chronic obstructive pulmonary disease or congestive heart failure exacerbation. One of the most important factors in making the diagnosis of influenza, whether on clinical grounds or through diagnostic testing, is the local influenza activity. That is, if a community is experiencing an outbreak of influenza, particularly if the incidence of influenza is at its

peak, fever and cough in an older person increase the likelihood of infection with influenza. In the nursing home setting, it is essential to obtain prompt diagnostic testing, because, as consistently demonstrated in longitudinal studies that have tied symptoms with specific etiologic agents, the clinical presentation is nonspecific. Even when there are peaks of influenza in the community, respiratory syncytial virus (RSV) or other respiratory viruses can circulate. It is essential to obtain testing, because it can lead to a change in management: an outbreak of influenza in nursing home warrants chemoprophylaxis (see further) as well as immunization of nonimmunized residents in whom it is safe to do so.

Specific Diagnostic Tests

The traditional method to detect influenza has been viral culture, which is limited by moderate diagnostic accuracy and delay in obtaining results (**Table 130-1**). Rapid tests include direct fluorescent antigen (DFA), or direct immunofluoresence, where monoclonal antibodies labeled with fluorescent material are directed to influenza cell coat antigens. A result can be reported within hours. Rapid enzyme-linked immunoassay (ELISA) tests are commercially available, but are very insensitive in older adults with sensitivities as low as 20%. Nucleic acid amplification testing, such as reverse transcription polymerase chain reaction (RT-PCR), is the most promising test since it is over 95% sensitive and specific and the turnaround time can be rapid. The drawback, however, is that not all laboratories are capable of performing PCR daily at this time.

TABLE 130-1 SUMMARY OF TEST CHARACTERISTICS OF DIFFERENT DIAGNOSTIC TESTS FOR VARIOUS RESPIRATORY VIRAL PATHOGENS IN OLDER ADULTS

	CULTURE	RAPID EIA	DFA/IFA	PCR	SEROLOGY
Influenza A	++	+	+	+++	++[a]
Influenza B	++	+	+	+++	++[a]
RSV	+	+/–	+/–	+++	+++

+/–, available but poor sensitivity; +, fair sensitivity; ++, good sensitivity; +++, optimal sensitivity.

[a]Interpretation complicated by vaccination.

Infection Control Aspects

The incubation period of influenza, the period of time from initial infection to development of symptoms, is typically 2 days, but can range from 1 to 4 days. An infected individual becomes contagious 1 day prior to the onset of symptoms. In adults, viral shedding at levels high enough to cause transmission occurs over 5 or 6 days. Although the extent to which influenza can be transmitted by airborne spread is controversial, the majority of spread of influenza is large droplet caused by coughing and sneezing hence medical workers should wear a mask to prevent infection and spread of infection. In terms of practical implications, use of “respiratory etiquette,” coughing, and sneezing into tissues, for example, may help prevent spread to older adults who are susceptible to complications, although supporting epidemiologic evidence is limited.

Immunization

Many influenza vaccine formulations are now available in the United States. Only three, all inactivated vaccines, are licensed for adults aged 65 years or more. The most well-known influenza vaccine is the trivalent inactivated vaccine, now abbreviated as IIV3, which contains components of an H1N1, an H3N2, and B strains. Due to difficulties anticipating that B viral lineage will circulate, many vaccine manufacturers have added an addition influenza B strain to the influenza vaccine. This quadrivalent vaccine is abbreviated as IIV4. Due to decreased immune responses and poorer clinical responses when IIV3 or IIV4 is administered in seniors (when compared with young adults), a new high dose influenza vaccine has been licensed. This vaccine only contains three influenza strains but has four times the dose of each component versus the regular IIV3 and is abbreviated as IIV3-HD. The IIV3-HD has been shown to generate higher antibody levels in older adults than IIV3, and is 24% more effective for the prevention of illness due to influenza. At this time, the advisory committee on immunization practices recommends use of any of these three vaccines in older adults.

For the same reasons that older adults are more likely to have complications due to influenza infection, older adults

respond less well to influenza immunizations. A recent systematic review summarized 35 influenza vaccine effectiveness studies. These studies were performed in 15 countries. Cases were influenza positive; controls were patients who also had an acute respiratory illness but who tested negative for influenza. Vaccine effectiveness for the prevention of medically attended acute respiratory illness was found to be 38% to 70% during seasons of vaccine and circulating strain match and 15% to 59% during seasons of mismatch. These data show that influenza immunization plays an important but modest role in prevention.

Studies using seasonal regression modeling with both United States and Italian data show no reduction in mortality among older adults with increased influenza vaccine coverage. These studies assessed trends in excess mortality after adjusting for age. One possible explanation of the results in these studies is that the influenza vaccine failed to protect older adults against death because of immune senescence (see Chapter 3).

Influenza and Long-Term Care

Residents of nursing homes and other long-term care facilities are at high risk for complications of influenza, including pneumonia, death, and hospitalization. This is likely because there is close contact between residents and staff in these facilities, increasing the exposure to and transmission of influenza, and because the majority of residents have comorbidities, including cognitive impairment, chronic lung diseases, and strokes. Outbreaks of influenza are well characterized in nursing homes, often described as “explosive” in that the onset is relatively abrupt. Such outbreaks are usually first detected by nursing home staff who notice a higher incidence of respiratory symptoms than usual on specific long-term units, although at least one surveillance study has shown that such outbreaks are commonly missed even when active surveillance by trained nurses is performed. Such outbreaks are best managed using a multifaceted approach that includes the following: cohorting residents, increasing adherence to hand hygiene, chemoprophylaxis with antiviral agents, and immunization of those not previously vaccinated. It should be noted that because of space limitations, it is usually not feasible to cohort ill residents together as a means of separating them from noninfected residents in long-term care facilities. Administering neuramindase inhibitors, such as oseltamivir or zanamavir, as chemoprophylaxis to noninfected residents helps to reduce further spread. In one randomized controlled trial where long-term units were randomized to zanamivir or to rimantidine, the risk of influenza was 3% in the zanamivir arm versus 8% in the rimantidine arm ($P = 0.038$). More recent data suggest that immunizing staff in nursing homes against influenza benefits residents. There have been four cluster-randomized controlled trials showing that immunizing health care workers against influenza reduces mortality in residents of long-term care facilities. Vaccinating nursing home staff against influenza may prevent deaths, use of health services, and influenza-like illness in nursing home residents.

Use of Antivirals to Prevent and Treat Influenza in Older Adults in the Community

There are five antivirals that are approved for treating influenza: amantadine (oral), rimantadine (oral), zanamivir (inhaled), oseltamivir (oral), and peramivir (IV). Amantadine and rimantadine are only active against influenza A and currently circulating influenza A strains are predominantly resistant to both amantadine and rimantadine. The neuraminidase inhibitors zanamivir and oseltamivir are active against influenza A and B are 70% to 90% effective for prophylaxis in preventing influenza and when used as treatment to reduce clinical severity when given within 48 hours of symptom onset. However, the feasibility of using these agents for treatment is reduced since the majority of patients in the community present over 48 hours following symptom onset. It is important to note that the doses of treatment and prophylaxis are different. Hence it is important, to use treatment doses if a patient is symptomatic. Zanamivir and oseltamivir are associated with few adverse effects. Zanamivir may worsen or provoke respiratory distress in those with underlying obstructive disease. Oseltamivir should be dosed based on renal function. In early 2015, the FDA approved a third neuraminidase inhibitor, peramivir, for the treatment of influenza which is only available in an IV formulation.

Indirect Benefit of Immunization in Children to Protect Older Adults

There is observational data to suggest that children play an important role in the spread of influenza in the community. For example, data from a 3-year longitudinal surveillance study of children and adults in New York State demonstrated that children were about twice as likely to acquire and shed influenza as compared to adults. In a longitudinal study conducted in Seattle from 1968 to 1974, elementary and junior high school students had the highest rates of influenza during epidemics, reaching 54%. In the Tecumseh, Michigan, studies from 1976 to 1981, over one-third of children between the ages of 5 and 14 years had influenza virus isolated from specimens, and the highest rate

was among persons with febrile respiratory illness. Serological data revealed similar results; from 1977 to 1978, children in 5 to 9, 10 to 14, and 15 to 19 age groups had approximately a 30% infection rate with H3N2. This was over twice the rate seen in adults. There were similar infection rates with influenza B in children aged 5 to 14 years, rates 14-fold higher than those in adults older than 20 years of age.

Given that school-aged children appear to play an important role in introducing and transmitting influenza into households, and hence into the community, immunizing these children may interrupt spread to older adults who are at high risk for complications. In the Tecumseh studies, Monto and colleagues demonstrated that selectively immunizing 86% of children in this 7500-person community with inactivated influenza vaccine reduced influenza in adults by a third when compared to an adjacent community, where children were not immunized. More evidence for the potential benefit of immunizing children with inactivated vaccine has been derived from an analysis of the effect of influenza vaccination in Japan. Japan began a program of immunizing school-aged children in 1962 and continued this policy until 1994. The effect of this policy was to dramatically reduce excess mortality rates to values similar to those in the United States. The fact that there was a rapid increase in excess deaths after 1994, the year in which mass immunization formally ended, supports the conclusion that the effects observed in earlier years were because of vaccine-induced herd immunity, although it is possible that social factors may have amplified the effects of this program. The authors explain their findings by hypothesizing that the high levels of vaccination in school children protected transmission of influenza to their grandparents. There have been several more recent observational studies where children have been immunized showing a reduced attack rate of influenza in adults. However, randomized clinical trial evidence of immunizing children to prevent influenza in older adults is limited.

RESPIRATORY SYNCYTIAL VIRUS

RSV has been long recognized as the major cause of bronchiolitis in children. Since the 1970s, there have been numerous reports about the burden of RSV in older adults, particularly those residing in nursing homes. RSV is now recognized as an important contributor to morbidity in both community-dwelling older adults as well as in residents of long-term care facilities. This section will describe the epidemiology of RSV in both settings including clinical, diagnostic, and management issues.

Characteristics of Respiratory Syncytial Virus

RSV is an enveloped RNA virus that can be classified into two major groups, A and B, based on antigenic and genetic properties. An important feature of RSV is that reinfections occur frequently throughout life and into older age. Because RSV infection does not produce robust immunity, developing a vaccine has been a major challenge. In addition, RSV is a very labile virus meaning it can be difficult to grow if it is not transported very carefully. This makes diagnoses difficult outside of the hospital setting.

General Epidemiology

Like influenza, RSV circulates during winter months in temperate climates roughly beginning in November and lasting until early spring. Often clinical cases precede influenza epidemics. The incubation period of RSV is 3 to 5 days. The majority of those who are infected show respiratory symptoms. In contrast to infants who shed higher titers ($10^{5–6}$ plaque forming units/mL of secretion) for longer time periods (10–14 days), adults tend to shed lower titers of the virus ($10^{2–3}$ plaque forming units/mL of secretion for 3 to 6 days). RSV is spread primarily by large droplets and fomites.

Community-Dwelling Older Adults and Respiratory Syncytial Virus

The best data about RSV in older persons living in the community are derived from a cohort study conducted in Rochester, New York, from 1999 to 2003. This cohort was comprised of 608 healthy persons aged 65 years and older. Forty-six (8%) of the 608 participants developed RSV, compared to 56 (10%) of high-risk older participants (defined as having congestive heart failure or chronic pulmonary disease). The impact of RSV infection was important in both the healthy older adults group and in the high-risk group: 17% and 23%, respectively, in these groups made physician office visits. Morbidity was greater in the high-risk group, where 16% required hospitalization. The study was also useful because it allowed for a comparison to influenza: 42% of healthy older participants and 60% of high-risk participants required office visits for influenza, rates statistically significantly higher than for RSV. Since then, RSV

has been shown in other studies to cause similar if not higher hospitalization rates than influenza in older adults.

Epidemiology of Respiratory Syncytial Virus in Long-Term Care Facilities

Respiratory syncytial virus attack rates during nursing home outbreaks have been reported to be variable, ranging from 2% to 90%. However, most involved relatively small numbers of residents and included the use of diagnostic assays with varying levels of sensitivity. In one prospective study conducted in Rochester, where a sensitive enzyme immunoassay was used, the overall attack rate was 7% and the virus was identified as a cause of 27% of illness. One retrospective cohort study estimated the burden of illness in nursing homes in Tennessee by linking cardiopulmonary hospitalization, medical utilization, and death to viral activity in the general community during a period of 88,581 person-years. According to these data, RSV accounted for 15 hospitalizations and 17 deaths per 1000 residents.

Clinical Features of Respiratory Syncytial Virus in Older Adults

It is important to note that the clinical features of RSV cannot be distinguished from those of other viruses, such as influenza, with the exception that fever is less pronounced than for influenza. The nonspecific nature of the clinical presentation indicates the need for diagnostic testing. Signs and symptoms include rhinorrhea, nasal congestion, sore throat, cough, and dyspnea. Similar to patients infected with influenza, patients with RSV may present with exacerbation of underlying conditions such as chronic obstructive pulmonary disease and congestive heart failure.

Diagnosis

This can be done by viral culture, antigen detection in respiratory secretions, nucleic acid amplification, or serology. For diagnosis in real time, only the first three tests are appropriate. It is important to note that viral culture is only 50% sensitive. Similarly, detection of RSV antigens using immunofluorescence is very insensitive in older adults. In contrast, reverse transcriptase-polymerase chain reaction (RT-PCR) is relatively sensitive and specific. As the use of multiplex PCR systems increases, RSV will likely be recognized more often as the causative agent in the clinical setting.

Therapy

Care is mainly supportive in the older adult with RSV infection, the only licensed antiviral with activity versus RSV is ribavirin, but there are sparse data on which to base treatment recommendations in adults. Practical considerations about ribavirin include that the administration of this aerosolized drug to older adults using face masks may be difficult and ribavirin is teratogenic, which is important for the health care provider who is delivering care and the family that is entering the patient's room.

Prevention

Transmission of RSV is believed to be caused by large droplets and fomites. Strategies such as increasing hand hygiene, particularly in nursing homes, may help to reduce spread. Isolation practices for RSV include gowning and gloving when taking care of a patient with RSV. At the present time, there are no licensed RSV vaccines.

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